The International Pharmaceutical Excipients Council

& The Pharmaceutical Quality Group

The Joint Good Manufacturing Practices Guide

For Pharmaceutical Excipients

Version 5
2022

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.

This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

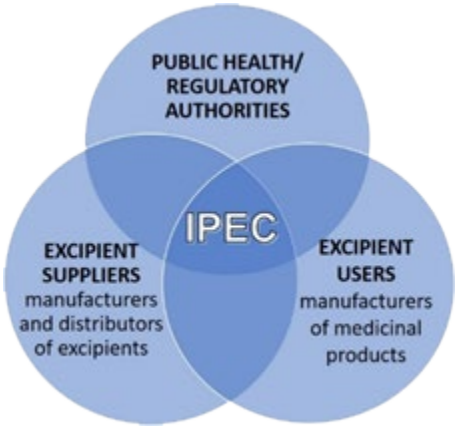
FOREWORD

IPEC

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and users. At the current writing there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the international excipient standards development and harmonization, provide information useful for new excipient development and introduction, and offer best practice and guidance concerning excipient manufacture.

IPEC has three major stakeholder groups:

1. excipient manufacturers and distributors, defined as suppliers in IPEC documents,
2. pharmaceutical manufacturers, defined as users in this document, and
3. public health and regulatory authorities.



The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

PQG

The PQG was formed in 1977 to promote development of a consistent approach to pharmaceutical quality and good manufacturing practice. The group has since expanded, and in 1990 the PQG published three codes of practice to cover pharmaceutical raw materials, printed and contact packaging materials. In 1995 the codes were revised and were integrated with ISO 9002:1994. The code for raw materials was revised and reissued as PS 9100:2002 Pharmaceutical excipients, an application standard and GMP guide for pharmaceutical excipients.

For further information, visit www.pqg.org.

This guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the rules and regulations applying to excipients will vary from region to region and country to country. In addition, the rules and regulations are continually evolving. It is the responsibility of the reader to review the latest version of the applicable regulatory guidance; however, the version referenced in the guide will be based on the version available at the time the guide was published.

In this guide, pharmaceutical excipient(s) will be referred as excipient(s). This guide may be applied to veterinary medicines, as appropriate with reference to specific veterinary guidance and regulations.

Throughout the guide, justification implies that a decision is made based on a scientific, quality and/or regulatory considerations.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

Table of Contents

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

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Part 1

IPEC-PQG GMP Guide

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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

ACKNOWLEDGEMENTS

This guide was developed by representatives from International Pharmaceutical Excipients Council (IPEC) and the Pharmaceutical Quality Group (PQG) member companies. IPEC is an industry association whose members consist of excipient manufacturers, distributors, and users.

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.

The company representatives who worked on this guide are listed below:

List of Contributors from IPEC-Americas

William Dale Carter*, Evonik

George Collins, Vanderbilt Chemicals LLC

Ann Gulau, IFF

List of Contributors from IPEC Europe

Jeffrey Brambora, Consultant

Roberto Mastrantonio, Eli Lilly

Astrid Stockrahm-Uhling*+, DFE Pharma

Beverley Stout, GSK

List of Contributors from PQG

Ian McKeown, PQ Silicas

* co-chair
+ task force team leader

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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PART 1 - IPEC-PQG GMP GUIDE

1 Introduction

1.1 Purpose and scope

Excipients are essential components of the medicinal product formulation. The quality of excipients is critical to ensure the safety, quality, and efficacy of medicinal products, because excipients provide a wide range of functionality.

Excipients can have multiple uses in medicinal products (see 4.1 Note 1). Therefore, it is essential to apply principles of appropriate **Good Manufacturing Practices** (**GMP**) to excipients. Additionally, excipient GMP provides the foundation for the understanding and implementation of all **IPEC guide**s.

Users of excipients are increasingly required by regulatory authorities to ensure patient safety through the evaluation of risks and application of suitable GMP to the **manufacture** and supply of each excipient. This document provides GMP appropriate to the manufacture of all excipients and to GMP services provided by excipient manufacturers. It covers the **quality management system**, including the GMP necessary throughout manufacturing, based on **risk assessment**s, for both batch and continuous processes.

It should be recognized that once the excipient is in the **supply chain**, it may be subjected to further GMP related activities, such as re-packaging or re-**labeling**, before it reaches the final user. Such activities should be performed in compliance with GMP principles as described in this guide.

This guide is the result of a joint initiative between the International Pharmaceutical Excipients Council (IPEC), and the Pharmaceutical Quality Group (PQG).

1.2 Principles adopted

1.2.1 *The guide and its use*

Excipients are diverse materials that often have uses other than pharmaceutical applications. Therefore, each **manufacturer** should consider how this guide applies to their processes, products, and GMP services (see 4.1).

This revised guide incorporates the principles of risk assessment to identify the controls needed for GMP according to the manufacturer's intended use of the excipient. The need for risk assessments is identified throughout this guide. This approach allows the guide to be used for all

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

excipients, including those that are supplied sterile and / or pyrogen free, and those intended for parenteral, ocular, inhalation, or open wound use.

For the purposes of this guide, the terms “Good Manufacturing Practices (GMP)” and “current Good Manufacturing Practices (**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*

This international guide applies to all excipients and excipient-related GMP services. Therefore, it cannot specify the manufacturing knowledge or competencies required, the national legal requirements, or consider excipient characteristics (e.g., chemical, or physical properties) for every excipient or GMP service. It is the responsibility of each excipient manufacturer to utilize appropriate expertise when identifying and implementing applicable requirements (see 4.2).

1.2.3 *Quality System standard*

The quality management system standard chosen as a framework for this guide is **ISO** 9001:2015.

IPEC and **PQG** support merging GMP principles for excipient manufacturing with the **ISO 9001** quality management system because these principles enhance the organization’s quality management system, operational processes, and related procedures. The organization may also seek certification to an excipient GMP standard.

1.3 Layout and definitions

1.3.1 *Layout*

Revised in its entirety, this version of the guide, its headings and clause numbers have been developed to align with ISO 9001:2015. Additional headings are included as required to introduce the additional **guidance** on GMP when not covered by ISO 9001:2015 clauses.

This guide is published in two parts:

- Part 1 includes Good Manufacturing Practices for excipients.
- Part 2 includes Good Manufacturing Practices for excipients together with notes that offer examples for GMP interpretation and implementation without adding further requirements.
    - Notes may provide common examples but are not intended as an exhaustive list.
    - Notes are presented as indented, *italicized text*.

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Each part of the guide has the following sections:

Section 1, Introduction

Section 2, General guidance, identifies the regulatory expectation of following excipient GMP.

Section 3, Excipient GMP implementation, provides an overview of the GMP criteria applicable to services and excipient manufacture from the point where excipient GMP starts.

Sections 4 through 10 provide guidance on the GMP principles and implementation of a quality management system suitable for excipient manufacture and service provision.

1.3.2 *Definitions*

ALCOA+:

The acronym ALCOA defines that data should be Attributable, Legible, Contemporaneous, Original, and Accurate. In addition, ALCOA+ guidance defines that data should also be Complete, Consistent, Enduring, and Available.

GMP Service:

GMP-related activities performed by an organization on behalf of their customer, where the organization's output is not the product (excipient) but either a tangible or intangible output of an activity.

Manufacture/Manufacturing Process:

All operations from receipt of materials through production, packaging, **repackaging**, labeling, **relabeling**, quality control, release, storage and **distribution** of excipients and related controls.

Regulatory requirement:

ISO 9000 defines "regulatory requirement" as "obligatory requirements specified by an authority mandated by a legislative body".

Statutory requirement:

ISO 9000 defines "statutory requirement" as "obligatory requirement specified by a legislative body".

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

ISO 9000:2015:

ISO 9000:2015 specifies the terms and definitions that apply to all quality management and quality management system standards (developed by ISO/TC 176). Reference to ISO 9000 is used in Notes, when definitions are provided for generic terms, such as “nonconformity”. These definitions are taken from ISO 9000, because they are not available in ISO 9001.

For further definitions refer to the International Pharmaceutical Excipient Council Glossary: General Glossary of Terms and Acronyms. The first use of a term found in the Glossary will be in **bold**.

2 General Guidance

Conforming with **excipient** GMP is a best practice that benefits excipient users and the patient.

Complying with excipient GMP is a regulatory expectation when statutory or regulatory requirements exist either in the location of excipient manufacture or intended market.

3 Excipient GMP implementation

The objective of excipient GMP is to ensure that:

- excipients are consistently manufactured with the intended quality and performance characteristics;
- GMP services lead to consistent results.

The excipient manufacturer should design, control, document, and maintain its manufacturing processes. Justification is required to determine the point at which excipient GMP should be applied. This justification should be based on thorough process knowledge and recorded in a documented risk assessment. GMP usually begins well before the final finishing operation.

Implementation of excipient GMP should also consider at a minimum:

- **batch** versus **continuous processing**;
- dedicated versus multi-purpose **equipment**;
- open versus closed processes.

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Throughout this guide, the use of “GMP” will mean “excipient GMP” as outlined in this document.

4 Context of the organization

In a GMP context, the excipient manufacturer is the organization. The two terms are used interchangeably throughout this guide.

4.1 Understanding the organization and its context

Manufacturers should identify, within their portfolio, those products manufactured and marketed as excipients. Excipient manufacturers should define and document the intended use(s) of their excipients, considering the potential impact on patient safety. They should determine and monitor external and internal issues that are relevant to the manufacture and marketing of excipients. These should include outsourced activities that can affect excipient quality and for which the organization has control and responsibility.

Excipient manufacturers should identify the quality management system processes required to assure excipient quality, accounting for customer, social, legal, technological, and cultural environments.

4.2 Understanding the needs and expectations of interested parties

The excipient manufacturer should determine the interested parties that are relevant to the GMP quality system being maintained. Current applicable customer, compendial, statutory, and regulatory requirements should be determined and met (see 6.1.1).

The excipient manufacturer should monitor information about interested parties and their relevant requirements (see 4.3, 5.3 and 6.1.1).

4.3 Determining the scope of the Quality Management System

The organization’s overall intentions and approach to GMP should be documented to facilitate common understanding and consistent application. The excipient manufacturer should have:

- a documented description of the quality management system;
- a quality policy (see 5.2);
- commitment to apply the appropriate quality management principles contained in this guide, including GMP.

The documented description of the quality management system should include the scope of the quality management system and reference to supporting procedures, considering:

- boundaries and applicability of GMP;
- products and GMP services in scope;
- external and internal issues (see 4.1);
- requirements of relevant interested parties (see 4.2);
- the interaction between quality management system processes (see 4.4).

Documentation should identify and justify the starting point in the process (manufacturing or service provision) from which the full excipient GMP principles of this guide apply.

4.4 Quality Management System and its processes

Excipient manufacturers should define, implement, maintain, and continually improve the quality management system and its processes. These processes and their interactions should be documented.

This documentation should include:

- inputs required and outputs expected from these processes;
- process sequence and interaction;
- criteria and methods needed to ensure the effective operation and control of these processes;
- resources needed for these processes and ensure their availability;
- responsibilities and authorities for these processes;
- risks and opportunities as determined in accordance with the requirements of 6.1 and how they are addressed;
- evaluation of processes and implementation of any changes needed to ensure that these processes achieve their intended results;
- evaluation of risk assessments and improvements to the quality management system (see 10.1).

Records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality management system.

Where manufacturing, testing or other operations that could affect excipient quality are outsourced (i.e., externally provided), the responsibility for quality remains with the excipient

manufacturer and control measures should be defined. The organization should define which records, results and reports of subcontractor activities are retained and by whom.

5 Leadership

5.1 Leadership and commitment

5.1.1 *General*

Top management should be identified.

Top management should demonstrate their commitment to the quality management system and be accountable for its maintenance and effectiveness. This should be accomplished through the development of a quality policy (see 5.2.1) and establishment of quality and GMP objectives (see 6.2). Current applicable customer, compendial, statutory, and regulatory requirements should be determined and met.

Top management should promote risk-based thinking (see 6.1).

Top management should provide adequate resources to ensure conformance to the principles of this guide. There should be a process for the identification of resources needed for adherence to GMP.

Top management should ensure that the quality policy, the quality and GMP objectives, and the definition of roles, responsibilities and authorities are communicated, understood, and applied across the organization. They should ensure that the quality management system achieves its intended result and should promote continual improvement (see 10.3). Progress towards the documented quality and GMP objectives should be reviewed at planned intervals.

5.1.2 *Customer focus*

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

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

5.2 Quality policy

5.2.1 *Establishing the quality policy*

Top management should participate in and provide the resources necessary for the development, implementation, and maintenance of the organization's quality policy. The quality policy should include commitment to appropriate GMP, compliance with applicable requirements and continual improvement of the quality management system.

5.2.2 *Communicating the quality policy*

Top management should demonstrate its commitment to the quality policy and appropriate GMP, and ensure that this is communicated and implemented within the organization.

5.3 Organizational roles, responsibilities, and authorities

Top management should ensure that responsibility and authority are clearly defined, communicated, and understood within the organization.

Top management should assign the responsibility and authority for:

- ensuring that the quality management system conforms to the provisions of this guide;
- ensuring that the processes are delivering their intended outputs;
- reporting to top management on the performance of the quality management system, opportunities for improvement (see 9.3.2) and changes to applicable customer, compendial, statutory and regulatory requirements (see 4.2);
- ensuring the promotion of customer focus throughout the organization;
- ensuring that the integrity of the quality management system is maintained when changes to the quality management system are planned and implemented.

Top management should ensure that a quality unit or other appropriate unit, independent of production, has the responsibility and authority to:

- ensure **quality-critical** activities are identified and undertaken as defined;
- review and approve documents that have the potential to impact product quality;
- approve external providers (**supplier**s) of quality-critical processes, services and materials;
- ensure that providers of outsourced processes and services comply with the relevant sections of this guide (see 8.4);
- approve or reject **raw material**s, packaging components, intermediates and finished excipients, according to current approved **specification**s and procedures;

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- approve or reject the excipient if it is produced, processed, packaged or held under contract by another company;
- ensure that there is a review of production records prior to excipient release;
- ensure that where errors, deviations, or nonconformities have occurred or are identified in the review process, they are appropriately investigated and documented;
- ensure corrective and preventative actions are implemented and effective;
- participate in reviewing and authorizing **significant change**s that have the potential to impact quality (see 8.5.6);
- review and approve the results of investigations into deviations from production instructions, test or measurement failures, customer complaints, or other nonconformities;
- develop and implement an internal audit program of the quality management system.

Some of the quality unit's activities may be delegated if appropriate controls are in place and documented. However, in all cases the quality unit should be responsible for performing:

- review and approval of documents that impact excipient or GMP service quality;
- approval of significant changes that may impact excipient or GMP service quality;
- approval of quality-critical suppliers;
- release of the finished excipient;
- release of GMP services;
- approval of **reworking**;
- evaluating and determining the disposition of returned excipients, including recalled excipients.

For all of the quality unit's activities listed in this section, whether performed by the quality unit or another appropriate unit, records should be available to demonstrate review and approval / rejection. Although quality unit activities may be delegated, the quality unit is ultimately responsible for the final output and should approve the controls used by any other unit to perform the delegated activity.

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An organizational chart by function should show inter-departmental relationships as well as relationships to top management. Personnel who have an impact on excipient quality should have job descriptions (see 7.2).

6 Planning

6.1 Actions to address risks and opportunities in the Quality Management System

6.1.1 *Risk Assessment*

The excipient manufacturer should conduct risk assessments of the issues referred to in 4.1 and the requirements referred to in 4.2 to determine the risks and opportunities that need to be addressed to:

- give assurance that the quality management system can achieve its intended result(s);
- enhance desirable effects;
- prevent, or minimize, undesirable effects;
- achieve continual improvement.

See also “The IPEC Risk Assessment Guide for Pharmaceutical Excipients”.

6.1.2 *Preventive action and continual improvement*

The excipient manufacturer should plan actions to address risks and opportunities in the quality management system (see 6.1.1), by:

- initiating preventive actions including assignment of responsibilities and timelines for implementation, to deal with problems at a level corresponding to the risks;
- initiating actions to enhance desirable effects or remove barriers to improvement;
- ensuring that actions are implemented and effective;
- implementing and recording changes in processes or procedures resulting from actions.

6.2 Quality and GMP objectives and planning to achieve them

Top management should set appropriate quality and GMP objectives to ensure that the excipient manufacturer maintains and improves its performance. These objectives should be:

- consistent with the quality policy;

- measurable;
- monitored;
- communicated;
- documented;
- updated as appropriate.

When planning to meet these objectives, the excipient manufacturer should determine:

- what will be done;
- who will be responsible;
- what additional resources will be required;
- when it will be completed;
- how results will be evaluated.

6.3 Planning of changes

The excipient manufacturer should establish and maintain documented procedures to evaluate and approve changes that may have an impact on the excipient or GMP service.

Prior to implementation, evaluation and approval of changes should be documented (see 7.5) and, where appropriate, a formal risk assessment conducted. Consideration should include potential impact on **validation** (see 8.5.1.8) or regulatory submissions made by the excipient supplier. Procedures should describe the means by which a change is determined to be significant. Where the impact is determined to be significant, such changes should be communicated to customers and, as applicable, to regulatory authorities. See also “The IPEC Significant Change Guide for Pharmaceutical Excipients”.

7 Support

7.1 Resources

7.1.1 *General*

The organization should, in a manner consistent with this guide, determine and provide adequate resources to:

- implement, maintain and improve the quality management system;

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- produce, package, test, store and release each excipient;
- supply each GMP service.

7.1.2 *People*

The organization should determine and provide adequate numbers of qualified personnel.

7.1.3 *Infrastructure*

The infrastructure should be designed, managed, operated, cleaned, and maintained in accordance with GMP principles to ensure excipient quality as well as to minimize the risk of **contamination**, including **cross-contamination**. It should be designed and controlled to prevent unauthorized access.

An infrastructure risk assessment should be documented (see 7.1.3.1 - 7.1.3.5), based on the intended use of the excipient, to identify areas in which the excipient is at risk of contamination from infrastructure design and / or deficiencies. See also “The IPEC Risk Assessment Guide for Pharmaceutical Excipients”.

7.1.3.1 *Buildings and facilities*

The ability to clean and minimize the risk of contamination (including pest infestation (see 7.1.4.4) and cross-contamination) should be considered in the design of the manufacturing processes and facilities, particularly where the excipient is exposed to the environment.

To facilitate cleaning, maintenance, and correct operation appropriate to the type of processing, buildings and facilities used in the supply of GMP services or the production, processing, packaging, testing or storage of an excipient should be:

- appropriate for their purpose,
- maintained in a good state of repair, and
- of suitable size, construction, and location.

Manufacturing processes using **allergens**, highly sensitizing or toxic materials should be located in dedicated facilities and / or use equipment not used for excipient manufacture. In some jurisdictions this is a regulatory requirement. If allowed by regulation and when non-dedicated facilities or equipment are used, appropriate measures, resulting from a specific risk assessment, should be implemented to minimize the risk of cross-contamination. The effectiveness of these measures should be demonstrated.

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7.1.3.2 *Equipment*

To facilitate cleaning, maintenance, and correct operation for the type of processing, equipment used in the supply of GMP services or the production, processing, transfer, packaging, testing or storage of an excipient should be:

- appropriate for its purpose,
- maintained in a good state of repair, and
- of suitable size, construction, and location.

Consideration of the risk of breakage or damage should be given.

Equipment should be qualified and commissioned before use to ensure that it is functioning as intended. See also “The IPEC Validation Guide for Pharmaceutical Excipients”.

The use, cleaning and maintenance of quality-critical equipment should be recorded (see 8.5.1.1). The status of equipment should be readily identifiable.

Where equipment is located outdoors there should be suitable controls to minimize the risk to excipient quality from the environment.

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 not come into contact with raw materials, packaging materials, intermediates or finished excipients. Where contact with such substances is possible, substances at least suitable for use in food applications should be utilized.

Equipment should be designed to minimize the possibility of contamination caused by direct personnel contact. The sanitary design of transfer and processing equipment should be evaluated using a risk assessment.

Equipment and its components should be assessed regarding their potential for erosion and degradation to control the risk of contamination, including cross-contamination.

Equipment maintenance:

Documented procedures should be established and followed for maintenance of quality-critical equipment used in the production, processing, packaging, testing, or holding of excipients. There should be records of the use and maintenance of quality-critical equipment.

Computer systems:

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

Computer systems (i.e., software, hardware, data) that may impact excipient quality should have sufficient controls for operation and maintenance to ensure that the system is performing as intended, including:

- procedures for periodic system **verification**;
- back-up or archiving (see 7.5.1);
- preventing unauthorized access;
- assurance that changes are traceable, verified, documented, and only made by authorized personnel (see 6.3 and 7.5).

See also “The IPEC Validation Guide for Pharmaceutical Excipients”.

Records demonstrating proper performance of the computer systems should be maintained.

7.1.3.3 *Utilities*

A risk assessment should be performed to consider the risk to excipient quality from utilities used in the production, storage, or transfer of materials. Appropriate action should be taken to eliminate or, at a minimum, control the identified risks. Utilities that could impact excipient quality should have documented specifications and be of suitable quality for their intended use. **Quality critical** parameters of these specifications should be monitored at a documented frequency (see 8.5.1).

7.1.3.4 *Water*

A risk assessment should be performed to consider the risk to excipient quality from water used in the manufacture of excipients. Appropriate action should be taken to eliminate or, at a minimum, control the identified risks. Water that could impact excipient quality, regardless of its source, should have documented specifications and be of suitable quality for its intended use. Quality critical parameters of these specifications should be monitored at a documented frequency (see 8.5.1).

Unless otherwise justified, water used in the manufacture of excipients should, at a minimum, meet **WHO guideline**s for drinking (potable) water. When drinking water quality is insufficient to ensure excipient quality, appropriate chemical and / or microbiological water quality limits should be defined.

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 contacting the excipient should be produced and distributed to minimize the risk of contamination or backflow in the system.

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

7.1.3.5 *Recycled or recovered materials*

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.

Activities to recycle or recover materials should be documented in production records or logs to enable traceability (see 8.5.2).

7.1.4 *Environment for the operation of processes*

Where the excipient is exposed during manufacture it should be in an appropriately controlled environment to minimize the risk of degradation and contamination, including cross-contamination.

A documented assessment should be carried out to identify the related risks and to determine the necessary controls. The following should be considered, as applicable:

- air handling systems, see 7.1.4.1;
- need for specific environments (controlled environments), see 7.1.4.2;
- cleanliness and sanitary conditions, see 7.1.4.3;
- pest control, see 7.1.4.4;
- personnel hygiene, see 7.1.4.5;
- material (including waste) segregation, see 7.1.4.8;
- waste disposal, see 7.1.4.8;
- other potential sources of contamination, including cross-contamination.

Special consideration should be taken in multi-use areas, where several products are processed simultaneously.

Where maintaining the work environment is critical to excipient quality, the controls should be documented and, as appropriate, monitored.

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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

7.1.4.1 *Environmental air handling*

Where the documented risk assessment has identified risks associated with air handling, the system should be designed and controlled to minimize the risk of degradation, contamination, and cross-contamination of the excipient.

The effectiveness of the air handling system should be demonstrated.

7.1.4.2 *Controlled environment*

Where the documented risk assessment has identified the need for a controlled environment, it should be monitored and controlled to assure excipient quality.

Such controlled environments should be designed to minimize the risk of contamination, including cross-contamination, or degradation of the excipient. The degree of protection required may vary depending on the stage of the process.

Where the documented risk assessment has identified the need for an inert atmosphere, the inerting gas should be treated as a raw material.

If interruptions to the controlled environment occur, sufficient evidence and appropriate rationale should be documented to show that such interruptions have not compromised the quality of the excipient.

7.1.4.3 *Clean and sanitary conditions*

Buildings used in the production, processing, packaging, or holding of an excipient should be maintained in an appropriately clean and sanitary condition.

Where the documented risk assessment has identified the need for clean / sanitary conditions, documented procedures should be in place according to the type of processing conducted:

- assigning responsibility for cleaning / sanitizing;
- describing in sufficient detail the schedules, methods, equipment, and materials to be used in cleaning / sanitizing the buildings and facilities.

These activities should be documented (see 7.5.1).

Where disinfectants and / or detergents are used, a documented risk assessment should demonstrate their suitability. The quality unit should approve the use of quality-critical cleaning and sanitizing agents.

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7.1.4.4 *Pest control*

A documented risk assessment should be carried out by an internal or external pest control specialist. This risk assessment should consider the potential for infestation by rodents, birds, flying and crawling insects and other vermin.

Some raw materials, particularly agriculturally sourced materials, may contain unavoidable contamination, such as rodent or other animal filth. Appropriate control methods should be in place to prevent the increase of such contamination in holding areas and its spread to other areas of the manufacturing facility.

Where the risk assessment has identified the need for pest control, the organization should document the pest control program, including the use of suitable rodenticides, insecticides etc.

Where a service provider is used, there should be a contract in place (see 8.4).

7.1.4.5 *Personnel hygiene*

Where the documented risk assessment has identified areas in which the excipient is at risk of contamination, including cross-contamination, from personnel or their activities, controls should be put in place to minimize the risk. At a minimum the following should be considered and documented:

- the personnel themselves;
- suitability of clothing and protective equipment for the activity;
- provision of facilities for showering and / or changing clothes;
- removal or covering of jewelry and other loose items, including those in pockets;
- reporting to supervisory personnel any health conditions, apparent illness or open lesions, that may have an adverse effect on excipients;
- restricting the storage and consumption of food, drink, personal medication, tobacco products or similar items to designated locations separate from manufacturing areas.

Adequate washing facilities and supplies should be provided so that suitable hygiene standards can be maintained. Toilet facilities should be clean and separate from but easily accessible to working areas.

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7.1.4.6 *Lighting*

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

7.1.4.7 *Drainage*

In areas where the excipient is open to the environment or stored, drains should be of adequate size. Where connected directly to a sewer, drains should be provided with air breaks or mechanical devices to minimize the risk of back-siphoning. Drains should be maintained appropriately.

7.1.4.8 *Waste*

Waste should be segregated and disposed of in a timely manner by means appropriate to its type. If waste is not disposed of immediately, it should be suitably labeled and stored. Excipient packaging should not be used to hold waste unless clearly labeled as waste.

7.1.5 ***Monitoring and measuring resources***

7.1.5.1 *General*

The excipient manufacturer should identify measuring and monitoring equipment necessary to adequately control manufacturing processes. Equipment critical to quality should be qualified, commissioned, calibrated, and, where appropriate, maintained.

The control program should include:

- the standardization or calibration of instruments and equipment at suitable intervals in accordance with a documented program;
- specific instructions, schedules, limits for accuracy and precision;
- provisions for remedial action if accuracy and / or precision limits are not met, including:
    - prevention of future use until suitability can be demonstrated;
    - documented investigation to determine the validity for results reported since the last successful qualification / **commissioning** / calibration.

Instruments and equipment not meeting established calibration limits should not be used.

For quality-critical monitoring and measurement equipment, the excipient manufacturer should retain documented evidence demonstrating fitness for purpose.

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7.1.5.2 *Measurement traceability*

Standards used for the calibration of measuring and monitoring equipment should be traceable to recognized national, international, or compendial standards, as appropriate.

The qualification / commissioning / calibration status of quality-critical equipment should be known and verifiable to users.

7.1.6 *Organizational knowledge*

The excipient manufacturer should determine, apply, and maintain the knowledge necessary for manufacturing and marketing of excipients. Knowledge of current regulations should be aligned to the labeling claims made about the excipient, intended use, and the countries in which it is marketed.

7.2 Competence

The excipient manufacturer should determine, and document in a written job description, the appropriate combination of education, training and experience for roles / personnel performing tasks that may affect excipient quality (see 5.3). These tasks should be considered in the training plan.

The excipient manufacturer should establish and maintain procedures for identifying the training needs of its employees and contracted personnel. A process should be established to provide effective training to all personnel who perform activities that may affect excipient quality. Training should be provided prior to independently performing those activities.

Training should address the particular GMP operations that the employee performs as well as detailed GMP related to the employee's role.

Appropriate records of training should be maintained.

Retraining requirements should be defined and documented.

Consultants advising on 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 advice they provide.

7.3 Awareness

Qualified individuals should develop and provide general GMP training. This training should be consistent with the quality policy and provided with sufficient frequency to ensure that employees remain familiar with applicable GMP principles. Training content should include the following topics – at a minimum – as they relate to the individual's role and function:

- importance of following instructions and prompt notification of any deviation;
- data integrity;
- precautions necessary to minimize the risk of contamination, including cross-contamination, through personal hygiene practices;
- understanding of other precautions necessary to minimize the risk of contamination of excipients, including cross-contamination;
- potential to impact patient safety should the above expectations not be met.

The training program should ensure personnel understand that deviations from procedural instructions may impact the safety, quality, or efficacy of medicinal products.

The training program should also ensure that personnel know what to do when a deviation has taken place.

7.4 Communication

The excipient manufacturer should ensure that internal and external communication processes are established.

Processes for internal communication should be in place for:

- GMP and regulatory requirements;
- quality-relevant policies, including the organization's overall quality policy;
- quality-relevant procedures;
- quality and GMP objectives;
- effectiveness of the quality management system;
- prompt notification to top management of quality-critical situations, including excipient retrievals (see 8.7.4).

External communication processes should include:

- accurate and pertinent information, which may include regulatory documents (see 7.5);
- replies to customer enquiries, contracts and order handling requirements;
- origin and traceability of the excipient to the customer;
- issues detected after delivery of the excipient (see 8.7.1 and 8.7.4);

- responses to customer complaints and feedback;
- significant changes (see 6.3 and 8.2.4).

7.5 Documented information

7.5.1 *General documentation requirements*

The organization's overall intentions and approach to GMP should be described and documented to facilitate common understanding and consistent application.

Procedures for manufacturing, control of data and records, as well as other documents related to requirements of the quality management system should be implemented, controlled, and maintained. This includes regulatory documents and documents of external origin that are part of the quality management system.

The excipient manufacturer should establish and maintain procedures for the lifecycle of documented information covering:

- Review, approval, distribution, access, retrieval, and use:
    - current versions of applicable documents should be available at points of use;
    - prevent unintended use of obsolete documents;
- storage and preservation, including preservation of readability and integrity:
    - prevent unintended and / or unauthorized changes;
    - minimize the risk of accidental deletion or damages;
- control of changes (e.g., correction, version control);
- periodic review to ensure the document remains current with practice;
- retention, including:
    - process for identifying and labeling obsolete documents;
    - retention time;
- destruction.

Records should be maintained to demonstrate achievement of the required excipient quality and the effective operation of the quality management system. Records should be legible and identifiable with the product or process involved.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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The organization should define which results, records and reports of subcontractor activities are retained, by whom, and for how long.

If electronic signatures are used, they should be authenticated, provide equivalent security to handwritten signatures, and comply with relevant regulatory requirements.

Data integrity principles i.e., of ALCOA+ should be incorporated throughout the procedures and systems used for managing documented information.

Data integrity controls for excipient manufacturing and distribution processes should be commensurate with risks associated with the use of the data. A higher level of control should be implemented where the loss of data integrity could compromise compliance with excipient GMP, impact confidence in excipient quality, cause the failure or rejection of the medicinal product, or pose potential **harm** to the patient.

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.

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 records should be signed and dated, leaving the original entry legible.

7.5.2 *Creating and updating*

Documents should include a unique identifier, date of issue and revision number to facilitate identification of the most recent document.

Documents that have the potential to impact product quality should have a defined owner and be reviewed and approved by the quality unit (see 5.3) before issuance to the appropriate areas. Additionally, procedures and forms should indicate from which date they are valid. This date should allow sufficient time to provide for employee training (see 7.2).

The department with the responsibility for issuing the documents should be identified.

Changes to approved, quality-relevant documents should be reviewed and approved by the quality unit (see 5.3) before use.

Changes and the reasons for the change should be documented.

All quality-related documented information (i.e., data, records, documents) should meet the above, independent of the storage medium (i.e., paper, electronic, **mixture** of both).

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
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7.5.3 *Control of documented information*

Documented information should be controlled. Controls should provide assurance that only the current version is being used in operational areas and that previous versions of documents have been removed.

Copies of controlled documents should be readily identifiable as either controlled or uncontrolled.

Records should be kept for a defined period appropriate to the excipient and as specified in applicable:

- regulations;
- certification standards;
- customer agreements.

The excipient manufacturing record retention period should be at least one year past the excipient's expiry or last **re-evaluation date**, or at least five years from the **date of manufacture**.

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

8 Operation

8.1 Operational planning and control

The excipient manufacturer should plan, implement, and control the processes needed for provision of excipients and GMP services. According to the actions determined in section 6, the excipient manufacturer should:

- determine the requirements for the excipients and GMP services;
- establish criteria for excipient manufacturing that include:
    - documented processes;
    - documented testing programmes for quality-critical materials including intermediates and finished excipients;
    - appropriate specifications;
    - sampling plans;
    - environmental and hygiene control programmes (see 7.1.4) to minimize the risk of contamination, including cross-contamination;

- test and release procedures;
- determination and provision of resources to implement these plans and controls.

- document procedures describing activities related to the storage and distribution of excipients;
- implement actions from relevant documented risk assessments (see 7.1 including sub-sections);
- generate and maintain records providing evidence that the controls have been followed and met.

The excipient manufacturer should control planned changes (see 6.3) and have a process to manage the consequences of deviations (i.e., unintended changes).

The excipient manufacturer should ensure that outsourced processes are controlled (see 8.4) and notify customers as applicable (see 8.2.1).

8.2 Requirements for excipients and GMP services

8.2.1 *Customer communication*

There should be processes in place for communication to the customer, including:

- provision of accurate and pertinent information, which may include regulatory documents (see 7.5);
- provision of replies to enquiries, contracts and order handling requirements;
- handling or controlling customer property, as applicable;
- communicating the **original manufacturer**'s identity and production **site**;
- notifying customers of outsourced activities that may affect excipient quality (see 8.4);
- provision of **certificate of analysis** for each **batch** shipped (see 8.6);
- notifying customers of significant changes (see 6.3);
- documenting and responding to customer complaints and feedback;
- informing customers of issues, including recalls and critical deviations detected after delivery of the excipient or provision of the GMP service (see 8.7.1, 8.7.2, and 8.7.4);
- informing if customers are impacted by activation of contingency plans.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
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8.2.2 *Determining the requirements for excipients and GMP services*

The excipient manufacturer should determine the requirements for manufacture of excipients and provision of GMP services based on the intended use. Customer-specific, legal, and regulatory requirements should be considered, as found in “The IPEC Qualification of Excipients for Use in Pharmaceuticals Guide and Checklist”.

8.2.3 *Review of the requirements for excipients and GMP services*

The excipient manufacturer and customer should review and mutually agree upon the requirements identified in 8.2.2 before supply begins. The manufacturer should have the facility and process capability (see 8.5.1) to consistently meet the mutually agreed specifications and GMP services.

Customer requirements may be documented in agreements, revision of which can be initiated by either party.

Where the requirements determined in 8.2.2 are changed, this review should be repeated before supply resumes.

8.2.4 *Changes to requirements for excipients and GMP services*

The excipient manufacturer should have a process for handling changes related to customer and regulatory requirements. See 6.3 for changes initiated by the excipient manufacturer.

8.3 Design and development of excipients and GMP services

8.3.1 *General*

In the design and development of excipients and GMP services, the GMP principles of this guide may not always be fully applicable.

The excipient manufacturer should document in a risk assessment those parts of the guide that are not applied when developing excipients.

8.3.2 *Design and development planning*

When designing and developing excipients and GMP services, the excipient manufacturer should consider the processes and activities necessary to control the desired result, including:

- the type, duration, and complexity of the development activities associated with the excipient or GMP service;
- stages of the plan, including reviews and approvals;
- verification or validation activities;

- roles and responsibilities (see 5.3);
- resources (internal and external) (see 7.1);
- interface(s) between people involved;
- customer and user involvement (see 5.1.2);
- customer and user requirements (see 8.2.2);
- facilities and process capabilities needed to consistently meet the desired result (see 8.5.1);
- documented evidence needed to demonstrate that planning requirements have been met.

8.3.3 *Design and development inputs*

The excipient manufacturer should determine the requirements specific to the excipients and GMP services being designed and developed, considering, at a minimum:

- **functionality** and performance;
- information available from similar design and development activities;
- statutory and regulatory environments;
- standards or codes of practice implemented by the organization;
- potential consequences of failure attributable to the type of the excipient or GMP service.

Design and development inputs should be:

- adequate for their intended purposes;
- clear and comprehensive;
- consistent in their approach.

Evidence of these inputs should be documented and retained (see 7.5).

8.3.4 *Design and development controls*

The excipient manufacturer should control the design and development process to ensure that:

- desired results are defined;

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- review of results is performed to assess if requirements can be realized;
- verification activities are conducted to confirm that the design and development outputs meet the input requirements;
- actions verify resulting excipients and GMP services meet the organization's intended use, and customer and user requirements;
- actions are performed to address problems identified during reviews or verification activities, as applicable;
- control activities are documented and retained (see 7.5).

8.3.5 *Design and development outputs*

The excipient manufacturer should ensure that outputs for design and development of excipients and GMP services:

- meet all input requirements;
- satisfy requirements of the standards and codes of practice implemented by the organization;
- identify process **control strategy** requirements, as appropriate, and corresponding acceptance criteria;
- identify release specifications and / or other requirements consistent with the intended marketed purpose and safe use by the customer, or
- identify other requirements essential for the intended purpose.

Evidence of these outputs should be documented and retained (see 7.5).

8.3.6 *Design and development changes*

In order to minimize the potential for nonconformance to requirements (see 8.3.3), the excipient manufacturer should appropriately control changes (see 6.3) made during the design and development of excipients and GMP services. Documented evidence should be maintained to record:

- the scope of the change;
- review of the change;
- authorization of the change;
- actions implemented to minimize potential negative effects caused by the change.

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8.4 Control of externally provided quality critical processes, services and materials

8.4.1 *General*

Externally-provided quality-critical processes, services and materials should be described in written agreements and the excipient manufacturer should ensure that these activities and materials conform to the documented requirements (see 8.4.3).

A documented process should be used to identify quality-critical processes, services and materials, and their necessary controls.

Suppliers of quality-critical processes, services and materials should be approved by the quality unit after a documented evaluation of the supplier's quality management system, including adequate evidence that they can consistently meet agreed requirements (see 8.4.3). Documented information of these activities should be retained (see 7.5).

8.4.2 *Type and extent of control*

The excipient manufacturer should determine the controls necessary to ensure that the externally-provided quality-critical processes, services and materials meet agreed requirements (see 8.4.3). These activities should be documented, including controls that apply to both:

- the external provider, and
- their provided process, service, or material.

These controls may require periodic audits of the supplier’s operations.

8.4.2.1 *Control of externally-provided processes and services*

Where manufacturing, testing, other operations, or services that could affect excipient quality are outsourced, the responsibility for quality ultimately remains with the excipient manufacturer, and control measures should be defined. The excipient manufacturer should be able to demonstrate that the applicable GMP principles, in accordance with this guide, are followed for those operations and services.

8.4.2.2 *Control of externally-provided materials*

There should be procedures for control of incoming materials. These should describe the process for approval and release of quality-critical materials, including handling of out-of-specification test results (see 8.6.4).

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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Incoming quality-critical materials, including packaging and preprinted materials, should be physically or administratively quarantined until they have been tested or otherwise verified and approved for use by the quality unit or their delegate (see 5.3).

Sampling activities should be conducted under defined conditions in accordance with a defined sampling method and using approved procedures and sampling tools designed to minimize the risk of contamination, including cross-contamination.

Bulk deliveries should have appropriate controls to minimize the risk of contamination, including cross-contamination.

When quarantine and stock control are managed with computer systems, there should be system controls to prevent the use of unreleased material.

Quarantine may not be feasible for materials supplied through 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.

8.4.3 *Information for external providers*

Excipient manufacturers should have documented agreements with external providers, communicating:

- the quality-critical processes, services and / or materials to be provided, including where applicable:
    - 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;
    - requirements for the approval of:
        - materials and services;
        - methods, processes, and equipment;
        - the release of processes, services, and materials.
    - requirements for personnel competence, including appropriate regulatory qualifications.
- the need for adherence to the applicable GMP principles in accordance with this guide;
- which records, results and reports need to be retained, by whom, and for how long;
- how control and monitoring of external provider performance will be applied;

- **change control** requirements, including subcontracting;
- requirements for verification or validation activities by the external provider, if applicable;
- any need for periodic audits by the excipient manufacturer of the external supplier's operations.

8.5 Production and GMP service provision

8.5.1 *Control of production and GMP service provision*

Activities for provision of excipients and GMP services should be carried out under controlled conditions (see 8.1). There should be evidence defining:

- the characteristics of the excipients to be produced;
- the GMP services to be provided;
- the activities to be performed;
- the results to be achieved.

Specific controls detailed in sections 8.5.1.1 through 8.5.1.8 apply for the excipients or GMP services within the scope of operations (see 8.1).

8.5.1.1 *Instructions and records*

Documents and records (see 7.5.1) describing how the excipient is manufactured or distributed, or GMP service is provided, should be maintained. Written instructions and forms that become records should be available at point of use and may differ based on the activity.

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 based on time or quantity produced and / or packaged. Records should also be available for each GMP service provided.

Where critical to demonstrate compliance with this guide and as applicable, records should comply with data integrity principles (see 7.5.1) and include:

- date / time each step was completed;
- documentation of key parameters together with conformance check against specified operating ranges;
- identification of persons:

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- performing / checking each operation;
- verifying control parameters.

- identification of major equipment and lines used;
- cleaning activities for equipment, lines, and utensils (see 8.5.1.2);
- material inputs (to enable traceability, see 8.5.2);
- in-process control results (see 8.5.1.6);
- inspection of the packaging and labeling area(s) before use, to ensure that materials not required for the current operation have been removed or destroyed;
- labeling controls performed;
- description of excipient containers and closures;
- description of sampling performed;
- failures, deviations, and their investigations;
- visual inspection results of packaged excipient (see 9.1.3 for analytical testing of final excipient);
- the quantity produced for the defined batch and a statement of the percentage of theoretical yield, as applicable.

8.5.1.2 *Equipment cleaning*

Equipment and utensils should be cleaned and, if critical to excipient quality, sanitized. Cleaning can be achieved in several ways, some of which may not result in visually clean equipment. The excipient manufacturer should design and justify cleaning and sanitization intervals and procedures and provide documented evidence of their effectiveness based on pre-determined acceptance criteria.

Cleaning and sanitization procedures should be documented. Where disinfectants or detergents are required, an assessment of suitability should be documented. Procedures should contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner (see 7.1.4.3). There should be a record confirming that these procedures have been followed. The cleanliness and, where appropriate, sanitization status of equipment should be identifiable and documented.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.5.1.3 *Recovery and reuse of materials*

Where materials are recovered and reused, they should meet appropriate specifications prior to reuse or mixing with other approved materials. Processes for recovery and reuse of materials should be justified. These processes should be documented, and records maintained to enable traceability.

8.5.1.4 *Blending of excipients*

If excipients are blended (without the manufacturing elements of **co-processing**) the process should ensure homogeneity and should be reproducible from batch to batch (see 8.5.1.8). The process should be controlled and documented to allow traceability back to the individual batches that make up the blend.

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

Blending should not be used to dilute contamination (see 8.7.1). Blending should also not be used where the performance of the resulting excipient could be impacted.

8.5.1.5 *Co-processing of excipients*

For co-processing of excipients, different technologies such as granulation, melt extrusion, spray drying, or milling may be used.

To ensure that specified properties and quality are obtained:

- the co-processing of excipients should be:
    - adequately controlled in-process (see 8.5.1.6);
    - documented to allow traceability back to the **component** excipient batches (see 8.5.2.1);
- finished **co-processed excipients** should be tested to ensure the product conforms to specifications (see 9.1.3).

The expiry or re-evaluation date of the co-processed excipient should be justified.

See also “The IPEC Co-Processed Excipient Guide for Pharmaceutical Excipients”.

8.5.1.6 *In-process control*

In-process controls may be based upon in-line monitoring of the process or actual sample analysis at defined locations and times. In-process sampling, inspection and testing should be performed by trained personnel on representative samples according to documented procedures. In-process samples should be clearly labeled and not returned to the GMP-process production stream.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

The results of in-process controls should be recorded and should be verified against established process limits. Written instructions should describe the use of inspection and test data to control the process. These instructions should detail actions to be taken when the results are outside specified limits.

8.5.1.7 *Packaging and labeling of excipients*

Packaging and labeling procedures should be employed to ensure excipient identity, quality, and purity. To prevent mix-ups, procedural controls should be implemented to ensure:

- correct labels are printed and issued;
- labels contain the correct information;
- printed information is indelible;
- packaging and labeling facilities are inspected immediately before use, confirming that materials not required for the current packaging operation have been removed or destroyed;
- excipient is packaged into the correct packaging system (see 8.5.4.2);
- excess batch-specific labels are destroyed immediately following packaging operations.

If not required for the subsequent packaging and labeling operation, excess product containers, closures and / or labels without batch- or product-specific information should be destroyed or returned to controlled storage immediately following operations.

Repackaging / relabeling activities should follow the same principles outlined above.

8.5.1.8 *Validation for production and GMP service provision*

The excipient manufacturer should demonstrate consistent operations for the provision of excipients and GMP services based on knowledge of operational parameters, requirements, and their inter-relationship.

The concept of validation is a key element in ensuring that processes are capable of consistently producing an excipient that meets specifications. The excipient manufacturer may not perform validation activities in the same manner or to the same extent as the pharmaceutical industry. However, many activities leading to the same degree of assurance are performed within the excipient industry.

Validation should be used:

- where testing alone may not be sufficient to reveal variations outside the process limits, or

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- where the resulting output cannot be verified by subsequent monitoring or measurements.

The excipient manufacturer should have a process for assessing and documenting the impact of change on the **validated state** of the system.

See also the IPEC Validation Guide.

8.5.2 *Identification and traceability*

Quality-critical materials and services, including GMP services, should be identifiable and traceable through records to demonstrate conformance with the principles of this guide.

8.5.2.1 *Traceability*

Records should allow traceability of the service, including GMP services, or, for excipients, from receipt of raw materials through delivery to initial customers and vice versa.

Methods should be defined for traceability and identification of raw materials, equipment used in excipient manufacturing, and GMP service provision to customers.

Even though one-to-one **lot** traceability is not possible with continuously supplied materials or bulk deliveries, traceability of use should still be documented in production records.

8.5.2.2 *Inspection and test status*

The inspection status of quality-critical materials and services, including GMP services, should be identifiable. Methods for identifying test status should be defined.

8.5.2.3 *Labels*

Excipient container labels may be subject to regulatory and / or compendial requirements (see 8.2.2).

Labels should include at a minimum:

- the names of the excipient (tradename and generic name(s)) and, if applicable, grade, or material code which specifies the grade
- the excipient manufacturer's and / or supplier's name and address,
- the **batch number** from which the complete batch history can be determined,
- special storage conditions, if applicable.

Labeling for excipient packages is subject to national and international regulatory requirements, which may include transportation and safety measures.

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W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.5.3 *Property belonging to customers or external providers*

The excipient manufacturer should establish and maintain procedures for verification, storage and maintenance of customer and externally-supplied materials intended for incorporation into the customer's excipient. Verification by the manufacturer does not relieve the customer or external provider of the responsibility to provide acceptable material.

Material that is lost, damaged or is otherwise unsuitable for use should be recorded and reported to the customer or external provider. 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 or external provider.

8.5.4 *Preservation*

8.5.4.1 *Handling, storage, and preservation*

Appropriate storage conditions should be maintained. If critical to maintaining the quality of materials used in excipient production and packaging, storage conditions should be specified, monitored, and recorded. Deviations from specified storage conditions should be assessed (see 8.7). Storage and handling procedures should be defined to:

- protect containers, labels, closures, and security seals,
- minimize the risk of contamination, damage, or deterioration, and
- prevent mix ups.

Bulk storage containers should be identified and labeled with their contents. Outdoor storage of materials and excipients is acceptable provided the containers give suitable protection against deterioration, contamination, and loss of traceability.

See also the IPEC **Good Distribution Practices** Guide.

8.5.4.2 *Packaging*

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

- documented specifications, based on the excipient’s properties, including stability,
- packaging systems that provide adequate protection against deterioration, moisture uptake or contamination of the excipient during transportation and recommended storage,
- packaging system components that do not interact with or contaminate the excipient,

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- tamper-evident seals, where feasible

If containers are to be reused for the excipient, verified cleaning procedures should be followed and should include instructions for removing previous labels. Records of cleaning should be retained.

Excipient packaging should not be used to hold waste unless clearly labeled as waste.

8.5.4.3 *Delivery and distribution*

Excipients should only be supplied within their **expiry date** or reevaluation period and, where applicable, according to customer and / or regulatory requirements.

Distribution records of excipient shipments to initial customers should be kept. To facilitate retrieval if necessary, distribution records should include:

- batch number,
- customer name and address,
- quantity shipped,
- shipment date, and
- where critical to maintaining excipient quality, conditions were met during transportation to the initial customer.

Where applicable, excipient manufacturers should define and provide transportation conditions to service providers and customers (see 8.6.8).

For bulk transport, verified cleaning procedures should be justified and applied. Records of cleaning should be retained. A list of prohibited and / or allowed previous cargos should be supplied to transportation companies.

See also the IPEC Good Distribution Practices Guide.

8.5.5 *Post-delivery activities*

The excipient manufacturer should determine and meet post-delivery activities, based on the intended use of the excipient, including:

- informing customers of issues, including recalls and critical deviations detected after delivery of the excipient (see 8.7.1 and 8.7.4), and significant changes (see 6.3),
- provision for country-specific legal and regulatory requirements,
- provision for a complaint handling process (see 8.7.3),

- provision for a returned goods handling process (see 8.7.1.3),
- provision for replies to enquiries and requests

8.5.6 *Control of changes*

For planning of changes, and changes to requirements for excipients and GMP services, see 6.3 and 8.2.4, respectively.

8.6 Release of excipients and GMP services

The excipient manufacturer should establish procedures and test methods to ensure excipients and GMP services meet requirements and specifications prior to release. Details are provided in sections 8.6.1 through 8.6.9.

8.6.1 *Monitoring and measurement*

Analytical procedures and test methods should be evaluated and verified to demonstrate they provide reliable test results and are fit for purpose. These may be included in the current edition of the appropriate pharmacopoeia or another accepted standard, but the methods may also be non-compendial. The responsibility for monitoring the current pharmacopeia or official compendium should be assigned.

If the excipient is labeled with a compendial designation, then it must meet all requirements of the designated compendia.

Without the corresponding GMP, it is not acceptable to upgrade non-excipient **grade** materials for excipient use based only on testing results.

Non-compendial, including in-house, analytical test methods should be demonstrated to be at least equivalent to those in the compendia.

See also the IPEC Validation Guide for Pharmaceutical Excipients, 2.5 “Analytical Methods”.

8.6.2 *Laboratory controls*

Data integrity principles, i.e., ALCOA+, should be incorporated throughout laboratory procedures and systems to always maintain data integrity (see 7.5.1).

The excipient manufacturer should establish laboratory controls, requiring complete data derived from tests, necessary to ensure conformance with specifications and standards. Records (see 7.5.3) of these controls should include:

- identification and traceability of samples, i.e., a description of the sample received for testing together with:

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

    - the material name;
    - batch number or other distinctive code;
    - identity of the person taking the sample (if applicable);
    - date the sample was taken;
    - time the sample was taken (where appropriate).
- test method reference(s);
- for each analysis, raw data required to confirm the test result, including sample preparation, graphs, chromatograms, charts, and spectra from laboratory instrumentation, identifying the specific material and batch tested;
- calculations performed;
- test results compared with specifications;
- date and identity of the person who performed each test, including time (where appropriate);
- the equipment, including ancillary equipment, used to perform the test when multiple equipment options are available.

Laboratory reagents, solutions, and reference standards may be purchased or prepared internally. There should be documented procedures for the labeling, handling, use, and storage of laboratory reagents, solutions, and reference standards. Procedures should also be available for the preparation and standardization of internally prepared materials.

Purchased materials should be verified on receipt.

Purchased and internally prepared materials should be stored appropriately and labeled with the name, concentration, and expiry or re-evaluation date. Purchased materials, once opened, should also be labelled with the remaining usage period.

Records for the preparation and standardization of reagents, solutions, and reference standards should be maintained and include at a minimum:

- identity of the prepared material,
- identity, quantities, and batch numbers of components used in the preparation,
- name of preparer,
- equipment used for preparation,

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- date of preparation,
- expiry or re-evaluation date of the prepared material.

When secondary reference standards are used, there should be a documented procedure for their qualification against primary reference standards. This procedure should include requirements for preparation, testing, approval, use, and storage.

Expiry or re-evaluation periods should be defined for secondary reference standards. For secondary reference standards with re-evaluation periods, requalification should be performed according to a documented procedure.

8.6.3 *Finished excipient testing and release*

Routine finished excipient testing should be performed on each batch to ensure that the excipient conforms to documented specifications. Nonroutine testing should be scheduled and justified to confirm the finished excipient complies with all specifications.

Results from in-process testing, **process analytical technology** (**PAT**), or from other process control records may be used to demonstrate that the finished excipient conforms to documented specifications.

The quality unit should be responsible for the release of the finished excipient. 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. Excipient shipped to the customer prior to quality unit release should follow a documented quarantine-shipping process that includes acknowledgement by the customer and any relevant authority.

8.6.4 *Out-of-specification test results*

Out-of-specification (OOS) test results should be investigated and documented according to a written procedure (see 10.2).

Results obtained by retesting may only be used to replace original test results if a documented investigation concludes that the original results are 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.

Retesting may not be necessary when product is released under a different specification. However, an OOS investigation should still be performed and documented.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
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Original and retest data should be included in the investigation report, including when the sample is suspected of not being representative of the material from which it was taken.

8.6.5 *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 sample**s should be stored in a secured location, readily retrievable and in conditions consistent with the recommended storage conditions for the finished excipient.

Unless otherwise justified, retained 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.

8.6.6 *Certificates of analysis*

Excipient manufacturers should provide certificates of analysis to the required specification for each batch of excipient. See the IPEC Certificate of Analysis Guide for Pharmaceutical Excipients for details on the suitable contents of a certificate of analysis.

8.6.7 *Impurities*

Where possible, excipient manufacturers should identify impurities as part of the **composition profile**. See also the IPEC Composition Guide.

Appropriate limits for impurities should be based upon safety data, limits as described in official compendia, or other requirements and sound GMP considerations. Manufacturing processes should be adequately controlled so that impurities do not exceed established limits.

Excipient manufacturers should conduct documented risk assessments to determine whether the excipient specifications should include tests and limits for impurities. At a minimum, microbiological **bioburden** and impurities from raw materials of natural origin should be considered.

In some manufacturing processes, insoluble and visible particles cannot be fully excluded. These particles should not necessarily be considered impurities. However, the excipient manufacturer should implement mitigation strategies based on a documented risk assessment to maintain the occurrence of such particles at an acceptable level. See also the IPEC **TUPP** Guide for guidance related to **technically unavoidable particles**.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.6.8 *Stability*

The stability of excipients is an important factor contributing to the overall safety, quality, and efficacy of the medicinal products in which they are used. Excipient manufacturers should determine the stability of their excipients. They should also consider stability when defining storage and transportation conditions.

See the IPEC Excipient Stability Program Guide.

8.6.9 *Expiry date or re-evaluation period*

Based on excipient stability, an **expiry** date or **re-evaluation** period should be assigned to each excipient and communicated to the customer.

8.7 Control of nonconforming outputs

8.7.1 *Control of nonconforming intermediates and finished excipients*

Intermediates and finished excipients not meeting analytical specifications or other quality indicators should be clearly identified and controlled to prevent inadvertent use or release for sale.

It is not acceptable to blend contaminated or adulterated batches to reduce the contamination or adulteration below an acceptable or detectable limit (see 8.5.1.4).

Incidences of nonconformance should be investigated and addressed according to a documented procedure in order to:

- identify the root cause(s),
- assess the potential impact on other:
    - batches;
    - intermediates, finished excipients and other product lines;
    - processes.
- evaluate and determine the disposition of the nonconforming intermediate or finished excipient in one or more of the following ways:
    - **reprocess**ing (see 8.7.1.1);
    - reworking (see 8.7.1.2);
    - authorization for release by customer concession (see 8.2.1);
    - re-grading for use in other applications;

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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- disposal.

- define and implement actions to prevent recurrence (see 6.1.2 and 10.2), as appropriate.

All activities of the above-mentioned investigation should be documented and records maintained. The quality unit should review and approve the results of this investigation (see 5.3).

8.7.1.1 *Reprocessing*

Reprocessing should only occur when it has been assessed and documented that the intermediate or excipient may be made in this manner (see 8.5.1). Records of reprocessing should be maintained (see 8.5.1.1 and 8.5.2.1).

8.7.1.2 *Reworking*

Reworking should only be conducted following a documented risk assessment 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 intermediate and / or finished excipient, including equivalence to established specifications;
- impact on stability or the validity of the re-evaluation period;
- impact on performance of the intermediate and / or finished excipient;
- additional controls needed to minimize the risk to excipient quality;
- customer notification.

The method of reworking should be documented and in compliance with the outputs of the risk assessment. Records of reworking should be maintained.

8.7.1.3 *Returned excipients*

There should be a documented procedure detailing the process for handling returned excipients from receipt through quarantine and final disposition.

The quality unit should approve disposition of the returned excipient (e.g., resale, re-grade, reprocess, rework, or disposal).

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Returned excipients should only be considered for resale when the quality unit has evaluated and confirmed that the excipient's integrity and conformance to the required storage and / or transportation conditions have been met for each package.

Excipient integrity factors include at a minimum:

- no evidence of tampering;
- original packaging is not compromised;
- remaining **shelf life** does not preclude resale.

Records of the quality unit's confirmation should be maintained and include at a minimum:

- name of the excipient;
- **batch (lot) number;**
- reason for return;
- quantity returned;
- identification of customer who returned the excipient;
- any evaluation that was performed;
- final disposition of the returned excipient.

8.7.2 *Control of nonconforming GMP services*

Incidences of nonconformance should be investigated and addressed according to a documented procedure in order to:

- identify the root cause(s),
- assess the potential impact on:
    - batches that are in scope of the nonconforming GMP service;
    - other GMP services that could be affected by the identified root cause(s).
- notify customer(s) (see 8.2.1),
- define and implement actions to prevent recurrence (see 6.1.2 and 10.2), as appropriate.

All activities of the above-mentioned investigation should be documented, and records maintained. The quality unit should review and approve the results of this investigation (see 5.3).

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8.7.3 *Customer complaint handling*

There should be a documented procedure for management of customer complaints within a timely manner.

This procedure should include at a minimum:

- receiving and documenting the complaint;
- investigating the complaint;
- concluding and documenting the investigation, identifying:
    - root cause;
    - whether the complaint is justified;
    - impact on other intermediates, finished excipients (see 8.7.1), or GMP services (see 8.7.2);
    - corrective and / or preventive actions as needed (see 10.2);
- responding to the customer and, as appropriate, other interested parties (see 4.2).

Records of complaints, complaint investigations, and resulting actions should be maintained. Complaints should be regularly evaluated for trends, including recurrence and criticality, in order to identify needs for corrective or preventive actions.

8.7.4 *Recall / Retrieval*

There should be a documented procedure for effectively and promptly recalling from the market, excipients known or suspected to be nonconforming (see 8.7.1). This procedure should include at a minimum:

- how the **recall** of an excipient should be conducted;
- which interested parties require notification (see 4.2);
- how, through a mock recall, the effectiveness of this procedure is periodically evaluated;
- how reconciliation discrepancies are addressed.

Recalled excipients should be identified and quarantined until final disposition by the quality unit. Records of recalls and mock recalls should be maintained.

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9 Performance evaluation

9.1 Monitoring, measurement, analysis and evaluation

9.1.1 *General*

The excipient manufacturer should identify, plan, and implement the monitoring and measurement activities required to demonstrate conformity and effectiveness:

- of the organization's quality management system according to this guide;
- to applicable requirements (see 4.2).

Monitoring and measurement activities should be documented and consider:

- what needs to be monitored and measured;
- what methods are needed to ensure valid results are obtained;
- when these activities should be performed;
- when results should be analyzed and evaluated.

9.1.2 *Customer satisfaction*

The excipient manufacturer should establish monitoring and measurement activities to assess customer satisfaction including the methods for obtaining, monitoring, and reviewing this information. This information should drive activities to continuously improve customer satisfaction.

9.1.3 *Analysis and evaluation*

The excipient manufacturer should analyze results obtained from monitoring and measurement activities (see 9.1.1) to evaluate:

- conformity of excipients and GMP services;
- the degree of customer satisfaction (see 9.1.2);
- the performance and effectiveness of its quality management system;
- if planning has been implemented effectively;
- the effectiveness of actions taken to address risks and opportunities (see 6.1);
- the performance of external providers (see 8.4.3);
- the need or opportunity for improvements to the quality management system (see 10).

9.2 Internal audit

The excipient manufacturer should plan, establish, implement, and maintain an internal audit program to:

- consider whether its quality management system (see 4.4) conforms to the organization's own requirements, and to the GMP principles of this guide;
- confirm that the implementation and maintenance of the quality management system are effective.

This program should be based on risk and carried out following documented procedures.

For internal audits, the procedures should:

- include the frequency, methods, responsibilities, planning requirements and reporting, considering the site's activities, changes affecting the organization, and previous audit results;
- require the identification of audit criteria and scope;
- define auditor qualification requirements;
- require that auditors are selected to ensure objectivity and impartiality of the audit process;
- describe requirements for audit documentation and reporting, including, at a minimum, report distribution to relevant management;
- where nonconformity is identified, require timely identification of follow-up actions (see 10.2).

Records should be maintained as evidence of audit program implementation and audit results.

9.3 Management review

9.3.1 *General*

Top management of the organization should review the quality management system at planned intervals to verify the organization's continued conformance to this guide.

The review should be documented and include a process for:

- identifying opportunities for improvement;
- assessing the alignment with the excipient manufacturer's strategic direction;
- identifying any need for changes to the quality management system (see 4.3);
- checking suitability of the quality policy (see 5.2).

Records should be maintained as evidence of management review, including actions recommended and taken.

9.3.2 *Management review inputs*

Management review should be carried out taking into consideration, at a minimum:

- status of action items from previous management review;
- changes in external and internal issues that are relevant to the quality management system (see 4.1);
- information on the performance and effectiveness of the quality management system, including trends in:
    - customer satisfaction (see 9.1.2);
    - customer complaints (see 8.7.3);
    - feedback from relevant interested parties (see 4.2);
    - the extent to which quality and GMP objectives have been met (see 6.2);
    - process performance;
    - conformity of excipients and GMP services;
    - nonconforming outputs (see 8.7) and resulting actions;
    - status of corrective and preventive actions;
    - monitoring and measurement results (see 9.1.3);
    - internal and external audit results;
    - performance of external providers (see 8.4.3);
- adequacy of resources (see 7.1);
- effectiveness of actions taken to address risks and opportunities (see 6.1);
- opportunities for improvement (see 10).

9.3.3 *Management review outputs*

Management review outputs should include decisions and actions related to:

- opportunities for improvement (see 10);

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W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- resource needs;
- any need for changes to the quality management system (see 4.3);
- any need to update the quality policy (see 5.2).

10 Improvement

10.1 General

The excipient manufacturer should select opportunities for improvement (see 9.3.3), and plan and implement activities to improve:

- performance and effectiveness of the quality management system and its processes (see 4.4);
- excipients and GMP services to enhance customer satisfaction, considering the potential impact on patient safety.

Improvement activities should also include correction, prevention, or reduction of undesired effects.

Any changes should be assessed and implemented following the change control procedure (6.3).

10.2 Nonconformity and corrective action

The excipient manufacturer should have a documented procedure to:

- define the management of nonconformities, as applicable and commensurate with risk;
- control and correct nonconformities;
- address the consequences of nonconformities;
- investigate each nonconformity, determining:
    - the root cause(s),
    - the need for actions, including the prevention of recurrence of the same, similar, or potentially similar nonconformities (see 10.3).
- define actions as applicable, including responsibilities and timelines for implementation;
- evaluate and optimize the effectiveness of actions taken;

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- evaluate and update risk assessments as described in this guide (see 3, 7.1.3, 7.1.4, 7.1.4.3, 7.1.4.4, 8.3.1, 8.6.7, and 8.7.1.2), if necessary;
- update the quality management system (see 4.4), if necessary;
- record changes (see 6.3) resulting from actions, if necessary.

Records should be maintained as evidence of these activities.

10.3 Continual improvement

The excipient manufacturer should continually improve the quality management system and its processes (see 4.4). Improvement activities should consider suitability, adequacy, and effectiveness.

To identify opportunities for continual improvement of the quality management system, the excipient manufacturer should consider results from analysis and evaluation (see 9.1.3) and the outputs from management review (see 9.3.3).

11 References

IPEC References:

IPEC Certificate of Analysis Guide for Pharmaceutical Excipients 2013

IPEC Composition Guide For Pharmaceutical Excipients 2020

IPEC Co-Processed Excipient Guide For Pharmaceutical Excipients 2017

IPEC Excipient Information Package User Guide and Templates 2020

IPEC Excipient Stability Program Guide 2010

IPEC General Glossary of Terms and Acronyms For Pharmaceutical Excipients 2021

IPEC GMP Certification Scheme and Certification Body Qualification Guide For Pharmaceutical Excipients 2020

IPEC Good Distribution Practices Guide For Pharmaceutical Excipients 2017

IPEC Position Paper: Data Integrity for Pharmaceutical Grade Excipients 2020

IPEC Qualification of Excipients for Use in Pharmaceuticals Guide and Checklist 2020

IPEC Quality Agreement Guide and Template(s) For Pharmaceutical Excipients 2017

IPEC Risk Assessment Guide for Pharmaceutical Excipients, Part 1: Risk Assessment for Excipient Manufacturers 2017

IPEC Significant Change Guide for Pharmaceutical Excipients 2014

IPEC Technically Unavoidable Particle Profile (TUPP) Guide 2015

IPEC Validation Guide For Pharmaceutical Excipients 2021

Other References:

EXCiPACT cGDP 2021 standard

EXCiPACT cGMP 2021 standard

EXCiPACT cGWP 2021 standard

ISO 9000:2015 Quality management systems – Fundamentals and vocabulary

ISO 9001:2015 Quality management systems — Requirements

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

NSF/IPEC/ANSI 363 – 2019 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients

WHO Guidelines for drinking-water quality 2022

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

Part 2

IPEC-PQG GMP Guide + Notes

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

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The company representatives who worked on this guide are listed below:

List of Contributors from IPEC-Americas

William Dale Carter*, Evonik

George Collins, Vanderbilt Chemicals LLC

Ann Gulau, IFF

List of Contributors from IPEC Europe

Jeffrey Brambora, Consultant

Roberto Mastrantonio, Eli Lilly

Astrid Stockrahm-Uhling*+, DFE Pharma

Beverley Stout, GSK

List of Contributors from PQG

Ian McKeown, PQ Silicas

* co-chair
+ task force team leader

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

PART 2 - IPEC-PQG GMP GUIDE AND NOTES

1 Introduction

1.1 Purpose and scope

Excipients are essential components of the medicinal product formulation. The quality of excipients is critical to ensure the safety, quality, and efficacy of medicinal products, because excipients provide a wide range of functionality.

Excipients can have multiple uses in medicinal products (see 4.1 Note 1). Therefore, it is essential to apply principles of appropriate **Good Manufacturing Practices** (**GMP**) to excipients. Additionally, excipient GMP provides the foundation for the understanding and implementation of all **IPEC guide**s.

Users of excipients are increasingly required by regulatory authorities to ensure patient safety through the evaluation of risks and application of suitable GMP to the **manufacture** and supply of each excipient.

*Note: EC document 2015/C 95/02 is one example regulation that requires users to **perform risk assessment** of their excipient **supplier**s. PIC/S PI-045-1 provides **guideline**s for implementation.*

This document provides GMP appropriate to the manufacture of all excipients and to GMP services provided by excipient manufacturers. It covers the **quality management system**, including the GMP necessary throughout manufacturing, based on risk assessments, for both batch and continuous processes.

It should be recognized that once the excipient is in the **supply chain**, it may be subjected to further GMP related activities, such as re-packaging or re-**labeling**, before it reaches the final user. Such activities should be performed in compliance with GMP principles as described in this guide.

This guide is the result of a joint initiative between the International Pharmaceutical Excipients Council (IPEC), and the Pharmaceutical Quality Group (PQG).

1.2 Principles adopted

1.2.1 *The guide and its use*

Excipients are diverse materials that often have uses other than pharmaceutical applications. Therefore, each **manufacturer** should consider how this guide applies to their processes, products, and GMP services (see 4.1).

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

This revised guide incorporates the principles of risk assessment to identify the controls needed for GMP according to the manufacturer's intended use of the excipient. The need for risk assessments is identified throughout this guide. This approach allows the guide to be used for all excipients, including those that are supplied sterile and / or pyrogen free, and those intended for parenteral, ocular, inhalation, or open wound use.

For the purposes of this guide, the terms "Good Manufacturing Practices (GMP)" and "current Good Manufacturing Practices (**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*

This international guide applies to all excipients and excipient-related GMP services. Therefore, it cannot specify the manufacturing knowledge or competencies required, the national legal requirements, or consider excipient characteristics (e.g., chemical, or physical properties) for every excipient or GMP service. It is the responsibility of each excipient manufacturer to utilize appropriate expertise when identifying and implementing applicable requirements (see 4.2).

1.2.3 *Quality System standard*

The quality management system standard chosen as a framework for this guide is **ISO** 9001:2015.

IPEC and **PQG** support merging GMP principles for excipient manufacturing with the **ISO 9001** quality management system because these principles enhance the organization's quality management system, operational processes, and related procedures. The organization may also seek certification to an excipient GMP standard.

1.3 Layout and definitions

1.3.1 *Layout*

Revised in its entirety, this version of the guide, its headings and clause numbers have been developed to align with ISO 9001:2015. Additional headings are included as required to introduce the **additional guidance** on GMP when not covered by ISO 9001:2015 clauses.

This guide is published in two parts:

- Part 1 includes Good Manufacturing Practices for excipients.
- Part 2 includes Good Manufacturing Practices for excipients together with notes that offer examples for GMP interpretation and implementation without adding further requirements.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- Notes may provide common examples but are not intended as an exhaustive list.
- Notes are presented as indented, *italicized text*.

Each part of the guide has the following sections:

Section 1, Introduction

Section 2, General guidance, identifies the regulatory expectation of following excipient GMP.

Section 3, Excipient GMP implementation, provides an overview of the GMP criteria applicable to services and excipient manufacture from the point where excipient GMP starts.

Sections 4 through 10 provide guidance on the GMP principles and implementation of a quality management system suitable for excipient manufacture and service provision.

1.3.2 *Definitions*

ALCOA+:

The acronym ALCOA defines that data should be Attributable, Legible, Contemporaneous, Original, and Accurate. In addition, ALCOA+ guidance defines that data should also be Complete, Consistent, Enduring, and Available.

GMP Service:

GMP-related activities performed by an organization on behalf of their customer, where the organization's output is not the product (excipient) but either a tangible or intangible output of an activity.

Note: 1. ISO 9001:2008 used the term "product" to include all output categories. ISO 9001:2015 uses "products and services". The specific inclusion of "services" in ISO 9001:2015 and, therefore, this guide is intended to highlight the differences between products and services in the application of some requirements. For example, conformity to requirements cannot necessarily be confirmed before service delivery.

2. The organization may sell both GMP services and excipients. For example, an excipient manufacturer may sell their excipient (product) but also manage their customer's inventory to ensure a safety stock of the excipient is always available to the customer (an intangible GMP service).

3. Alternatively, an excipient manufacturer may only sell GMP services, tangible or intangible. For example:

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *a GMP contract manufacturer who does not sell the excipient that they produce but instead sells their (intangible) manufacturing services (to custom-make the excipient) for their customer;*
- *a contract testing lab sells the GMP service of testing excipients for their customers. The **certificate of analysis** provided by the contract testing laboratory would be the tangible output of the GMP service.*

Manufacture/Manufacturing Process:

All operations from receipt of materials through production, packaging, **repackaging**, labeling, **relabeling**, quality control, release, storage and **distribution** of excipients and related controls.

Regulatory requirement:

ISO 9000 defines ”regulatory requirement” as “obligatory requirements specified by an authority mandated by a legislative body”.

*Note: The US**FDA** is an example of an authority mandated by a legislative body, in this case, the US Congress.*

Regulatory requirements specified by the USFDA are found in Title 21 of the US Code of Federal Regulations (21 CFR).

Statutory requirement:

ISO 9000 defines ”statutory requirement” as “obligatory requirement specified by a legislative body”.

Note: The US Food Drug and Cosmetic Act is an example of an obligatory requirement specified by a legislative body, in this case, the US Congress.

ISO 9000:2015:

ISO 9000:2015 specifies the terms and definitions that apply to all quality management and quality management system standards (developed by ISO/TC 176). Reference to ISO 9000 is used in Notes, when definitions are provided for generic terms, such as “nonconformity”. These definitions are taken from ISO 9000, because they are not available in ISO 9001.

For further definitions refer to the International Pharmaceutical Excipient Council Glossary: General Glossary of Terms and Acronyms. The first use of a term found in the Glossary will be in **bold**.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

2 General Guidance

Conforming with **excipient** GMP is a best practice that benefits excipient users and the patient.

Complying with excipient GMP is a regulatory expectation when statutory or regulatory requirements exist either in the location of excipient manufacture or intended market.

3 Excipient GMP implementation

The objective of excipient GMP is to ensure that:

- excipients are consistently manufactured with the intended quality and performance characteristics;
- GMP services lead to consistent results.

The excipient manufacturer should design, control, document, and maintain its manufacturing processes. Justification is required to determine the point at which excipient GMP should be applied. This justification should be based on thorough process knowledge and recorded in a documented risk assessment. GMP usually begins well before the final finishing operation.

*Note: 1. Examples of methods for identifying when **excipient** GMP should begin include:*

- ***HACCP** (**Hazard** Analysis and Critical Control Point);*
- ***FMEA** (Failure Mode and Effects Analysis).*

2. Examples of documenting where excipient GMP begins include:

- *risk assessment;*
- *process flow diagram.*

Implementation of excipient GMP should also consider at a minimum:

- **batch** versus **continuous processing**;
- dedicated versus multi-purpose **equipment**;
- open versus closed processes.

Throughout this guide, the use of “GMP” will mean “excipient GMP” as outlined in this document.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

4 Context of the organization

In a GMP context, the excipient manufacturer is the organization. The two terms are used interchangeably throughout this guide.

Note: ISO 9000 defines the organization as "person or group of people that has its own functions with responsibilities, authorities and relationships to achieve its objectives".

*The organization can include one or more manufacturing **site**(s), and outside support references (e.g., company headquarters, regional testing facilities, centralized human resources, etc.).*

4.1 Understanding the organization and its context

Manufacturers should identify, within their portfolio, those products manufactured and marketed as excipients. Excipient manufacturers should define and document the intended use(s) of their excipients, considering the potential impact on patient safety. They should determine and monitor external and internal issues that are relevant to the manufacture and marketing of excipients. These should include outsourced activities that can affect excipient quality and for which the organization has control and responsibility.

Note: 1. Examples for intended use of excipients include:

- *function (e.g., pH adjuster, color, flavor, binder, disintegrant);*
- ***dosage form** (e.g., tablets, capsules, liquids, aerosols, patch, cream);*
- *route of administration (e.g., parenteral, topical, oral);*
- ***grade** (suitable for use in e.g., food or medicinal products).*

2. Examples of how the intended use of excipients relates to patient safety include:

- *particle size may impact controlled release in the medicinal product;*
- *excipient bioburden and the route of administration;*
- *colors used in coatings for tablet identification.*

For guidance on information needed to support marketing a material for use as an excipient, refer to the International Pharmaceutical Excipients Council Guide for Qualification of Excipients for Use in Pharmaceuticals.

3. Examples of external issues affecting the manufacture and marketing of excipients include changes to:

- *regulations;*

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *compendia;*
- *requirements for composition / **specification**;*
- *import / export / transportation requirements.*

4. Examples of internal issues include:

- *succession planning to ensure knowledge is maintained;*
- *changes in organizational structure (e.g., access to expertise and responsibility for monitoring external issues);*
- *changes in operational strategy (e.g., outsourcing, insourcing);*
- *changes to and use of infrastructure (see 7.1.3 for more information on infrastructure).*

Excipient manufacturers should identify the quality management system processes required to assure excipient quality, accounting for customer, social, legal, technological, and cultural environments.

Note: Examples of environmental aspects include:

- *customer aspects such as:*
  - *specifications compliant to multiple compendia;*
  - *customer-specific requirements.*
- *social aspects such as:*
  - *regional differences in animal welfare concerns may result in different pest control practices;*
  - *differences in privacy concerns may have legal consequences and could limit availability of records during audits (e.g., health records, training records).*
- *legal aspects such as:*
  - *regulations applicable to excipients;*
  - *non-permitted ingredients, e.g., **GMO**;*
  - *confidential Disclosure Agreement;*
  - *contractual Agreements (e.g., Supply Agreement, **Quality Agreement**);*

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *privacy protection, such as reporting names of personnel on **COA**s, external review (e.g., customer audits) of individual job descriptions and training records, use of biometrics (e.g., fingerprint, retina scan);*
- *use of employee background checks or monitoring cameras.*

- *technological aspects such as:*
  - *contingency plans for failure of automation / computer systems;*
  - *Enterprise Resource Planning - software, use of smart packaging (to control / monitor storage conditions or **shelf life**), electronic record keeping and electronic signature software;*
  - *electronic data integrity and storage;*
  - *updates and improvements to **equipment**.*
- *cultural aspects such as:*
  - *religious purity laws, e.g., **Kosher**, **Halal**:*
  - *ethical sourcing, e.g., conflict minerals, child labor;*
  - *consumer preferences, e.g., animal versus plant sourcing.*

4.2 Understanding the needs and expectations of interested parties

The excipient manufacturer should determine the interested parties that are relevant to the GMP quality system being maintained. Current applicable customer, compendial, statutory, and regulatory requirements should be determined and met (see 6.1.1).

Note: Examples of interested parties include:

- *internal:*
  - *personnel (permanent and temporary; internal and external), top management;*
  - *other departments in the organization (e.g., quality assurance, regulatory affairs, sales, marketing).*
- *external:*
  - *patients;*
  - *customers;*
  - *competitors, e.g., market intelligence;*

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *regulatory authorities, e.g., health, compendial, supervising / notified bodies, safety, environmental, transportation;*
- *suppliers, consultants, contractors, and service providers (pest control, **QC** lab, calibration, warehousing, tolling, contract manufacturer, freight forwarders, transport companies).*

The excipient manufacturer should monitor information about interested parties and their relevant requirements (see 4.3, 5.3 and 6.1.1).

Note: Examples of where monitoring information could be found include:

- *management review inputs including results from internal and external audits;*
- *incident reports and trends;*
- *relevant industry journals and trade shows;*
- *trade association and regulatory websites;*
- *regulatory updates and newsletters;*
- *information requests from interested parties;*
- *agreed customer requirements (e.g., as defined in Quality / Supply Agreements).*

4.3 Determining the scope of the Quality Management System

The organization's overall intentions and approach to GMP should be documented to facilitate common understanding and consistent application. The excipient manufacturer should have:

- a documented description of the quality management system;
- a quality policy (see 5.2);
- commitment to apply the appropriate quality management principles contained in this guide, including GMP.

The documented description of the quality management system should include the scope of the quality management system and reference to supporting procedures, considering:

- boundaries and applicability of GMP;
- products and GMP services in scope;
- external and internal issues (see 4.1);

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- requirements of relevant interested parties (see 4.2);
- the interaction between quality management system processes (see 4.4).

Documentation should identify and justify the starting point in the process (manufacturing or service provision) from which the full excipient GMP principles of this guide apply.

Note: 1. Examples for documented description of the quality management system include Quality Manual, procedures, work instructions.

2. Examples for commitment of the organization to applying the appropriate GMP include participation in IPEC, tracking quality metrics, GMP certification, presentations, and posters.

3. How to determine boundaries and applicability of GMP?

- *Starting from the specification of **raw material**s, the excipient manufacturer applies a justified level of GMP to each operational step to ensure excipient quality.*
- *Define at what point industrial production is diverted to excipient or other markets (e.g., food, cosmetic).*
- *Initial manufacturing steps may not require full excipient GMP.*
- *A risk assessment (e.g., **HACCP**, FMEA) may help identify the point from which GMP will be applied.*

4.4 Quality Management System and its processes

Excipient manufacturers should define, implement, maintain, and continually improve the quality management system and its processes. These processes and their interactions should be documented.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

Note: An example of the interaction between quality management processes is illustrated in the following diagram:

This documentation should include:

- inputs required and outputs expected from these processes;
- process sequence and interaction;
- criteria and methods needed to ensure the effective operation and control of these processes;
- resources needed for these processes and ensure their availability;
- responsibilities and authorities for these processes;
- risks and opportunities as determined in accordance with the requirements of 6.1 and how they are addressed;
- evaluation of processes and implementation of any changes needed to ensure that these processes achieve their intended results;
- evaluation of risk assessments and improvements to the quality management system (see 10.1).

Records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality management system.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

Where manufacturing, testing or other operations that could affect excipient quality are outsourced (i.e., externally provided), the responsibility for quality remains with the excipient manufacturer and control measures should be defined. The organization should define which records, results and reports of subcontractor activities are retained and by whom.

Note: See 8.4 for more information about "Control of externally provided quality-critical processes, materials and services".

5 Leadership

5.1 Leadership and commitment

5.1.1 *General*

Top management should be identified.

Top management should demonstrate their commitment to the quality management system and be accountable for its maintenance and effectiveness. This should be accomplished through the development of a quality policy (see 5.2.1) and establishment of quality and GMP objectives (see 6.2). Current applicable customer, compendial, statutory, and regulatory requirements should be determined and met.

Top management should promote risk-based thinking (see 6.1).

Top management should provide adequate resources to ensure conformance to the principles of this guide. There should be a process for the identification of resources needed for adherence to GMP.

Note: See 7.1 for more information about resources.

Top management should ensure that the quality policy, the quality and GMP objectives, and the definition of roles, responsibilities and authorities are communicated, understood, and applied across the organization. They should ensure that the quality management system achieves its intended result and should promote continual improvement (see 10.3). Progress towards the documented quality and GMP objectives should be reviewed at planned intervals.

Note: 1. Examples of communication tools include:

- *posters, bulletin boards, monthly reports, email messages, intranet postings;*
- *reports from management review meetings;*
- *training and availability of quality policy, organization charts and job descriptions.*

2. Examples for review at planned intervals include:

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *management reviews, monthly team meetings;*
- *depending on the size of the organization, corporate reviews, not necessarily limited to the local level.*

5.1.2 *Customer focus*

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

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

Note: 1. Examples for determining and understanding customer requirements include:

- *review of intended uses;*
- *sharing of product application information;*
- *supplying information for regulatory filings.*

2. Examples of other related matters include:

- *logistical requirements and details (e.g., delivery times, pallet height);*
- *correct tools (e.g., hoses, couplings) for unloading bulk tanker deliveries.*

3. Examples of other means to demonstrate to the customer the quality management system's effectiveness include:

- *virtual meetings (teleconference or videoconference), filming;*
- *completing written questionnaires;*
- *provision of certification of conformance to other GMP, e.g., food;*
- *on site meetings (F2F) with business, technical or development functions.*

5.2 Quality policy

5.2.1 *Establishing the quality policy*

Top management should participate in and provide the resources necessary for the development, implementation, and maintenance of the organization's quality policy. The quality policy should include commitment to appropriate GMP, compliance with applicable requirements and continual improvement of the quality management system.

Note: Frequently asked questions to consider with regards to the quality policy include:

- *Is the quality policy a controlled document?*
- *Is it reviewed at an adequate frequency to ensure the policy remains appropriate to the purpose and context of the organization?*
- *Who reviews the established policy?*
- *How is it communicated internally and to interested parties?*

5.2.2 *Communicating the quality policy*

Top management should demonstrate its commitment to the quality policy and appropriate GMP, and ensure that this is communicated and implemented within the organization.

Note: 1. Examples for demonstration of top management's commitment include:

- *signing the quality policy;*
- *attending annual review meetings;*
- *providing resources for voluntary certification to a GMP standard.*

2. Examples for communicating the quality policy and appropriate GMP include:

- *facility posters;*
- *confirmation that the policy has been read and understood by all employees;*
- *distribution of quality reports and results of annual reviews.*

5.3 Organizational roles, responsibilities, and authorities

Top management should ensure that responsibility and authority are clearly defined, communicated, and understood within the organization.

Note: Job descriptions, organization charts and training, may be used to communicate organizational roles, responsibilities, and authorities.

Top management should assign the responsibility and authority for:

- ensuring that the quality management system conforms to the provisions of this guide;
- ensuring that the processes are delivering their intended outputs;
- reporting to top management on the performance of the quality management system, opportunities for improvement (see 9.3.2) and changes to applicable customer, compendial, statutory and regulatory requirements (see 4.2);
- ensuring the promotion of customer focus throughout the organization;

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
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- ensuring that the integrity of the quality management system is maintained when changes to the quality management system are planned and implemented.

Top management should ensure that a quality unit or other appropriate unit, independent of production, has the responsibility and authority to:

- ensure **quality-critical** activities are identified and undertaken as defined;
- review and approve documents that have the potential to impact product quality;
- approve external providers (suppliers) of quality-critical processes, services and materials;
- ensure that providers of outsourced processes and services comply with the relevant sections of this guide (see 8.4);
- approve or reject raw materials, packaging components, intermediates and finished excipients, according to current approved specifications and procedures;
- approve or reject the excipient if it is produced, processed, packaged or held under contract by another company;
- ensure that there is a review of production records prior to excipient release;
- ensure that where errors, deviations, or nonconformities have occurred or are identified in the review process, they are appropriately investigated and documented;
- ensure corrective and preventative actions are implemented and effective;
- participate in reviewing and authorizing **significant change**s that have the potential to impact quality (see 8.5.6);
- review and approve the results of investigations into deviations from production instructions, test or measurement failures, customer complaints, or other nonconformities;
- develop and implement an internal audit program of the quality management system.

Note: Examples for other appropriate unit, independent of production include:

- *regulatory group;*
- *technical service;*
- *product development (R&D).*

Some of the quality unit's activities may be delegated if appropriate controls are in place and documented. However, in all cases the quality unit should be responsible for performing:

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- review and approval of documents that impact excipient or GMP service quality;
- approval of significant changes that may impact excipient or GMP service quality;
- approval of quality-critical suppliers;
- release of the finished excipient;
- release of GMP services;
- approval of **reworking**;
- evaluating and determining the disposition of returned excipients, including recalled excipients.

For all of the quality unit's activities listed in this section, whether performed by the quality unit or another appropriate unit, records should be available to demonstrate review and approval / rejection. Although quality unit activities may be delegated, the quality unit is ultimately responsible for the final output and should approve the controls used by any other unit to perform the delegated activity.

Note: 1. Examples of activities that may be delegated include:

- *complaint investigations;*
- *approval of incoming raw materials and / or packaging components based on written procedures approved by the quality unit;*
- *review of pest control reports and responding to actions.*

2. Examples of controls for delegated responsibilities include:

- *design and / or approval of the delegated process, including corresponding records;*
- *clear definition of when to notify the quality unit (i.e., well-defined boundaries of the delegated responsibility);*
- *periodic review of delegated responsibility (e.g., by internal audit);*
- *individuals performing the delegated activity are trained, and qualified by the quality unit.*

An organizational chart by function should show inter-departmental relationships as well as relationships to top management. Personnel who have an impact on excipient quality should have job descriptions (see 7.2).

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Note: 1. An organizational chart may be embedded into the information technology (IT) systems in use in the company rather than exist as a record.

2. Details in an organization chart may include:

- *all functions on site with site manager as "top management";*
- *all functions on site and remote functions to the business organization with, e.g., CEO as "top management";*
- *separation of the quality unit from production unit;*
- *reporting relationships between departments indicating direct and indirect reporting (e.g., using bold or dotted lines).*

6 Planning

6.1 Actions to address risks and opportunities in the Quality Management System

6.1.1 *Risk Assessment*

The excipient manufacturer should conduct risk assessments of the issues referred to in 4.1 and the requirements referred to in 4.2 to determine the risks and opportunities that need to be addressed to:

- give assurance that the quality management system can achieve its intended result(s);
- enhance desirable effects;
- prevent, or minimize, undesirable effects;
- achieve continual improvement.

See also "The IPEC Risk Assessment Guide for Pharmaceutical Excipients".

Note: 1. Examples to achieve intended results include:

- *complying with **IPEC PQG** GMP;*
- *developing and achieving quality objectives.*

2. Examples of desirable effects include:

- *customer satisfaction;*
- *satisfactory regulatory inspections and customer audits;*
- *minimal quality issues (OOS, complaints, rejected batches);*

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- *obtaining / maintaining certifications;*
- *innovation, new and improved excipients, and more sustainable and efficient processes.*

3. Examples of undesirable effects include:

- *regulatory sanctions and legal ramifications;*
- *customer complaints, returns, retrieval / recalls;*
- *loss of current or future business;*
- *increased waste and / or environmental impact;*
- *loss of reputation or shareholder value;*
- *loss of ability to supply customer;*
- *failures to make excipients or provide GMP services to the defined process;*
- *deviations.*

6.1.2 *Preventive action and continual improvement*

Note: What is a preventive action?

ISO 9000 defines "preventive action" as "action to eliminate the cause of a potential nonconformity or other potential undesirable situation." ISO 9000 goes on to explain that a "preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence."

The excipient manufacturer should plan actions to address risks and opportunities in the quality management system (see 6.1.1), by:

- initiating preventive actions including assignment of responsibilities and timelines for implementation, to deal with problems at a level corresponding to the risks;
- initiating actions to enhance desirable effects or remove barriers to improvement;
- ensuring that actions are implemented and effective;
- implementing and recording changes in processes or procedures resulting from actions.

Note: 1. Examples of preventive action include developing, verifying, and maintaining:

- *production and supply contingency plans;*
- *disaster recovery plan;*

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- *business continuity plans.*

2. Examples of actions to enhance desirable effects include:

- *enhancing security of supply;*
- *making processes more sustainable, efficient, and reliable;*
- *expanding markets, and developing new and improving existing products for new applications;*
- *creating a quality culture where all personnel can make suggestions to improve GMP efficiency and performance.*

6.2 Quality and GMP objectives and planning to achieve them

Top management should set appropriate quality and GMP objectives to ensure that the excipient manufacturer maintains and improves its performance. These objectives should be:

- consistent with the quality policy;
- measurable;
- monitored;
- communicated;
- documented;
- updated as appropriate.

Note: Examples for objectives include:

- *reduction in number of manufacturing deviations or out-of-specification test results;*
- *improvement in right-first-time product quality;*
- *favorable customer audit findings and customer ratings;*
- *compliance with additional compendia;*
- *upgrades in facilities / systems to support use in expanded markets.*

When planning to meet these objectives, the excipient manufacturer should determine:

- what will be done;
- who will be responsible;
- what additional resources will be required;

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- when it will be completed;
- how results will be evaluated.

6.3 Planning of changes

The excipient manufacturer should establish and maintain documented procedures to evaluate and approve changes that may have an impact on the excipient or GMP service.

Prior to implementation, evaluation and approval of changes should be documented (see 7.5) and, where appropriate, a formal risk assessment conducted. Consideration should include potential impact on **validation** (see 8.5.1.8) or regulatory submissions made by the excipient supplier. Procedures should describe the means by which a change is determined to be significant. Where the impact is determined to be significant, such changes should be communicated to customers and, as applicable, to regulatory authorities. See also “The IPEC Significant Change Guide for Pharmaceutical Excipients”.

7 Support

7.1 Resources

7.1.1 *General*

The organization should, in a manner consistent with this guide, determine and provide adequate resources to:

- implement, maintain and improve the quality management system;
- produce, package, test, store and release each excipient;
- supply each GMP service.

Note: Recurring GMP and / or quality deficiencies may indicate a lack of adequate resources.

7.1.2 *People*

The organization should determine and provide adequate numbers of qualified personnel.

Note: No single formula can accurately determine the adequate number of personnel for all excipient manufactures. Examples of how to determine the number of qualified personnel necessary include:

- *resource mapping;*
- *work studies of output versus time;*

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- *management system reviews (input from internal / external audits, nonconformances, etc.).*

7.1.3 *Infrastructure*

The infrastructure should be designed, managed, operated, cleaned, and maintained in accordance with GMP principles to ensure excipient quality as well as to minimize the risk of **contamination**, including **cross-contamination**. It should be designed and controlled to prevent unauthorized access.

An infrastructure risk assessment should be documented (see 7.1.3.1 - 7.1.3.5), based on the intended use of the excipient, to identify areas in which the excipient is at risk of contamination from infrastructure design and / or deficiencies. See also “The IPEC Risk Assessment Guide for Pharmaceutical Excipients”.

Note: Risks associated with deficiencies inherent to the design and location of the facility may be mitigated using additional controls from the risk assessments described in the following sub-sections.

7.1.3.1 *Buildings and facilities*

The ability to clean and minimize the risk of contamination (including pest infestation (see 7.1.4.4) and cross-contamination) should be considered in the design of the manufacturing processes and facilities, particularly where the excipient is exposed to the environment.

Note: 1. Examples of how to minimize the risk of contamination and cross-contamination include:

- *allowing adequate space for activities, including:*
  - *controlled areas for sampling or dispensing of raw materials, intermediates and final product;*
  - *ability to access equipment that needs cleaning or maintenance;*
  - *ability to separate processing of different materials.*
- *use of dedicated pipelines;*
- *pipelines and tanks from which the previous material can effectively be removed.*

2. Examples of where the excipient is exposed to the environment include:

- *manual additions of raw materials, including seed crystals, to production equipment;*
- *open transport of materials (e.g., on a conveyer belt);*

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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *packaging or repackaging operations, especially those that take place outdoors.*

To facilitate cleaning, maintenance, and correct operation appropriate to the type of processing, buildings and facilities used in the supply of GMP services or the production, processing, packaging, testing or storage of an excipient should be:

- appropriate for their purpose,
- maintained in a good state of repair, and
- of suitable size, construction, and location.

Manufacturing processes using **allergens**, highly sensitizing or toxic materials should be located in dedicated facilities and / or use equipment not used for excipient manufacture. In some jurisdictions this is a regulatory requirement. If allowed by regulation and when non-dedicated facilities or equipment are used, appropriate measures, resulting from a specific risk assessment, should be implemented to minimize the risk of cross-contamination. The effectiveness of these measures should be demonstrated.

Note: 1. Examples for toxic materials include: pesticides, carcinogens.

2. Examples for highly sensitizing materials include: antibiotics, hormones.

3. Cleaning and inactivation are examples of appropriate measures that minimize the risk of cross-contamination, when it is not possible to locate highly sensitizing or toxic materials in dedicated facilities or to use separate equipment.

4. To demonstrate effectiveness of these measures, the following could be documented:

- *segregation;*
- *studies of cleaning effectiveness and repeatability;*
- *environmental monitoring;*
- *monitoring of cleaning effectiveness.*

7.1.3.2 *Equipment*

To facilitate cleaning, maintenance, and correct operation for the type of processing, equipment used in the supply of GMP services or the production, processing, transfer, packaging, testing or storage of an excipient should be:

- appropriate for its purpose,
- maintained in a good state of repair, and

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- of suitable size, construction, and location.

Consideration of the risk of breakage or damage should be given.

Note: 1. Examples of equipment used for transfer include pipelines, hoses, hoppers, intermediate storage containers and utensils such as scoops.

2. Examples of how the type of processing could affect size, construction and location of equipment include:

- *batch processing equipment may need to be designed to allow for more frequent cleaning or maintenance versus equipment used in continuous processing;*
- *equipment which must be opened for charging may be inappropriate for outdoor use;*
- *for handling materials requiring low bioburden, the need for different surface finishes, materials of construction, types of welds, etc.*

3. Examples of where breakage or damage may occur, include:

- *glass equipment, e.g., glass-lined reactors, vessels or tanks, sight glasses (also called viewing ports), in-line probes e.g., pH or temperature;*
- *metal sieves, milling equipment and moving parts;*
- *filters, gaskets, seals.*

Equipment should be qualified and commissioned before use to ensure that it is functioning as intended. See also “The IPEC Validation Guide for Pharmaceutical Excipients”.

The use, cleaning and maintenance of quality-critical equipment should be recorded (see 8.5.1.1). The status of equipment should be readily identifiable.

Note: Examples of readily identifying the status of equipment include labels, calibration status sticker, equipment power lock, equipment use log, etc.

Where equipment is located outdoors there should be suitable controls to minimize the risk to excipient quality from the environment.

Note: Examples of how to minimize the risk to excipient quality where equipment is located outdoors include:

- *processing within a closed system;*
- *use of temporary enclosures when equipment must be opened;*
- *use of inline samplers to avoid opening equipment.*

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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 not come into contact with raw materials, packaging materials, intermediates or finished excipients. Where contact with such substances is possible, substances at least suitable for use in food applications should be utilized.

Equipment should be designed to minimize the possibility of contamination caused by direct personnel contact. The sanitary design of transfer and processing equipment should be evaluated using a risk assessment.

Note: Examples of direct personnel contact include:

- *open unloading of centrifuges;*
- *manual sampling from open equipment;*
- *open operating and maintaining of equipment.*

Equipment and its components should be assessed regarding their potential for erosion and degradation to control the risk of contamination, including cross-contamination.

Note: Examples of equipment and components with potential for erosion or degradation include:

- *lubricants, coolants;*
- *filter screens;*
- *ball bearings.*

Equipment maintenance:

Documented procedures should be established and followed for maintenance of quality-critical equipment used in the production, processing, packaging, testing, or holding of excipients. There should be records of the use and maintenance of quality-critical equipment.

Note: These records can be in the form of a paper log, computer database (e.g., maintenance software) or other appropriate documentation. See 7.5.

Computer systems:

Computer systems (i.e., software, hardware, data) that may impact excipient quality should have sufficient controls for operation and maintenance to ensure that the system is performing as intended, including:

- procedures for periodic system **verification**;

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- back-up or archiving (see 7.5.1);
- preventing unauthorized access;
- assurance that changes are traceable, verified, documented, and only made by authorized personnel (see 6.3 and 7.5).

See also “The IPEC Validation Guide for Pharmaceutical Excipients”.

Records demonstrating proper performance of the computer systems should be maintained.

7.1.3.3 *Utilities*

A risk assessment should be performed to consider the risk to excipient quality from utilities used in the production, storage, or transfer of materials. Appropriate action should be taken to eliminate or, at a minimum, control the identified risks. Utilities that could impact excipient quality should have documented specifications and be of suitable quality for their intended use. **Quality critical** parameters of these specifications should be monitored at a documented frequency (see 8.5.1).

Note: 1. Examples of utilities include steam, water, process air, and compressed gasses.

2. Examples of how improperly controlled utilities could pose a risk to excipient quality include:

- *Incorrect air pressure might change a powder’s particle size,*
- *Introducing contaminants, e.g., moisture, microorganisms, oil, particles.*

3. More guidance on water is given in 7.1.3.4.

4. Environmental air handling is not a utility. Section 7.1.4.1 provides relevant requirements for environmental air handling.

7.1.3.4 *Water*

A risk assessment should be performed to consider the risk to excipient quality from water used in the manufacture of excipients. Appropriate action should be taken to eliminate or, at a minimum, control the identified risks. Water that could impact excipient quality, regardless of its source, should have documented specifications and be of suitable quality for its intended use. Quality critical parameters of these specifications should be monitored at a documented frequency (see 8.5.1).

Note: 1. Examples of water used in the manufacture of excipients include:

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- *process water that contacts the excipient or intermediate (e.g., diluting, dissolving, washing);*
- *steam / water used for heating or cooling that has potential for product contact;*
- *water used to flush a line after material transfer;*
- *steam / water used for cleaning.*

2. Examples of water sources include:

- *well;*
- *municipality;*
- *condensate;*
- *recycled.*

3. Based on the risk assessment, monitoring activities could include:

- *continuous monitoring (inline);*
- *periodic sampling at appropriate intervals and locations;*
- *periodically receiving documentation attesting to potable water quality from the water treatment facility.*

Unless otherwise justified, water used in the manufacture of excipients should, at a minimum, meet **WHO** guidelines for drinking (potable) water. When drinking water quality is insufficient to ensure excipient quality, appropriate chemical and / or microbiological water quality limits should be defined.

Note: How might a manufacturer determine the quality of water needed?

- *Some **process step**s (e.g., washing of raw or intermediate materials) may not require WHO quality water if further purification steps take place later in the manufacturing process.*
- *Drinking water quality may not be sufficient based on the manufacturing process (e.g., reaction or sanitization) or customer requirements (e.g., intended use of the excipient).*
- *Where water is used to wash the final excipient, WHO quality water (or higher) may be necessary, because there is no further purification.*

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.

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Water contacting the excipient should be produced and distributed to minimize the risk of contamination or backflow in the system.

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

Note: Examples of interruptions include:

- *planned or unplanned stoppage of the water flow;*
- *loss of ability to monitor or maintain specified water quality.*

7.1.3.5 *Recycled or recovered materials*

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.

Activities to recycle or recover materials should be documented in production records or logs to enable traceability (see 8.5.2).

7.1.4 *Environment for the operation of processes*

Where the excipient is exposed during manufacture it should be in an appropriately controlled environment to minimize the risk of degradation and contamination, including cross-contamination.

Note: For examples of potential excipient exposure to the environment refer to first "Note 2" in 7.1.3.1.

A documented assessment should be carried out to identify the related risks and to determine the necessary controls. The following should be considered, as applicable:

- air handling systems, see 7.1.4.1;
- need for specific environments (controlled environments), see 7.1.4.2;
- cleanliness and sanitary conditions, see 7.1.4.3;
- pest control, see 7.1.4.4;
- personnel hygiene, see 7.1.4.5;
- material (including waste) segregation, see 7.1.4.8;

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- waste disposal, see 7.1.4.8;
- other potential sources of contamination, including cross-contamination.

Special consideration should be taken in multi-use areas, where several products are processed simultaneously.

Where maintaining the work environment is critical to excipient quality, the controls should be documented and, as appropriate, monitored.

7.1.4.1 *Environmental air handling*

Where the documented risk assessment has identified risks associated with air handling, the system should be designed and controlled to minimize the risk of degradation, contamination, and cross-contamination of the excipient.

The effectiveness of the air handling system should be demonstrated.

Note: 1. Process air is a utility, see 7.1.3.3.

2. Environmental air handling describes the management of ambient air to be acceptable for excipient exposure, e.g., heating / cooling / recirculation or isolation of room / facility air.

3. Inadequate or malfunctioning air handling systems could cause degradation or contamination of the excipient by, for example, introduction of:

- *moisture;*
- *microorganisms;*
- *foreign materials,*
- *industrial / agricultural emissions.*

4. Means of demonstrating effectiveness of the air handling system could be described in a procedure and may include:

- *regular checks of the air pressure differential;*
- *reviewing trend data (e.g., continuous dew point monitoring);*
- *inspection of filters.*

7.1.4.2 *Controlled environment*

Where the documented risk assessment has identified the need for a controlled environment, it should be monitored and controlled to assure excipient quality.

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Note: Examples of controlled environments include:

- *protection from light;*
- *humidity control;*
- *inert atmosphere;*
- *temperature control;*
- *classified areas.*

Such controlled environments should be designed to minimize the risk of contamination, including cross-contamination, or degradation of the excipient. The degree of protection required may vary depending on the stage of the process.

Where the documented risk assessment has identified the need for an inert atmosphere, the inerting gas should be treated as a raw material.

Note: When the gas is manufactured on site, it is a utility (see 7.1.3.3). When the gas is purchased, it is an externally-provided quality-critical material (see 8.4).

If interruptions to the controlled environment occur, sufficient evidence and appropriate rationale should be documented to show that such interruptions have not compromised the quality of the excipient.

Note: Examples for interruptions to the controlled environment include:

- *opening of lines or tanks for maintenance that interrupt the flow of inert gas;*
- *power outages that interrupt monitoring or control activities;*
- *filter breach.*

7.1.4.3 *Clean and sanitary conditions*

Buildings used in the production, processing, packaging, or holding of an excipient should be maintained in an appropriately clean and sanitary condition.

Note: Cleaning / sanitizing in this context refers to buildings and facilities. Cleaning / sanitizing of equipment is discussed in 8.5.1.2.

Where the documented risk assessment has identified the need for clean / sanitary conditions, documented procedures should be in place according to the type of processing conducted:

- assigning responsibility for cleaning / sanitizing;

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- describing in sufficient detail the schedules, methods, equipment, and materials to be used in cleaning / sanitizing the buildings and facilities.

Note: Examples of different types of processing include open system versus closed system, continuous production versus batch production, and dedicated equipment versus multi-purpose equipment.

These activities should be documented (see 7.5.1).

Where disinfectants and / or detergents are used, a documented risk assessment should demonstrate their suitability. The quality unit should approve the use of quality-critical cleaning and sanitizing agents.

Note: Examples of what to consider for suitability include:

- *intended use as determined by the manufacturer, for example: "technical grade" may not be appropriate for use in an excipient manufacturing facility;*
- *effective for their intended use;*
- *evaluate if odors or residues may adversely affect packaging material or the excipient (e.g., chemical composition, stability);*
- *other requirements, such as **Halal** or **Kosher**.*

7.1.4.4 *Pest control*

A documented risk assessment should be carried out by an internal or external pest control specialist. This risk assessment should consider the potential for infestation by rodents, birds, flying and crawling insects and other vermin.

Some raw materials, particularly agriculturally sourced materials, may contain unavoidable contamination, such as rodent or other animal filth. Appropriate control methods should be in place to prevent the increase of such contamination in holding areas and its spread to other areas of the manufacturing facility.

Note: 1. Infestation means the presence of the actual vermin or the evidence that they were there, e.g., bird droppings.

2. In case of open facilities, risk mitigation may be used, as appropriate (e.g., usage of bird net or other screening measures).

Where the risk assessment has identified the need for pest control, the organization should document the pest control program, including the use of suitable rodenticides, insecticides etc.

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Note: As determined by the documented risk assessment, the quality unit should approve the use of such rodenticides and / or insecticides.

Where a service provider is used, there should be a contract in place (see 8.4).

7.1.4.5 *Personnel hygiene*

Where the documented risk assessment has identified areas in which the excipient is at risk of contamination, including cross-contamination, from personnel or their activities, controls should be put in place to minimize the risk. At a minimum the following should be considered and documented:

- the personnel themselves;
- suitability of clothing and protective equipment for the activity;
- provision of facilities for showering and / or changing clothes;
- removal or covering of jewelry and other loose items, including those in pockets;
- reporting to supervisory personnel any health conditions, apparent illness or open lesions, that may have an adverse effect on excipients;
- restricting the storage and consumption of food, drink, personal medication, tobacco products or similar items to designated locations separate from manufacturing areas.

Note: 1. Examples of personnel activities that could introduce contamination include:

- *maintenance;*
- *sampling;*
- *packaging;*
- *other manual process operations.*

2. Jewelry and other loose items could include pens, ID cards, piercings, artificial nails, other cosmetic applications such as nail polish, perfume, after shave, lipstick, false eye lashes and personal protective equipment such as ear plugs, safety monitors, and bandages.

Adequate washing facilities and supplies should be provided so that suitable hygiene standards can be maintained. Toilet facilities should be clean and separate from but easily accessible to working areas.

Note: Adequate washing facilities and supplies can include hot and cold water, soap or detergent, air dryers or single service towels.

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7.1.4.6 *Lighting*

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

Note: 1. Examples of proper operations include:

- *ability to see instrument read-outs and read batch numbers on labels;*
- *sufficient lighting to perform visual controls, e.g., titration, identifying the interface in a phase separation, discerning colors in test methods;*
- *protecting light sensitive excipients from exposure to light.*

2. Temporary lighting (e.g., torches / hand-held flashlights) should be subject to the same controls as fixed lighting.

7.1.4.7 *Drainage*

In areas where the excipient is open to the environment or stored, drains should be of adequate size. Where connected directly to a sewer, drains should be provided with air breaks or mechanical devices to minimize the risk of back-siphoning. Drains should be maintained appropriately.

Note: Based on the results of the documented risk assessment, maintenance of drains could include, for example, routine:

- *visual inspection;*
- *flushing / rinsing;*
- *cleaning / sanitizing.*

7.1.4.8 *Waste*

Waste should be segregated and disposed of in a timely manner by means appropriate to its type. If waste is not disposed of immediately, it should be suitably labeled and stored. Excipient packaging should not be used to hold waste unless clearly labeled as waste.

Note: 1. Waste types could include chemical, biological, and hazardous.

2. Examples of labeling include:

- *text labels (container labels, tank labels, area labels, etc.);*
- *color coding (colored containers, colored tape).*

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7.1.5 *Monitoring and measuring resources*

7.1.5.1 *General*

The excipient manufacturer should identify measuring and monitoring equipment necessary to adequately control manufacturing processes. Equipment critical to quality should be qualified, commissioned, calibrated, and, where appropriate, maintained.

Note: 1. Examples of equipment critical to quality may include:

- *in-process instruments;*
- *equipment used in the laboratory;*
- *equipment used for the calibration of measuring and monitoring equipment;*
- *computerized systems.*

2. Some quality-critical equipment, based on a documented risk assessment, can be run to failure provided they are calibrated before each use. In some cases, it might be necessary to calibrate after use as well to ensure equipment suitability. Examples include pH probes and chromatography columns.

The control program should include:

- the standardization or calibration of instruments and equipment at suitable intervals in accordance with a documented program;
- specific instructions, schedules, limits for accuracy and precision;
- provisions for remedial action if accuracy and / or precision limits are not met, including:
  - prevention of future use until suitability can be demonstrated;
  - documented investigation to determine the validity for results reported since the last successful qualification / **commissioning** / calibration.

Instruments and equipment not meeting established calibration limits should not be used.

Note: Examples to prevent usage of instruments and equipment not meeting established calibration limits include:

- *labeling;*
- *lock-outs;*
- *removal from area, where feasible, or barrier tape.*

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For quality-critical monitoring and measurement equipment, the excipient manufacturer should retain documented evidence demonstrating fitness for purpose.

Note: Examples of documented evidence include:

- *equipment qualification (design, installation, operation, performance) reports;*
- *calibration records and certificates of calibration;*
- *maintenance records;*
- *computerized system validation reports.*

7.1.5.2 *Measurement traceability*

Standards used for the calibration of measuring and monitoring equipment should be traceable to recognized national, international, or compendial standards, as appropriate.

The qualification / commissioning / calibration status of quality-critical equipment should be known and verifiable to users.

Note: User in this context means "analyst / person qualified to use such equipment", not excipient user

7.1.6 *Organizational knowledge*

The excipient manufacturer should determine, apply, and maintain the knowledge necessary for manufacturing and marketing of excipients. Knowledge of current regulations should be aligned to the labeling claims made about the excipient, intended use, and the countries in which it is marketed.

Note: 1. Application of organizational knowledge can be based on:

- *internal sources (e.g., intellectual property; knowledge gained from experience; lessons learned from failures and successful projects; deviation and complaint investigations; capturing and sharing knowledge and experience so that it is not dependent upon an individual; the results of improvements in processes, excipients and GMP services);*
- *external sources (e.g., standards; academia; conferences; gathering knowledge from customers or external providers).*

2. Examples of knowledge include information related to:

- *formulas and recipes;*
- *manufacturing equipment;*

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- *test methods;*
- *regulatory / compendial requirements;*
- *customer specifications.*

3. Examples of maintaining the knowledge include:

- *succession planning;*
- *mentoring;*
- *technical reports, databases, e.g., regulatory, product safety;*
- *ensuring that key knowledge is appropriately shared.*

7.2 Competence

The excipient manufacturer should determine, and document in a written job description, the appropriate combination of education, training and experience for roles / personnel performing tasks that may affect excipient quality (see 5.3). These tasks should be considered in the training plan.

The excipient manufacturer should establish and maintain procedures for identifying the training needs of its employees and contracted personnel. A process should be established to provide effective training to all personnel who perform activities that may affect excipient quality. Training should be provided prior to independently performing those activities.

Training should address the particular GMP operations that the employee performs as well as detailed GMP related to the employee's role.

Note: Examples for detailed GMP related to the employee's role include:

- *supply chain: stock reconciliation deviations are GMP deviations / failures, not only financial transactions to be made;*
- *security personnel: allowing visitors entry to the facility;*
- *production operators: impact of process interruptions, e.g., restarting equipment during production, unplanned maintenance and return to service.*

Appropriate records of training should be maintained.

Note: Examples of appropriate records of training include:

- *documented content and evaluation of "training on the job" by e.g., instructor, supervisor or line manager;*

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- *attendance log of internal or external training supported by contents of the course and demonstration of effectiveness (e.g., testing).*

Retraining requirements should be defined and documented.

Note: Examples for when retraining could apply:

- *after job reassignments or extended absences;*
- *when job details change, i.e., new equipment, procedure changes, new testing and / or regulations;*
- *following human errors, accidents, or process incidents.*

Consultants advising on 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 advice they provide.

Note: 1. Consultants are subject matter experts who share their knowledge, in contrast to service providers, e.g., calibration technicians, who do the actual work.

2. Consultants can advise on topics such as:

- *engineering;*
- *experimental design;*
- *method validation;*
- *conformance of the quality management system to excipient GMP;*
- *development of training materials.*

7.3 Awareness

Qualified individuals should develop and provide general GMP training. This training should be consistent with the quality policy and provided with sufficient frequency to ensure that employees remain familiar with applicable GMP principles. Training content should include the following topics – at a minimum – as they relate to the individual's role and function:

- importance of following instructions and prompt notification of any deviation;
- data integrity;
- precautions necessary to minimize the risk of contamination, including cross-contamination, through personal hygiene practices;

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- understanding of other precautions necessary to minimize the risk of contamination of excipients, including cross-contamination;
- potential to impact patient safety should the above expectations not be met.

Note: Examples of other precautions include:

- *equipment cleaning after invasive maintenance;*
- *use of approved cleaning materials and lubricants.*

The training program should ensure personnel understand that deviations from procedural instructions may impact the safety, quality, or efficacy of medicinal products.

Note: Examples of deviations include:

- *charging raw materials in wrong order;*
- *stirring the reactor longer or shorter than the instructions allow;*
- *using an expired reagent to perform an analytical test;*
- *using the wrong lubricant during maintenance.*

The training program should also ensure that personnel know what to do when a deviation has taken place.

Note: See 8.7 for more information about control of nonconforming outputs.

7.4 Communication

The excipient manufacturer should ensure that internal and external communication processes are established.

Processes for internal communication should be in place for:

- GMP and regulatory requirements;
- quality-relevant policies, including the organization's overall quality policy;
- quality-relevant procedures;
- quality and GMP objectives;
- effectiveness of the quality management system;
- prompt notification to top management of quality-critical situations, including excipient retrievals (see 8.7.4).

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External communication processes should include:

- accurate and pertinent information, which may include regulatory documents (see 7.5);
- replies to customer enquiries, contracts and order handling requirements;
- origin and traceability of the excipient to the customer;
- issues detected after delivery of the excipient (see 8.7.1 and 8.7.4);
- responses to customer complaints and feedback;
- significant changes (see 6.3 and 8.2.4).

Note: Examples of external parties include:

- *contractors;*
- *suppliers and service providers;*
- *customers and **distributor**s;*
- *regulatory agencies;*
- *certification bodies;*
- *compendial organizations.*

7.5 Documented information

7.5.1 *General documentation requirements*

The organization's overall intentions and approach to GMP should be described and documented to facilitate common understanding and consistent application.

Procedures for manufacturing, control of data and records, as well as other documents related to requirements of the quality management system should be implemented, controlled, and maintained. This includes regulatory documents and documents of external origin that are part of the quality management system.

Note: 1. Examples of data, including raw data, include:

- *direct measurements, e.g., weights, temperatures, pH;*
- *calculated results, e.g., yield, concentration.*

2. Data reported in a formatted document is called a record. Examples of records include:

- *batch (production) records;*

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- *training records;*
- *laboratory data sheets;*
- *certificates of analysis and certificates of conformity;*
- *cleaning lists;*
- *shipping records;*
- *maintenance logs;*
- *equipment use record (sometimes available as a log);*
- *qualification reports.*

3. Examples of documents include:

- *procedures;*
- *blank forms and logs;*
- *master production instruction (also known as master batch record or master production record);*
- *training materials;*
- *quality manual and policies.*

4. Examples of regulatory documents and documents of external origin include:

- *excipient **DMF** and / or **CEP**;*
- *EXCiPACT and / or ISO certificate;*
- *Halal and / or Kosher certificate;*
- *raw material certifications, e.g., GMO, **BSE** / **TSE**.*

The excipient manufacturer should establish and maintain procedures for the lifecycle of documented information covering:

- Review, approval, distribution, access, retrieval, and use:
  - current versions of applicable documents should be available at points of use;
  - prevent unintended use of obsolete documents;
- storage and preservation, including preservation of readability and integrity:
  - prevent unintended and / or unauthorized changes;

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- minimize the risk of accidental deletion or damages;

- control of changes (e.g., correction, version control);
- periodic review to ensure the document remains current with practice;
- retention, including:
  - process for identifying and labeling obsolete documents;
  - retention time;
- destruction.

Records should be maintained to demonstrate achievement of the required excipient quality and the effective operation of the quality management system. Records should be legible and identifiable with the product or process involved.

Note: Records may be in different locations and / or formats.

The organization should define which results, records and reports of subcontractor activities are retained, by whom, and for how long.

If electronic signatures are used, they should be authenticated, provide equivalent security to handwritten signatures, and comply with relevant regulatory requirements.

Note: 1. What does it mean to authenticate electronic signatures? Authentication is a method to verify signer's identity. Examples include:

- *unique UserID + personal password;*
- *biometric identification (retina scan or fingerprint);*
- *RFID identity badge + PIN code.*

2. Information about electronic signatures and expectations of how to control them, including regulatory requirements and the meaning of equivalent security, can be found in:

- *U.S. FDA Code of Federal Regulation, Title 21 Part 11 (**21 CFR** 11), Electronic Records; Electronic Signatures;*
- *EU GMP Annex 11, Computerised Systems, January 2011;*
- *MHRA: GxP Data Integrity Definitions and Guidance for Industry, July 2016;*
- *US FDA Guidance for Industry: Part 11, Electronic Records; Electronic Signatures-Scope and Application, 2003;*

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- *WHO: TRS 996, Annex 05, Guidance on good data and record management practices, 2016.*

Data integrity principles i.e., of ALCOA+ should be incorporated throughout the procedures and systems used for managing documented information.

Note: Compliance with ALCOA+ data integrity principles can be met when data and records are:

- ***A**ttributable (i.e., you know who acquired the data or performed an action and when);*
- ***L**egible (i.e., you can easily read the data);*
- ***C**ontemporaneous (i.e., data are documented at the time of the activity);*
- ***O**riginal (i.e., data are recorded from original observations or taken from certified copies);*
- ***A**ccurate (i.e., data, including metadata (e.g., audit trail) and edits, where applicable, are complete and correct);*
- ***+**Complete (i.e., for each activity, records include all data collected, including, where applicable, metadata (e.g., audit trail), and edits);*
- ***+**Consistent (i.e., entries in records include all elements in the expected sequence);*
- ***+**Enduring (i.e., data are maintained throughout their defined lifecycle on media proven to last throughout the retention period);*
- ***+**Available (i.e., records can be readily accessed - in human readable form - during their lifecycle).*

Data integrity controls for excipient manufacturing and distribution processes should be commensurate with risks associated with the use of the data. A higher level of control should be implemented where the loss of data integrity could compromise compliance with excipient GMP, impact confidence in excipient quality, cause the failure or rejection of the medicinal product, or pose potential **harm** to the patient.

*Note: Data integrity controls for excipients may be different from controls used for manufacturing of **Active Pharmacuetical Ingredients (APIs)** and medicinal products.*

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.

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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 records should be signed and dated, leaving the original entry legible.

7.5.2 *Creating and updating*

Documents should include a unique identifier, date of issue and revision number to facilitate identification of the most recent document.

Documents that have the potential to impact product quality should have a defined owner and be reviewed and approved by the quality unit (see 5.3) before issuance to the appropriate areas. Additionally, procedures and forms should indicate from which date they are valid. This date should allow sufficient time to provide for employee training (see 7.2).

The department with the responsibility for issuing the documents should be identified.

Note: 1. Examples of how ownership is defined include:

- *name and / or function of the owner identified within the document;*
- *list of procedures with owners for each.*

The owner does not have to be the quality unit.

2. How can the quality unit review and approve a document?

- *signing off as reviewed and accepted for final draft version;*
- *signing off as final approver.*

Changes to approved, quality-relevant documents should be reviewed and approved by the quality unit (see 5.3) before use.

Changes and the reasons for the change should be documented.

Note: It may be practical to only maintain the most recent reasons for revision in an effective procedure while maintaining the complete revision history offline in a controlled and restricted space.

All quality-related documented information (i.e., data, records, documents) should meet the above, independent of the storage medium (i.e., paper, electronic, **mixture** of both).

7.5.3 *Control of documented information*

Documented information should be controlled. Controls should provide assurance that only the current version is being used in operational areas and that previous versions of documents have been removed.

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Note: Examples how to control data, records, and documents, including access, include management by:

- *procedures;*
- *computerized systems;*
- *combination of both.*

Copies of controlled documents should be readily identifiable as either controlled or uncontrolled.

Note: Examples of identification include:

- *watermark;*
- *date and signature;*
- *stamping;*
- *use of colored paper;*
- *expiration date (for printed electronic copies)*.

Records should be kept for a defined period appropriate to the excipient and as specified in applicable:

- regulations;
- certification standards;
- customer agreements.

The excipient manufacturing record retention period should be at least one year past the excipient's expiry or last **re-evaluation date**, or at least five years from the **date of manufacture**.

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

Note: Examples of how to apply these controls to electronic records include:

- *controlled and limited access;*
- *audit trail;*
- *back-up systems;*
- *readability of records in obsolete software.*

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8 Operation

8.1 Operational planning and control

The excipient manufacturer should plan, implement, and control the processes needed for provision of excipients and GMP services. According to the actions determined in section 6, the excipient manufacturer should:

- determine the requirements for the excipients and GMP services;
- establish criteria for excipient manufacturing that include:
    - documented processes;
    - documented testing programmes for quality-critical materials including intermediates and finished excipients;
    - appropriate specifications;
    - sampling plans;
    - environmental and hygiene control programmes (see 7.1.4) to minimize the risk of contamination, including cross-contamination;
    - test and release procedures;
    - determination and provision of resources to implement these plans and controls.
- document procedures describing activities related to the storage and distribution of excipients;
- implement actions from relevant documented risk assessments (see 7.1 including sub-sections);
- generate and maintain records providing evidence that the controls have been followed and met.

The excipient manufacturer should control planned changes (see 6.3) and have a process to manage the consequences of deviations (i.e., unintended changes).

The excipient manufacturer should ensure that outsourced processes are controlled (see 8.4) and notify customers as applicable (see 8.2.1).

8.2 Requirements for excipients and GMP services

8.2.1 *Customer communication*

There should be processes in place for communication to the customer, including:

- provision of accurate and pertinent information, which may include regulatory documents (see 7.5);
- provision of replies to enquiries, contracts and order handling requirements;
- handling or controlling customer property, as applicable;
- communicating the **original manufacturer**'s identity and production site;
- notifying customers of outsourced activities that may affect excipient quality (see 8.4);
- provision of **certificate of analysis** for each **batch** shipped (see 8.6);
- notifying customers of significant changes (see 6.3);
- documenting and responding to customer complaints and feedback;
- informing customers of issues, including recalls and critical deviations detected after delivery of the excipient or provision of the GMP service (see 8.7.1, 8.7.2, and 8.7.4);
- informing if customers are impacted by activation of contingency plans.

Note: 1. Examples for information communicated to customers include:

- ***Excipient Information Package**, Specification, Product Information Brochure (refer to IPEC Excipient Information Package User Guide and Templates);*
- *GMP certification from an accredited certification body (refer to IPEC GMP Certification Scheme and Certification Body Qualification Guide).*

2. Information could be communicated in a variety of ways, e.g., company website, electronic portal, customer's monitored mailbox.

8.2.2 *Determining the requirements for excipients and GMP services*

The excipient manufacturer should determine the requirements for manufacture of excipients and provision of GMP services based on the intended use. Customer-specific, legal, and regulatory requirements should be considered, as found in "The IPEC Qualification of Excipients for Use in Pharmaceuticals Guide and Checklist".

8.2.3 *Review of the requirements for excipients and GMP services*

The excipient manufacturer and customer should review and mutually agree upon the requirements identified in 8.2.2 before supply begins. The manufacturer should have the facility and process capability (see 8.5.1) to consistently meet the mutually agreed specifications and GMP services.

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Customer requirements may be documented in agreements, revision of which can be initiated by either party.

Note: 1. Examples of agreements include Quality Agreement, Supply Agreement, Purchase Agreement, and Service Level Agreement.

2. For guidance on quality agreement responsibilities and review, refer to the IPEC Quality Agreement Guide and Template(s) for Pharmaceutical Excipients.

Where the requirements determined in 8.2.2 are changed, this review should be repeated before supply resumes.

8.2.4 *Changes to requirements for excipients and GMP services*

The excipient manufacturer should have a process for handling changes related to customer and regulatory requirements. See 6.3 for changes initiated by the excipient manufacturer.

8.3 Design and development of excipients and GMP services

Note: Section 8.3 including its sub-sections may not apply to all excipient manufacturers (see section 4, Context of the Organization).

8.3.1 *General*

In the design and development of excipients and GMP services, the GMP principles of this guide may not always be fully applicable.

The excipient manufacturer should document in a risk assessment those parts of the guide that are not applied when developing excipients.

Note: 1. Examples of excipients and GMP services include:

- *extension of portfolio with different type of excipient;*
- *use of an existing product as an excipient (e.g., food ingredient to be offered into pharma market);*
- *offering customized GMP services, e.g., non-standard packaging.*

2. Adjustments to the established manufacturing and GMP service provision processes are managed as changes, see 6.3.

8.3.2 *Design and development planning*

When designing and developing excipients and GMP services, the excipient manufacturer should consider the processes and activities necessary to control the desired result, including:

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- the type, duration, and complexity of the development activities associated with the excipient or GMP service;
- stages of the plan, including reviews and approvals;
- verification or validation activities;
- roles and responsibilities (see 5.3);
- resources (internal and external) (see 7.1);
- interface(s) between people involved;
- customer and user involvement (see 5.1.2);
- customer and user requirements (see 8.2.2);
- facilities and process capabilities needed to consistently meet the desired result (see 8.5.1);
- documented evidence needed to demonstrate that planning requirements have been met.

Note: 1. Examples of customers include:

- *distributor;*
- *medicinal product manufacturer.*

2. Examples of users include:

- *medicinal product manufacturer;*
- *contracted 3rd party.*

8.3.3 *Design and development inputs*

The excipient manufacturer should determine the requirements specific to the excipients and GMP services being designed and developed, considering, at a minimum:

- **functionality** and performance;
- information available from similar design and development activities;
- statutory and regulatory environments;
- standards or codes of practice implemented by the organization;
- potential consequences of failure attributable to the type of the excipient or GMP service.

Note: 1. Examples of standards (other than GMP) include:

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- ***FSSC 22000****, Food Safety Management Systems;*
- ***ISO 14001****, Environmental Management Systems;*
- *ISO 50001, Energy Management Systems.*

2. Examples of codes of practice include:

- ***NACD*** *Responsible Distribution;*
- ***Responsible Care®****;*
- *WHO Sustainable Development Goals.*

Design and development inputs should be:

- adequate for their intended purposes;
- clear and comprehensive;
- consistent in their approach.

Evidence of these inputs should be documented and retained (see 7.5).

8.3.4 *Design and development controls*

The excipient manufacturer should control the design and development process to ensure that:

- desired results are defined;
- review of results is performed to assess if requirements can be realized;
- verification activities are conducted to confirm that the design and development outputs meet the input requirements;
- actions verify resulting excipients and GMP services meet the organization's intended use, and customer and user requirements;
- actions are performed to address problems identified during reviews or verification activities, as applicable;
- control activities are documented and retained (see 7.5).

8.3.5 *Design and development outputs*

The excipient manufacturer should ensure that outputs for design and development of excipients and GMP services:

- meet all input requirements;

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- satisfy requirements of the standards and codes of practice implemented by the organization;
- identify process **control strategy** requirements, as appropriate, and corresponding acceptance criteria;

Note: Examples of process steps for which controls might be needed include:

- *phase changes involving the desired molecule, solvent, inert carrier or vehicle (for example dissolution, crystallization, 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**).*

- identify release specifications and / or other requirements consistent with the intended marketed purpose and safe use by the customer, or
- identify other requirements essential for the intended purpose.

Evidence of these outputs should be documented and retained (see 7.5).

8.3.6 *Design and development changes*

In order to minimize the potential for nonconformance to requirements (see 8.3.3), the excipient manufacturer should appropriately control changes (see 6.3) made during the design and development of excipients and GMP services. Documented evidence should be maintained to record:

- the scope of the change;
- review of the change;
- authorization of the change;
- actions implemented to minimize potential negative effects caused by the change.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.4 Control of externally provided quality critical processes, services and materials

8.4.1 *General*

Externally-provided quality-critical processes, services and materials should be described in written agreements and the excipient manufacturer should ensure that these activities and materials conform to the documented requirements (see 8.4.3).

Note: Examples of:

- *"processes" include contracted manufacturing operations related to the excipient such as micronization, packaging, coating, and irradiation;*
- *"services" include additional activities such as warehousing, transportation, pest control, cleaning, and laboratory testing;*
- *"materials" include purchased products such as raw materials, pre-printed labels, lubricants, **process aid**s, (primary or **barrier**) packaging materials.*

A documented process should be used to identify quality-critical processes, services and materials, and their necessary controls.

Note: Examples of documented processes to identify quality-critical processes, services and materials include:

- *risk assessment;*
- *supplier qualification and approval.*

Suppliers of quality-critical processes, services and materials should be approved by the quality unit after a documented evaluation of the supplier's quality management system, including adequate evidence that they can consistently meet agreed requirements (see 8.4.3). Documented information of these activities should be retained (see 7.5).

8.4.2 *Type and extent of control*

The excipient manufacturer should determine the controls necessary to ensure that the externally-provided quality-critical processes, services and materials meet agreed requirements (see 8.4.3). These activities should be documented, including controls that apply to both:

- the external provider, and
- their provided process, service, or material.

These controls may require periodic audits of the supplier's operations.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.4.2.1 *Control of externally-provided processes and services*

Where manufacturing, testing, other operations, or services that could affect excipient quality are outsourced, the responsibility for quality ultimately remains with the excipient manufacturer, and control measures should be defined. The excipient manufacturer should be able to demonstrate that the applicable GMP principles, in accordance with this guide, are followed for those operations and services.

Note: Examples for controls of outsourced operations and services include:

- *specific agreed controls and procedures, based on outcome of risk assessment, e.g.,:*
  - *review of records and approval of operations or services by the excipient manufacturer;*
  - *on-site presence of the excipient manufacturer during execution of outsourced activity;*
  - *analytical testing of the externally-processed excipient.*
- *review and approval for use of cleaning agents and pest control materials;*
- *inspections of the supplier's operations and / or services;*
- *periodic audits of the supplier.*

8.4.2.2 *Control of externally-provided materials*

There should be procedures for control of incoming materials. These should describe the process for approval and release of quality-critical materials, including handling of out-of-specification test results (see 8.6.4).

Incoming quality-critical materials, including packaging and preprinted materials, should be physically or administratively quarantined until they have been tested or otherwise verified and approved for use by the quality unit or their delegate (see 5.3).

Note: 1. Quality-critical preprinted materials provide information as described in section 8.5.2.3, Labels.

2. Examples of verification include:

- *confirming that material received from approved supplier matches purchase order, which may be done manually or by a computer system;*
- *check of the supplier certificate of analysis or certificate of conformance;*
- *identification testing;*

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *testing of quality-critical specifications.*

Sampling activities should be conducted under defined conditions in accordance with a defined sampling method and using approved procedures and sampling tools designed to minimize the risk of contamination, including cross-contamination.

Bulk deliveries should have appropriate controls to minimize the risk of contamination, including cross-contamination.

Note: Examples of controls for bulk deliveries include verification of:

- *dedicated tankers and, where appropriate, couplings and hoses;*
- *details of prior container contents;*
- *tamper-evident seals;*
- *certificate of cleaning;*
- *analytical results (i.e., supplier certificate of analysis, in-house testing).*

When quarantine and stock control are managed with computer systems, there should be system controls to prevent the use of unreleased material.

Note: For more information about control of computer systems refer to section 7.1.3.2, sub-paragraph "Computer Systems".

Quarantine may not be feasible for materials supplied through 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.

8.4.3 *Information for external providers*

Excipient manufacturers should have documented agreements with external providers, communicating:

- the quality-critical processes, services and / or materials to be provided, including where applicable:
  - 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;
  - requirements for the approval of:
    - materials and services;
    - methods, processes, and equipment;

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

        - the release of processes, services, and materials.
    - requirements for personnel competence, including appropriate regulatory qualifications.
- the need for adherence to the applicable GMP principles in accordance with this guide;
- which records, results and reports need to be retained, by whom, and for how long;
- how control and monitoring of external provider performance will be applied;
- **change control** requirements, including subcontracting;
- requirements for verification or validation activities by the external provider, if applicable;
- any need for periodic audits by the excipient manufacturer of the external supplier's operations.

Notes: 1. Examples of documented agreements with external providers include:

- *purchasing agreement;*
- *quality agreement;*
- *service level agreement;*
- *supply agreement.*

2. Examples of regulatory qualifications of personnel competence include:

- *pest control applicator's license;*
- *permit for bio**IID** handling;*
- *license for transporting hazardous materials.*

3. Examples of requirements for verification or validation activities include:

- *on-site presence during manufacturing activities;*
- *review and approval of critical process steps or operations by excipient manufacturer that are subcontracted to another external provider;*
- *permission for excipient manufacturer's customer to visit and / or audit;*
- *defining any revalidation frequency.*

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.5 Production and GMP service provision

8.5.1 *Control of production and GMP service provision*

Activities for provision of excipients and GMP services should be carried out under controlled conditions (see 8.1). There should be evidence defining:

- the characteristics of the excipients to be produced;
- the GMP services to be provided;
- the activities to be performed;
- the results to be achieved.

Specific controls detailed in sections 8.5.1.1 through 8.5.1.8 apply for the excipients or GMP services within the scope of operations (see 8.1).

8.5.1.1 *Instructions and records*

Documents and records (see 7.5.1) describing how the excipient is manufactured or distributed, or GMP service is provided, should be maintained. Written instructions and forms that become records should be available at point of use and may differ based on the activity.

Note: Examples of how written instructions and forms may differ based on the activity, include:

- *batch process may have a blending record whereas continuous process may have a **statistical process control** (SPC) chart;*
- *customer specific requirements for packaging / labeling;*
- *consideration of seasonal effects on shipping e.g., due to temperature and humidity variations.*

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 based on time or quantity produced and / or packaged. Records should also be available for each GMP service provided.

Where critical to demonstrate compliance with this guide and as applicable, records should comply with data integrity principles (see 7.5.1) and include:

- date / time each step was completed;
- documentation of key parameters together with conformance check against specified operating ranges;

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- identification of persons:
    - performing / checking each operation;
    - verifying control parameters.
- identification of major equipment and lines used;
- cleaning activities for equipment, lines, and utensils (see 8.5.1.2);
- material inputs (to enable traceability, see 8.5.2);

Note: Examples of material input traceability include batch numbers, quantities, time added, etc.

- in-process control results (see 8.5.1.6);
- inspection of the packaging and labeling area(s) before use, to ensure that materials not required for the current operation have been removed or destroyed;
- labeling controls performed;
- description of excipient containers and closures;
- description of sampling performed;
- failures, deviations, and their investigations;
- visual inspection results of packaged excipient (see 9.1.3 for analytical testing of final excipient);

Note: Examples of visual inspection controls of packaged excipient include:

- *seal integrity;*
- *package integrity;*
- *correct label;*
- *external surface cleanliness.*

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

Note: Continuous processes are an example where the calculation of theoretical yield may not be applicable because the theoretical yield is not quantifiable.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.5.1.2 *Equipment cleaning*

Equipment and utensils should be cleaned and, if critical to excipient quality, sanitized. Cleaning can be achieved in several ways, some of which may not result in visually clean equipment. The excipient manufacturer should design and justify cleaning and sanitization intervals and procedures and provide documented evidence of their effectiveness based on pre-determined acceptance criteria.

Note: 1. Equipment cleaning and sanitization justification may be documented in a risk assessment. For example, during a production campaign incidental carry-over frequently occurs and can be acceptable when cleaning between successive batches of the same excipient is not required to maintain quality.

2. The use of a model product (i.e., groups of products of similar type) approach or matrix design may be used in justifying a suitable procedure.

3. Provided that risks from bioburden or degradation are appropriately controlled, product flushes may be an adequate method for cleaning dedicated equipment. This method is often used with powdered excipients and may not result in visually clean equipment, i.e., residue of the flush material will still be visible after cleaning.

4. Evidence of effectiveness may be provided in various ways, e.g., in a cleaning validation report, cleaning effectiveness assessment report, video recording of visual inspections, or through analytical test results.

Cleaning and sanitization procedures should be documented. Where disinfectants or detergents are required, an assessment of suitability should be documented. Procedures should contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner (see 7.1.4.3). There should be a record confirming that these procedures have been followed. The cleanliness and, where appropriate, sanitization status of equipment should be identifiable and documented.

8.5.1.3 *Recovery and reuse of materials*

Where materials are recovered and reused, they should meet appropriate specifications prior to reuse or mixing with other approved materials. Processes for recovery and reuse of materials should be justified. These processes should be documented, and records maintained to enable traceability.

Note: Examples of process streams from which materials may be recovered and reused include:

- *solvents;*
- *mother liquors;*

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- *second crop crystallizations.*

8.5.1.4 *Blending of excipients*

If excipients are blended (without the manufacturing elements of **co-processing**) the process should ensure homogeneity and should be reproducible from batch to batch (see 8.5.1.8). The process should be controlled and documented to allow traceability back to the individual batches that make up the blend.

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

Note: Examples of acceptable blending operations include:

- *blending that is part of the defined manufacturing process;*
- *blending small batches to increase batch size;*
- *blending batch tailings (i.e., relatively small quantities of isolated excipient) from batches of the same excipient to form a single batch;*
- *blending of packages that do not conform to weight specifications (i.e., under or over weight);*
- *blending of different excipients to produce a **mixed excipient**.*

Blending should not be used to dilute contamination (see 8.7.1). Blending should also not be used where the performance of the resulting excipient could be impacted.

Note: 1. Examples of unacceptable blending operations include:

- *blending contaminated excipients to dilute contamination below detectable limits;*
- *blending to bring the **technically unavoidable particles profile** into the typical profile range (refer to IPEC Technically Unavoidable Particle Profile (**TUPP**) Guide).*

2. Examples where the performance of the resulting excipient could be impacted include:

- *if blending alters the particle size distribution profile outside normal ranges;*
- *if blending introduces undesirable characteristics, e.g., changes in bulk density, flowability, viscosity.*

8.5.1.5 *Co-processing of excipients*

For co-processing of excipients, different technologies such as granulation, melt extrusion, spray drying, or milling may be used.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

To ensure that specified properties and quality are obtained:

- the co-processing of excipients should be:
    - adequately controlled in-process (see 8.5.1.6);
    - documented to allow traceability back to the **component** excipient batches (see 8.5.2.1);
- finished **co-processed excipients** should be tested to ensure the product conforms to specifications (see 9.1.3).

The expiry or re-evaluation date of the co-processed excipient should be justified.

See also “The IPEC Co-Processed Excipient Guide for Pharmaceutical Excipients”.

8.5.1.6 *In-process control*

In-process controls may be based upon in-line monitoring of the process or actual sample analysis at defined locations and times. In-process sampling, inspection and testing should be performed by trained personnel on representative samples according to documented procedures. In-process samples should be clearly labeled and not returned to the GMP-process production stream.

Note: An example of why in-process control samples should not be returned to the GMP-process production stream is because the handling of samples increases the risk of contamination to the sample. Returning samples contradicts the overall effort to reduce risk of contamination during excipient manufacturing.

The results of in-process controls should be recorded and should be verified against established process limits. Written instructions should describe the use of inspection and test data to control the process. These instructions should detail actions to be taken when the results are outside specified limits.

8.5.1.7 *Packaging and labeling of excipients*

Packaging and labeling procedures should be employed to ensure excipient identity, quality, and purity. To prevent mix-ups, procedural controls should be implemented to ensure:

- correct labels are printed and issued;
- labels contain the correct information;
- printed information is indelible;
- packaging and labeling facilities are inspected immediately before use, confirming that materials not required for the current packaging operation have been removed or destroyed;

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- excipient is packaged into the correct packaging system (see 8.5.4.2);
- excess batch-specific labels are destroyed immediately following packaging operations.

If not required for the subsequent packaging and labeling operation, excess product containers, closures and / or labels without batch- or product-specific information should be destroyed or returned to controlled storage immediately following operations.

Repackaging / relabeling activities should follow the same principles outlined above.

8.5.1.8 *Validation for production and GMP service provision*

The excipient manufacturer should demonstrate consistent operations for the provision of excipients and GMP services based on knowledge of operational parameters, requirements, and their inter-relationship.

Notes Examples of how to demonstrate knowledge of operational parameters include:

- *process capability studies;*
- *development and scale-up reports;*
- *periodic product reviews.*

The concept of validation is a key element in ensuring that processes are capable of consistently producing an excipient that meets specifications. The excipient manufacturer may not perform validation activities in the same manner or to the same extent as the pharmaceutical industry. However, many activities leading to the same degree of assurance are performed within the excipient industry.

Validation should be used:

- where testing alone may not be sufficient to reveal variations outside the process limits, or
- where the resulting output cannot be verified by subsequent monitoring or measurements.

Note: Examples where process output cannot be verified by subsequent monitoring or measurement include:

- *where hazardous environments and / or materials prohibit sampling or exposure;*
- *when sampling or sampling techniques expose the material to degradation or contamination;*
- *where the process requires heat treatment to reduce or eliminate bioburden.*

The excipient manufacturer should have a process for assessing and documenting the impact of change on the **validated state** of the system.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

See also the IPEC Validation Guide.

8.5.2 *Identification and traceability*

Quality-critical materials and services, including GMP services, should be identifiable and traceable through records to demonstrate conformance with the principles of this guide.

Note: Examples of quality-critical materials and services include:

- *raw materials, packaging materials, intermediates and finished excipients;*
- *calibration and maintenance;*
- *testing services (insourced and outsourced);*
- *vendor managed inventory services.*

8.5.2.1 *Traceability*

Records should allow traceability of the service, including GMP services, or, for excipients, from receipt of raw materials through delivery to initial customers and vice versa.

Note: This traceability applies to the excipient manufacturer. However, the end user will want to document the entire supply chain.

Methods should be defined for traceability and identification of raw materials, equipment used in excipient manufacturing, and GMP service provision to customers.

Note: Examples of traceability and identification methods include:

- *batch numbering system;*
- *system based on time or quantity produced and / or packaged;*
- *documents that facilitate traceability, e.g., logbooks, worksheets.*

Even though one-to-one **lot** traceability is not possible with continuously supplied materials or bulk deliveries, traceability of use should still be documented in production records.

Note: 1. "One-to-one lot traceability" refers to the batch of raw material which is used in a particular lot of finished excipient.

2. Traceability of continuously supplied materials or bulk deliveries may be possible by using time and production rates, relating a period of raw material receipt to a period of production.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.5.2.2 *Inspection and test status*

The inspection status of quality-critical materials and services, including GMP services, should be identifiable. Methods for identifying test status should be defined.

8.5.2.3 *Labels*

Excipient container labels may be subject to regulatory and / or compendial requirements (see 8.2.2).

Labels should include at a minimum:

- the names of the excipient (tradename and generic name(s)) and, if applicable, grade, or material code which specifies the grade
- the excipient manufacturer's and / or supplier's name and address,
- the **batch number** from which the complete batch history can be determined,
- special storage conditions, if applicable.

Labeling for excipient packages is subject to national and international regulatory requirements, which may include transportation and safety measures.

8.5.3 *Property belonging to customers or external providers*

The excipient manufacturer should establish and maintain procedures for verification, storage and maintenance of customer and externally-supplied materials intended for incorporation into the customer's excipient. Verification by the manufacturer does not relieve the customer or external provider of the responsibility to provide acceptable material.

Material that is lost, damaged or is otherwise unsuitable for use should be recorded and reported to the customer or external provider. 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 or external provider.

Note: Examples of customer or externally provided property include:

- *test equipment;*
- *test methods;*
- *specifications.*

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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

8.5.4 *Preservation*

8.5.4.1 *Handling, storage, and preservation*

Appropriate storage conditions should be maintained. If critical to maintaining the quality of materials used in excipient production and packaging, storage conditions should be specified, monitored, and recorded. Deviations from specified storage conditions should be assessed (see 8.7). Storage and handling procedures should be defined to:

- protect containers, labels, closures, and security seals,
- minimize the risk of contamination, damage, or deterioration, and
- prevent mix ups.

Note: 1. Examples of materials used in excipient production and packaging include:

- *raw materials;*
- *intermediates, including those processed by third parties*
- *process aids;*
- *packaging materials (primary and secondary), printed and unprinted.*

2. Examples of specified storage conditions include:

- *temperature;*
- *humidity;*
- *light;*
- *atmosphere;*
- *sanitary (e.g., odorless, free from pest infestation, visibly clean).*

Bulk storage containers should be identified and labeled with their contents. Outdoor storage of materials and excipients is acceptable provided the containers give suitable protection against deterioration, contamination, and loss of traceability.

Note: Examples of outdoor storage and controls include:

- *movable containers designed to withstand weather are kept in designated locations;*
- *unpackaged pre-GMP materials (e.g., minerals or vegetation) that will undergo extensive processing (e.g., dissolving, extraction, washing, melting, etc.);*

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- *isolation pads for highly explosive or corrosive materials;*
- *tank farms and silos designed to provide adequate protection and segregation to prevent mix ups.*

See also the IPEC **Good Distribution Practices** Guide.

8.5.4.2 *Packaging*

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

- documented specifications, based on the excipient's properties, including stability,
- packaging systems that provide adequate protection against deterioration, moisture uptake or contamination of the excipient during transportation and recommended storage,
- packaging system components that do not interact with or contaminate the excipient,

Note: Examples of packaging system components include:

- *containers (small volume and bulk), closures, and seals;*
- *inert gas blanket;*
- *moisture barriers;*
- *desiccants.*

- tamper-evident seals, where feasible

If containers are to be reused for the excipient, verified cleaning procedures should be followed and should include instructions for removing previous labels. Records of cleaning should be retained.

Excipient packaging should not be used to hold waste unless clearly labeled as waste.

8.5.4.3 *Delivery and distribution*

Excipients should only be supplied within their **expiry date** or reevaluation period and, where applicable, according to customer and / or regulatory requirements.

Distribution records of excipient shipments to initial customers should be kept. To facilitate retrieval if necessary, distribution records should include:

- batch number,
- customer name and address,

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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- quantity shipped,
- shipment date, and
- where critical to maintaining excipient quality, conditions were met during transportation to the initial customer.

Where applicable, excipient manufacturers should define and provide transportation conditions to service providers and customers (see 8.6.8).

Note 1. Defined transportation conditions may be applicable, e.g., in the case of excipients for which transportation conditions outside recommended storage conditions have the potential to result in deterioration of the excipient.

2. Examples of defined transportation conditions include:

- *temperature;*
- *humidity;*
- *light;*
- *atmosphere;*
- *sanitary (e.g., odorless, free from pest infestation, visibly clean).*

3. Examples of how transportation conditions may be provided include:

- *container label;*
- *shipping documents;*
- *product specification;*
- *safety data sheet.*

For bulk transport, verified cleaning procedures should be justified and applied. Records of cleaning should be retained. A list of prohibited and / or allowed previous cargos should be supplied to transportation companies.

See also the IPEC Good Distribution Practices Guide.

8.5.5 *Post-delivery activities*

The excipient manufacturer should determine and meet post-delivery activities, based on the intended use of the excipient, including:

- informing customers of issues, including recalls and critical deviations detected after delivery of the excipient (see 8.7.1 and 8.7.4), and significant changes (see 6.3),

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VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- provision for country-specific legal and regulatory requirements,
- provision for a complaint handling process (see 8.7.3),
- provision for a returned goods handling process (see 8.7.1.3),
- provision for replies to enquiries and requests

Note: 1. Examples of:

- *enquiries include:*
  - *material handling;*
  - *disposal topics;*
  - *safety data questions;*
  - *allergens;*
  - *compendia changes.*
- *requests include:*
  - *retain samples;*
  - *shelf-life extension;*
  - *technical support.*

2. Enquiries and requests may originate from customers, authorities (e.g., regulatory bodies), or other interested parties (e.g., distributors, agents, contract manufacturers, and third-party service providers).

8.5.6 *Control of changes*

For planning of changes, and changes to requirements for excipients and GMP services, see 6.3 and 8.2.4, respectively.

8.6 Release of excipients and GMP services

The excipient manufacturer should establish procedures and test methods to ensure excipients and GMP services meet requirements and specifications prior to release. Details are provided in sections 8.6.1 through 8.6.9.

8.6.1 *Monitoring and measurement*

Analytical procedures and test methods should be evaluated and verified to demonstrate they provide reliable test results and are fit for purpose. These may be included in the current edition of the appropriate pharmacopoeia or another accepted standard, but the methods may also be

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

If the excipient is labeled with a compendial designation, then it must meet all requirements of the designated compendia.

Note: The word "must" is used instead of the word "should" because use of the compendial designation requires compliance with all compendial requirements including:

- *material **monograph**;*
- *general notices;*
- *mandatory general chapters.*

Without the corresponding GMP, it is not acceptable to upgrade non-excipient grade materials for excipient use based only on testing results.

Non-compendial, including in-house, analytical test methods should be demonstrated to be at least equivalent to those in the compendia.

Note: Sources of non-compendial analytical test methods include:

- *national testing standards, e.g., ASTM (American Society for Testing and Materials), EN (European Norms), BS (British Standards);*
- *industry testing standards, e.g., AOAC (Association of Official Analytical Chemists), ICUMSA (International Commission for Uniform Methods of Sugar Analysis);*
- *customer specific analytical test methods*

See also the IPEC Validation Guide for Pharmaceutical Excipients, 2.5 "Analytical Methods".

8.6.2 *Laboratory controls*

Data integrity principles, i.e., ALCOA+, should be incorporated throughout laboratory procedures and systems to always maintain data integrity (see 7.5.1).

The excipient manufacturer should establish laboratory controls, requiring complete data derived from tests, necessary to ensure conformance with specifications and standards. Records (see 7.5.3) of these controls should include:

- identification and traceability of samples, i.e., a description of the sample received for testing together with:
  - the material name;

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

- batch number or other distinctive code;
- identity of the person taking the sample (if applicable);
- date the sample was taken;
- time the sample was taken (where appropriate).

- test method reference(s);
- for each analysis, raw data required to confirm the test result, including sample preparation, graphs, chromatograms, charts, and spectra from laboratory instrumentation, identifying the specific material and batch tested;
- calculations performed;
- test results compared with specifications;
- date and identity of the person who performed each test, including time (where appropriate);

Note: Examples of reasons to provide time of analysis include:

- *unstable samples or reagents may deliver invalid results over time;*
- *the order of testing may impact analytical results;*
- *documenting time may support root cause investigations.*

- the equipment, including ancillary equipment, used to perform the test when multiple equipment options are available.

Note: 1. Examples of ancillary equipment include:

- *thermometers;*
- *electronic pipettes;*
- *pH-meters;*
- *balances.*

2. Examples of reasons to document laboratory equipment used include:

- *to facilitate laboratory investigations, e.g., information about correct setup, traceability to equipment qualification / calibration status (see 7.1.5.1);*
- *to facilitate other investigations, e.g., manufacturing investigations, customer complaints.*

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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Laboratory reagents, solutions, and reference standards may be purchased or prepared internally. There should be documented procedures for the labeling, handling, use, and storage of laboratory reagents, solutions, and reference standards. Procedures should also be available for the preparation and standardization of internally prepared materials.

Purchased materials should be verified on receipt.

Purchased and internally prepared materials should be stored appropriately and labeled with the name, concentration, and expiry or re-evaluation date. Purchased materials, once opened, should also be labelled with the remaining usage period.

Records for the preparation and standardization of reagents, solutions, and reference standards should be maintained and include at a minimum:

- identity of the prepared material,
- identity, quantities, and batch numbers of components used in the preparation,
- name of preparer,
- equipment used for preparation,
- date of preparation,
- expiry or re-evaluation date of the prepared material.

When secondary reference standards are used, there should be a documented procedure for their qualification against primary reference standards. This procedure should include requirements for preparation, testing, approval, use, and storage.

Expiry or re-evaluation periods should be defined for secondary reference standards. For secondary reference standards with re-evaluation periods, requalification should be performed according to a documented procedure.

Note: Examples of secondary reference standards include:

- *microbiological stock cultures, which may be used for positive and negative control testing, for media testing;*
- *internally produced material tested against a primary reference standard, which may be used for performing system suitability.*

Secondary reference standards may also be referred to as working standards (FDA. Guidance for industry: analytical procedures and methods validation—chemistry, manufacturing, and controls documentation. Rockville: FDA; 2000.)

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8.6.3 *Finished excipient testing and release*

Routine finished excipient testing should be performed on each batch to ensure that the excipient conforms to documented specifications. Nonroutine testing should be scheduled and justified to confirm the finished excipient complies with all specifications.

Note: Examples of nonroutine testing (i.e., not performed on each lot) include:

- *micro testing when verified by process controls;*
- *functionality related characteristics.*

Results from in-process testing, **process analytical technology** (**PAT**), or from other process control records may be used to demonstrate that the finished excipient conforms to documented specifications.

The quality unit should be responsible for the release of the finished excipient. 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. Excipient shipped to the customer prior to quality unit release should follow a documented quarantine-shipping process that includes acknowledgement by the customer and any relevant authority.

8.6.4 *Out-of-specification test results*

Out-of-specification (OOS) test results should be investigated and documented according to a written procedure (see 10.2).

Results obtained by retesting may only be used to replace original test results if a documented investigation concludes that the original results are erroneous due to an assignable root cause.

Note: Examples of assignable root cause that invalidates original results include:

- *sampling error (e.g., pulled from wrong tank, used uncleaned sampling device);*
- *test equipment settings were incorrect;*
- *wrong weight of sample used in analysis;*
- *wrong analytical procedure used.*

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.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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Retesting may not be necessary when product is released under a different specification. However, an OOS investigation should still be performed and documented.

Original and retest data should be included in the investigation report, including when the sample is suspected of not being representative of the material from which it was taken.

8.6.5 *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 sample**s should be stored in a secured location, readily retrievable and in conditions consistent with the recommended storage conditions for the finished excipient.

Unless otherwise justified, retained samples should be maintained in a packaging format that is equivalent to or more protective than the commercial packaging system.

Note: Reasons for using more protective packaging for retained samples include:

- *to ensure the results obtained at retesting are on a sample that has not changed during storage;*
- *because finished packaging sizes may not be practical for sample storage;*
- *because samples for microbiological testing need to be stored in specialized containers.*

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

8.6.6 *Certificates of analysis*

Excipient manufacturers should provide certificates of analysis to the required specification for each batch of excipient. See the IPEC Certificate of Analysis Guide for Pharmaceutical Excipients for details on the suitable contents of a certificate of analysis.

8.6.7 *Impurities*

Where possible, excipient manufacturers should identify impurities as part of the **composition profile**. See also the IPEC Composition Guide.

Appropriate limits for impurities should be based upon safety data, limits as described in official compendia, or other requirements and sound GMP considerations. Manufacturing processes should be adequately controlled so that impurities do not exceed established limits.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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Excipient manufacturers should conduct documented risk assessments to determine whether the excipient specifications should include tests and limits for impurities. At a minimum, microbiological **bioburden** and impurities from raw materials of natural origin should be considered.

*Note: Reasons for adding **impurity** limits to specifications include:*

- *use of metal catalysts;*
- *presence of impurities in raw materials*
- *potential presence of pyrogen for parenteral excipients;*
- *use of solvents;*
- *use of processing aids such as flocculants or filter aids;*
- *reprocessing or reworking.*

In some manufacturing processes, insoluble and visible particles cannot be fully excluded. These particles should not necessarily be considered impurities. However, the excipient manufacturer should implement mitigation strategies based on a documented risk assessment to maintain the occurrence of such particles at an acceptable level. See also the IPEC TUPP Guide for guidance related to technically unavoidable particles.

8.6.8 *Stability*

The stability of excipients is an important factor contributing to the overall safety, quality, and efficacy of the medicinal products in which they are used. Excipient manufacturers should determine the stability of their excipients. They should also consider stability when defining storage and transportation conditions.

See the IPEC Excipient Stability Program Guide.

8.6.9 *Expiry date or re-evaluation period*

Based on excipient stability, an **expiry** date or **re-evaluation** period should be assigned to each excipient and communicated to the customer.

Note: Examples of how to communicate expiry date or re-evaluation period to customers include:

- *printed information on packages, certificate of analysis;*
- *shelf-life statement, which may be included in an excipient information package or made available separately.*

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8.7 Control of nonconforming outputs

Note: 1. Outputs include intermediates, finished excipients and GMP services.

2. ISO 9000 defines:

- *"Output" as the result of a process.*
- *"Process" as a set of interrelated or interacting activities that use inputs to deliver an intended result.*

8.7.1 *Control of nonconforming intermediates and finished excipients*

Intermediates and finished excipients not meeting analytical specifications or other quality indicators should be clearly identified and controlled to prevent inadvertent use or release for sale.

Note: Examples of other quality indicators include:

- *compliance with GMP;*
- *free of foreign matter;*
- *required documentation available and complete, e.g., deviations closed prior to release.*

It is not acceptable to blend contaminated or adulterated batches to reduce the contamination or adulteration below an acceptable or detectable limit (see 8.5.1.4).

Incidences of nonconformance should be investigated and addressed according to a documented procedure in order to:

- identify the root cause(s),
- assess the potential impact on other:
  - batches;
  - intermediates, finished excipients and other product lines;
  - processes.

    Note: Examples of other processes to be assessed for potential impact, include:

    - *maintenance;*
    - *inspections;*
    - *cleaning.*

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- evaluate and determine the disposition of the nonconforming intermediate or finished excipient in one or more of the following ways:
    - **reprocess**ing (see 8.7.1.1);
    - reworking (see 8.7.1.2);
    - authorization for release by customer concession (see 8.2.1);
    - re-grading for use in other applications;
    - disposal.
- define and implement actions to prevent recurrence (see 6.1.2 and 10.2), as appropriate.

All activities of the above-mentioned investigation should be documented and records maintained. The quality unit should review and approve the results of this investigation (see 5.3).

8.7.1.1 *Reprocessing*

Reprocessing should only occur when it has been assessed and documented that the intermediate or excipient may be made in this manner (see 8.5.1). Records of reprocessing should be maintained (see 8.5.1.1 and 8.5.2.1).

8.7.1.2 *Reworking*

Reworking should only be conducted following a documented risk assessment 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 intermediate and / or finished excipient, including equivalence to established specifications;
- impact on stability or the validity of the re-evaluation period;
- impact on performance of the intermediate and / or finished excipient;
- additional controls needed to minimize the risk to excipient quality;
- customer notification.

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The method of reworking should be documented and in compliance with the outputs of the risk assessment. Records of reworking should be maintained.

8.7.1.3 *Returned excipients*

There should be a documented procedure detailing the process for handling returned excipients from receipt through quarantine and final disposition.

The quality unit should approve disposition of the returned excipient (e.g., resale, re-grade, reprocess, rework, or disposal).

Returned excipients should only be considered for resale when the quality unit has evaluated and confirmed that the excipient's integrity and conformance to the required storage and / or transportation conditions have been met for each package.

Excipient integrity factors include at a minimum:

- no evidence of tampering;
- original packaging is not compromised;
- remaining shelf life does not preclude resale.

Records of the quality unit's confirmation should be maintained and include at a minimum:

- name of the excipient;
- **batch (lot) number;**
- reason for return;
- quantity returned;
- identification of customer who returned the excipient;
- any evaluation that was performed;
- final disposition of the returned excipient.

8.7.2 *Control of nonconforming GMP services*

Incidences of nonconformance should be investigated and addressed according to a documented procedure in order to:

- identify the root cause(s),
- assess the potential impact on:

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- batches that are in scope of the nonconforming GMP service;
- other GMP services that could be affected by the identified root cause(s).

- notify customer(s) (see 8.2.1),
- define and implement actions to prevent recurrence (see 6.1.2 and 10.2), as appropriate.

All activities of the above-mentioned investigation should be documented, and records maintained. The quality unit should review and approve the results of this investigation (see 5.3).

8.7.3 *Customer complaint handling*

There should be a documented procedure for management of customer complaints within a timely manner.

Note: The procedure for management of customer complaints may also be applied to complaints from internal customers, i.e., intra-company or inter-departmental complaints.

This procedure should include at a minimum:

- receiving and documenting the complaint;
- investigating the complaint;
- concluding and documenting the investigation, identifying:
  - root cause;
  - whether the complaint is justified;
  - impact on other intermediates, finished excipients (see 8.7.1), or GMP services (see 8.7.2);
  - corrective and / or preventive actions as needed (see 10.2);
- responding to the customer and, as appropriate, other interested parties (see 4.2).

Records of complaints, complaint investigations, and resulting actions should be maintained. Complaints should be regularly evaluated for trends, including recurrence and criticality, in order to identify needs for corrective or preventive actions.

8.7.4 *Recall / Retrieval*

*Note: Is there a difference between the terms "**recall**" and "retrieval"?*

In some regions / countries regulatory authorities may have specific definitions for these terms.

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In this document "recall" has the same meaning as "retrieval".

There should be a documented procedure for effectively and promptly recalling from the market, excipients known or suspected to be nonconforming (see 8.7.1). This procedure should include at a minimum:

- how the recall of an excipient should be conducted;
- which interested parties require notification (see 4.2);
- how, through a mock recall, the effectiveness of this procedure is periodically evaluated;
- how reconciliation discrepancies are addressed.

Recalled excipients should be identified and quarantined until final disposition by the quality unit. Records of recalls and mock recalls should be maintained.

9 Performance evaluation

9.1 Monitoring, measurement, analysis and evaluation

9.1.1 *General*

The excipient manufacturer should identify, plan, and implement the monitoring and measurement activities required to demonstrate conformity and effectiveness:

- of the organization's quality management system according to this guide;
- to applicable requirements (see 4.2).

Monitoring and measurement activities should be documented and consider:

- what needs to be monitored and measured;
- what methods are needed to ensure valid results are obtained;
- when these activities should be performed;
- when results should be analyzed and evaluated.

9.1.2 *Customer satisfaction*

The excipient manufacturer should establish monitoring and measurement activities to assess customer satisfaction including the methods for obtaining, monitoring, and reviewing this information. This information should drive activities to continuously improve customer satisfaction.

Note: Examples of monitoring and measurement activities include:

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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- *trending of customer complaints (see 8.7.3) and customer audit results;*
- *surveying and evaluation of customer perceptions, including business review meetings, sales contacts, and activities at expositions;*
- *trending of customer returns (see 8.7.1.3) and rejections.*

9.1.3 *Analysis and evaluation*

The excipient manufacturer should analyze results obtained from monitoring and measurement activities (see 9.1.1) to evaluate:

- conformity of excipients and GMP services;

Note: Examples include process capability, product / service reviews and customer complaints.

- the degree of customer satisfaction (see 9.1.2);
- the performance and effectiveness of its quality management system;

Note: Examples include results from internal and certification audits.

- if planning has been implemented effectively;

Note: Examples include planned actions completed on time and in full.

- the effectiveness of actions taken to address risks and opportunities (see 6.1);
- the performance of external providers (see 8.4.3);
- the need or opportunity for improvements to the quality management system (see 10).

Note: The results of these evaluations may be used as part of the input for management review (see 9.3.2).

9.2 Internal audit

The excipient manufacturer should plan, establish, implement, and maintain an internal audit program to:

- consider whether its quality management system (see 4.4) conforms to the organization's own requirements, and to the GMP principles of this guide;
- confirm that the implementation and maintenance of the quality management system are effective.

This program should be based on risk and carried out following documented procedures.

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Note: A review of the internal audit program performed not less than once per year is considered best practice (see 9.3.2).

For internal audits, the procedures should:

- include the frequency, methods, responsibilities, planning requirements and reporting, considering the site's activities, changes affecting the organization, and previous audit results;

Note: 1. Frequency of internal audits may be determined based on risk assessment.

2. Examples of internal audit methods include:

- *onsite, remote, and desktop audits;*
- *checklist and systems-based audits;*
- *face-to-face interviews and written questionnaires.*

3. Examples of changes affecting the organization include:

- *changes in strategy by top management;*
- *changes in organizational structure (e.g., access to expertise and responsibility for monitoring external issues);*
- *changes in operational strategy (e.g., outsourcing, insourcing);*
- *changes to and use of infrastructure (see 7.1.3).*

- require the identification of audit criteria and scope;

Note: 1. Examples of audit criteria include the internal and external requirements used as references during internal audits.

Examples of these requirements and references include policies and procedures, IPEC Guides, and external standards or regulations, as applicable.

2. Examples of audit scope include the extent and boundaries of an audit, such as physical locations, departments, activities, processes, and product grades.

3. Where applicable, audit criteria and audit scope may need to consider corporate and local aspects.

- define auditor qualification requirements;
- require that auditors are selected to ensure objectivity and impartiality of the audit process;

Note: An example of how auditors can be selected to ensure objectivity and impartiality is by ensuring that auditors are independent of the area / process being audited.

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- describe requirements for audit documentation and reporting, including, at a minimum, report distribution to relevant management;
- where nonconformity is identified, require timely identification of follow-up actions (see 10.2).

Records should be maintained as evidence of audit program implementation and audit results.

9.3 Management review

9.3.1 *General*

Top management of the organization should review the quality management system at planned intervals to verify the organization's continued conformance to this guide.

Note: Management review performed not less than once per year is considered best practice.

The review should be documented and include a process for:

- identifying opportunities for improvement;
- assessing the alignment with the excipient manufacturer's strategic direction;
- identifying any need for changes to the quality management system (see 4.3);
- checking suitability of the quality policy (see 5.2).

Records should be maintained as evidence of management review, including actions recommended and taken.

9.3.2 *Management review inputs*

Management review should be carried out taking into consideration, at a minimum:

- status of action items from previous management review;
- changes in external and internal issues that are relevant to the quality management system (see 4.1);
- information on the performance and effectiveness of the quality management system, including trends in:
    - customer satisfaction (see 9.1.2);
    - customer complaints (see 8.7.3);
    - feedback from relevant interested parties (see 4.2);
    - the extent to which quality and GMP objectives have been met (see 6.2);

- process performance;
- conformity of excipients and GMP services;
- nonconforming outputs (see 8.7) and resulting actions;
- status of corrective and preventive actions;
- monitoring and measurement results (see 9.1.3);
- internal and external audit results;
- performance of external providers (see 8.4.3);

- adequacy of resources (see 7.1);
- effectiveness of actions taken to address risks and opportunities (see 6.1);
- opportunities for improvement (see 10).

Note: 1. Trending may include statistical analysis.

2. The term "resulting actions" includes immediate corrections (i.e., actions to eliminate a detected nonconformity), corrective actions and preventive actions.

9.3.3 *Management review outputs*

Management review outputs should include decisions and actions related to:

- opportunities for improvement (see 10);
- resource needs;
- any need for changes to the quality management system (see 4.3);
- any need to update the quality policy (see 5.2).

10 Improvement

10.1 General

The excipient manufacturer should select opportunities for improvement (see 9.3.3), and plan and implement activities to improve:

- performance and effectiveness of the quality management system and its processes (see 4.4);

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- excipients and GMP services to enhance customer satisfaction, considering the potential impact on patient safety.

Improvement activities should also include correction, prevention, or reduction of undesired effects.

Any changes should be assessed and implemented following the change control procedure (6.3).

10.2 Nonconformity and corrective action

Note: 1. What is a nonconformity?

ISO 9000 defines "nonconformity" as "non-fulfilment of a requirement". "Nonconformity" is also known as "nonconformance". These terms may be used interchangeably.
See 4.2 for more information about determining applicable requirements. See 8.7 for more information about control of nonconforming outputs.

2. What is a corrective action?

ISO 9000 defines "corrective action" as "action to eliminate the cause of a nonconformity and to prevent recurrence". ISO 9000 goes on to explain that a "corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence."

The excipient manufacturer should have a documented procedure to:

- define the management of nonconformities, as applicable and commensurate with risk;
- control and correct nonconformities;
- address the consequences of nonconformities;
- investigate each nonconformity, determining:
    - the root cause(s),

      Note: Identifying "human error" as a root cause may overlook a deficiency of systems, such as training, procedures, or tools.

    - the need for actions, including the prevention of recurrence of the same, similar, or potentially similar nonconformities (see 10.3).

      Note: Examples of identification of (potential) similar nonconformities include:

        - *impact on other batches of the same or different product;*
        - *impact on other systems or processes.*

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- define actions as applicable, including responsibilities and timelines for implementation;
- evaluate and optimize the effectiveness of actions taken;

Note: Optimizing the effectiveness of actions may be achieved through risk assessment. For example, it would not be necessary to install a new reactor for a light sensitive excipient when covers on the windows can provide adequate protection.

- evaluate and update risk assessments as described in this guide (see 3, 7.1.3, 7.1.4, 7.1.4.3, 7.1.4.4, 8.3.1, 8.6.7, and 8.7.1.2), if necessary;
- update the quality management system (see 4.4), if necessary;
- record changes (see 6.3) resulting from actions, if necessary.

Records should be maintained as evidence of these activities.

10.3 Continual improvement

The excipient manufacturer should continually improve the quality management system and its processes (see 4.4). Improvement activities should consider suitability, adequacy, and effectiveness.

To identify opportunities for continual improvement of the quality management system, the excipient manufacturer should consider results from analysis and evaluation (see 9.1.3) and the outputs from management review (see 9.3.3).

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

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The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region