The International Pharmaceutical Excipients Council

Risk Assessment Guide

for Pharmaceutical Excipients

Risk Assessment for Excipient Manufacturers

Version 1
2025

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.

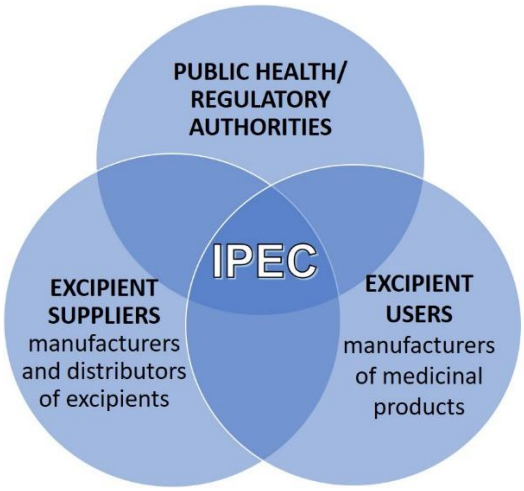
This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient **manufacture**rs, distributors, and end-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 development.

IPEC has three major stakeholder groups:

1. Excipient manufacturers and distributors, defined as suppliers in this document,
2. Medicinal (drug) product manufacturers, defined as *excipient users* in this document, and
3. Public health and regulatory authorities.



This guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the laws and regulations applying to excipients will vary

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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 most current version of any applicable regulatory requirement. Versions referenced in the guide were based on versions available at the time the guide was published.

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

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

This document offers best practice and guidance in **risk assessment** related to excipients covering the principles of quality **risk management**, including risk assessment methodologies and providing an overview of methods in the ICH Q9 **guideline**. It includes areas where risk assessment may be used by the excipient manufacturer in the lifecycle of excipient.

This document is a revised version of The IPEC Risk Assessment Guide for Pharmaceutical Excipients, first published in 2017 by IPEC-Americas and IPEC Europe.

NOTE: Refer to the "International Pharmaceutical Excipients Council Glossary: General Glossary of Terms and Acronyms" for definitions [1]. The first use of a term found in the glossary will be in ***BOLD.***

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ACKNOWLEDGEMENTS

This guide was developed by representatives of the associations which constitute the IPEC Federation (IPEC). The IPEC Federation greatly appreciates 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 extends its thanks to the employers of those same contributors who provided the necessary time and resources, without which this guide would not be possible.

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1 INTRODUCTION

1.1 Purpose

The primary intent of the IPEC Risk Assessment Guide for Pharmaceutical Excipients is to provide a systematic and scientifically sound methodology for the evaluation of risk to **excipient** quality and to facilitate more effective and consistent risk-based decisions by excipient makers, distributors, and **users**. Guidance is provided herein on “How to” conduct a risk assessment from the perspective of an excipient manufacturer or distributor.

Risk assessment is the process of identifying which **hazard**s exist, or may appear in the workplace, and how they may cause **harm** to patients and steps which should be taken to minimise it.

1.2 Scope

The scope of this guide is to provide **excipient supplier**s with an overview of risk assessment tools, and resources that they can use, when conducting risk assessments required by both NSF/IPEC/ANSI 363 [2] and EXCiPACT® [3] excipient GMP standards to identify and mitigate for potential risks to excipient quality.

However, IPEC Guidelines on **Good Manufacturing Practices** (IPEC-PQG GMP Guide [4]) and **Good Distribution Practices** [5] should be the primary references for readers to better understand considerations when and how to perform risk assessments in various operational areas.

The guide provides an overview of 1) quality risk management, 2) the scientific principles of **risk identification** and assessment and 3) an outline of the process and use of appropriate risk assessment methodologies. In addition, the guide identifies areas where risk assessment requirements are found in the IPEC-PQG GMP Guide and suggests documentation to demonstrate adequacy of risk assessment and GMP controls.

The IPEC Risk Assessment Guide is designed to provide excipient manufacturers and distributors with a common starting point to evaluate risks and develop risk management plans, as appropriate. The guide can help users in assessing their suppliers’ risk assessment plans.

Throughout the guide, questions suggested help with the risk evaluation. Note that these questions are not intended to be comprehensive lists, since specific requirements should be considered for evaluation of the risk for any given excipient.

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1.3 Background

IPEC has developed and promoted the implementation of appropriate and scientifically valid voluntary industry guides for excipients [4] for many years. IPEC's unique combination of experts from excipient makers, distributors and users makes this association uniquely positioned and qualified to understand the underlying risks to excipient quality. IPEC guides were developed to address these risks as they were identified to the organization. IPEC's mission is to ensure that excipients meet the highest appropriate standards for quality, safety and **functionality** throughout their manufacturing process and **supply chain**. The use of risk management principles applied to excipients furthers this cause.

In the current regulatory environment surrounding excipients, pharmaceutical manufacturers are under increasing pressure to develop better knowledge of their excipients and excipient supply chain. Pharmaceutical manufacturers are required to ensure that excipients used in the **drug products** are fit for their intended use. The diversity of excipient manufacture, type of **material** and application means that a "one size fits all" approach to excipients does not provide the necessary assurances of product quality and patient safety. Supplier led risk assessments to determine the threats to quality and patient safety are mandated in EXCiPACT®, GMP, GDP and GWPs and the American National Standard GMP for Pharmaceutical Excipients, NSF/IPEC/ANSI 363. Both standards utilize quality risk-management principles to ensure that proportionate controls are applied in manufacturing and **distribution** to produce and deliver excipients that are safe, of appropriate quality and of consistent composition. These voluntary standards using risk assessment tools are mirrored by the authorities in Europe with the Falsified Medicines Directive (FMD) legislation (2011/62/EU) requiring Manufacturing Authorization Holders (MAH) [6] to perform and document a formalized risk assessment and consider the source and intended use of excipients as well as previous instances of quality defects. These guidelines have been subsequently adopted by PIC/S, where each PIC/S participating authorities will decide whether it should become a legally binding standard [7]. As part of the excipient evaluation and **qualification** process, the drug manufacturer/ MAH holder should perform risk assessments to evaluate the excipient supplier, quality systems, manufacturing operations, etc. Risk assessments by excipient users are performed by taking into account:

- The type of excipient
- The manufacturer of the excipient
- The quality history of the excipient supplier, including changes, and the **reliability** and integrity of the supply chain
- The use of the excipient in the finished product and its route of administration

The PDA-IPEC Federation document "Formalized Risk Assessment for Excipients" can be accessed on the IPEC Federation website. [8] This provides guidance on risk assessment for

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excipients by presenting a model risk assessment, guidance on key elements and examples to complete risk assessments meeting regulatory requirements. MAH-led risk assessments relative to a specific application / use of an excipient may require, in agreement with the excipient manufacturer, additional steps to be taken to mitigate risks.

This guide is intended to provide excipient manufacturers, **distributor**s and users with guidance on risk assessment methodologies and assessment techniques for identifying and assessing potential risks.

1.4 Layout

This guide includes the following sections:

- Principles of risk assessment and management
- Risk assessment methods, including an overview of basic risk facilitation methods as outlined in the ICH Q9 [9] guideline
- Risk assessment by excipient manufacturer, including expectations described in the IPEC-PQG GMP Guide [4]

The first use of a term defined in IPEC General Glossary of Terms and Acronyms [1] is noted by the use of **bold** type with no underline.

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2 PRINCIPLES OF RISK ASSESSMENT AND MANAGEMENT

Risk assessment is a basic principle to support decision making in the IPEC-PQG GMP Guide [4], where it is used to define the GMP controls necessary to mitigate those risks that have been identified as potentially posing a threat to excipient quality. The implementation of specific GMP controls is dependent upon the evaluation of risk to the excipient quality. Performing risk assessments in accordance with a defined quality risk management procedure ensures a consistent assessment of risk and facilitates communication of the identified risks throughout the organization. A documented risk assessment also provides for periodic review of the risk to verify the output of the assessment has remained valid.

Quality risk management requires a documented science-based, objective evaluation of risk with focus on the quality of the excipient and the potential impact of the excipient on patient safety. This evaluation facilitates conformance to the risk assessment requirements of the Guide, as follows:

- The risk
- Consequences
- Likelihood
- Detectability
- Level of risk
- Measure(s) to mitigate risk
- Risk-benefit balance
- Consequences of risk mitigation implementation
- **Risk communication**

Note: Depending on the risk management method or approach not all bullet points are applicable or reasonable, for example formal risk assessment or FMEA procedure.

The extent of the assessment of risk should be commensurate with the hazard posed to excipient quality. If a section in the GMP Guide does not apply, then justification should be documented.

The Quality Risk Management procedure should address the four phases involved with assessing a potential hazard as discussed below.

2.1 Phase I: Risk Assessment

The first phase, **risk assessment**, begins with a well-defined problem definition, referred to as **risk identification** or hazard identification. Identification of the risk can be framed by asking the following fundamental questions:

- What might go wrong (the hazard)?

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- What are the consequences of the hazard (severity)?
- What is the likelihood it will go wrong (probability)?
- Can the presence of the hazard be identified (detectability)?

Hazard identification addresses the question “What might go wrong?” and includes the possible consequences. Examples of hazard identification are the failure of a valve that results in **contamination** of the excipient, poor housekeeping that allows accumulated dust to become airborne and settle on the exposed excipient, the presence of rodents in the facility, etc. Once the hazard has been identified, it is appropriate to gather a team of subject matter experts and risk assessment experts to perform the risk assessment. During this phase, background information such as historical data, theoretical analysis, informed opinions and **stakeholder** concerns is assembled.

Following hazard identification, **risk analysis** provides an estimation of the risk associated with the identified hazard. Depending upon the risk analysis tool selected, the analysis is either a qualitative or quantitative process that links the severity of the harm with the probability of occurrence. Certain tools also add the ability to detect the harm (detectability) in order to provide an estimate of the magnitude of the risk.

Once the risk analysis has been completed, **risk evaluation** is used to compare the level of perceived risk against established risk criteria. Risk evaluation considers the response to the fundamental questions; severity, probability of occurrence, and, where assessed, detectability. The risk criteria determine the need to implement **risk control** or **risk reduction** and develop a **control strategy**.

The quality of a risk assessment rests on the data used. Disclosing the assumptions and sources of uncertainty enhances confidence in the evaluation and identifies its limitations. Typical sources of uncertainty include gaps in:

- Excipient knowledge and process knowledge
- Understanding of potential harm to the pharmaceutical manufacturer from an excipient that is not of acceptable quality, and is used in a drug product (such as the impact on manufacturing the drug product, impurities, stability, etc.)
- Understanding of potential harm to the patient from an excipient that is not of acceptable quality, and is used in a drug product (such as affecting the drug bioavailability, patient acceptance, presence of contaminants, etc.)

The output of phase 1 is a qualitative or quantitative level of risk based on the potential hazard(s) identified.

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2.2 Phase 2: Risk Control

In the second phase, **risk control,** the decision is made to either accept the level of risk or take measures to reduce the risk to an acceptable level. The following questions help guide this effort:

- Is the risk higher than a level deemed acceptable?
- What measures will reduce or eliminate a risk that exceeds an acceptable level?
- What is the proper balance between the benefit, risk and resources needed to affect reduction?
- Will a new risk be introduced as a consequence of **risk reduction**?

Risk acceptance recognizes that the level of risk is not high enough to negatively impact either the pharmaceutical user or their patients. Where the risk may impact the pharmaceutical user or patient, risk reduction should be considered. Reduction measures can reduce the probability, or increase detectability or any combination thereof.

Risks may be reduced through measures such as a change in materials, process, **equipment**, personal protective equipment (PPE) etc. For example, the risk of **transmissible spongiform encephalopathy (TSE)** can be mitigated by sourcing the animal derived **raw material** from a lower risk supplier or switching to a non-animal source. Changes should be evaluated based on the IPEC **Significant Change** Guide [10].

Detectability might be improved through more reliable or sensitive quality control testing; implementation of in-process testing, either in-line or at-line; expansion of finished excipient sampling, etc. The ability to detect the consequence of a hazard may reduce the potential for non-compliant excipients being shipped to a customer.

Once a risk reduction decision has been made, it is appropriate to repeat the risk analysis in order to assess whether implementation of the risk reduction measures introduced any new risks to the excipient. The review of the risk analysis results should show reduction of the risk to an acceptable level or one that is commensurate based upon cost/benefit analysis. The impact of any significant change on the risk assessment assumptions and results should be evaluated consistent with **change control** processes and, if necessary, appropriate actions should be taken to mitigate further risks.

2.3 Phase 3: Risk Communication

The third phase, **risk communication** involves communication of the conclusions from the first two phases and involves sharing of the risk assessment and risk control with interested and affected parties. Interested parties often include operators and department personnel within the

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site and company that implement the risk reduction measures or are potentially impacted by them. Of particular importance is the communication of risk reduction activities for evaluation under management of change (change control). Impacted activities may include changes in production, **quality control**, **quality assurance**, internal audit(s), marketing, etc. External interested parties include customers that may be impacted by the risk and regulators who are aware of the risk.

2.4 Phase 4: Risk Review

The final step in quality risk management is **risk review**. Risk assessments completed should be periodically reviewed in order to ensure that their conclusions remain valid. The quality risk management procedure should include a rationale for when a risk review should be performed.

The review should examine any changes to the excipient quality or conformance to the standard(s) since the original risk assessment or previous risk review. More frequent reviews should be performed in response to:

- Customer complaints resulting from the risk that was assessed
- Finished excipient test failure for a risk that was mitigated
- **Deviation**s which can impact quality
- Significant changes, where appropriate
- Change to regulatory requirement or customer expectation related to the risk

2.5 Documentation

The quality risk management procedure should describe the documentation required to demonstrate that the risk was evaluated in accordance with the procedure.

The IPEC-PQG GMP Guide [4] and related standards require that a risk assessment is used to justify any section of these documents that is not applicable. Documentation of such risk assessments need only provide the rationale as to why the section does not apply.

The objective of documentation is to show that a systematic assessment was conducted by knowledgeable individuals and provides the basis for the decision made. The common supporting documentation for a risk assessment, regardless of the assessment technique, should include:

- Members of the risk assessment team, along with their role on the team
- Meeting agendas

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- Meeting minutes
- Outcome of risk assessment activities
- Communication of the risk mitigation under change control.

3 RISK ASSESSMENT METHODS

There are many different methods for performing a risk assessment. The reader should refer to authoritative guides, such as ICH Q9 [9], or other alternative methods such as GAMP 5 [11] and HACCP [12], for a detailed description.

4 RISK ASSESSMENT BY EXCIPIENT MANUFACTURER

The IPEC-PQG GMP Guide and related standards expect application of risk-assessment principles to define and justify appropriate GMP controls in order to mitigate risk to prevent contamination from personnel, equipment, and facilities. Risk assessment is also used for supplier qualification, change management, and rework activities. [13]

4.1 Risk Assessment Documentation

There are many acceptable techniques to address the requirements for conducting risk assessment. To meet the requirements of the guide(s) and standard(s), a risk assessment may be conducted at either the corporate or facility level. Dedicated risk assessment teams or ad hoc teams are assembled to address a specific risk. A single document may be used to document all the risk assessments required by the standard or individual risk assessment documentation can be created for each relevant section. These risk assessments can be used as a basis for specific market-based risk assessments.

The justification and documentation required for each risk assessment depends on the complexity of the assessment. For sections that do not apply, a justification of why the section is not applicable can be sufficient. Justification including rationale to demonstrate conformance to the standard should be completed and documented. The actual process for conducting a risk assessment may vary depending on the scope of the exercise but the documentation should follow the four phases of quality risk management described in Section 2 of this guide.

Note: *it is acceptable to perform a single risk assessment covering more than one section of the guide(s) and standard(s), provided that the documentation links the assessment to each applicable section.*

As with all records, documentation of the risk assessment should be maintained and available during an audit. In addition, the risk assessment(s) should be periodically reviewed to ensure continuing validity and suitability of the excipient based on any new information. A procedure for

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conducting the risk assessment and periodic review should be included in the **Quality Management System** (QMS).

4.2 Areas Requiring Risk-Based Decision Making

The information provided in this section represents the current thinking of IPEC on the application of risk assessment techniques. While this guide provides approaches to address those clauses of the IPEC-PQG GMP Guide [4] and related standards requiring risk assessments, alternative approaches that satisfy the intent of the clause are acceptable. The reader should evaluate their specific manufacturing process, facility and excipients to identify a suitable risk assessment approach.

This section is organized as follows:

- The title of the section and the wording from IPEC-PQG GMP Guide. For wording, please refer to the latest version of this Guide
- An explanation of the potential risks associated with the section
- Discussion of techniques to identify potential risks and establish mitigation plans to manage risk(s)
- Special considerations for documentation and records related to the risk assessment beyond information disclosed in section 2.5 of this guide

Regardless of the risk assessment techniques used, the following general principles apply to many of the risk assessment requirements defined in these standards.

Of the three categories of risk to excipient quality, physical hazards often pose the lowest quality and safety risk for use of the excipient by the pharmaceutical user and subsequent use of the drug product by the patient. Physical hazards such as the presence of sampling devices, safety glasses, tools and disposable gloves are usually visible to operating personnel at both the excipient manufacturer and user. Relatively large physical objects can be collected by screens and filters during pharmaceutical manufacture. Because of their relative size in comparison to the **dosage form**, it is unlikely for physical objects to become incorporated unnoticed into a drug product; however, the presence of any foreign object implies that the manufacture of the excipient did not comply with GMP.

Chemical hazards may pose a higher risk than physical hazards since chemicals can become incorporated in the dosage form without detection by pharmaceutical operating personnel or their quality control organization. The presence of chemical contaminants can present hazards to patient safety due to:

1. Toxicity from the chemical hazard

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2. Interference with the bioavailability of the **Active Pharmaceutical Ingredient** (API) due to reaction with the chemical
3. Reduced **shelf life** of the drug product if the chemical reacts with the API or another excipient
4. Inability to accurately assay the API in the final dosage due to interference with the test method

Biological hazards, as a category, often present the highest risk to patient safety though not necessarily to the manufacture of the drug product using the excipient. Biological hazards may arise from poor hygienic practices. Biological hazards affect human health and can be difficult to detect since biological agents are generally not widely dispersed throughout the excipient. Excipient manufacturers typically do not sample and test each **lot** for the presence of pathogenic organisms. This may also be true for their pharmaceutical users, depending on specific risks presented by the nature of the material. Therefore, it is important to prevent biological contamination especially with pathogenic organisms.

4.2.1 Hygienic Practices

Please refer to section 7.1.4.5 “Personnel Hygiene” of the IPEC-PQG GMP Guide.

4.2.1.1 Understanding the Requirement for Risk Assessment for Hygienic Practices

Poor practices where the excipient is exposed to the environment can expose the excipient to various contaminants from personnel, their activities and the equipment they use.

Certain hazards present the impression that the excipient was not produced under GMP such as the presence of food, tobacco or beverage in the excipient.

4.2.1.2 Implementation of the Risk Assessment for Hygienic Practices

The following questions help to identify risks to excipient quality during manufacturing and packaging steps where the excipient is exposed:

- Physical hazards are caused by the presence of foreign substances:

1. Is there a possibility that portable equipment such as sampling scoops, tools, etc. used by personnel during maintenance, sampling or inspection may fall or be left inside production equipment or packaging?
2. Is there a possibility that items used by personnel such as pens, **label**s, twist ties and seals may fall into the excipient?
3. Is there a risk from contamination to equipment during maintenance and inspections by personnel?

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- Chemical hazards arise from the presence of unintended foreign substances:

    1. Is there a risk of contamination from soiled personal clothing including dust from production activities that is carried by clothing between different unit operations, lines, buildings or carried in on clothing from home?
    2. Can food, beverage or tobacco products consumed nearby contact the excipient?
    3. Can medication used by personnel fall into the excipient?
    4. Is there a risk of contamination from the reuse of gloves or other protective gear that may contain chemicals from other operations or activities?

- Biological hazards result from exposure of the excipient to biological organisms:

    1. Is there a risk of excipient contamination from poor personal hygiene practices at the facility?
    2. Is there a risk from the lack of adequate facilities for hand washing?
    3. Is there a risk of contamination from clothing?
    4. Is there a risk of contamination from personnel with open lesions or illness?
    5. Is there a risk from hair falling into the excipient?
    6. Is there a risk when employees perspire, cough, sneeze, etc., where the excipient may become contaminated?
    7. Is there a risk from unauthorized and/or unintentional access of persons not properly gowned or having proper personal protective equipment (PPE)?
    8. Is there risk of contamination from the reuse of gloves or other protective gear that may contain biological organisms or body fluids?

Risk mitigation measures may include, as appropriate, a combination of:

- Personnel hygiene training - improves compliance with the expectation for adequate hand washing after eating, using toilet facilities or otherwise getting soiled hands

- Procedures and training - informs employees of the importance to report any exposure due to illness or the presence of open sores or lesions

- Procedures and training - establishes appropriate personal attire to protect the excipient from employee contamination, e.g. no pockets above the waist where there is a risk items may fall into the bulk excipient, hair covering or no loose buttons on outer garments

- Portable equipment stored clean in a designated location – ensures continued equipment cleanliness and **traceability**. Equipment not stored in their designated location should be reported promptly to supervisors, thoroughly investigated and the findings discussed with employees

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- Procedures and security measures - prevents access from designated operating areas
- Designated consumption and storage of food, drink, personal medication and tobacco products – reduces risk of potential exposure and impact on excipient quality
- Dedicated protective clothing – such clothing and shoes or shoe covers for use with specific processing equipment or excipient manufacture reduces the likelihood of contamination from dust and dirt on clothing.
- Equipment inspection – after maintenance and other non-routine activity, a designated individual inspects equipment for the presence of contaminants and tools.
- Washing facilities – adequately designed facilities should be provided, maintained and stocked with supplies

4.2.1.3 Documentation and Records Supporting Hygienic Practices

Documentation and records requirements are discussed in section 2.5.

Key items for the manufacturer to consider include determining the risk of contamination from personnel, the utensils and tools they use, and their activities where the excipient is exposed. The risk assessor should consider the possibility for items to contaminate the excipient at those locations. Of particularly interest are likely to be:

- Employee attire
- Loose items particularly tools and sampling utensils
- Contamination from unprotected hair, skin and perspiration
- Evidence of consumption of food, beverage and tobacco products outside designated areas.

Where it is observed that there is a risk to contamination of the excipient, the documented assessment for hygienic practices should ascertain if the risk has been identified and mitigation measures considered.

4.2.2 Building and Facilities

Please refer to section 7.1.3 “Infrastructure” of the IPEC-PQG GMP Guide.

4.2.2.1. Understanding the Requirement for Risk Assessment for Building and Facilities

Buildings and facilities can present many potential risks to excipient quality. These risks may involve risk of contamination of biological, chemical or physical nature, as discussed earlier.

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Buildings and facilities that are in a good state of repair, closed and easy to clean represent a lower risk than those with portions exposed to the outside environment, have numerous process openings and/or are difficult to clean.

Where excipients are exposed within the structures (e.g. packaging and loading operations), the potential risks to excipient quality are greater.

4.2.2.1 Implementation of the Risk Assessment for Building and Facilities

The following questions help with risk evaluation. Note that this is not intended to be a comprehensive list since facility and operation-specific issues should be considered in evaluation of the risk. In each unit operation, the questions should be posed to identify if there is potential risk.

- Consider the following physical hazards from buildings and facilities:
    1. Is the state of repair of the building such that there are holes or unsealed penetrations in walls, roof leaks, rust, doors and windows that cannot close tightly?
    2. Does the building allow entry and activity by pests such as flying insects and birds during operations requiring open doors or other entry points?
    3. Is there abandoned piping and equipment that can collect dust and/ or be inadvertently used?
    4. Is there evidence of inadequate temporary repairs such as use of tape, plastic ties and wire?
    5. Are materials of construction used in buildings and building maintenance where there is a potential they can enter the product?
    6. Are there asbestos products where there is the potential for the asbestos to contaminate the excipient?
- Chemical hazards that can be present in buildings and facilities where the excipient is exposed such as:
    1. Are pest control chemicals not meant for food manufacturing plants used for pest control?
    2. Are chemical cleaning agents used to clean the building?
    3. Is there peeling paint or other coatings?
    4. Is there loose or flaking insulation?

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5. Are building maintenance items such as lubricants, paint, etc. stored in a manner that can contaminate the excipient?
6. Is there evidence that exhaust gases or materials (e.g. steam, exhaust from internal combustion engines, etc.) can enter the area? Are there airborne contaminants from nearby operations, particulates or chemical odours/fumes?
7. Is there uncontrolled storage of other chemicals such as **solvent**s, reagents, or other highly sensitizing or toxic materials?

- Biological hazards that can occur from deficiencies with building and facilities where the excipient is exposed:

1. Is the state of repair of the building such that there are holes or unsealed penetrations in walls, roof leaks, rust, doors and windows that cannot close tightly?
2. Does the excipient during processing, packaging or loading operations come in contact with unfiltered air in the environment or unfiltered process air or gas (which may contain microbial contamination)?
3. Is there standing water that can promote microbial growth in the processing area?
4. Is there evidence of leaks (water or chemicals)?
5. Do internal structures allow for collection of dust, pollen and mould on structures such as ledges, light fixtures, hanging utilities or piping?
6. Is there overhead open floor grating that can scrape dirt off shoes?
7. Does Preventive Maintenance require normally closed equipment and buildings to be opened?
8. Do procedures for return to operation after maintenance include confirmation of cleanliness before use?
9. Are there unprotected opened doors, windows and other entry points into the building that allow for entry and activity by birds, pests and insects?

Risk mitigations may include, as appropriate, a combination of:

- Ensure that air contacting the excipient in open equipment is of appropriate quality
- Maintain buildings and facilities in a good state of repair
- Ensure materials of construction are suitable for their application

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- Ensure procedures prevent building maintenance activities when excipient processing may be contaminated
- Designate storage area(s) for cleaning agents, pest control chemicals and maintenance chemicals
- Prevent backflow in gas, water and vacuum lines by mitigating with backflow preventers or check valves
- Ensure that there are adequate inventory controls to minimize the potential for mix-ups and errors

4.2.2.2 Documentation and Records Supporting Building and Facilities

In addition to the documentation noted in section 2.5 of this guide, piping and instrumentation drawings (P&IDs) and a site map may be reviewed as appropriate. The following considerations may be applicable:

- Documented assessment of the physical, chemical and biological risks associated with buildings and facilities
- Procedures for inspecting the facility for state of repair

4.2.3 Equipment Construction

Please refer to section 7.1.3.2 “Equipment” of the IPEC-PQG GMP Guide.

4.2.3.1 Understanding the Requirement for Risk Assessment for Equipment Construction

The risk to be assessed includes chemical and physical risks from process materials and media contaminating the excipient.

4.2.3.2 Implementation of the Risk Assessment for Equipment Construction

Excipient manufacturers should have procedures that provide for the assessment of risk from process materials and media beginning with the design of equipment and use of existing installations. The procedure should address equipment **specification**s and the use of food **grade** process materials.

The following questions help with chemical and physical risks evaluation:

1. Are food grade and/or regulatory agency approved equipment **component**s required due to their potential to contact the excipient?

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2. Are there supplier assurance statements referring to equipment quality and/or suitability?
3. Do maintenance and operating work instructions require the use of appropriate process materials and/or media?
4. Are the materials of construction of the equipment appropriate to prevent their erosion and degradation?

4.2.3.3 Documentation and Records Supporting Equipment Construction

No additional expectations beyond that in section 2.5 of this guide.

4.2.4 Equipment Maintenance

Please refer to section 7.1.3.2 “Equipment” of the IPEC-PQG GMP Guide.

4.2.4.1 Understanding the Requirement for Risk Assessment for Equipment Maintenance

Proper maintenance of equipment is an important measure to prevent contamination of the excipient from equipment. The risk mitigation strategy included in this section is threefold:

1. Written maintenance procedures for all quality-critical equipment,
2. Scheduled maintenance for all quality-critical equipment, and
3. Adherence to the maintenance schedule

If an organization concludes that scheduled maintenance or maintenance procedures are unnecessary, a documented justification should explain why such scheduled maintenance is not required.

4.2.4.2 Implementation of the Risk Assessment for Equipment Maintenance

The best practice is to ensure that all quality-critical equipment has a procedure for routine maintenance, routine maintenance is scheduled, and the schedule is followed. Procedures with appropriate detail for maintenance and manageable schedules should take into consideration the risk of equipment failure to the final product and appropriately match the maintenance details and frequency toward the critical equipment.

If an organization decides not to have a maintenance procedure for specific equipment or decides to exclude equipment from a schedule, then the risk assessment should justify how the quality or functionality of the excipient will be maintained in the event of unexpected failure or a decrease in equipment performance. As input to the risk assessment, the purpose and function of the equipment should be presented along with a description of how the equipment fails and

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the consequences of the failures described. To justify that equipment has no effect on production, the organization needs to prove that the process operates as designed when the equipment fails. Data showing that the process behaves normally and that quality of the product is unchanged when the equipment fails or is otherwise shut down during production can be used to provide evidence to support exclusion of the equipment from the preventative maintenance program. The risk assessment should show that the manner of failure would not contribute foreign matter, result in deviations to product attributes or result in significant production delays affecting the availability of product to meet customer orders.

The risk to the excipient is from physical hazards, chemical or biological. Physical hazards can be identified by asking questions such as:

1. What foreign objects may enter the process during maintenance or if maintenance doesn't occur as scheduled; what could the consequences be?
2. What are maintenance practices and equipment failures that can lead to foreign material hazards to the product?
3. What are the risks to product quality, including functionality, of running outside of the maintenance schedule to the equipment?
4. Is equipment taken into the processing area reconciled when maintenance is completed?

Chemical hazards can be identified by asking questions such as:

1. What chemical contaminants can enter the process when maintenance fails or doesn't occur as scheduled; what could the consequences be?
2. What is the highest-level risk that would contribute to deviations in product quality attributes and functionality?

Biological hazards can be identified by asking questions such as:

1. If equipment fails due to a lack of routine maintenance, can process water enter the manufacturing process?
2. If equipment fails due to a lack of routine maintenance, can the excipient become contaminated with airborne biological organisms and extraneous matters?

When the schedule is missed, the justification should show how the product was protected from the risk. The justification should state the reason for the scheduled deviation, such as plant shut down and wait for start-up, and show the additional measure taken to mitigate the risk if product was made. Where the missed scheduled deviations cannot be justified, the deviation should be noted as a non-conformance and corrective action taken (please refer to Section 10.2 "Nonconformity and corrective action" of IPEC-PQG GMP Guide).

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4.2.4.3 Documentation and Records Supporting Equipment Maintenance

Documentation and records requirements are discussed in section 2.5.

Maintenance procedures and equipment schedules should be considered. The risk assessment should include justification when equipment does not have a procedure for maintenance or is not on schedule.

4.2.5 Utilities

Please refer to section 7.1.3.3 “Utilities” of the IPEC-PQG GMP Guide.

4.2.5.1 Understanding the Requirement for Risk Assessment for Utilities

The purpose of this clause is to reduce the risk of contaminating the excipient or producing a poor quality excipient due to failures in the utility system, from contaminants in the utility or contaminants formed by the failure of the utility. Contamination from utilities can be physical, chemical or biological in nature. Rust is an example of physical contamination while boiler **additive**s illustrate chemical hazards, and environmental conditions can contribute to microbial contamination.

4.2.5.2 Implementation of the Risk Assessment for Utilities

The goal is to have a list of all hazards associated directly with the utility (such as contamination from or reactions with impurities in the utility) or the hazards resulting from the failure of the utility system (such as degradation or side reactions due to loss of an inert environment). Design documents or a process flow diagram showing all utilities used in producing, storing and transferring the excipient should be used to make a complete list. The utilities on the list should then be evaluated to identify which utilities contact or have the potential to contact the excipient. The risk assessment should include relevant utilities, specify the method used and document results. Relevant questions aiding in conducting a complete risk assessment may include:

- Physical hazards that can be present in utilities can be identified by the following:
    1. If the utility malfunctioned; what physical contaminants may be introduced into the excipient?
    2. What foreign matter that may be present in the utility can transfer to the excipient?
    3. How is utility system/equipment maintained and what are the consequential physical contamination prevented by this maintenance?
- Chemical hazards that can be present in utilities can be identified by the following:

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1. What chemical hazards are to be prevented by the utility in processing the excipient?
2. If the utility malfunctioned; what's the effect on the chemical quality and functionality of the excipient?
3. What chemical impurities, such as compressor oil, could be present in the utility that may transfer to the excipient?
4. How is utility system/equipment maintained and what are the consequential chemical contamination prevented by this maintenance?

- Biological hazards that can be present in utilities can be identified by the following:
  1. If the utility malfunctioned; what's the potential impact on biological contamination in the excipient?
  2. What biological contaminants that could be present in the utility, such as slime or biofilm, may transfer to the excipient?
  3. How are utility system/equipment maintained and what are the consequential biological contamination prevented by this maintenance?

Risk mitigation for utilities usually involves the installation and maintenance of filters and traps to ensure the excipient is not exposed to physical and chemical hazards. Physical and biological hazards may be prevented through routine maintenance of the utility distribution system by removing rust and trapped water in the lines. Chemical hazards may be prevented through measures taken by the supplier of the utility in their manufacture and supply of the utility.

4.2.5.3 Documentation and Records Supporting Utilities

In addition to the documentation discussed in section 2.5 of this guide, for new or updated installations, a risk assessment should define GMP controls.

A process diagram or a list showing all utilities used in the production, storage, and transfer of excipient that contacts or has the potential to contact the excipient may be considered.

4.2.6 Water

Please refer to section 7.1.3.4 "Water" of the IPEC-PQG GMP Guide.

4.2.6.1 Understanding the Requirement for Risk Assessment for Water

The intent of this clause is to reduce the risk of contamination or poor quality excipient from the quality of water when used in contact with the excipient. The control measure applied is to set the minimum quality as the WHO guidelines for drinking water quality. [14]

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The risk assessment should determine the quality of water depending on the manufacturer's intended use of the product.
Where a lesser quality of water is used, justification showing that excipient quality and functionality are met should be documented. The expectation is to also have a sanitary distribution system and continuous flow or back flow prevention.

Any deviation in the distribution of water should be justified.

Water poses a risk of chemical and biological contamination to the excipient. Chemical hazards arise from the presence of impurities from the water source as well as water treatment chemicals. Biological hazards result from the presence of microorganisms in the feed water and distribution system as well as from water treatment on-site.

4.2.6.2 Implementation of the Risk Assessment for Water

Specifications should be written for water quality. Different water quality specifications could be used at different steps in the process and there should be an explanation offered in the design documentation to support the specified attributes. Early stages of the process where crude materials are washed or diluted and further purification occurs may be able to make use of recycled process water or raw water not treated to drinking water standards. Many counter current wash processes use pure water in the final wash that is recycled through the earlier steps for conservation and yield recovery. Process **validation** should show that these practices and specifications are appropriate. To further the argument for alternative specifications best practices would be to note the differences between the WHO guidelines [14] and the chosen specification and explain why the attribute specified in the WHO Guideline is not needed or can have higher limits.

The following risk questions illustrate potential contamination from water that comes into contact with the excipient from the starting point of GMP:

- Chemical hazards that may arise from water can be identified by asking:

    1. Is process water treated on-site?
    2. What water treatment chemicals are used?
    3. What measures are taken to remove chemical contaminants?
    4. What is the consequence if there is a failure in the removal of the chemical treatment?
    5. What chemical contaminants are present in the water source?
    6. What measures are taken on-site to remove the contaminants?
    7. What is the consequence if there is a failure to remove the contaminants?

- Biological hazards that may arise from water can be identified by asking:

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1. Is process water treated on-site?
2. Does on-site water treatment have the potential to allow microbiological contamination?
3. If the water is deionized, has the operation of the deionizer been shown to inhibit microbial growth in the water?
4. What measures are taken to control microbiological contaminants?
5. What is the consequence if there is a failure to remove microbiological contaminants?
6. Has the water at the point of use been shown to meet the microbiological requirements for potable water?

Risk mitigation may include validation of process water purification that demonstrates non-potable water can be made to predetermined water quality standards [4], and that the distribution system delivers the specified water quality from the source to the point of use. If on-site purification of water is not cost-effective, potable water from a municipality is a suitable alternative. Also, potable water may be purchased and delivered in bulk transport, and should be treated and handled as a raw material or reagent.

4.2.6.3 Documentation and Records Supporting Water

In addition to the documentation discussed in section 2.5 of this guide, for existing installations, **verification** that water quality meets specified requirements at the point of use can be used to demonstrate that water purification and distribution is adequate.

Use of water, other than that which meets the WHO guidelines [14], should be justified as appropriate to maintain the quality of the excipient or shown not to have an impact on excipient quality.

4.2.7 Recycled or recovered materials

Please refer to section 7.1.3.5 of the IPEC-PQG GMP Guide.

4.2.7.1 Understanding the Requirement for Risk Assessment for Recycled or recovered materials

A recycled material / recovered material may be defined as an output of a process containing the remaining value of excipient that can be reused either in the same process or for another use.

*Example : recycling of output product with low concentration after a **process step** to ensure the maximum amount is captured.*

The intent of this clause is to ensure that the use of recycled / recovered materials containing excipient is justified and that the recycled / recovered product meets pre-defined specification.

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The activities related to recycling or recovery should be documented to ensure traceability.

4.2.7.2 Implementation of the Risk Assessment for Recycled or recovered materials

A specification should be written for any case of use of recycled / recovered material prior to reuse.

The objective is to ensure that there is no risk of **cross contamination** or mixing of non-conforming material with conforming product.

- What type of material is authorized for reuse / recycle / recover in the process?
- What specification limit should be fixed for this material (prior to reuse)?
- At which process steps the material is reused / recycled / recovered?
- Is the material reused / recycled / recovered in the same process or in another process?
- How is it recorded / documented to ensure traceability?

4.2.8 Air Handling Systems

Please refer to section 7.1.4.1 “Environmental air handling” of the IPEC-PQG GMP Guide.

4.2.8.1 Understanding the Requirement for Risk Assessment for Air Handling Systems

Section 4.2.5 of this guide, “Utilities”, addresses the risk of using air; however:

1. In the processing and storage of the excipient, this section is directed to the use of air in moving the excipient while in process, to storage or packaging
2. To protect the excipient where exposed to the environment during processing and/or storage

Air used to convey the excipient poses some of the same risk of contamination as noted in section 4.2.5 of this guide. The air quality should be based on the manufacturer's intended use of the excipient.

The air may contain foreign objects from failures in machinery, screens or filters. Also, the air may contain dust and dirt from failure of screens and filters that can cause the excipient to be contaminated with these materials as well as microorganisms that are sometimes carried by dust and dirt. Where the air contains chemicals from other operations, filtration such as with HEPA filter or activated carbon may be used to remove them.

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Where air is used to protect the excipient where exposed to the environment, the risk arises from the presence of dust, dirt and airborne insects. The principle preventive measure is to filter the air, often HVAC, used to put the area under positive pressure. The lack of adequate maintenance can cause collected dust and dirt to be forced through the filter or a broken filter to be in-use. The resulting contaminants could be dust, dirt and airborne microorganisms. Where the air contains chemicals from other operations, filtration such as with HEPA filter or activated carbon may be used to remove them.

4.2.8.2 Implementation of the Risk Assessment for Air Handling Systems

The risk to excipient quality can be from physical, chemical and biological hazards.

- Physical hazards that may arise from or are to be prevented by air handling can be identified by asking:

  1. Is filtration used and required?
  2. What level of filters and/or controls are required?
  3. Would there be visible and sub visible particulates in the area where the excipient is exposed if the air was not filtered?
  4. If a filter fails, what is the consequence?
  5. Can the temperature or humidity of the air impact excipient quality?

- Chemical hazards that are to be prevented by air handling can be identified by asking:

1. Are there odours or fumes in the general area that may contaminate the excipient where exposed to the environment?

2. Are there odours or fumes in the general area of the inlet air?

- Biological hazards that are to be prevented by air handling can be identified by asking:

  1. Is there a potential for microbial contamination from air used for moving the excipient or preventing airborne contamination where the excipient is exposed?

  2. Are there any requirements for microbial quality that may be impacted by contact of the excipient with air?

The area where the excipient is exposed or where air handling is used to move the excipient can be assessed using environmental monitoring techniques to identify the risk of contamination. Where the risk is from airborne microorganisms, seasonality should be considered. Risk mitigation can involve the use of appropriate preventive measures such as filters and activated carbon to remove contaminants from the air. These items should be included on an appropriate preventive maintenance schedule.

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4.2.8.3 Documentation and Records Supporting Air Handling Systems

In addition to the documentation discussed in section 2.5 of this guide, the data from scientific studies should be included to support preventive measures such as the performance requirements of filters.

Control measures where the excipient is exposed to the environment or where the excipient is moved with air may be considered. Finished excipient quality control data, deviations and complaints should be reviewed to determine whether control measures are working adequately to assure that the excipient meets all requirements.

4.2.9 Controlled Environments

Please refer to section 7.1.4.2 “Controlled environment” of the IPEC-PQG GMP Guide.

4.2.9.1 Understanding the Requirement for Risk Assessment for Special Environments

Contamination, degradation or moisture pickup by the excipient should be considered in areas (e.g. weighing, packaging and sampling) that were designed for control of environmental factors. What is the cause of degradation? Controlled environment with elevated temperature, humidity could contribute to degradation.

4.2.9.2 Implementation of the Risk Assessment for Special Environments

The risk to excipient quality can be from physical hazards.

- Common questions to consider include:
- Physical hazards that may arise from or are to be prevented by air handling can be identified by asking:
    1. Can the temperature or humidity of the environment impact excipient quality?
    2. Is the design of the environment adequate for the desired outcome?
    3. What is the risk to excipient physical properties in the environment?
    4. Are the control procedures relating to the environment adequate and are they being followed?
    5. Are measurements, e.g. differential pressure, air quality, temperature, pressure adequate to detect excursions from requirements?
    6. Is the special environment design and the controls adequate to minimize the occurrence of excursions?

Potential risk control measures include:

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- Environmental monitoring
- Effectiveness of preventive maintenance program for special environment
- Procedures to manage short term excursions in special environment
- Management of change process considers special environment.

4.2.9.3 Documentation and Records Supporting Special Environments

Documentation requirements are discussed in section 2.5 of this guide.

Scientific validity of the risk assessment and assessment of the procedures for ongoing monitoring of control measure effectiveness may be considered. It may also be useful to determine if procedures are being followed (by reviewing related records) and evaluate finished excipient quality control data, deviations and complaints to determine if control measures are working adequately to assure that the excipient meets all requirements.

4.2.10 Cleanliness and Sanitary Conditions

Please refer to section 7.1.4.3 “Clean and sanitary conditions” of the IPEC-PQG GMP Guide.

4.2.10.1 Understanding the Requirement for Risk Assessment for Cleanliness and Sanitary Conditions

Physical and microbiological contamination of the excipient may result from unclean or unsanitary conditions where the excipient comes into contact with surfaces, such as manufacturing/packaging equipment and/or transport containers and work areas. Also, in areas where the product is exposed to the environment, there may be a risk of physical contamination (trash or dirt) or mix-up from poor housekeeping. Finally, there is a contamination risk presented from sanitizing agents.

4.2.10.2 Implementation of the Risk Assessment for Cleanliness and Sanitary Conditions

Physical, chemical, and biological hazards can contaminate the excipient from work areas that are unclean and unsanitary.

- Physical hazards that may arise from an unclean work environment can be identified by asking:

    1. What is the cleaning procedure for product contact surfaces? Is this procedure effective? Is routine testing performed to verify the effectiveness of cleaning?
    2. Do material properties, e.g., solubility, facilitate or impede cleaning?
    3. Can unclean piping or hoses contact the excipient?

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4. Is there a process for management and disposition of scrapped product?
5. What procedures are in place regarding segregation, **labelling** and disposal of waste?
6. How is waste contained? How is it labelled? How is it removed? At what frequency?
7. Is there any waste with impact on worker exposure?
8. Is there any waste with impact on the environment?
9. How is waste awaiting disposal stored?

- Chemical hazards that may arise from an unsanitary work environment can be identified by asking:
    1. Are sanitizing agents that may come into contact with the excipient used?
    2. Have any chemicals that come into contact with the excipient being appropriately assessed (for example, food-grade lubricants)?
    3. Can a mix-up contaminate the excipient with chemical waste?
    4. Is there a potential risk from recycled material (**mother liquor** or recycled solvent)?
- Biological hazards that may arise from an unsanitary work environment can be identified by asking:
    1. Is there a risk of microbiological contamination from an unsanitary work environment where the excipient is exposed?

Risk mitigation may include:

- Using sanitizing agents that are readily removed from equipment
- Promptly cleaning equipment after use if the equipment is to be kept idle
- Testing of finished excipient for physical and microbiological contamination
- Testing of product contact surfaces, periodic and/or routine
- Housekeeping per procedures. Internal audit to assess conformance
- Using automated cleaning, e.g., clean-in-place
- Training employees pertaining to personal hygiene and gowning

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- Process for management and identification of waste material
- Properly containment of waste
- Labelling of waste
- Promptly removing waste
- Proper storing of waste awaiting disposal.

4.2.10.3 Documentation and Records Supporting Cleanliness and Sanitary Conditions

Documentation requirements are discussed in section 2.5 of this guide.

Scientific validity of the risk assessment and assessment of the procedures for ongoing monitoring of control measure effectiveness may be considered. It may also be useful to determine if procedures are being followed (by reviewing related records) and evaluate finished excipient quality control data, deviations and complaints to determine if control measures are working adequately to assure that the excipient meets all requirements.

4.2.11 Pest Control

Please refer to section 7.1.4.4 “Pest Control” of the IPEC PQG GMP Guide.

4.2.11.1 Understanding the Requirement for Risk Assessment for Pest Control

Excipient manufacture, where the excipient is exposed, and storage areas should be free from the presence of pests including insects, rodents and other animals. Pests present a risk of contaminating the excipient with biological hazards. There is also a risk of contamination from the rodenticides, insecticides, fungicides and fumigation agents that may be used for risk control as well as physical hazards presented from traps and similar mechanical control devices. Each manufacturing area is to be assessed for risk from pests and adequate management measures taken, as required, including monitoring and eradication to control them.

4.2.11.2 Implementation of the Risk Assessment for Pest Control

The following questions illustrate how the risk from physical, chemical and biological hazards can be identified.

- Potential physical hazards can occur from mechanical control of pests
    1. Is there a risk that components of pest traps and other similar equipment can get into the excipient?
    2. Are insectocutors situated such that insect fragments may contaminate the excipient?

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- Potential chemical hazards can result from the use of chemicals for pest control.
    1. If pesticides and rodenticides are authorised to control pests, are they managed so as not to present a risk to the excipient?
    2. Is fumigation or spraying done in the area where the excipient is exposed or stored?
    3. Are bait stations that use pesticides used?
- Potential biological hazards can occur from pests and their associated particulates.
    1. Is there a potential for contamination from incoming pallets, **packaging material**s, material supplies, etc.?
    2. Can pests approach the perimeter of the excipient manufacturing or storage facility due to insufficient maintenance of the external environment (area around plant facility)?
    3. Can pests enter the facility due to maintenance of the manufacturing, packaging, or storage facility perimeter (e.g., walls, floors, drains, roof, doors, windows, storm sewers, and penetrations through walls, windows, doors, vent pipes, etc.)?
    4. Are there food sources that attracts pests (e.g., open food waste containers or storage of food in the vicinity) in manufacturing, packaging or storage facilities?

Risk mitigation controls include:

- Inspection of incoming material such as pallets, packaging and raw materials for evidence of pest infestation
- Elimination of incoming materials that are known to be contaminated with pest droppings
- Documented pest management program which includes:
    - processes with facility mapping showing locations of traps
    - chemical management measures allowed in the facility
- Approval of pest control services
- Reports from the pest control service that identify evidence of activity and actions taken
- Review of reports from pest control services

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- Responsibility for inspection and control of the entire risk area at specific frequency; including roofs, basements, entries and exits
- SOPs and training on pest control measures
- Inspection of areas surrounding the outside of the facility are managed such as: spraying with pesticides, draining standing water, maintaining a perimeter landscape inhospitable to pests and periodic visual inspections
- Cracks in the walls are filled and any holes and ventilation system holes are equipped with screens to prevent entry of pests
- Placement of traps
- Traps inspected regularly and maintained
- Automatic door closures
- Automation of rodent station examination for activity with automatic scanners

4.2.11.3 Documentation and Records Supporting Pest Control

Documentation requirements are discussed in section 2.5 of this guide.

Signs of activity by pests in areas where the excipient is manufactured, packaged or stored should be assessed. Other things to consider include risk mitigation measures to control pests in all areas where the excipient is exposed during manufacturing and packaging as well as areas where finished excipient is stored.

4.2.12 Planning for excipient realization

Please refer to section 8.1 “Operation planning and control” of the IPEC-PQG GMP Guide.

4.2.12.1 Understanding the Requirement for Planning for Excipient Realization

The intent here is to ensure that risk evaluation and mitigation measures above have been taken into consideration for excipient realization.

4.2.13 Customer Communication

Please refer to section 7.4 “Communication” of the IPEC PQG GMP Guide.

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4.2.13.1 Understanding the Requirement for Risk Assessment for Customer Communication

The definition of how changes are assessed to identify those that are potentially significant is discussed in the IPEC Significant Change guide. [10]

4.2.13.2 Implementation of the Risk Assessment for Customer Communication

The criteria for assessing changes for their potential to impact the excipient is discussed in the IPEC Significant Change guide. [10]

4.2.13.3 Documentation and Records Supporting Customer Communication

See the IPEC Significant Change guide. [10]

Periodic review of changes through Management of Change (Change Control) is useful to determine if changes are assessed for impact to the customer.

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

Please refer to section 8.4 “Control of externally provided **quality critical** processes, services and materials” of the IPEC-PQG GMP Guide.

4.2.14.1 Understanding the Requirement for Risk Assessment for Purchasing Process

Materials and services that are procured by an excipient supplier can be intended for a variety of markets and an even wider variety of applications. The excipient supplier assesses the level of risk that the raw material or service presents to the quality of the excipient being manufactured, to identify the level of control to ensure the risk remains acceptable.

Any material that is a component of or has the potential to impact excipient conformance to the final release specification (quality, safety and/or performance) potentially represents a risk to the excipient and the supplier should be approved by the **quality unit**. This should include materials that the excipient manufacturing process cannot control.

Any service provided that has the potential to impact confirmation that the excipient was produced in conformance to GMP requirements or meets quality requirements is to be approved by the quality unit.

Contractors such as for pest control, metrology, and preventive maintenance require approval by the quality unit.

The primary goals are the use of raw materials that do not represent an unacceptable level of risk to the production of the excipient, and excipient that is acceptable for use in the

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pharmaceutical industry. The following key factors should be considered in evaluation of the excipient supplier:

- Ensure that the excipient supplier's system will consistently provide the same quality of product
- Records are maintained to ensure the raw material supplier or service provider is monitored as the risk level warrants
- The supplier will inform the customer of significant changes or have other agreements with their customer.

There is a risk that a significant change made by a material supplier will result in a change in the **composition profile** of the excipient. Where the material supplier does not agree to notify the excipient manufacturer of significant change, the change in chemical composition may go unidentified.

4.2.14.2 Implementation of the Risk Assessment for Externally provided Processes, Services and Materials

The excipient supplier should assess the raw materials or service providers for their corresponding criticality to the operation, and the potential risk they pose to the quality of the excipient. Distributors should conduct an appropriate risk assessment of the manufacturers for whom they distribute.

The outcome of the assessment should be approved by quality and the attributes of the raw material supplier or service providers (e.g. supplier's QMS), that comprise the evaluation and qualification process, documented. Specifications to be documented and maintained for critical materials, including quality critical attributes (e.g. stability).

Change control should be established with the raw material supplier or service provider, and if this is not possible, a documented risk assessment should demonstrate that an acceptable mitigation plan (e.g. control mechanisms) exists to manage the risk. Key service providers within the supply chain should also be considered within the assessment (e.g. testing laboratories).

The first question to ask is whether a raw material is critical to the quality, safety and performance of the excipient. If yes, then the following questions may assist with evaluating potential risks associated with the raw material supplier, the raw material and/or the service provider:

- Does the manufacturing location of the raw material have the potential to impact safety or quality of the excipient?

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- Example: site of the supply of cellulose used to make modified cellulose excipient is important to achieving desired performance
- **Country of origin** for animal derived raw materials is critical to complying with **BSE**/TSE risk mitigation

- Does the supplier have a quality system similar to ISO 9001 in place? Does the manufacturer have a supplier qualification program?
  - Does the manufacturer perform incoming testing on the raw materials, and what quality standards do they comply with?
  - Does the manufacturer have traceability from incoming raw materials to final product?
- What is the risk to the excipient from the process used to manufacture the raw material?
  - Is the equipment cleaned between runs? Cleaned between product change-over?
  - Is there a preventive maintenance program and/or a housekeeping program in place?
- Is the raw material from plant, animal, mineral or **synthetic** origin?
- Does the origin present a risk to the excipient quality?
  - Are there any special or unique process steps involved in the production of the raw material?
- Does the manufacturer have product specifications and **CoA**s for the raw material?
  - What are the solvents used in the manufacturing of the raw material (e.g. compliance with USP General Chapter 467, ICH Q3C)?
  - What are the typical concentrations of these solvents in the final product?
  - Does the manufacturer have a change control program in place?
- Are there any consequences to excipient quality to not storing the raw material to manufacturer's recommendation?
  - If the storage condition is not ambient, how long can the raw material remain outside of the recommended storage condition?
  - What is the recommended shelf life for the raw material? Is the raw material's shelf life based on stability studies?

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- How is a service provider evaluated?
    - Evaluate relevant experience and certifications to provide the service?
    - Do they have a documented quality system in place?
    - Do they provide services to the pharma, health care, food and cosmetic industry in general? It is preferred if the service provider has significant experience.
    - Do they notify customers of significant change and supply to agreed requirements?

The assessment for continued use of a supplier that does not agree to notification of significant change considers the possibility of a change in excipient composition. The following questions illustrate the type of questions that may be used:

1. How extensively is the quality control testing of the raw material provided by the supplier?
2. What information from a site audit assesses the potential for the supplier to make a significant change?
3. Is there any reason why the supplier cannot provide notification of significant change, i.e. their product is fed into a pipeline also used by other manufacturers of that material?

4.2.14.3 Documentation and Records Supporting Purchasing Process

Documentation may include a process flow diagram to demonstrate where raw materials are used in the process, as well as a list of all raw materials involved in the production of the excipient.

Consider documenting what areas of the operation/process are potentially impacted by the service(s) provided.

The documentation should provide objective evidence relating to the qualification process and include the corresponding rationale, via a documented risk assessment, to support the level of controls established in relation to qualification and management of the materials and the suppliers. The documentation may include:

- Product specification sheet or **certificate of analysis**
- Certificate of origin, if applicable
- **Certificate of suitability**, if applicable

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- BSE/TSE statement, if applicable
- Any other pertinent animal or plant sourced information
- **Residual solvents** list or residual solvents statement letter
- Summary of stability studies
- Summary of shipping studies
- Audit findings and assessment
- Quality and/or supply agreements
- Supplier's test methods
- Supplier's QMS and associated certification
- Supplier's change control system
- Safety data sheets (SDS)

Process flow diagram, indicating the raw materials used in the process, as well as the services employed to manufacture the excipient within the scope identified within the quality manual may be considered. Qualification process evaluation of the raw material supplier and/or service provider may be useful.

Objective evidence will be expected in relation to a documented risk assessment, the level of controls within the organization, and any supporting rationale provide for any risks that are documented as being acceptable. Those items that are deemed as critical to the quality of the excipient should have accompanying documented support, as well as documented controls that demonstrate an appropriate level of control in relation to the risks identified.

Existence of a documented system for the ongoing management of a supplier, including a process for disqualification of a previously approved supplier and/or material is important to consider.

Records for existing suppliers, materials, risk assessments, change control, agreements, audits, and the like shall be maintained, routinely evaluated as required, and stored appropriately.

4.2.15 Verification of Purchased Product

Please refer to section 8.4 "Control of externally provided quality critical processes, services and materials" of the IPEC-PQG GMP Guide.

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4.2.15.1 Understanding the Requirement for Risk Assessment for Verification of Purchased Product

Verification of the identity and quality of purchased materials used in processing and manufacturing is important as non-compliant material can impact the quality of the excipient and ultimately patient safety. For each purchased product, the standards require that a control to identify and verify that the material meets predetermined specifications and quality characteristics is in place. The risk to the excipient is a change in excipient composition.

4.2.15.2 Implementation of the Risk Assessment for Verification of Purchased Product

The following questions may assist with evaluating potential chemical hazards:

1. Is the raw material a direct component of the excipient product formulation?
2. Is it used as a **process aid** not intended to be part of the product formulation?
3. Is it used in multiple excipient products?
4. Is it supplied directly, or does it go through multiple parties in the supply chain?
5. Will a change in the composition (residual monomer, impurities) adversely impact the quality of the excipient?
6. Is the raw material from synthetic or natural origin? For **animal sourced** raw materials, traceability (country of origin) and evaluation of BSE/TSE risk is important.
7. Are there agreed specifications and CoAs for the raw material?
8. Is the raw material a compendial grade material?
9. Does the manufacturer identify any impurities and/or by-products that are not on the CoA? If so, are these quantified and controlled?
10. What are the expected ranges of **specified impurities**?
11. Does the manufacturer have a change control program in place? Is there an agreement with raw material supplier that significant changes will be communicated?
12. What is the justification if incoming testing is not performed on a specific raw material?
    a. Is there a risk the raw material will become contaminated during sampling?
    b. Is there a risk the raw material will have its quality impacted?
    c. Is it toxic or otherwise hazardous to employee health?
    d. Is it pipeline material (if feasible, in line sampling may be a suitable alternative)

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13. If testing is not performed, are there other controls to verify and approve the raw material such as:
    a. Information on process capability
    b. Corporate policies and procedures
    c. Regulatory compliance
    d. Other metrics, such as supplier performance history, that may be used to evaluate hazardous materials

Alternative approaches to sampling a material that is hazardous, or toxic includes reviewing accompanying documentation (bill of lading) and labelling (CoA and package label) to ensure that the correct purchased product was provided and to confirm that the material meets the agreed quality specifications.

4.2.15.3 Documentation and Records Supporting Verification of Purchased Product

In addition to the documentation discussed in section 2.5 of this guide, it is suggested that objective evidence to support the hazardous nature of material, such as the safety data sheet (SDS), is documented.

Incoming sampling and testing of raw materials identified in section 4.2.15.1 of this guide as having the potential to impact excipient quality may be considered. Where a raw material is not sampled and tested, justification should be provided to ensure the raw material has been properly identified. Justification maybe one or more of the following criteria:

1. Sampling exposes a significant risk the material will become contaminated
2. The material poses a significant hazard to employee health or safety, e.g. explosion hazard or burn risk
3. The quality of the material may be impacted by sampling, e.g. causing degradation such as in sampling organic peroxide initiator

Such exceptions should be justified and documented.

4.2.16 Preservation of Product

Please refer to section 8.5.4 “Preservation of product” of the IPEC-PQG GMP Guide.

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4.2.16.1 Understanding the Requirement for Risk Assessment for Preservation of Product

When raw materials and finished excipient are not stored under appropriate conditions, these materials may not continue to meet their quality requirements through the stated shelf life or **retest date**. This may result in a change in their chemical composition.

4.2.16.2 Implementation of the Risk Assessment for Preservation of Product

To assess the risk of change in chemical composition to materials, the following may be considered:

1. Does the material label state conditions for handling and storage?
2. Is the material handled according to the stated condition, such as dispense in a low humidity environment?
3. Is the material stored in an area that meets the labelled requirements?
4. Is the area where the material is stored monitored for the conditions on the label?

Risk mitigation would include mapping of the storage facility to identify those areas that either conform or do not meet the storage requirement. Where the labelled handling or storage information lacks clarity, the manufacturer should be contacted to quantify the requirements.

4.2.16.3 Documentation and Records Supporting Preservation of Product

In addition to the documentation requirements of section 2.5 of this guide, there should be a list of all raw materials and excipients that have labelled handling and storage conditions.

Examine the labels of raw materials and excipients to identify those which stipulate conditions for handling and storage and verify that they are being met.

4.2.17 Excipient Packaging Systems

Please refer to section 8.5.4.2 “Packaging” of the IPEC PQG GMP Guide.

4.2.17.1 Understanding the Requirement for Risk Assessment for Excipient Packaging Systems

The excipient container/closure system may be important in maintaining the excipient in conformance to its **monograph** or specification through its stated shelf life or retest interval. The packaging protects the excipient from physical hazards encountered during storage and transport such as moisture, chemical hazards and biological hazards. Chemical hazards might include volatile chemicals which could leach ingredients into or extract ingredients from contact packaging. Biological hazards are particularly important for sterile and low **bioburden** excipients.

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4.2.17.2 Implementation of the Risk Assessment for Excipient Packaging Systems

Where the excipient container/closure system has a history of use, examination of records can be used to demonstrate the packaging is adequate. Records such as stability testing, customer complaints, retest of excipient, and reported performance problems at the customer may be useful in this regard. New packaging should be justified through scientific studies that show the excipient will conform to the monograph or specification through its retest interval or shelf life. Also, a leachable and extractable study of contact packaging that contains any additives should be considered. The following questions may assist with evaluating excipient- packaging systems:

- Does the excipient supplier have agreed specifications for the packaging components
- Has packaging been evaluated to be non-reactive to the product?
- Are **tamper evident** seals used?
- Does the packaging comply with relevant regulatory requirements?
- Do procedures exist to adequately explain reusing containers?

4.2.17.3 Documentation and Records Supporting Excipient Packaging Systems

Documentation of the supporting data that shows the suitability of the container/closure system should be available for review.

Review of supporting data for the packaging system may be considered if there is an indication that the system does not adequately protect the excipient.

4.2.18 Control of Monitoring and Measuring Equipment

Please refer to section 8.6.1 “Monitoring and Measuring” of the IPEC PQG GMP Guide.

4.2.18.1 Understanding the Requirement for Risk Assessment for Control of Monitoring and Measuring Equipment

The validity of measurements rests on the foundation of measuring and test devices that have been calibrated and suitably maintained. Actions taken as a consequence of erroneous measurements can impact the quality of the excipient.

4.2.18.2 Implementation of the Risk Assessment for Control of Monitoring and Measuring Equipment

Use of an instrument that is out of **calibration** or otherwise not operating reliably can present a physical, chemical or biological hazard to the excipient. The following questions can be used to identify if a measuring or test device does not need calibration or maintenance:

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1. Is the instrument capable of calibration?
2. Is there any preventive maintenance that can be performed?
3. Does the instrument have a “calibration due” date prior to which it is expected to remain reliable?
4. What is the consequence of an unreliable measurement to the excipient?

4.2.18.3 Documentation and Records Supporting Control of Monitoring and Measuring Equipment

Documentation requirements are discussed in section 2.5 of this guide.

Justification for any measuring or test device that is not in the calibration program should be considered.

4.2.19 Reworking

Please refer to section 8.7.1.2 “**Reworking**” of the IPEC PQG GMP Guide.

4.2.19.1 Understanding the Requirement for Risk Assessment for Reworking

Reworking an excipient involves utilizing processing steps and/or equipment not routinely used to manufacture the excipient. Therefore, there is a risk to excipient quality from physical hazards resulting from the use of new equipment, chemical hazards to excipient compositions such as new by-products or decomposition products, and biological hazards from environment exposure.

4.2.19.2 Implementation of the Risk Assessment for Reworking

These general questions may apply to rework activities:

1. Has the rework process removed the non-conforming properties of the affected excipient? And how is this demonstrated?
2. Will the reworked product have the same performance and specification properties as normal production?
3. What additional testing is used to monitor and control rework processes?
4. What additional **acceptance criteria** are needed for reworked excipients?
5. Is there any impact on stability and retest intervals?
    - Will the reworked product have equivalent stability?

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- If product is needed in a relatively short time, can accelerated stability studies be used?

6. Are there possible composition changes?
    - How can we measure possible changes to the **impurity profile**/composition?
7. Are there possible performance changes?
    - What type of performance testing should be considered?
8. How is the need to notify customers for reworked excipients addressed?
    - Is the Disposition Process dependent on sale of the material?
    - Will certain customers not be considered?
    - What type of customer notification is needed?
9. Will the **batch**es be repeatable when scaled up for manufacturing?
10. Are any new safety or environmental risks possible in the manufacturing steps?
11. Can the reworked batch be sufficiently isolated from routine production?
12. Will different cleaning procedures be necessary?
13. How can we evaluate risks with downgrading the product?
14. Should we consider validating the rework for future possible **reprocess**ing?

4.2.19.3 Documentation and Records Supporting Reworking

Documentation requirements are discussed in section 2.5 of this guide.

The risk assessment for reworked excipient along with affirmation from the customer that the excipient is acceptable should be considered.

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