# The IPEC Risk Assessment Guide for Pharmaceutical Excipients

## Part 1 – Risk Assessment for Excipient Manufacturers

**First Version**
**2017**

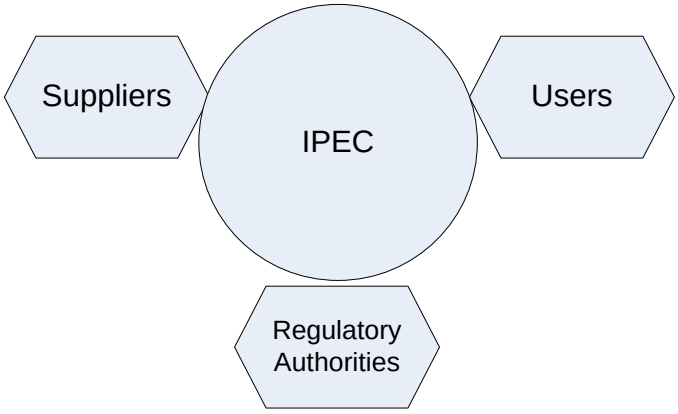
This document represents voluntary guidance for the pharmaceutical excipient industry and the contents should not be interpreted as regulatory requirements. Alternative approaches to those described in this guide may be implemented.

## FOREWORD

International Pharmaceutical Excipients Council (IPEC) is an international industry association formed in 1991 by manufacturers, distributors and end-users of excipients. At the time of writing there are regional pharmaceutical excipient industry associations including the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace, and the development of best practice and guidance concerning excipients.

IPEC has three major stakeholder groups;

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




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

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This guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas®), an industry association headquartered in Arlington, Virginia whose principal members consist of excipient manufacturers, distributors, and users. The company representatives who worked on this guide are listed below:

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# 1. INTRODUCTION

## 1.1. Purpose

The primary intent of the IPEC Risk Assessment Guide for Pharmaceutical Excipients (RAG) 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.

## 1.2. Scope

The scope of this guide is to provide excipient suppliers with an overview of risk assessment tools, and resources that they can use, when conducting risk assessments required by both NSF/IPEC/ANSI 363[1] and EXCiPACT™ [2] excipient GMP standards, in order to identify and control for potential risks to excipient quality. 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 assessments requirements are found in both the NSF/IPEC/ANSI 363 and EXCiPACT™ excipient GMP standards and suggests documentation to demonstrate adequacy of risk assessment and GMP controls.

The IPEC Risk Assessment Guide Part 1 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. We expect to include additional sections to the risk assessment guide in the future and this edition reflects the first part.

## 1.3. Background

IPEC has developed and promoted the implementation of appropriate and scientifically valid voluntary industry guides for excipients[3] for many years. IPEC's unique combination of experts from excipient makers, distributors and users makes this association uniquely positioned 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 and GDPs and the American National Standard *GMP for Pharmaceutical Excipients*, NSF/IPEC/ANSI 363. Both of these 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

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[1] NSF/IPEC/ANSI 363 -2014 *Good Manufacturing Practices (GMP) for Pharmaceutical Excipients*

[2] EXCiPACT™ *Certification Standards for Pharmaceutical Excipients: Good Manufacturing Practices, Good Distribution Practices, 2012*

[3] IPEC Guides are available as a free download from https://ipecamericas.org/ipec-store (Americas) and http://www.ipec-europe.org/page.asp?pid=59 (Europe).

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)[4] 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. 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 manufacture of the excipient
- The quality history of the excipient supplier and the reliability and integrity of the supply chain
- The use of the excipient in the finished product and its route of administration

The "IPEC Europe "How-To" Document on EU Guidelines on Risk Assessment for Excipients, 2016" can be accessed on the IPEC Europe web site (IPEC Europe Guidelines) which was created to give excipient users and suppliers additional information and guidance to accurately complete a risk assessment specifically to meet the EU FMD requirements.[5]

This guide is intended to provide excipient manufacturers, distributors 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[6] guideline
- Risk assessment by excipient manufacturer, including requirements described in NSF/IPEC/ANSI 363 and EXCiPACT™

The first use of a term defined in IPEC's Glossary of Official Definitions of Excipients[7] is noted by the use of **bold** type with no underline.

[4] EU Guidelines of 19 March 2015 on the formalized risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (QJ 2015/C 95/02)

[5] *IPEC Europe "How-To" Document* for "Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use." http://ipec-europe.org/UPLOADS/160318_IE_How-to_do_RAGuidelines_v1_2.pdf

[6] International Conference on Harmonisation, ICH Q9: *Quality Risk Management*, November 2005.

[7] International Pharmaceutical Excipient Council Glossary: *Glossary of Official Definitions for Excipients.*

## 2. PRINCIPLES OF RISK ASSESSMENT AND MANAGEMENT

Risk assessment is a basic principle to support decision making in the NSF/IPEC/ANSI 363 and EXCiPACT™ standards, 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 evaluation of risk with focus on quality of the excipient and potential impact of the excipient on patient safety. This facilitates conformance to the risk assessment requirements of the standard.

The extent of the assessment of risk should be commensurate with the hazard posed to excipient quality. If a section in the GMP standard 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)?
- 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 assessment and develop the control strategy. 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**.

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 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 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.

## 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 customer or their patients. Where the risk may impact the pharmaceutical customer 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[8].

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 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 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.

[8] The International Pharmaceutical Excipients Council Significant Change Guide, Third Revision, 2014.

## 2.4. Phase 4: Risk Review

The final step in quality risk management is **risk review**. The risk assessments completed to comply with NSF/IPEC/ANSI 363 and EXCiPACT™ standards should be periodically reviewed in order to ensure that their conclusions remain valid. The quality risk management procedure should include a maximum time interval for performing a risk review. 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
- Deviations 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 documentation required to demonstrate that the risk was evaluated in accordance with the procedure. NSF/IPEC/ANSI 363 requires that a risk assessment be used to justify any section of the standard 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
- Meeting minutes
- Outcome of risk assessment activities
- Communication of the risk mitigation under change control.

# 3. RISK ASSESSMENT METHODS

There are many methods for performing a risk assessment. This guide will refer to the techniques listed in ICH Q9:

1. Failure Mode Effects Analysis (FMEA)
2. Failure Mode Effects and Criticality Analysis (FMECA, aka FMEA)
3. Fault Tree Analysis (FTA)
4. Hazard Analysis and Critical Control Points (HACCP)
5. Hazard Analysis and Risk-Based Preventive Controls (HARPC)
6. Hazard Operability Analysis (HAZOP)
7. Preliminary Hazard Analysis (PHA)
8. Risk Ranking and Filtering

The common elements of each technique discussed below are:

1. A clear definition of the goal of the assessment, including the scope of the hazard, real or potential, that is being assessed.

2. A team typically comprised of a facilitator, a team lead, and functional experts, as appropriate. Dividing the assessment into unit operations can facilitate the evaluation of an entire manufacturing process.
3. Risk assessment documentation sufficient to demonstrate that relevant site procedures were followed.

## 3.1. Failure Mode Effects Analysis (FMEA)

FMEA is used to assess the potential failure modes of equipment and facilities in order to identify the potential impact of failure on product or process. FMEA is a qualitative tool typically used to identify the root cause of risks and develop mitigation to prevent failure. A key difference between FMEA and FMECA is that FMECA extends the assessment by assigning a rating to the criticality of the hazard, the severity, probability of occurrence, and detectability. Assigning a rating facilitates the prioritization of hazards, through the development of a risk score, which allows one to prioritize mitigation efforts and to make an objective decision on risk tolerance.

FMEA has been widely supplanted by FMECA for the purpose of quantifying and prioritizing risk. Since the fundamentals of FMECA rests on those of FMEA, the guide will only provide details on FMECA; often referred to in the literature as FMEA. Therefore, further reference to FMEA in this guide will refer to "Failure Mode, Effects and Criticality Analysis."

## 3.2. Failure Mode, Effects and Criticality Analysis (FMECA, aka, FMEA)

Components of the FMECA are:

- Severity: if a failure were to occur, what effect would that failure have on the product quality and on the patient (if any)?
- Probability of occurrence: how likely is it for a particular failure to occur?
- Detectability: what mechanisms are in place (if any) to detect a failure if it were to occur?

Each of the above metrics require clear definitions and a corresponding scale to rank or score the projected impact (i.e. a scale for severity; probability; and detectability). A composite score can to be calculated (e.g. severity multiplied by probability multiplied by detectability) and matrixed so that final team recommendations are based on a calculated risk ranking.

This technique lends itself to a quantitative assessment of the risk resulting from equipment and facilities and allows for the analysis of manufacturing's effect on the excipient or the excipient manufacturing process. However, FMEA can only assess a single mode of failure not a combination of failure modes. This technique is useful for assessing the impact of potential failures and the development of effective preventive measures. FMECA is useful during the design process as a bottom up analysis.

### 3.2.1. **Establish Clear Definitions**

As described in section 2.1 of this guide, there are three components to a risk assessment: severity, probability, and detectability. The definitions for the various rankings of severity, probability, and detectability should be clearly articulated in the assessment documentation.

The multiplication of the ratings for severity, probability, and detectability produce a risk priority number (RPN). A full discussion of this technique is provided in the PQRI *Failure Modes and Effects Analysis Guide*.[9].

#### 3.2.1.1. *Severity Criteria*

Severity takes into account the impact of the risk to the pharmaceutical manufacturer and, where the intended market for the excipient or the drug product is known, the patient who consumes the drug product. Severity includes the impact to the manufacturer of the drug product as well as conformance of the finished pharmaceutical to specification, safety, and efficacy.

#### 3.2.1.2. *Probability Criteria*

Probability of occurrence relates the frequency of the risk with the likelihood that the effect occurs as a result of the specified failure mode. The preference is to relate the frequency of occurrence to prior experience.

#### 3.2.1.3. *Detectability Criteria*

Detectability evaluates the likelihood the failure will be detected before the excipient is released. The detectability rating can assess the ability of quality control testing in conjunction with manufacturing experience in identifying the failure.

### 3.2.2. **Risk score matrix**

As described above, the relative risk is defined by a risk priority number (RPN) that is calculated based on severity (S), probability (P), and detectability (D).

$$\text{RPN} = S \times P \times D$$

The RPN should take into consideration other applicable risk factors outside the scope of the evaluation. The RPN establishes a relative priority for addressing the potential failure - the bigger the RPN, the higher the priority to address the potential failure being assessed.

## 3.3. Fault Tree Analysis (FTA)

FTA is a visual technique that shows the links between the effect and the potential causes. This technique uses all possible root causes of a potential failure or problem to evaluate failures one at a time. The results of the assessment are presented pictorially as a tree of fault modes. Each level of the tree presents combinations of fault modes described using Boolean logic[10], operators such as "and", "or" etc., to combine lower-level causal factors until the potential root causes have been identified. The logic operators "and" and "or" prevent the failure at the next higher level unless specific conditions are met. When a failure can only occur if several conditions are met ("and"), prevention only requires the control of one failure mode.

FTA establishes the path by which a root cause leads to failure; starting with the failure and proceeding to the root cause. Therefore, the technique is more valuable as a retrospective tool. FTA can combine multiple root causes by visualizing causal chains. Also the technique can be used to assure risk mitigation will prevent the failure while not creating a new failure mode. It is often used in conjunction with FMEA.

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[9] Pharmaceutical Quality Research Institute (PQRI) Manufacturing Technology Committee-Risk Management Working Group, Risk Management Training Guides, draft proposal May 29, 2008, Revision 04.

[10] Boolean logic is a form of algebra in which all values are reduced to either TRUE or FALSE

## 3.4. Hazard Analysis and Critical Control Points (HACCP)

HACCP is "*A systematic, proactive and preventive method for assuring product quality, reliability, and safety*."[11] This technique applies technical and scientific principles to analyze, evaluate, prevent and control risk due to design and production of products. HACCP helps to prevent or reduce known hazards through the identification and monitoring of critical control points. The hazards addressed by this technique are strictly defined as biological, chemical or physical contaminates that are reasonably likely to cause injury or illness if consumed. HACCP is a seven principles technique[6]:

1. Perform hazard analysis and identify preventive measures
2. Identify critical control points (CCP)
3. Establish limits for each CCP
4. Establish monitoring of CCP
5. Develop corrective action when CCP is not in a state of control
6. Verify that the HACCP is working effectively
7. Establish a recordkeeping system.

The HACCP assessment can identify and manage risks associated with excipient physical, chemical and biological hazards. HACCP integrates risk mitigation and communication with risk identification. The technique does not identify quality failures that may impact the performance and function of the excipient in the drug product formulation. A major drawback to this technique is that there is no quantification of risk and thus no priority ranking of hazards.

### 3.4.1. **Describe the Product, Intended Use and Process**

The HACCP team should first define the excipient associated with the HACCP. The excipient should be defined through its physical, chemical and biological characteristics. It is also important to consider the intended use of an excipient so that the assessment can identify the hazards associated with the pharmaceutical manufacturing process and drug product. This allows the HACCP team to define the process. The process should be sufficiently detailed to allow for highlighting process hazards and potential control points.

"*There are a total of twelve tasks required to develop a HACCP Plan, and these are designed to ensure that the seven principles are applied correctly*."[12] The tasks are:

1. Establish a HACCP team
2. Describe the product
3. Identify the product's intended use
4. Draw up the process flow diagram
5. On-site confirmation of the flow diagram
6. Identify and analyze hazards
7. Determine the critical control points
8. Establish critical limits for each critical control point
9. Establish a monitoring procedure

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[11] International Conference on Harmonisation, ICH Q9: *Quality Risk Management*, November 2005 Annex 1: Methods & Tools, Annex 1.5, Hazard Analysis and Critical Control Points, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Q9_Briefing_Pack/PPT/Tools/Q9_HAZOP.ppt

[12] José Rodríguez-Pérez, *Quality Risk Management in the FDA-Regulated Industry*, ASQ Quality Press, 2012, pp. 124-127.

10. Establish corrective action
11. Verify the HACCP plan
12. Keep records.

### 3.5. Hazard Analysis and Risk-Based Preventive Controls (HARPC) from 21CFR117 Subpart C

HARPC is typically applied to food but can provide a good model to address some concepts of risk assessment in the NSF/IPEC/ANSI 363 standard, such as personal hygiene.

As part of the Food Safety Modernization Act of 2010, the United States Food and Drug Administration (U.S. FDA) published new food GMPs under 21 CFR Part 117. Subpart C introduces the concept of preventive controls that go beyond the traditional process based critical control points of HACCP. The regulation defines preventive controls as "*those risk-based, reasonably appropriate procedures, practices and processes that a person knowledgeable about the safe manufacturing, processing, packing or holding of food would employ to significantly minimize or prevent the hazards identified under the hazard analysis that are consistent with the current scientific understanding of safe food manufacturing, processing, packing or holding at the time of the analysis*".[13] The regulation requires a "Food Safety Plan" whose contents must include the written:

- Hazard analysis
- Preventive controls
- Supply-chain program
- Recall plan
- Procedures for monitoring the implementation of the preventive controls
- Corrective actions procedures
- Verification procedures

The tasks are similar to those in HACCP given above except that the critical control points are expanded to also include other controls that are appropriate for food safety including specifically:

- Process controls
- Food allergen controls
- Sanitation controls
- Supply-chain controls
- Recall plan
- Other controls including hygienic training and current good manufacturing practices

### 3.6. Hazard Operability Analysis (HAZOP)

HAZOP is a structured and systematic assessment of a planned or existing product, process, or procedure.[12] This technique assumes that failures are caused by deviating from design or operating intentions. The technique relies on brainstorming using certain guide words to stimulate the thinking of team members to identify deviations that may result in a failure. Guide words such as "no", "none", "more", and "less" are combined with the design or operating intention to identify the potential deviation. The deviations are then discussed to identify the hazard, evaluate the risk and controls, and make recommendations for reduction. HAZOP relies on subject matter experts to predict deviations based upon their knowledge and past

[13] 21 CFR Part 117 – Current Good Manufacturing Practice, Hazard Analysis, and Risk Based Preventative Controls for Human Food. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=117&showFR=1

experience. HAZOP is often used as a starter for HACCP. HAZOP is a qualitative technique that does not facilitate the prioritization of the risks identified.

HAZOP is particularly suited to examining system design for the ability to meet user specifications and identifying weaknesses. It is also useful for assessing the physical and operational environment and the operational and procedural controls. The technique involves four phases:

1. Definition of the assessment scope
2. Preparation, which involves gathering supporting information, identifying the study output and preparing for the study
3. Execution where the system or process is examined
4. Documentation and follow-up

### 3.7. Preliminary Hazard Analysis (PHA)

PHA relies on prior experience, knowledge or failure to identify potential future hazards. PHA provides an estimate of likelihood of occurrence for an activity, equipment or process. The technique involves four phases:

1. Identification of the potential risk event
2. Evaluation of the potential for harm
3. Ranking of the hazard by combining severity and probability
4. Identification of risk mitigation.

PHA lends itself to new processes and excipients, particularly where the process has been used before or the new excipient is a line extension. Often PHA is used to identify hazards early in a product lifecycle that are further assessed using other techniques; however, PHA does not result in rating or ranking risks nor does it help in developing preventive measures.

### 3.8. Risk Ranking and Filtering

Risk ranking and filtering facilitates focusing on critical risks that are part of a large and complex set of risks. It is often used for complex systems, where the technique allows the system to be broken down into components. Each component is assessed and then all of the risks are combined into a relative risk score. This tool allows the evaluation of qualitative and quantitative assessments together. Risk ranking and filtering is also used for comparing and ranking various related risks. A full discussion of this technique is provided in the PQRI Risk Management Training Guides, *Risk Ranking and Filtering.*[9]

Application of the technique starts with defining the head topics and subtopics associated with the risk question. Head topics are related risk factors while subtopics are factors that directly impact the risk associated with a head topic. Topics are the source of risk to be assessed and scored. Evaluation criteria to quantify the risk posed by the risk components, severity and probability, are then established. Scoring of each risk component is completed based upon a scoring scheme. Finally, the scores for the head topics and subtopics are ranked. Frequently low scoring risk components are filtered out of the assessment. Often a rating is assigned to the severity resulting from the hazard and probability of the failure being assessed.

The technique is useful for establishing area priorities for internal audit and for evaluating recurring problems.

## 4. RISK ASSESSMENT BY EXCIPIENT MANUFACTURER –

The NSF/IPEC/ANSI 363 standard requires 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 also is used for supplier qualification, change management, and rework activities.[14]

### 4.1. Risk Assessment Documentation

There are many acceptable techniques to address the requirements for conducting risk assessment. To meet the requirements of the standard(s), a risk assessment may be conducted at either the corporate level 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 assessments documentation can be created for each relevant section. Risk assessments performed for other markets can provide the basis for the excipient risk assessment and the risk information from other market assessments can be included with the excipient assessment documentation. The justification and documentation required for each risk assessment depends on the complexity of the assessment. For sections that do not apply, a simple explanation of why the section is not applicable can be sufficient. Justification including rationale to demonstrate conformance to the standard should be complete 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 NSF/IPEC/ANSI 363 standard as long as the documentation links the assessment to each applicable section of the standard.

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 conducting the risk assessment and periodic review should be included in the quality management system.

### 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 the guide provides approaches to address those clauses of the NSF/IPEC/ANSI 363 and EXCiPACT™ 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 both EXCiPACT™ GMP and NSF/IPEC/ANSI 363 standards
- 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

[14] Risk Assessment of Excipients, Patricia Van Arnum, Pharmaceutical Technology, September 2013 (5) http://www.pharmtech.com/risk-assessment-excipients.

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 customer 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
2. Interference with the bioavailability of the **Active Pharmaceutical Ingredient** (API) due to reaction with the chemical
3. Shortened 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 customers. Therefore, it is important to prevent biological contamination especially with pathogenic organisms.

#### 4.2.1. **Hygienic Practices**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 6.2.3 Personnel Hygiene | Section 6.2.3 Hygienic Practices |
| To protect excipients from contamination, the organization shall conduct a risk assessment to identify areas in which the excipient is at risk of contamination from personnel or their activities. The following shall be considered at a minimum to prevent excipient contamination:<br>a) the personnel themselves and their attire, including personal protective equipment,<br>b) loose items, including those in pockets,<br>c) unauthorized access to designated areas (see 6.3),<br>d) the potential impact of any person with an apparent illness or open lesions, | To protect excipients from contamination, the organization shall conduct a risk assessment to identify areas where the excipient is at risk of contamination from personnel and/or their activities. The following shall be considered at a minimum to protect the excipient from contamination:<br>a) the personnel, including their hygiene, any apparent illness or open lesions, and their attire;<br>b) the equipment used by the personnel;<br>c) the opportunity for loose items to fall into the excipient;<br>d) the access of unauthorized personnel to designated areas; and |

| EXCiPACT™ GMP and GDP Standard | NSF/IPEC/ANSI 363 GMP Standard |
|---|---|
| Section 6.2.3 Personnel Hygiene | Section 6.2.3 Hygienic Practices |
| e) the storage and use of food, drink, personal medication, tobacco products or similar items.<br><br>Where existing controls to minimize the risks of excipient contamination are not considered effective then additional measures shall be documented and implemented. | e) the storage and use of food, drink, personal medication, tobacco products, or similar items.<br><br>Suitable control measures shall be implemented to mitigate the identified risks.<br><br>Personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients. |

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 cGMP 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, labels, twist ties and seals may fall into the excipient?
    3. Is there a risk from contamination to equipment during maintenance and inspections by personnel?
- 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 fall into the excipient?
    3. Can medication used by personnel fall into the excipient?
    4. Is there 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 protective gear?
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 hands soiled
- 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
- 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.

#### 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 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 is 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**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 6.3 Infrastructure | Section 6.3 Infrastructure |
| The infrastructure shall be designed, operated, cleaned and maintained to avoid contamination and mix-ups of the excipient.<br><br>The organization shall conduct a risk assessment based on the organization's intended use of the infrastructure to identify areas in which the excipient is at risk for contamination from deficiencies in buildings and/or facilities. The risk assessment shall consider the following at a minimum to identify where the excipient is at risk from contamination:<br><br>a) Location of the operations (e.g. internal, external),<br>b) State of repair of the building and facility,<br>c) Suitable size, construction and location,<br>d) Ability to maintain a suitably clean building and facility environment,<br>e) Operations that can affect the excipient quality,<br>f) Presence of airborne contaminants, especially highly sensitizing or toxic substances.<br><br>Where existing controls to minimize the risks of excipient contamination are not considered effective, then additional measures shall be documented and implemented. | Contamination prevention shall be considered in the design, maintenance, refurbishing, or upgrading of buildings and facilities.<br><br>The organization shall conduct a risk assessment based on the organization's expressed, intended use of the excipient (see 7.2.3) to identify areas in which the excipient is at risk of contamination, cross contamination, or mix-ups due to deficiencies in buildings and/or facilities.<br><br>The risk assessment shall consider the following, at a minimum, to identify where the excipient is at risk of contamination:<br><br>a) state of repair of the building and facility;<br>b) suitable size, construction and location;<br>NOTE − Where equipment is located outdoors there shall be suitable control to minimize the risk to excipient quality from the environment, including seasonal variations.<br>c) ability to maintain a suitably clean building and facility environment;<br>d) operations inside or outside of the building or facility that may affect the excipient quality; and<br>e) presence of environmental contaminants, including microorganisms.<br><br>Suitable control measures shall be implemented to mitigate the identified risks. Access to areas of the buildings and facilities designated as limited access areas shall be controlled. |

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. 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.

#### 4.2.2.2. *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 tight?
    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?
    5. Are building maintenance items such as lubricants, paint, etc. stored in a manner that can contaminate the excipient?
    6. Is there exhaust such as steam, internal combustion, etc.?
    7. Are there airborne contaminants from nearby operations, particulates or chemical odors/fumes?
    8. Is there uncontrolled storage of other chemicals such as solvents, 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. Does the excipient during processing, packaging or loading operations come in contact with unfiltered air in the environment or unfiltered process air (which may contain microbial contamination)?
    2. Is there standing water that can promote microbe growth in the processing area?
    3. Is there evidence of leaks; water or chemicals?
    4. Do internal structures allow for collection of dust, pollen and mold on structures such as ledges, light fixtures, hanging utilities or piping?
    5. Is there overhead open floor grating that can scrape dirt off of shoes?
    6. Does Preventive Maintenance require normally closed equipment and buildings to be opened?
    7. Do procedures for return to operation after maintenance include confirmation of cleanliness before use?
    8. 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
- 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.

#### 4.2.2.3. *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

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 6.3 Infrastructure | Section 6.3.2.1 Equipment design and construction |
| Under section 6.3, Infrastructure, the standard emphasizes:<br>• Defective equipment shall not be used<br>• Equipment which can impact excipient quality shall be commissioned before use<br>Equipment shall be placed and constructed to facilitate cleaning and maintenance. | New installations or replacement equipment shall be designed and constructed to minimize the possibility of contamination and shall be commissioned before use to ensure it is functioning as intended.<br>In the design and construction of equipment, the risk of contamination from process materials or other media used for proper equipment operation (e.g. lubricants and heat transfer fluids) coming into contact with raw materials, packaging materials, intermediates or finished excipients shall be identified. When risks are identified, they shall be mitigated so as to minimize the possibility of contact with the process stream. Where contact is possible, materials suitable for food contact shall be used unless otherwise justified. |

#### 4.2.3.1. *Understanding the Requirement for Risk Assessment for Equipment Construction*

The risk to be assessed includes chemical risk 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 specifications and the use of food grade process materials.

The following questions help with chemical risk evaluation:

1. Are food grade and/or FDA approved equipment components required due to their potential to contact the excipient?
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?

#### 4.2.3.3. *Documentation and Records Supporting Equipment Construction*

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

### 4.2.4. Equipment Maintenance

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| | Section 6.3.2.2 Equipment maintenance |
| There are no requirements for risk assessment under ISO 9001 section 6.3 or the EXCiPACT™ GMP related to this section as all equipment is required to be maintained without exception. | If maintenance is performed without a procedure and associated schedule, this is to be justified based on a documented risk assessment. |

#### 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 three fold:

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

If an organization concludes that scheduled maintenance or maintenance procedures are unnecessary, they must justify why such scheduled maintenance is not required.

This section requires that "*deviation from the normal maintenance schedule shall be justified*." Though unstated, deviation from maintenance procedure should also be justified.

#### 4.2.4.2. *Implementation of the Risk Assessment for Equipment Maintenance*

The best practice is to ensure that all 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 must 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 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 when maintenance fails or 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?

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 organisms?

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 had to 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 (section 8.5.2 of the NSF/IPEC/ANSI 363 standard).

#### 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**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Excerpt from the Standard: 6.3 Infrastructure | Excerpt from the Standard: 6.3.3Utilities |
| "The organization shall conduct a risk assessment considering the risk to excipient quality from utilities" | "The organization shall conduct a risk assessment considering the risk to excipient quality from utilities intended or with the potential to contact the excipient. |

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 or from contaminates in the utility or contaminates 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 additives 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:
    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, 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**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Excerpt from the Standard: 6.3 Infrastructure | Excerpt from the Standard: 6.3.4 Water |
| "Unless otherwise justified, water shall, at a minimum meet WHO guidelines for drinking (potable) water quality." | "Unless otherwise justified, water shall, at a minimum, meet the WHO Guidelines for Drinking-Water Quality, be distributed in a well-designed sanitary system, and be provided either under continuous positive pressure or with other robust means of preventing back flow." |

#### 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 by the standard is to set the minimum quality as the WHO guidelines for drinking water quality.[15] Where a lessor quality of water is used, justification showing that excipient quality and functionality are met must be documented. The standards also requires a sanitary distribution system and continuous flow or back flow prevention. The NSF/IPEC/ANSI 363 standard allows deviations in the water system provided they are justified. The EXCiPACT™ GMP standard also requires the prevention of contamination during distribution. 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

[15] World Health Organization (WHO) Guidelines for drinking-water quality: Fourth edition incorporating the first addendum; http://www.who.int/water_sanitation_health/publications/drinking-water-quality-guidelines-4-including-1st-addendum/en/

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[15] 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:

    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?
    7. Does the excipient have anti-microbial properties?

Risk mitigation may include validation of process water purification that demonstrates non-potable water can be made potable 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.

#### 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.

Evidence that water, other than that which meets the WHO guidelines, 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. **Air Handling Systems**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 6.4.1 Air Handling | Section 6.4.1 Air handling |
| Under section 6.4, Work Environment, there is a requirement to perform a risk assessment for the excipient to become contaminated from exposure where an air handling system is used. | Under section 6.4, Work Environment, there is a requirement to perform a risk assessment for the excipient to become contaminated from exposure where an air handling system is used. |

#### 4.2.7.1. ***Understanding the Requirement for Risk Assessment for Air Handling Systems***

Section 4.2.5 of this guide, Utilities, addressed 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 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.

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, particularly mold and yeast. Where the air contains chemicals from other operations, filtration such as with HEPA filter or activated carbon may be used to remove them.

#### 4.2.7.2. ***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 odors or fumes in the general area that may contaminate the excipient where exposed to the environment?
    2. Are there odors 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 microbes, 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.

#### 4.2.7.3. *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.

### 4.2.8. **Special Environments**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 6.4.2 Controlled Environment | Section 6.4.2 Controlled environment |
| Under section 6.4, Work Environment, there is a requirement to perform a risk assessment where there is a need for a special environment to prevent contamination. | Under section 6.4, Work Environment, there is a requirement to perform a risk assessment where there is a need for a special environment to prevent contamination. |

#### 4.2.8.1. *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.

#### 4.2.8.2. *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:

- 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.

#### 4.2.8.3. *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.

### 4.2.9. **Cleanliness and Sanitary Conditions**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 6.4.3 Cleaning and Sanitary Conditions | Section 6.4 Work Environment. |
| Under section 6.4, Work Environment, there is a requirement to perform a risk assessment to determine if there is a need for clean and sanitary conditions to prevent excipient contamination. | Under section 6.4, Work Environment, there is a requirement to perform a risk assessment to determine if there is a need for clean and sanitary conditions and from waste segregation and disposal to prevent excipient contamination. |

#### 4.2.9.1. *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 come 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.

#### 4.2.9.2. *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?
    4. Is there a process for management and disposition of scrapped product?
    5. What procedures are in place regarding segregation, labeling and disposal of waste?
    6. How is waste contained? How is it labeled? 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. Can a mix-up contaminate the excipient with chemical waste?
  3. 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
- Process for management and identification of waste material
- Properly containing of waste
- Labeling of waste
- Promptly removing waste
- Proper storing of waste awaiting disposal.

#### 4.2.9.3. *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.

4.2.10. **Pest Control**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 6.4 Work Environment | Section 6.4.4 Pest control |
| Under section 6.4, Work Environment, there is a requirement to perform an assessment to determine if there is a risk of excipient contamination from pests. | Under section 6.4.4 Pest control, there is a requirement to perform an assessment to determine if there is a risk of excipient contamination from pests. |

4.2.10.1. ***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 form 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.

4.2.10.2. ***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 electrocuters situated such that insect fragments may contaminate the excipient?
- Potential chemical hazards can result from use of chemicals for pest control.
    1. Are pesticides and rodenticides used to control pests?
    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, other packaging materials, 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 (when possible) 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 extermination services
- Reports from the exterminator that identify evidence of activity and actions taken
- Review of reports from exterminator services
- Responsibility for inspection and control of the entire risk area at specific frequency; including roofs, basements, ingresses and egresses
- SOPs and training on pest control measures
- Inspection of facility outside surrounding areas 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

#### 4.2.10.3. *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.

### 4.2.11. Planning for excipient realization

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 7.1 h) | Section 7.1 Planning of excipient realization |
| The section establishes the expectation that risk mitigations identified through risk assessments are implemented | The section establishes the expectation that risk mitigations identified through risk assessments are implemented. |

#### 4.2.11.1. *Understanding the Requirement for Planning for Excipient Realization*

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

4.2.12. **Customer Communication**

| EXCiPACT™ GMP and GDP Standard | NSF/IPEC/ANSI 363 GMP Standard |
|---|---|
| | Section 7.2.3 Customer communication |
| No requirement (beyond ISO 9001) | The excipient manufacturer is expected to define how potentially significant changes are assessed and customers informed. |

4.2.12.1. ***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.[8]

4.2.12.2. ***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.[8]

4.2.12.3. ***Documentation and Records Supporting Customer Communication***

See the IPEC Significant Change guide.[8]

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

4.2.13. **Purchasing Process**

| EXCiPACT™ GMP and GDP Standard | NSF/IPEC/ANSI 363 GMP Standard |
|---|---|
| Section 7.4.1 Purchasing Process | Section 7.4.1 Purchasing process |
| Quality critical materials and services shall be identified through risk assessment. | Materials and services that may impact excipient quality are to be identified through risk assessment.<br>Where a supplier will not agree to provide notification of significant changes, a risk assessment will justify the continued use of the supplier. |

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

- Ensure that 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 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.

#### 4.2.13.2. *Implementation of the Risk Assessment for Purchasing Process*

The excipient supplier must 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 final 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 must be established with the raw material supplier or service provider, and if this is not possible, a documented risk assessment must demonstrate that an acceptable mitigation plan (e.g. control mechanisms) exists to manage the risk. Key service providers within the supply chain must 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 raw material have the potential to impact safety or quality of the excipient?
  - 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?
  - 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 other 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 CoAs for the raw material?
  - What are the solvents used in the manufacturing of the raw material (e.g. compliance with USP General Chapter 467)?
  - 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?
- 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? If they have significant experience, then it is a preferable.
  - 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?

#### 4.2.13.3. *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
- TSE statement, if applicable
- Any other pertinent animal or plant sourced information
- Residual solvents list or residual solvents statement letter
- Summary of stability study
- Summary of shipping study

- 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 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 must 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.

#### 4.2.14. **Verification of Purchased Product**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 7.4.3 Verification of purchased product | Section 7.4.3 Verification of purchased product |
| Materials that are not sampled shall have a process in place to ensure their quality. | There should be justification for not sampling an incoming material to provide a basis for quality approval. |

##### 4.2.14.1. ***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.

##### 4.2.14.2. ***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 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 to specifications and CoA 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 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)
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 labeling (CoA and package label) to ensure that the correct purchased product was provided and to confirm that the material meets the agreed quality specifications.

#### 4.2.14.3. *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 hazardous nature of material, such as the safety data sheet (SDS), is documented.

Incoming sampling and testing of raw materials identified in section 4.2.13.3 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 as falling within 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.

Preservation of Product

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 7.5.5 Preservation of product | Section 7.5.5 Preservation of product |
| Storage conditions are to be maintained. | The excipient manufacturer is to define and justify the handling and storage conditions of materials to maintain the validity of their shelf life or retest interval. |

#### 4.2.14.4. *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.

#### 4.2.14.5. *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 labeled 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.

#### 4.2.14.6. *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.

### 4.2.15. **Excipient Packaging Systems**

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 7.5.5 Preservation of Product | Section 7.5.5.2 Excipient packaging systems |
| There should be justification for the selection of the excipient packaging system. | The use of excipient packaging systems is to be justified. |

#### 4.2.15.1. *Understanding the Requirement for Risk Assessment for Excipient Packaging Systems*

The excipient container/closure system may be important to maintaining the excipient in conformance to their monograph or specification through their 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.

#### 4.2.15.2. *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 suitable. 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?

#### 4.2.15.3. *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.

### 4.2.16. Control of Monitoring and Measuring Equipment

| **EXCiPACT™ GMP and GDP Standard** | **NSF/IPEC/ANSI 363 GMP Standard** |
|---|---|
| Section 7.6 Control of Monitoring and Measuring Equipment | Section 7.6 Control of Monitoring and Measuring Equipment |
| No requirement to justify a lack of procedures for calibration and maintenance (beyond ISO 9001) | There should be justification for any measuring or test device without a calibration or maintenance procedure. |

#### 4.2.16.1. *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.

#### 4.2.16.2. *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:

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?

#### 4.2.16.3. *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.

### 4.2.17. Reworking

| EXCiPACT™ GMP and GDP Standard | NSF/IPEC/ANSI 363 GMP Standard |
|---|---|
| Section 8.3 f | Section 8.3.4 Reworking |
| A risk assessment is required that considers:<br>1. Additional testing to assure rework process was followed,<br>2. Additional acceptance criteria to show reworked excipient is suitable,<br>3. The impact to stability of the excipient,<br>4. Potential impact to composition of the excipient,<br>5. Potential to impact excipient performance | A risk assessment is required that considers:<br>1. Additional testing to assure rework process was followed,<br>2. Additional acceptance criteria to show reworked excipient is suitable,<br>3. The impact to stability of the excipient,<br>4. Potential impact to composition of the excipient,<br>5. Potential to impact excipient performance, and<br>The expectation to notify customers. |

4.2.17.1. ***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.

4.2.17.2. ***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 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?
   - 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 batches 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 for the customer?
14. Should we consider validating the rework for future possible reprocessing?

#### 4.2.17.3. ***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 was acceptable should be considered.

## 5. REFERENCES


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