IPEC EUROPE 'HOW-TO' DOCUMENT

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 (OJ 2015/C 95/02)

FOREWORD

This 'how-to' guide was developed by representatives of member companies of the International Pharmaceutical Excipients Council Europe – IPEC Europe.

Initially created in 1992, IPEC Europe is a not-for-profit association that brings together producers, distributors and **Users** of pharmaceutical excipients. IPEC Europe offers a unique forum to its members to exchange good practices and to develop harmonised standards for pharmaceutical excipients.

The company representatives who contributed to this 'how-to' guide, 2016 version, are:

Kaat Bracquiné, Capsugel
Frederik De Vos, Janssen Pharmaceutica
Laurence Galichet, Tereos
Geertrui Haest, Cargill
Frithjof Holtz, Merck
Armand Janssen, DMV International
Karl Kuma, AstraZeneca
Frank Milek, Aug. Hedinger
Iain Moore, Croda
Dan Pearce, Catalent Pharma Solutions
Andreas Pfrengle, Grace
Patricia Rafidison, Dow Corning
Angelica Rambaldi, Cargill
Beverley Stout, GSK
Allan Whiston, QA Resolutions
Michele Zandi, Cargill

This document offers a way to apply the EU 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 (OJ 2015/C 95/02) and represents IPEC Europe views and interpretation only.

IPEC Europe would like to stress that the content of its guide should neither be interpreted as regulatory requirements nor be considered as being endorsed by any legal authorities. This is a voluntary guide to help manufacturing authorisation holders and also producers and distributors of excipients. Alternative approaches to those described in this guide may be implemented.

Definitions of the terms in bold can be found in the IPEC Federation General Glossary of Terms and Acronyms.

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ACRONYMS

Acronyms used in the document:

CAPA: Corrective And Preventive Actions
EIP: Excipient Information Package
GDP: Good Distribution Practices
GMP: Good Manufacturing Practices
MAH: Manufacturing Authorisation Holders
PRDS: Harmonised IPEC-PQG Excipient Manufacturer Product Regulatory Data Sheet
QRM: Quality Risk Management
QIP: Quality Improvement Plan
TUPP: Technically Unavoidable Particle Profile

1. Introduction

The Falsified Medicines Directive (2011/62/EU) introduced, in Article 46 (f), a requirement that Manufacturing Authorisation Holders (MAHs) verify that the excipients they use are made according to appropriate Good Manufacturing Practices (GMP) standards. The Directive committed the European Commission to publish guidelines on the formalised risk assessment for ascertaining the appropriate GMP for excipients of medicinal products for human use (Article 47) and these were published on 19 March 2015 (OJ 2015/C 95/02). The goal of the Guidelines is to assure patient safety through the evaluation of risks and application of suitable GMPs to the manufacture and supply of each excipient. Manufacturing Authorisation Holders needed to be fully compliant with the new Guidelines by 21 March 2016.

The Guidelines require each excipient used to be assessed for the risks the excipient poses to the quality and purity of the medicinal product, and from these risks to determine the appropriate GMPs which are needed for mitigation. These GMP requirements should then be compared to those applied by each supplier of that excipient. The status of the GMP applied by the supplier should be determined and hence their overall risk profile confirmed. Steps should then be taken to remedy any shortfalls. A periodic review of the risk assessment is required to ensure it remains current to circumstances.

The figure below outlines the steps required in the EU Guidelines (OJ 2015/C 95/02) on the Formalised Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products for Human Use.

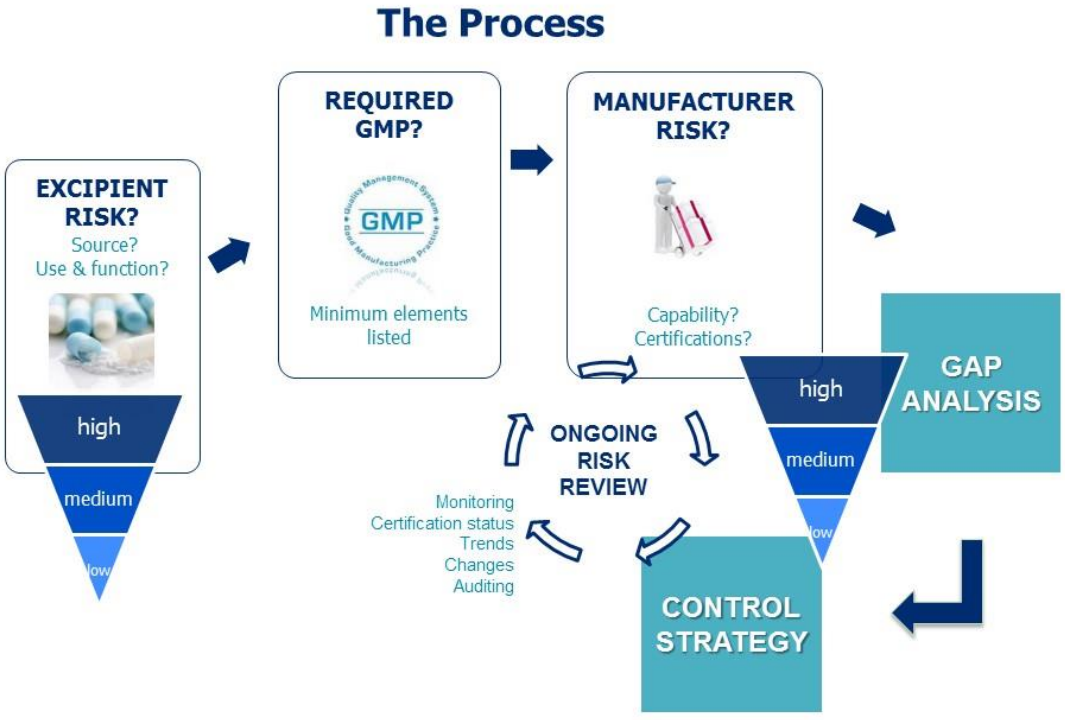


Figure 1: Risk Assessment Process
NB: a detailed process flow can be found in Annex I.

However, implementation of the Guidelines poses a number of challenges. For example, it should be recognised that quality systems applied during the manufacture of pharmaceutical excipients are diverse and generally based on the material's intended use which may not be primarily as a pharmaceutical excipient. Adjusting current quality systems to the pharmaceutical quality systems outlined in the Guidelines may be problematic for the supplier, particularly as the guidance does not provide any definitions for those quality systems or describe the expectations of regulators. A further problem is that an excipient can be used in many different dosage forms and by many Manufacturing Authorisation Holders which may result in different requirements for a single excipient from one supplier.

Therefore, IPEC Europe members, including representatives from both **Suppliers** and **Users** of excipients have prepared this 'How to' document to help Manufacturing Authorisation Holders comply with the new Guidelines, and to illustrate how excipient suppliers can facilitate the risk assessments and other steps needed for compliance. Use of this IPEC guide should support quick and efficient implementation and avoid duplication of work in the excipient industry.

2. Preamble

The unique nature of the 'excipient' industry, with its diverse technologies, industrial sources and origins of excipients, demands a risk based approach to the assurance of quality and purity. However, it should be remembered that the risk assessment in the Guidelines is to be applied to both existing as well as new uses of excipients. IPEC Europe believes that most of these risk processes and procedures already exist in excipient user organisations, and are already applied to excipients. However, the tools and insights provided in this guide will help users of excipients to proactively address this new GMP compliance assessment.

Bearing in mind the EU Guidelines (OJ 2015/C 95/02) have not introduced new or higher requirements for either **Users** or **Suppliers** of excipients with Quality Management Systems compliant with e.g. IPEC-PQG GMP Guide 2006, EXCiPACT or NSF/IPEC/ANSI-363 2014 standards, the decision to cease supply of excipient or withdraw an existing drug product from the market would be an extraordinary one.

This guide proposes risk assessment tools and ranking systems based on those detailed in ICH Q9. In addition, various excipients guidelines published by IPEC on GMP, Quality Agreements, Excipient Information Packages, etc. are referenced as these will aid the risk evaluation.

Fundamentally a successful risk assessment process requires input from excipient suppliers, and hence this guide illustrates how excipients suppliers along the supply chain can contribute efficiently to this risk analysis.

3. The Risk Assessment Process

As a prerequisite, the **User** should have in place a procedure for **risk management**. This will enable the **User** to address the requirements of Chapter 2 of the EU Guidelines (OJ 2015/C 95/02). This procedure should define **risk assessment**, **risk control** and **risk review** to ensure that the **User** is always following the most up-to-date and appropriate **risk assessment** methodology.

Before embarking on modifying their **risk assessment** programme, the **User** should conduct a gap analysis between their current **Supplier** qualification system and the requirements of the EU Guidelines. Adopting this approach will ensure that the **User** approaches this exercise in the most efficient manner and avoid duplication of effort.

Risk assessments are best conducted with a team of personnel with different experiences and competencies.

3.1 The Team: responsibilities, qualifications, training

The team should be led by a person with knowledge of and training in **risk management** tools and techniques and who has the competence, authority and respect to facilitate the process. This person will ensure that the ongoing **quality risk management (QRM)** system operates whilst coordinating the process across various functions, supporting the team and implementing effective communication throughout the organisation.

The team is usually formed from interdisciplinary members from areas appropriate to the risk being considered e.g.

Core Team:

- Subject matter experts in QRM processes
- Quality
- Supplier auditors
- Regulatory
- Technical/Operations
- Procurement

Extended Team:

- Development
- Engineering/Statistics
- Production
- Legal
- Medical/Clinical

3.2 The Plan

Once the team is assembled and briefed on the task, the first action is to define the question(s) which should be answered (e.g. a problem and/or risk question).

The four fundamental questions to be asked are:

- What might go wrong? (**Risk identification**)
- What is the likelihood it will go wrong? (Probability)
- What are the consequences of it going wrong? (Severity)
- What is the detectability?

Timelines and deliverables as well as the appropriate level of decision making should be established.

3.2.1 Data and Information Gathering

Gathering the necessary information and data is critical to an efficient **risk assessment**.

Background information and data need to be collected on the potential **hazard**, **harm** or impact on the final user (the patient), on the EU Guidelines (OJ 2015/C 95/02)' listed risk areas of consideration linked to the excipient source (Chapter 2; 2.3-2.4) and finally, on the excipient manufacturer.
Data gathering may include any pertinent assumptions but care should be taken to ensure that these do not lead the team to make unsupported decisions and thus to a wrong conclusion about the perceived risk.

The **User** should ensure there is a formal method of communication with the **Supplier** to obtain the details needed for the risk assessment.

Sources of information that can be used in risk identification can be data/information which are:

- Quantitative (i.e. numbers, figures, measurements, variables, etc.)
- Qualitative (i.e. attributes, subjective opinion, historical, experiences etc.)

3.2.1.1 Internal data gathering

The **User** should review internal documentation e.g. excipient and **Supplier** quality records to the risk assessment dossier, and from already implemented **Supplier** management records, where present.

3.2.1.2 External data gathering

It should be noted that **Suppliers** should have a comprehensive package of information specifically designed to support this process. They should assist in providing information in an easy to use format, e.g. certifications, Excipient Information Package (EIP), supply chain information/distributors. An overview of the available tools and documentation packages which can be gathered from the excipient manufacturer and supplier for the various sources (animal, mineral, vegetable, synthetic) and the areas of considerations listed in the EU Guidelines (OJ 2015/C 95/02 - § 2.3) can be found in Annex II.

As defined within the IPEC Excipient Composition Guide (2009), 'Mixed' and 'Co-processed' excipients are captured within the scope of '**composite excipients'**. By their nature they generally contain disparate components (some of which are considered excipients in their own right) where significant chemical change has not occurred. As expected for specific applications, the benefits offered by a composite is greater than the sum of its individual component parts. However, note that a composite excipient still reflects and retains the risks associated with the individual components, primarily due to the method of manufacture, e.g. mixing. Therefore, from a data gathering perspective, the **User** should not limit their scope to that of the final composite but should also include where possible, data on the individual components. For the **User**, this approach assures clarity of the risk contribution from each component within the composite and therefore further understanding regarding the appropriate GMP requirements, and the kinds of risk mitigation and control strategies that are to be applied as a result of the assessment process.

3.2.2 Risk Assessment Tools

Sections 2.1 and 2.2 of the EU Guidelines identify Eudralex Volume 4 and ICH Q9 Quality Risk Assessment as appropriate sources for **risk assessment** tools. If the **User** chooses not to use those listed within these references, which ever tool selected should support the principles of the reference as a minimum. There are many different tools available to conduct a **risk assessment** which support science-based decisions (refer to ICH Q9 Quality Risk Assessment). There is no single tool that is appropriate for all cases – see Annex III for further guidance on the suitability of selected tools.

3.2.3 Risk Types / Categories

- Risks may be identified both internally (**User**) and externally (**Supplier**); Dependent on the risk types / category identified one may wish to consider the type of tool used – see Annex II.
- System Risk (facility & people); e.g. interfaces, operators risk, environment, components.
- System Risk (organisation); e.g. Quality systems, controls, measurements, documentation, regulatory compliance.
- Process Risk; e.g. process operations and quality parameters.
- Product Risk (safety and efficacy); e.g. quality attributes: measured data according to specifications.

Note: The information gathered may not cover all details required, therefore the risk assessment team would need to apply some expert and professional judgement to determine what information is relevant to successfully complete the task.

Priorities should be established and resources allocated according to the potential for protection of patients.

3.3 Conducting risk assessment

The **User**'s formalised **risk assessment** should clearly identify and manage risks originating from and introduced by the following key contributing areas:

- Excipient Risks (intrinsic);
- Excipient **Supplier** Risks;
- Excipient **User** Risks.

Each of these areas should be assessed within whichever risk tool is chosen, with the aim of developing an overall risk picture. It is recommended that the **risk assessment** should consider and where applicable, include the following aspects:

- Risk assessment preparation:
  - ✓ Consideration should be given by the **User** regarding assessing their portfolio of excipients for risk assessment; Annex IV offers some guidance and outlines the benefits of Excipient Categorisation.
  - ✓ Information gathering relevant to the risk assessment discussion: **Supplier's** quality and safety, performance, history of supply, audits reports, certifications, etc.

- Risk identification and evaluation:
  - ✓ Identify and evaluate the potential risk factors that will impact the quality of the excipient used in the medicinal product (see Annex III).
  - ✓ Ensure the risk factors are clearly characterised in terms of understanding of their severity, probability and detectability.
  - ✓ Summarise the important risk factors identified and the likely effects of these on outcomes and/or excipient and product quality/performance.
  - ✓ Risk scoring may use different scales (see Annex VI), however it is important to ensure that scoring allows for differentiation and does not group risk outcomes so closely that it becomes difficult to appreciate the impact of changes within the risk assessment
  - ✓ Where the **User** is using a numerical scoring system it is recommended that they should develop a robust and consistent scoring range aligned to different levels of risk (e.g. Low/Medium/High), and subsequently to different levels of GMP. Otherwise for non-numerical systems the **User** should develop a set of criteria which once met would align the risk to levels of GMP.
  - ✓ The identified risks should be correlated with the GMP principles that mitigate or control the risks.

- Risk profile determination:
  - ✓ The determined minimum level of GMP should be used to perform the gap analysis to determine if the minimum quality standards determined for the excipient are sufficient versus what is delivered by the **Supplier** and required by the **User**'s formulation and use.
  - ✓ The **Suppliers** risk profile determined as a result of the gap analysis should provide an initial risk rating. Again where the **User** is using a numerical scoring risk tool system it is recommended that they should develop a robust and consistent scoring ranges aligned to different levels of risk (e.g. Low/Medium/High). Otherwise for non-numerical risk tool systems the User should develop a set of criteria which once met would determine a distinguishable level of risk.

- Risk mitigation or reduction:
  - ✓ A process for determining if the risk assessment outcome can be accepted, therefore no further action is required; reduced with the aid of a control strategy; or requires avoidance, in which case termination of the supply chain is the only action
  - ✓ Risk reduction strategy to reduce or control the potential failures with clearly defined actions for the **User** and/or **Supplier**.
  - ✓ Residual risk should be clearly defined based on the agreed mitigations.

- Risk review and monitoring:
  - ✓ New risk factors identified should be considered and included as part of the ongoing periodic risk review; a short summary used to highlight and provide context should be included.
  - ✓ A process for revisiting and refreshing the risk rating.
  - ✓ A process for monitoring the effectiveness of the risk control activities.

In general, care should be taken:

- During the process to identify the type of risk and appropriate tool to be used;
- Using assumption that may lead to incorrect conclusions;
- To conduct the assessment to the appropriate level to identify the true risks;
- To ensure common language and definitions associated with risk management;
- To consider how residual risk will be managed;
- To ensure that assessments are science-based, robust and defensible.

3.4 Output

A risk rating is then assigned to the trinomial 'excipient + excipient manufacturer + usage of the excipient' based on the outcome of the risk evaluation e.g.

- High/Medium/Low;
- Minimal/Moderate /Severe;
- Ascending numerical value;
- Critical/ Non Critical.

The risk rating should not be considered as an evaluation of the performance of the **Supplier** but as an attribution of the level of risk of the trinomial.

The output from the formalised risk assessment should be fully documented and contain:

- Residual risk;
- Remediation/Mitigation Plan – some of these actions might be internal and/or external, and need to be agreed by the interested parties according to local procedures;
- Communication (post-assessment) to the **Supplier** – already established communication processes should be used to communicate decisions and outcomes determined as a result of the risk assessment process.

The overall risk assessment and its constituent part should not be considered as a 'one-off' exercise and should be considered as a live document subject to review as and when changes are made internally and externally (e.g. significant change).

Supplier Risk Category	Material & Usage Risk Level			
	Low	**Medium**	**High**	
High	**Medium**	**High**	**High**	
Medium	**Low**	**Medium**	**High**	
Low	**Low**	**Low**	**Medium**	

Figure 2: Determination of risk level

4. Risk mitigation activity including communication with the Suppliers

A formal documented **risk mitigation** plan/control strategy should be created to address the gaps identified from the risk assessment in co-operation with the **Supplier**.

This may be achieved by means of:

- Quality Improvement Plan (QIP);
- Training;
- Audit / Corrective And Preventive Actions (CAPA);
- Modification to the **User**/**Supplier** agreement (e.g. Quality Agreement, Commercial agreement, etc.);
- Define appropriate audit frequency;
- Define appropriate inspection and testing regime;
- Quality Review Meetings at **User** site;
- Enhanced controls at manufacturer /**User** site;
- Assigning **User** personnel at **Supplier** Plant.

The control strategy should be commensurate with the risk rating identified e.g. where the risk is categorised as low/minimal, only limited controls are considered necessary (see Figure 3).

If the **Supplier** is unwilling or unable to implement mitigation of the risk, then the **User** needs to consider if risk mitigation can be managed internally. In the worst case scenario, the **User** may have to consider termination of supply. If termination is not a possibility, then consideration should be made internally on how to manage any ongoing risk.

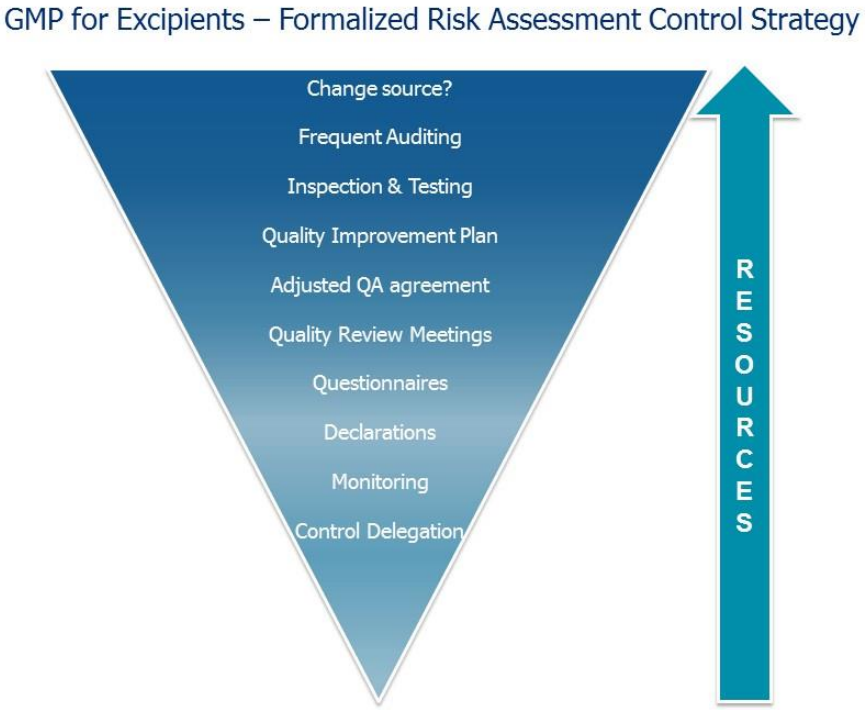


Figure 3: GMP for excipients – Formalised Risk Assessment Control Strategy

Based on the outcome of the risk review, the established control strategy should be reviewed and revised as necessary.

5. Residual risks resolution (e.g. Excipient risk classification)

It should be remembered that the EU Guidelines (OJ 2015/C 95/02) do not introduce any new GMP or GDP requirements for excipient **Suppliers** and **Distributors** who are already compliant with appropriate standards, e.g. the IPEC-PQG GMP Guide, EXCiPACT GMP and GDP standards or the NSF/IPEC/ANSI-363 2014 US national standard. Any risk assessment result that suggests a higher level GMP (e.g. ICH Q7) than the current expectations should be re-examined to confirm the outcome. This re-examination should include a challenge on the validity of any assumptions made during the initial assessment. If the re-examination confirms the initial decision, then the **User** should communicate with the **Supplier** on risk mitigation and agree upon any necessary actions.

Contradictory requirements for an excipient could arise for example when the **User** uses the same excipient in multiple drug products. In this instance the application of the EU Guidelines (OJ 2015/C 95/02) could result in the same excipient being classified differently (for example Medium in one application and Low in another). Therefore, it is important for the **User** to identify all excipients in their portfolio and where possible categorise, for example according to function and routes of administration.

Applying this approach should ensure consistency within the assessment process. In addition, this methodology also enables the **User** to challenge any differences internally in their risk assessment outcomes. It is recommended that this should be considered prior to engaging with the **Supplier** to discuss external control strategies or to recommend implementation increased levels of GMP.

Another situation could occur when a **Supplier** provides the same excipient to multiple customers and when the **Users** then respond with different risk mitigations (which would come from the different risk classifications).

The assumption hereinafter is that the communication from the **User** to the **Supplier** is not simply just the risk classification (e.g. High, Medium or Low) as the **Supplier** would have no or limited knowledge on how the **User** determined this outcome. What should be communicated are the appropriate standards of GMP or GDP required and the other risk mitigations that are needed as a result of the risk assessment.

5.1 Multiple results for an excipient – Users conundrum

Where the risk assessment process generates a different risk classification for an excipient then the **User** will need to evaluate some options before communicating to the **Supplier** what the overall result would be. In coming to a conclusion the answers to the following questions would be helpful:

- Are the mitigations required entirely 'in house' (i.e. applied by the **User**) and therefore one grade of the excipient can be used in the applications without requiring the excipient **Supplier** to provide different grades?
- Is it practical to segregate the deliveries of one excipient into different internal grades so that different mitigations can be applied and then these segregated stocks be used in different applications?

Although applying the highest standard to the excipient in question is the most robust and 'fail safe' from a quality system standpoint, the **Supplier** may not be able to accommodate the demands for one reason or another. Therefore, if the mitigations can be applied 'in house' then a single grade of excipient could be accepted and utilised in multiple applications.

Where the GMP required in the manufacture of the excipient is different for each application then the starting point would be to communicate the highest level to the **Supplier**. Where variation exists, communication between the **User** and **Supplier** is required to determine an agreed solution.

If the **Supplier** is unable or refuses to comply with the changes now required, or can only provide the excipient as suitable for one application then the hierarchy of mitigations in the guideline should be followed:

- Acceptance with additional mitigations on receipt at the **User**;
- Acceptance with targeted and/or increased frequency of targeted audits of the **Supplier**;
- Rejection of the **Supplier**'s excipient for that drug product.

The first two options allow for the continued use of the excipient, albeit with the application of additional controls. The latter presupposes that there is another **Supplier** of the excipient who is complying with the identified GMPs and risk mitigations. If this is not the case, then **User** should perform another risk assessment to decide if they can justify the continued use of the excipient from that **Supplier** for any

specific application (with or without additional risk mitigations at their end) or whether they have to withdraw the drug product from the market.

5.2 Multiple results for an excipient – Suppliers conundrum

Where an excipient **Supplier** has many customers for their excipient and these customers request multiple requirements for the same material then the excipient **Supplier** will be left with a similar conundrum. In deciding on a solution the answers to the following questions will be helpful:

- How much of the pharmaceutical excipient do I make and sell to pharmaceutical **Users**?
- Do I make it exclusively for one customer?
- What is the proportion sold to the pharmaceutical industry in relation to the total production?
- Is it technically feasible to make multiple grades on the same equipment but with different GMP standards?
- Could the highest standard be applied to all manufacture of the excipient?

Depending on the marketing and commercial approach of the **Supplier** in relation to the main use of the material then options to increase the GMPs, prepare special grades or undertake additional testing may be limited. In such cases **Suppliers** will have to indicate what they do and that they are not able to accommodate differing requirements.

Where segregation of production volumes and quality systems is possible then the **Supplier** may be able to provide different grades of the excipient under different conditions.

For example:

Production/Testing Controls
A batch could be made immediately after a total plant clean down (e.g. first batch after a shutdown, or a specially scheduled batch which included an exceptional and preceding total plant clean down). Additional checks may be introduced in production to provide direct evidence of homogeneity. Alternative final testing may be applied to provide additional assurance of the suitability of the specific batch for the **User**'s application.

Quality System Controls
Focused self-inspections could be made to specific equipment, processes etc. specific to the different grade, qualification of **Suppliers** used only for the different grade or improved change management and customer communication for certain material grades and equipment.

None of these options are themselves unusual or new, and **Suppliers** will already employ many of these to meet requirements, especially where the **Suppliers** intended market is not only pharmaceuticals.

Ultimately, if the **Supplier** is not able to be flexible in offering alternative grades to their customers then they will be left with two choices:

- Apply the highest standard required;
- State their degree of GMP applied and indicate this is not negotiable.

Applying a higher degree of GMP is not without its complications, not least as there could be substantial effort and cost required to meet those differences. For example in migrating from compliance with the IPEC-PQG GMP Guide to a system which encompasses full life cycle risk-based validation approach (e.g. in accordance with EU GMP Annex 15 Qualification and Validation will take many man years of effort, especially where the validation would have to be applied to computer systems and manufacturing plant). Such validation would also have to be retrospective.

5.3 Multiple results for an excipient – Suppliers and Users Iterations

Suppliers and **Users** should discuss the outcomes of the first pass assessments on each side as described above and identify if any mutually acceptable options could reduce the differences between them. It may be possible for the **Supplier** to provide some additional data for example to help the **User** justify the current arrangements. Every effort should be made to find an agreement to continue the collaboration. In the worst case scenario where no agreement can be reached then the relationship between the **Supplier** and **User** may cease.

6. Triggers for risk review

The most likely triggers for re-evaluation will be:

- Change in GMP or GDP for **User**;
- New product introductions by the **User**;
- Change in regulations for **User**;
- Significant change by the **Supplier**;
- Significant change in the excipient monograph/specification;

Also as listed in the EU Guidelines (OJ 2015/C 95/02 – § 4.1):

- Number of defects connected to batches of excipient received;
- Type/severity of such defects;
- Monitoring and trend analysis of excipient quality;
- Loss of relevant quality system and/or GMP certification by excipient manufacturer;
- Observation of trends in drug product quality attributes; this will depend on the nature and role of the excipient;
- Observed organisational, procedural or technical/process changes at the excipient manufacturer;
- Audit/re-audit of excipient manufacturer;
- Questionnaires.

For significant changes notified by the **Supplier** then the **Users** will have to revisit their risk assessment and ascertain the impact on the conclusions that were originally drawn. If these are now revised to require greater levels of assurance, then this has to be communicated to the **Supplier**. Again any changes to the risk assessment conclusions would have to be communicated to the **Supplier** and any differences resolved as indicated in Section 4.

Ideally, the **User** will communicate not only the conclusions of the risk assessment to their **Suppliers** but also some of the rationale for their conclusions. Where this is done the **Supplier** will be much better able to judge if a change is significant or not, and so identify if this is the best option and have a more clear view on when customers have to be notified about the change.

In all cases however, it is very clear that the risk assessment is a living document and has to be continually updated as new knowledge is obtained, experience gained and as changes occur external to the **User**.

Once GMP for the excipient and the risk rating of the excipient manufacturer has been defined, an ongoing risk review should be performed when following change control:

***

REFERENCES

References are listed in the order of appearance in the document:

1. EU 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 (OJ 2015/C 95/02)
2. IPEC Federation General Glossary of Terms and Acronyms
3. Falsified Medicines Directive (2011/62/EU)
4. IPEC-PQG GMP Guide 2006
5. EXCiPACT Standards
6. NSF/IPEC/ANSI-363 2014
7. ICH Q9
8. IPEC Excipient Information Package
9. IPEC Excipient Composition Guide 2009
10. Eudralex Volume 4
11. EU GMP Annex 15 Qualification and Validation
12. IPEC GDP Guide 2006
13. IPEC Technically Unavoidable Particle Profile (TUPP) Guide 2015
14. IPEC Significant Change guide 2014
15. IPEC Excipient Stability Program Guide 2010
16. ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
17. USP Chapter 1078 GMP for bulk pharmaceutical excipients
18. ISO 9001:2008 Quality Management Systems
19. ISO 9001:2015 Quality Management Systems

ANNEXES

ANNEX I**:** Process Flow of the Formalised Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products for Human Use

ANNEX II: General Documentation Packages or Compliance Declarations

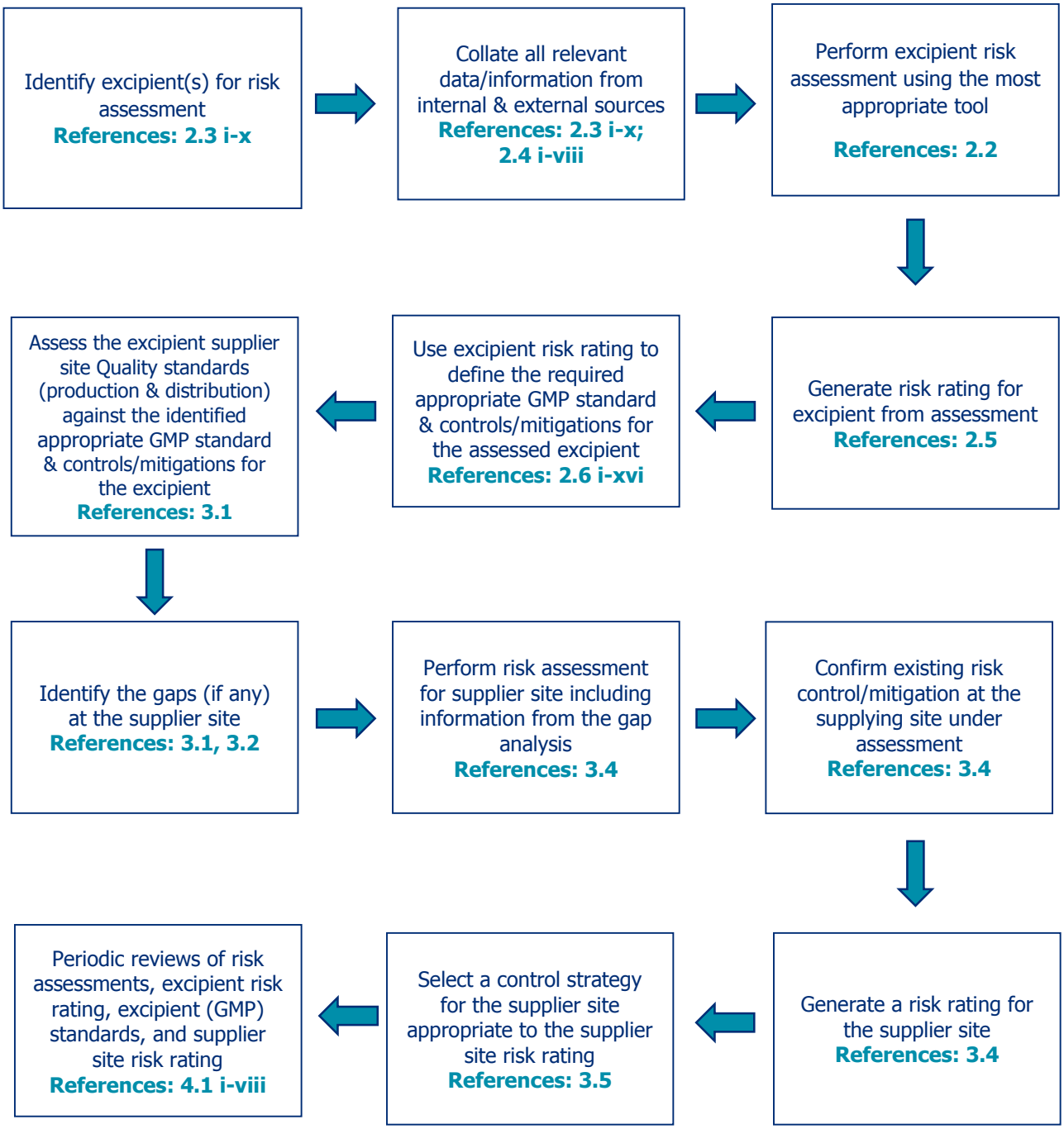
ANNEX III: Suitability of Risk Assessment tools

ANNEX IV: Excipient Categorisation (grouping of excipients, e.g. according to function/route of administration)

ANNEX V: Formalised Excipient Risk Assessment - Reference Table (GMP Principles)

ANNEX VI: Examples of risk scoring

ANNEX I - Process Flow of the Formalised Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products for Human Use



ANNEX II – General Documentation Packages or Compliance Declarations

As outlined in section 3.2.1., the starting point for assessing the risk of excipients is gathering data and information on the excipient risk linked to its source and origin.

The table below provides an overview of the available tools and documentation packages which can be gathered from the excipient manufacturer for the various sources and origins (animal, mineral, vegetable, synthetic), and the areas of considerations listed in the EU Guidelines (OJ 2015/C 95/02 - § 2.3).

Various legislative references do not directly apply to excipients, but are listed where excipients are part of the finished product assessment. Where judged relevant, legislative references applicable to food are listed in conjunction with the medicinal products references.

As such, the table serves as an illustration of applicable tools and legislative references, current at the moment of publishing this IPEC document.

Abbreviations:

- A: Animal
- M: Mineral
- V: Vegetable
- S: Synthetic
- ✓: to be considered
- N/A: not applicable
- TBD: to be defined

Excipient Source and Origin Risk Assessment - Information Gathering				
Examples of general Documentation Packages or Declarations for information				
General documentation packages which can be requested from the excipient manufacturer, based on following templates: • IPEC Excipient Information Package (EIP) • Harmonized IPEC-PQG Excipient Manufacturer Product Regulatory Data Sheet (PRDS) General Compliance declarations which can be requested from the excipient manufacturer, towards following IPEC Guides: • The Joint IPEC – PQG Good Manufacturing Practices Guide For Pharmaceutical Excipients; • The IPEC Good Distribution Practices Guide For Pharmaceutical Excipients; • The IPEC Technically Unavoidable Particle Profile (TUPP) Guide; • The IPEC Significant Change Guide for Pharmaceutical Excipients; • The IPEC Excipient Stability Program Guide; • The IPEC Excipient Composition Guide.				
Examples of specific information for the listed risk areas per source and origin				
Risk area	**A[1]**	**M**	**V**	**S**
LINKED TO ORIGIN / COMPOSITION				
Product composition:				
IPEC Excipient Composition Guide	✓	✓	✓	✓
TSE / BSE:				
OIE Terrestrial Animal Health Code – Chapter 11.5 BSE	✓	N/A	N/A	N/A
Ph Eur Gen. Monograph – Products with risk of TSE (1483)	✓	N/A	N/A	N/A
BSE/TSE Certificates of Suitability (EDQM)	✓	N/A	N/A	N/A
Potential for viral contamination:				
Ph Eur 5.1.7. Viral Safety	✓	N/A	N/A	N/A
Potential for microbiological or endotoxin/pyrogen contamination:				
Ph Eur Gen. Texts 5.1.4. Microbiological Quality of Substances For Pharmaceutical Use	✓	✓	✓	✓
ISO 29621:2011 Cosmetics: Microbiology - Guidelines for the risk assessment and identification of microbiologically low risk products	✓	✓	✓	✓
Potential for impurities from the raw materials of the excipient:				
Purity criteria for food additives used as excipients (e.g. colorants) Regulation (EC) 231/2012	✓	✓	✓	✓
Contaminants - Regulation (EC) 1881/2006 setting max limits for contaminants in foodstuffs	✓	N/A	✓	N/A
Veterinary residues (e.g. antibiotics) - Regulation (EC) 37/2010	✓	N/A	N/A	N/A
Allergens - EMA guideline on excipients in the label and leaflet of medicinal products (CPMP/463/00) + Q&A	✓	✓	✓	✓
Allergens - Regulation (EC) 1169/2011 (Food Information for Consumers)	✓	✓	✓	✓
Elemental Impurities - ICH Q3D	✓	✓	✓	✓
Elemental Impurities - USP <231> & <232>	✓	✓	✓	✓
GMO - Regulation (EC) n° 1829/2003 on genetically modified food and feed	N/A	N/A	✓	N/A
GMO - Regulation (EC) n° 1830/2003 concerning the traceability and labelling of GMO and the traceability of food and feed products from GMO	N/A	N/A	✓	N/A
Residual Solvents - ICH Q3C / Ph Eur 5.4.	✓	N/A*	✓	✓
Others to be defined, as deemed relevant	*TBD*	*TBD*	*TBD*	*TBD*

* *unless starting material is an intermediate*

[1] A: Animal; M: Mineral; V: Vegetable; S: Synthetic

Examples of specific information for the listed risk areas per source and origin				
Risk area	**A[2]**	**M**	**V**	**S**
LINKED TO MANUFACTURING PROCESS				
Potential for impurities from the manufacturing process:				
Allergens - EMA guideline on excipients in the label and leaflet of medicinal products (CPMP/463/00) + Q&A	✓	✓	✓	✓
GMO - Regulation (EC) n° 1829/2003 on genetically modified food and feed	✓	✓	✓	✓
GMO - Regulation (EC) n° 1830/2003 concerning the traceability and labelling of GMO and the traceability of food and feed products from GMO	✓	✓	✓	✓
Residual Solvents - ICH Q3C / Ph Eur 5.4. Residual Solvents	✓	✓	✓	✓
Elemental Impurities - ICH Q3D / USP <231> & <232> Elemental impurities	✓	✓	✓	✓
Particles - The IPEC Technically Unavoidable Particle Profile Guide	✓	✓	✓	✓
Potential for microbiological or endotoxin/pyrogen contamination Ph Eur Gen. Texts 5.1.4. Microbiological Quality of Substances For Pharma Use	✓	✓	✓	✓
Others to be defined, as deemed relevant	*TBD*	*TBD*	*TBD*	*TBD*
Potential for impurities from cross-contamination:				
EXCiPACT GMP/GDP Requirements – Sections 6.3 & 6.4	✓	✓	✓	✓
Sterility:	Only for excipients claimed to be sterile			
Quality System certifications currently in place:				
See annex with overview of typical quality system standards in place	✓	✓	✓	✓
LINKED TO SUPPLY CHAIN				
Stability of excipient:				
The IPEC Excipient Stability Program Guide	✓	✓	✓	✓
Environmental control and storage/transportation conditions:				
Based on excipient stability indicators and transport agreements, obtain compliance declarations towards made commitments	✓	✓	✓	✓
The Joint IPEC – PQG Good Manufacturing Practices Guide For Pharmaceutical Excipients	✓	✓	✓	✓
The IPEC Good Distribution Practices Guide For Pharmaceutical Excipients	✓	✓	✓	✓
Supply chain complexity:				
Obtain traceability to original manufacturer	✓	✓	✓	✓
The IPEC Good Distribution Practices Guide	✓	✓	✓	✓
PQG - A Guide to Supply Chain Risk Management	✓	✓	✓	✓
Packaging integrity evidence:				
Obtain information on tamper proof packaging evidence	✓	✓	✓	✓

[2] A: Animal; M: Mineral; V: Vegetable; S: Synthetic

ANNEX III – Suitability of Risk Assessment tools

The level of detail required for any assessment will vary case by case according to the risk(s). The following areas will contribute to the risk and will require careful consideration.

The most commonly used tool is FMEA but the following tabulation will help identify an appropriate tool.

The optimum risk assessment tool is indicated in the table. Other tools may be considered depending on each individual case.

A possible aid where to use methods/tools	General → Detail			
	System Risk (facility & people)	System Risk (organisation)	Process Risk	Product Risk (safety & efficacy)
Risk ranking & filtering	X	X	X	
Failure mode effect analysis		X	X	
Hazard analysis & critical control points		X	X	
Process mapping			X	
Flow charts			X	X
Statistical tools				X
Check sheets	X			X

ANNEX IV - Excipient Categorisation (grouping of excipients, e.g. according to function/route of administration)

Introduction

Users often have a large selection of excipients which have different properties and are used in different dosage forms. Performing the risk assessment for each excipient in each dosage form can be a very substantial task, therefore a categorisation approach can be used to perform a preliminary risk assessment in a bracketing approach. Any excipient combinations that are identified as high risk would then require an individual risk assessment. Where such approaches are applied the **User** should document their procedure and justify the risk assessment rationale.

Benefits of Categorisation

Where a **User** has many excipients, categorising can significantly reduce the risk assessment workload. It is possible to categorise initially by dosage form or route of administration, i.e. oral versus parenteral. Further categorisation can be introduced by segmenting by origin, i.e. animal versus synthetic. Other approaches also include categorising according to functionality of the excipient. In many cases to gain the benefit of categorising, the **User** should apply across all these key category section in combination. Categorisation in this way will assist the **User** in identifying areas of focus within the risk assessment and subsequently which areas need further examination when applying the confirmation of GMP step. Additional benefits of categorisation include ensuring a consistent understanding regarding the intrinsic risk associated with the excipient. However note that the overall benefit of categorisation is to assist in identifying which excipients need to be formally assessed as a priority to ascertain the appropriate GMP for excipients of medicinal products for human use.

Considerations when performing Categorisation

The following should be considered when categorising excipients. These factors can be used as the basis for generating some initial risk rating based on the intrinsic risks within the excipient.

Pertinent factors related and known (exclusively) to the excipient **User** are:

- The route of administration;
- The functional category of the excipient.

Within the Excipient Risk Assessment process the **User** could build further risk factors into their categorisation plan to segment their excipients into risk categories.

See below a working example of categorisation for information purpose.

Function	Presentation of Dosage Form	Description	Comment
Diluent	Tablets and Capsules	Increase dosage form volume or weight	Contributes to disintegration/dissolution (either water soluble or insoluble so providing something for the disintegrant to work on). Diluent is usually high proportion in formulation, has a large influence on flow & compaction. Very stable excipients. Can have high moisture content with impact on sterility
Stabiliser/Buffering agent		Maintain local pH in dosage form	Local pH can influence API solubility and therefore could impact dissolution of dose form. Materials are diluent like in their physical properties and could therefore impact flow/compaction. Often incorporated to help maintain API stability. Could have high moisture content with impact on sterility
Binder		Facilitate agglomeration into granules during mixing with a granulating fluid such as water	Has significant impact on disintegration/dissolution and processing (WG). Generally stable excipients and although hygroscopic they are used in low % in formulation
Disintegrant		Promote rapid disintegration into smaller units and allow drug substance to dissolve more rapidly	Has significant impact on disintegration/dissolution but not processing. Generally stable excipients and although hygroscopic they are used in low % in formulation
Lubricant		Reduce the frictional forces between particles	Levels selected specifically to have no impact on disintegration/dissolution. Significant impact on flow and compaction. Generally stable excipients and used in low % in formulation
Glidant		Promote powder flow	Has no impact on disintegration/dissolution. Significant impact on flow and compaction. Generally stable excipients and used in low % in formulation
Anticaking agent		Reduce caking or clumping that can occur when powders are stored in bulk	
Colouring Agent		Produce a distinctive appearance	Has no impact on disintegration/dissolution or processing. Generally stable excipients and used in very low % in formulation
Capsule Shell		Enable pharmaceutical powders and liquids to be formulated for dosing accuracy as well as ease of transportation	Has significant impact on disintegration/dissolution. Dimensional control important for compatibility with capsule filling equipment. Stability of capsule shell integrity impacts product stability

Function	Presentation of Dosage Form	Description	Comment
Coating Agent		Masking unpleasant tastes or odours, improving ingestion and appearance, protecting active ingredients from environment and modifying the release of the active ingredient (e.g. controlled release rates or gastrointestinal targeting).	Levels selected specifically to have no impact on disintegration/dissolution. Standard processing conditions. Coat may provide protection and therefore have an effect on product stability
Plasticizer		Added to another material - usually a polymer - to make the latter flexible, resilient and easier to handle.	E.g. solid dispersion. Should have no impact on disintegration/dissolution. Will impact process ability. Could make system more mobile so impact stability
Flavour/fragrance		Mask taste or odour of API.	Has no impact on disintegration/dissolution or processing. Generally stable excipients and used in very low % in formulation
Release modifying agent (includes enteric coatings)		Control drug release in extended-release formulations.	Critical for dissolution. For matrix tablets high quantity in formulation, physical properties impact process ability. Generally stable excipients and hygroscopic
pH Modifier (Acidifying / Alkalizing / Buffering agents)	Oral Liquids	Controlled pH of pharmaceuticals solutions to (1) maintain a pH close to that of the relevant body fluid to avoid irritation (2) improve drug stability that is pH dependant (3) control equilibrium solubility of weak acids or bases (4) maintain a consistent ionization state of molecules during chemicals analysis.	May be critical for drug solubility and therefore in-vivo exposure. No impact on processing. May be critical to maintain API stability
Wetting and/or Solubilising Agent		Dissolve insoluble molecules.	May be critical for drug solubility and therefore in-vivo exposure. Could impact processing. Excipient impurity profile could impact product stability
Antimicrobial Preservative		Used to kill or prevent growth of bacteria, yeast and mould in dosage form.	No impact on in-vivo exposure or process ability. Added to preserve and deliver product stability
Chelating and/or Complexing Agents		Remove the ions from solution to minimize or eliminate their ability to react with other elements and/or precipitate.	Driver is increased stability of product, also could impact stability during manufacture and bioavailability
Antioxidant		Used as in vitro stabilizers of pharmaceuticals preparations to mitigate oxidative processes.	Driver is increased stability of product, no impact on manufacture or bioavailability

Function	Presentation of Dosage Form	Description	Comment
Sweetening Agent		Sweeten oral dosage forms and to mask unpleasant flavours.	Has no impact on in-vivo exposure or processing. Generally stable excipients and used in low % in formulation
Suppository Base	Semisolids, Topicals and Suppositories	Used in the manufacture of suppositories (for rectal administration) and pessaries (for vaginal administration).	May impact processing
Suspending and/or Viscosity -Increasing Agent		Stabilize disperse systems (e.g. suspensions or emulsions), to reduce the rate of solute or particle transport, or to decrease the fluidity of liquid formulations.	Could impact dose delivery, process ability and stability. Water soluble polymers increased risk for sterility
Ointment Base		Serve as vehicles for topical application of medicinal substances and also as emollients and protective agents for skin.	No impact on exposure. Could impact processing. Little impact on stability. Water soluble polymers increased risk for sterility
Stiffening agent		Increase the viscosity or hardness of ointments and creams.	No impact on exposure. Could impact processing. Little impact on stability. Water soluble polymers increased risk for sterility
Emollient		To impart lubrication, spreading ease, texture and softening of the skin and to counter the potentially irritating impact of surfactants on the skin.	Could impact exposure and processing
Pharmaceutical Water	Parenterals	Used as solvent, vehicle, diluent or filler for many drug products, especially those supplied in liquid form.	No impact on exposure or processing. Could impact stability
Diluent		Liquid formulations: a solvent or vehicle. Lyophilized formulation: a material which provides a pharmaceutically elegant lyophilised cake with non-collapse structural integrity and to prevent drug loss due to blow out. In addition, to facilitate efficient drying and to provide a physically and chemically stable formulation matrix.	No impact on exposure. Could significantly impact processing. Large quantities in dosage form so could impact stability and sterility
Tonicity-adjusting Agent		Avoid crenation or haemolysis of red blood cells and to mitigate pain and discomfort if solutions are injected or introduced into the eyes or nose.	Could impact exposure
Solubilisers		Assist the dissolution of poorly soluble molecules.	May be critical for drug solubility and therefore in-vivo exposure. Could impact processing. Excipient impurity profile could impact product stability

Function	Presentation of Dosage Form	Description	Comment
Antimicrobial Preservative		Used to prevent or inhibit the growth of microorganisms which could present a risk of contamination or degradation of the medicinal product.	No impact on in-vivo exposure or process ability. Added to preserve and deliver product stability
Antioxidant		Used as in vitro stabilizers of pharmaceuticals preparations to mitigate oxidative processes.	Driver is increased stability of product, no impact on manufacture or bioavailability
pH Adjusters and Buffering agents		Controlled pH of pharmaceuticals solutions to (1) maintain a pH close to that of the relevant body fluid to avoid irritation (2) improve drug stability that is pH dependant (3) control equilibrium solubility of weak acids or bases (4) maintain a consistent ionization state of molecules during chemicals analysis.	May be critical for drug solubility and therefore in-vivo exposure. No impact on processing. May be critical to maintain API stability
Adjuvants		Component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses (mineral salts, e.g., aluminium hydroxide and aluminium or calcium phosphate gels, oil emulsions and surfactant based formulations, etc.).	Added to help and enhance the pharmacological effect of a drug or increases the ability of an antigen to stimulate the immune system"
Propellant	Aerosols	Provide force to expel contents from a container.	Critical for dose delivery

ANNEX V - Formalised Excipient Risk Assessment - Reference Table (GMP Principles)

This table represents a comparison of the appropriate GMP Principles required by the EU Guidelines (OJ 2015/C 95/02) with sections of other relevant quality standards. It is not intended to demonstrate comparability across different Standards and is up to the **User** to decide what is important for the excipient, within the dosage form and for patient safety based on the outcome of the risk assessment (e.g. high, medium or low). Although a certain quality standard may have comparable requirements with the minimum expectation of GMP Principles does not automatically mandate suitability for the highest risk excipients.

Legend:

- ✓: have to comply with
- **X** : does not exist/apply or it is not applicable to excipients.

I. GMP principles for excipients under pharmaceutical quality system

	GMP Principles	EU Vol.4 GMP Med Prod[1]	ICH Q7 GMP API[2]	ISO 9001		IPEC GMP 2006[3]	USP <1078>[4]	EXCiPACT™[5]	IPEC GDP 2006[6]	NSF/IPEC/ANSI 363 - 2014[7]
				2008[8]	2015[9]					
1	Establishment and implementation of an effective Pharmaceutical Quality system	1.3, 1.4	II.A	4.1	4.3, 4.4	4.1, 4.2.2	✓	4.1	1.1, 1.2	4.1
2	Sufficient competent and appropriately qualified personnel	2.1	III.A	6.2	7.2	6.1, 6.2.1	✓	6.2	1.5, 2.1	6.1
3	Defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities	2.1, 2.3	III.A	6.2.2	7.2, 7.3	6.2.2	✓	6.2.2	2.2	6.2.1
4	Training programmes for all staff involved in manufacturing and quality activities	2.10-2.12, 2.14	III.A	6.2.2	7.2, 7.3	6.21, 6.2.2	✓	6.2.2	2.2, 2.3, 2.4	6.2.2

[1] EudraLex – Volume 4 of "The rules governing medicinal products in the European Union" Guidelines
[2] ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
[3] IPEC-PQG Good Manufacturing Practice Guide 2006
[4] USP Chapter 1078 GMP for bulk pharmaceutical excipients
[5] EXCiPACT Standard
[6] IPEC Good Distribution Practice Guide 2006
[7] NSF/IPEC/ANSI 363-2014 GMP for pharmaceutical excipients
[8] ISO 9001:2008 Quality Management Systems
[9] ISO 9001:2015 Quality Management Systems

	GMP Principles	EU Vol.4 GMP Med Prod[1]	ICH Q7 GMP API[2]	ISO 9001 2008[8]	ISO 9001 2015[9]	IPEC GMP 2006[3]	USP <1078>[4]	EXCiPACT™[5]	IPEC GDP 2006[6]	NSF/IPEC/ANSI 363 - 2014[7]
5	Training programmes related to health, hygiene and clothing	2.15, 2.16, 3.31	III.B	**X**	**X**	6.2.2, 6.2.3	✓	6.2.2., 6.2.3.	2.6	6.2.2, 6.2.3
6	Provision and maintenance of premises and equipment appropriate to the intended operations	3, 3.1, 3.2	IV, V	6.3	7.1.3	6.3, 6.4	✓	6.3	3	6.3.1, 6.3.2, 6.3.2.2, 6.3.2.3, 6.4.5, 7.5.4, 7.6
7	Documentation system(s) covering all processes and specifications for the various manufacturing and quality operations	4	VI	4.2.2, 4.2.3	7.5.2, 7.5.3	4.2.3, 4.2.4	✓	4.2.2, 4.2.3	4	4.1, 4.2, 4.2.3, 4.2.4, 4.3
8	Systems for coding and identifying starting materials, intermediates and excipients to allow full traceability	4.8, 5.12, 5.29-30	VII	4.2.4, 7.1, 7.5.3	7.5.2, 7.5.3, 8.1, 8.5.2	4.2.4	✓	4.2.4, 7.1, 7.5.3	6.3, 6.5, 6.6	4.2.4, 7.5.3
9	Qualification program of **Suppliers**	1.4 (vi)	VII	7.4.1	8.4, 8.4.1, 8.4.2	7.4.1	✓	7.4.1	1.2	7.4.1
10	System for quality control of the excipient and a responsible person independent from production to release the batches	6.1, 6.2	II.A, II.B	8.2.4, 5.5.2	8.6, 5.3	5.5.1	✓	5.5.2	X	4.1.1, 5.5.1, 8.2.2

	GMP Principles	EU Vol.4 GMP Med Prod[1]	ICH Q7 GMP API[2]	ISO 9001 2008[8]	ISO 9001 2015[9]	IPEC GMP 2006[3]	USP <1078>[4]	EXCiPACT™[5]	IPEC GDP 2006[6]	NSF/IPEC/ANSI 363 - 2014[7]
11	Retention of records for incoming materials and excipients and retention of samples of excipients for the periods required by EudraLex Volume 4, Part II	6.7-10; 6.11, 6.14	VI.A	4.2.4	7.5.3	4.2.4	✓	4.2.4	6.1	4.2.4, 8.2.4.4
12	Systems to ensure that any activity contracted out is subject to a written contract	7 (Principle) 7.1	XVI	4.1	8.4	4.1., 7.4.2	✓	4.1, 7.4.2.	13	7.4.1
13	Maintenance of an effective system whereby complaints are reviewed and excipients may be recalled	8 (Principle), 8.2, 8.6, 8.9-16	XV	7.2.3, 8.2.1, 8.5.2	8.2.1, 9.1.2, 10.2	5.6, 8.2, 8.3, 8.4	✓	7.2.3, 8.2.1, 8.5.2	8, 9	5.6.2, 7.2.3, 7.2.3.1, 8.4
14	Change management system	1.4 xii - xiii	XIII, VI.E, VI.E, XIV.C	7.2.2, 7.2.3, 7.3.7,	8.2.1, 8.5.6	4.3, 7.2	✓	4.3, 7.2.2, 7.2.3, 7.3.7,	**X**	4.2.3, 4.3, 7.2.1, 7.2.2, 7.2.3,
	Deviation management system	1.8 vii, 1.10 iv		8.2.3, 8.3, 8.5.2, 8.5.3	9.11, 8.7, 10.2, 10.3, 6.1	8.2.3, 8.2.4.3, 8.3, 8.5	✓	8.2.3, 8.3, 8.5.2, 8.5.3	11	8.2.4.3, 8.3, 8.3.1, 8.3.2, 8.4
15	Self-inspection programme	9	D	8.2.2	9.2	8.2.2	✓	8.2.2	1.9	8.2.2
16	Environmental control and storage conditions.	5	**X**	7.5.5	8.5.4	7.5.5	✓	7.5.5	7.8, Section 12	7.5.5

II. GMP principles for excipient under food quality system

	GMP Principles	Title21 CFR Part 110 (food)[10]	ISO 9001		ISO 22000:2005[11]	Regulation (EC) No 852/2004[12]	BRC[13]
			2008[14]	2015[15]			
1	Establishment and implementation of an effective Quality Assurance system	110.80 (13) (i)	4.1	4.3,4.4	4.1 – 7.2	Art.3., 4., 5.	2.1 – 2.2
2	Sufficient competent and appropriately qualified personnel	110.10 c. d.	6.2	7.2	6.1 – 6.2.1 – 6.2.2	AI: II, 4.e.& 5.d AII: XII	
3	Defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities	**X**	6.2.2	7.2,7.3	6.2.2	5.4	1.1
4	Training programmes for all staff involved in manufacturing and quality activities	110.10 c	6.2.2	7.2, 7.3	6.2.1 - 6.2.2	AII: XII	7.1
5	Training programmes related to health, hygiene and clothing	110.10 a. b.	**X**	**X**	6.2.2.	AII: XII	7.2 – 7.4
6	Provision and maintenance of premises and equipment appropriate to the intended operations	110.20	6.3	7.1.3	6.3, 7.2.	6.3 – AII: I, II, III, V	4.6 – 4.7

[10] Code of Federation Regulation Title 21 Food & Drugs ; Chap I ; Subchap. B; Part 110 cGMP in manufacturing, packaging or holding human food
[11] ISO 22000:2005 Food safety management systems - Requirements for any organization in the food chain
[12] Regulation EC 852/2004 on hygiene of foodstuffs
[13] BRC Global Standards Self-Assessment Tool
[14] ISO 9001:2008 Quality Management Systems
[15] ISO 9001:2015 Quality Management Systems

	GMP Principles	Title21 CFR Part 110 (food)[10]	ISO 9001		ISO 22000:2005[11]	Regulation (EC) No 852/2004[12]	BRC[13]
			2008[14]	2015[15]			
7	Documentation system(s) covering all processes and specifications for the various manufacturing and quality operations	**X**	4.2.2, 4.2.3	7.5.2, 7.5.3	4.2.2, 4.2.3, 7.7	Art. 5: 2.g AI: III	3.2
8	Systems for coding and identifying starting materials, intermediates and excipients to allow full traceability	**X**	4.2.4, 7.1, 7.5.3	7.5.2, 7.5.3, 8.1, 8.5.2	4.2.3.,7.9	AI: III	3.6 – 3.9
9	Qualification program of **Suppliers**	**X**	7.4.1	8.4, 8.4.1, 8.4.2	**X**	**X**	3.5.1
10	System for quality control of the excipient and a responsible person independent from production to release the batches	**X**	5.5.2	8.6, 5.3	5.5.	Art. 4.e (QC)	
11	Retention of records for incoming materials and excipients and retention of samples of excipients for the periods required by EudraLex Volume 4, Part II	**X**	4.2.4	7.5.3	4.2.3	Art. 5: 2.g AI: III	3.3
12	Systems to ensure that any activity contracted out is subject to a written contract	**X**	4.1	8.4	4.1	**X**	3.5.3 – 3.5.4
13	Maintenance of an effective system whereby complaints are reviewed and excipients may be recalled	**X**	7.2.3, 8.2.1, 8.5.2	8.2.1, 9.1.2, 10.2	5.6.1 7.10.2	Art.6.2. (towards Authorities)	3.5.2 – 3.10 – 3.11

	GMP Principles	Title21 CFR Part 110 (food)[10]	ISO 9001		ISO 22000:2005[11]	Regulation (EC) No 852/2004[12]	BRC[13]
			2008[14]	2015[15]			
14	Change management system	**X**	7.2.2, 7.2.3, 7.3.7,	8.2.1, 8.5.6	**X**	Art. 5.2 Art.6.2. (towards Authorities	3.7 – 3.8
	Deviation management system	**X**	8.2.3, 8.3, 8.5.2, 8.5.3	9.11, 8.7, 10.2, 10.3, 6.1	7.6.4.,7.6.5.,7.10, 7.10.2, 5.7, 7.2	Art.5. c., e. (CCP)	
15	Self-inspection programme	**X**	8.2.2	9.2	8.4.1	**X**	3.4
16	Environmental control and storage conditions.	110.93	7.5.5	8.5.4	7.2	Art. 4. c.	4.4; 4.5; 4.8;4.12;4.14

ANNEX VI -Examples of risk scoring

Some examples of scales used are:

- Linear: 1, 2, 3, 4
- Exponential: 1, 2, 4, 8
- Logarithmic: 1, 10, 100, 1000
- Self-made: 1, 3, 7, 10