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White Paper

EU Excipient Risk Assessment Guidelines – Practical Implementation Experience

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The Challenges of Determining Excipient Quality

In the past years, the critical role of excipients in drug production has come into focus. This meant shaking off the long prevailing perception of excipients being passive additions to an active pharmaceutical ingredient (API). Now regulatory authorities are calling for more stringent quality management in excipient production and use, leading to new requirements for both excipient suppliers and drug manufacturers.

Regulating excipient quality, however, is no small task. More than one thousand different excipients are available, and only a small number of them are manufactured solely for pharmaceutical use. This heterogeneity and the resulting complexity have led to the EU Commission's approach to excipient quality. It is clearly risk-based; its core consists of general guidelines that offer a framework for excipient risk assessment. However, the guidelines provide neither detailed instructions for implementation nor a clear definition of appropriate Good Manufacturing Practices (GMP) for excipients. This is the responsibility of the manufacturing authorization holder – and evidently no small task either.

Readers of this white paper will find support in mastering the challenge of formalized excipient risk assessment. They will gain an overview of the relevant laws and guidelines, as well as voluntary standards developed by the industry to foster implementation. Most importantly, a case study on excipient risk assessment will provide valuable insights into risk assessment and preparing for inspections.

The EU Excipient Risk Assessment Guidelines

In 2011, the EU's Falsified Medicines Directive established that pharmaceutical manufacturers must conduct a formalized risk assessment for each excipient they use and determine its appropriate GMP (1). It also stated that the European Commission would develop guidelines offering direction on the risk management process and the appropriate level of GMP for excipients.

Based on this directive, the EU Excipient Risk Assessment Guidelines were drafted in 2013, published in March 2015 after intense discussion, and came into force one year later on March 21, 2016 (2). They were also referred to as binding guidelines in the revised EU rules governing GMP for medicinal products (3), which further underlines their importance.

In terms of content, the EU Excipient Risk Assessment Guidelines address both the intended use and source of excipients. The main topics are described in chapter 2 to 4, which cover:

- Determining appropriate GMP based on excipient type and use (chapter 2)
- Determining the excipient manufacturer's risk profile (chapter 3)
- Confirming the implementation of appropriate GMP (chapter 4).

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Relevance beyond the EU

The EU Excipient Risk Assessment Guidelines represent the first regulation dedicated to excipient GMP in the EU. They apply not only to medicinal products manufactured in Europe but also to those produced elsewhere if they are intended for the European market. The important role of the EU guidelines is also acknowledged beyond the EU, as for example by the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which adopted the guidelines on a voluntary basis in July 2018 (4).

Around the globe, other regions have also developed specific approaches to enhancing the safety and quality of pharmaceutical products, extending the requirements beyond APIs. The U.S. Food and Drug Administration (FDA) states that the current term GMP includes "establishing the safety of raw materials, materials used in the manufacture of drugs and finished products" (5).

Helpful Industry Standards

It is important to understand that the EU Excipient Risk Assessment Guidelines only provide a general framework. Developing a compliant risk assessment process and defining appropriate GMP for all excipients is clearly the responsibility of medicinal product manufacturers. However, they do not have to develop their own criteria. In fact, they can follow several well-established, voluntary industry standards. Based on the Manufacturing Authorization Holders classification of excipients into low, medium or high-risk categories as recommended by the EU guidelines, these voluntary industry standards help to define the appropriate GMP. These standards are not binding regulations, but are based on best industry practices, offering guidance and facilitating implementation.

The **IPEC PQG GMP Guide 2017** (6) is an important example. IPEC (International Pharmaceutical Excipient Council), the international organization representing excipient producers and users, provides excipient manufacturers with a voluntary standard on GMP for pharmaceutical excipients.

Combined with the **How-To document** (7) published by IPEC Europe in 2016, this gives pharmaceutical manufacturers a good initial guidance. The step-by-step document helps them to perform risk assessments to define appropriate GMP for excipients. It also offers a clearly arranged process overview of how to comply with the requirements outlined in the EU Excipient Risk Assessment Guidelines (see Table 1).

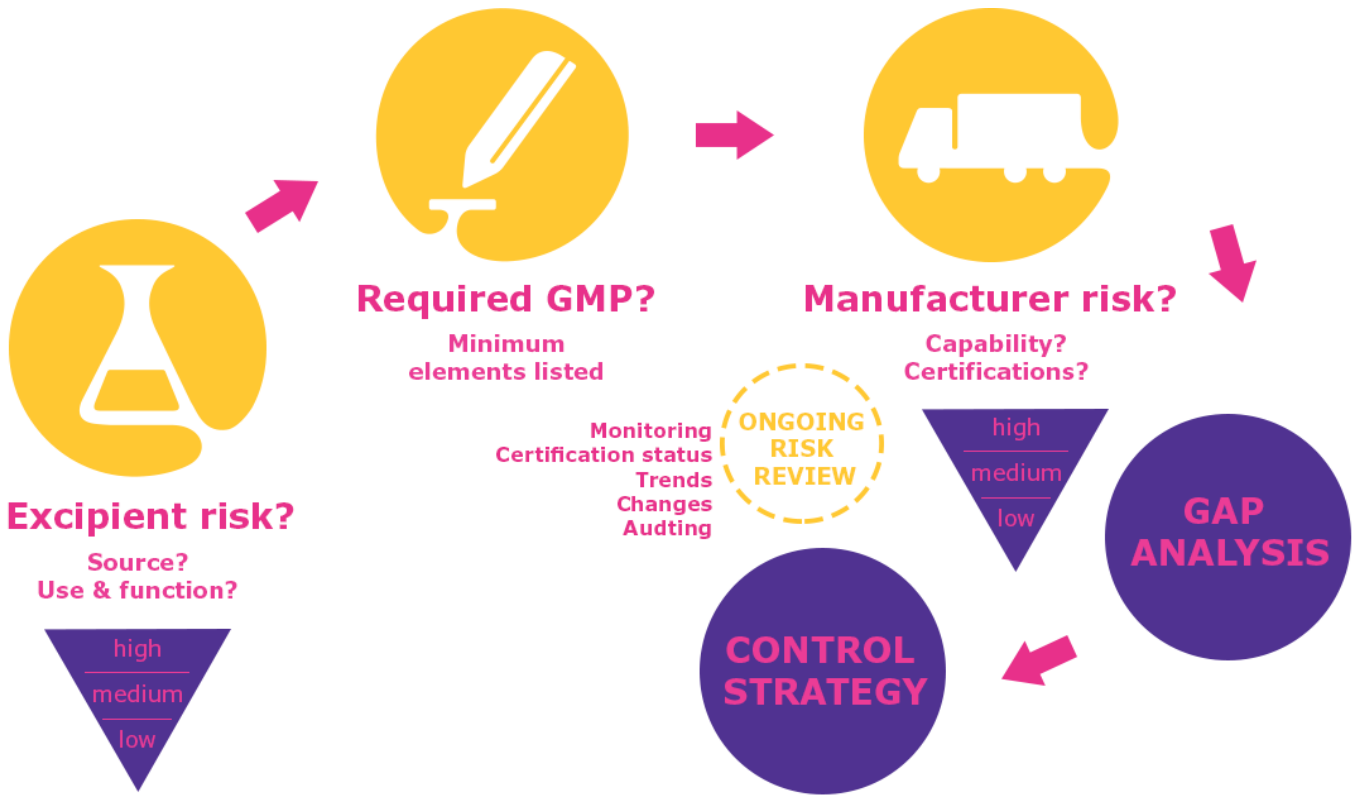


Table 1:
Risk assessment process to ensure appropriate GMP implementation, according to IPEC Europe's "How-To" document

In summary, the following list of voluntary standards should be appropriate in most cases:

- **IPEC-PQG GMP Guide 2017** (see above)
- **USP General Chapter 1078:** The standard issued by the United States Pharmacopeia (USP) includes in-depth descriptions of GMP for bulk pharmaceutical excipients (8).
- **EXCiPACT™:** The standard on GMP and GDP for excipients and the auditing scheme assists pharmaceutical companies ensure their regulatory compliance and strengthen safety and quality throughout the excipient supply chain (9).
- **NSF/IPEC/ANSI-363-2016:** This document is the first American national standard for pharmaceutical excipients, published by the global public health organization NSF International. It is based on the requirements of the EXCiPACT™ standard (10).

Learning from real Experience

Still, implementation remains a huge challenge for manufacturers and users of excipients. Given the abundance of excipients, formalized risk assessment might even seem infeasible. Also, the sheer number of supporting documents can be overwhelming, regardless of how helpful they are.

The following real-life case study was conducted to simplify the task and to enable effective learning through practical experience. The lessons learned by and with manufacturers will help to facilitate the efficient implementation of a risk assessment process that is both compliant and sustainable.

The starting point was to answer the key question "what do medicinal product manufacturers need to consider?" Two lists of criteria capture risks related to excipients based on the EU Guideline: on the one hand from a manufacturing or supply perspective and, on the other hand, from an application point of view.

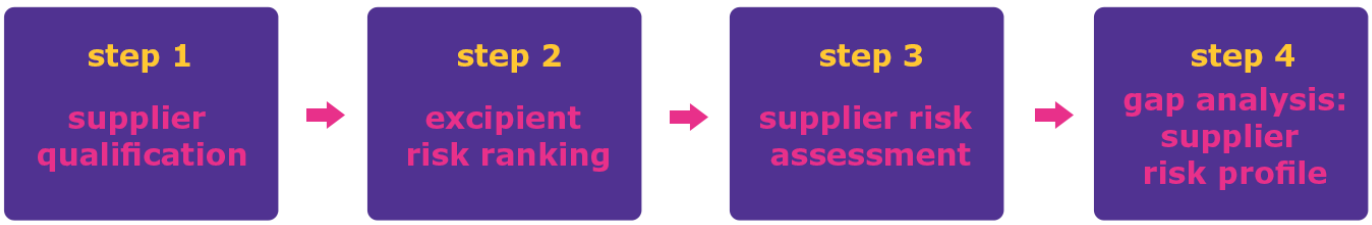
Risks from the excipient manufacturer or supplier perspective (SOURCE criteria):

- Quality Management System applied by the excipient supplier
- Contamination potential
- Impurities in general (regarding the excipient and the manufacturing process)
- TSE, viral safety
- Microbiological/endotoxin contamination
- Dedicated equipment/facilities (versus multi-purpose facilities involving higher risk)
- Environmental control and storage conditions
- Supply chain complexity

Risks regarding the application of excipients (USE criteria):

- Dosage form
- Route of administration (e.g. tablets, parenteral use involving higher risk)
- Functionality (e.g. colorant, filler, part of release system involving higher risk)
- Potential impact on critical quality attributes of the drug product
- Quantity, daily intake

By applying these criteria, five distinct **quality areas** were defined, and need to be considered: the Quality Management System (QMS), manufacturing of excipients, supply chain, route of administration and function of the excipient. Based on these initial considerations, the case study was conducted in four steps. Prior to the actual assessment process, the medicinal products produced under the responsibility of the pharmaceutical manufacturer were examined in order to identify all excipients to be assessed, as well as their respective use. This yielded 24 excipients to be investigated and assessed step-by-step:



Step 1 comprised the supplier qualification. Here, the EU guidelines were translated into a checklist, i.e., a supplier questionnaire. The responses were harmonized and collated in an Excel spreadsheet.

In step 2, an excipient risk ranking template covering all elements of the EU guidelines was developed. It provides a three-part risk score (low, medium and high) for each excipient, which reflects both the individual criteria and the resulting overall risk score (see Table 2). As guidance for risk prioritization, ICH Q9 Quality Risk Management (12) was used.

Step 3 involved determining the supplier risk, based on the previous definition of minimum requirements derived from documents such as the IPEC-PQG GMP Guide and EXCiPACT™.

Based on a gap analysis, a risk profile for each supplier was created in step 4, with the goal of also finding effective mitigation options, such as an update of the Quality Assurance Agreement (QAA) or intensified incoming goods control.

Risk Assessment						Result		
Excipient name	Any known quality defects/ fraudulent adulterations related to the excipient 1=no 2=yes, non-critical 3=yes, critical	Known of potential impact on the critical quality attributes of the medicinal product 1=no 3=yes	Function of excipient in the formulation 1=Processability 3=Bioavailability	Proportion of the excipient in the medicinal product composition 1=<5% 2=5-25% 3=>25%	Daily patient intake of the excipient for information only for information only	Sum of points	Amount of high risks	Risk Profile
Benzylalcohol	1	3	1	3	no	26	4	medium
Citric acid anhydrous	1	3	3	1	yes	28	5	medium
Citric acide monohydrate	1	3	1	1	no	22	2	medium
Creatinine	1	3	1	1	yes	20	1	medium
Disodium edetate	1	3	1	1	yes	24	3	medium
Ethanol	1	3	1	1	yes	24	3	medium
Glycerol	1	3	1	3	yes	25	3	medium
Glycine	1	3	1	1	no	22	2	medium
Hydrochloric acid	1	3	1	1	yes	26	4	medium

Table 2:
The assessment includes the ranking of single risks and the resulting overall risk profile by taking the sum of risk points and the amount of high risks into consideration (extract of the risk assessment).

The Overall Outcome Is Key

The excipient risk ranking through steps 1 and 2 resulted in all 24 excipients being classified as medium risk. It is important to note that this classification represents an overall ranking, as explicitly required by the guidelines. This means that excipients can have high single risks – which need to be closely looked into – but can still be classified as medium risk overall, as was the case here.

In summary, the high single risks identified showed that storage monitoring and packaging are important considerations regarding the excipient's source, whereas the dosage form (e.g. parenteral), permanent intake and function (e.g. excipient as part of the delivery system) are particularly relevant regarding the excipients' use.

The gap analysis at the supplier end (step 4) resulted in 14 excipients being classified as low risk, and 10 as medium risk. This classification was based on minimum requirements derived from the IPEC-PQG GMP Guide and EXCiPACT™ (step 3). The gaps identified included a potential for microbiological or endotoxin/pyrogen contamination – with the mitigation option of performing additional Quality Control (QC) testing in the manufacturing authorization holder's laboratory. Other gaps identified concerned environmental control and control of storage/transportation conditions including cold chain management and packaging integrity.

In summary, none of the 24 excipients assessed was classified as high-risk. 20 excipients showed high single risks. 14 excipients fulfilled all GMP requirements, meaning that no gap was identified at the supplier/manufacturer end.

Lessons Learned

One of the key lessons learned from the case study was that, in many cases, obtaining meaningful data posed a tremendous challenge. For example, suppliers did not provide data in a timely manner, the data was incomplete, contradictory or not delivered in the requested, or even in a uniform, format. Also, the sheer amount of data was overwhelming, making data transfer and dealing with huge spreadsheets both error-prone and time-consuming. All this shows that it takes significant resources to manage this task. Moreover, cross-functional teams are important to bring in all relevant competencies. In other words, a strong commitment and awareness on the part of the management are called for.

Another major challenge consisted in providing a sustainable risk assessment process, i.e. transferring it to daily business and keeping it up to date. The process should ideally be integrated into the QMS, considering both regular review and ad-hoc changes.

It is also important to note that the risk assessment is no substitute for regular audits, since the information provided by suppliers and manufacturers does not necessarily reflect the degree of compliance in day-to-day business.

By far the greatest challenge, however, was to translate the relevant points from the EU guidelines into a supplier questionnaire – and to find an appropriate procedure for risk prioritization on the basis of the responses. Some of the questions in this process were: "What are significant single risks?", "What is the best way of weighting risks?" and "Which risks generate points to be added, which risks should be considered as multipliers?". Here, the ICH Q9 Quality Risk Management offered a valuable resource, as foreseen by the EU guidelines. This document attaches particular importance to using scientific knowledge and balancing the level of formality of the risk management process with the level of risk posed by the excipient. This gives manufacturers and suppliers a certain degree of leeway in terms of defining a specific prioritization system.

Tried and Tested Tools

The case study also showed how important open and structured communication between the drug manufacturer and excipient supplier is. In addition, suppliers can actively contribute to a good risk assessment process by following established guidelines, fulfilling information needs and providing timely documentation, ideally bundled in packages and transmitted electronically.

The Emprove® Program was introduced in order to simplify this process and to help drug manufacturers overcome the challenges of supplying "inspection-friendly" documentation. It provides tried and tested tools, including comprehensive documentation packages. Regarding excipient risk assessment, the tools and information help to efficiently implement a compliant and sustainable risk assessment process, which optimally prepares pharmaceutical manufacturers for inspections.

Learn more about the Emprove® Program here:
MerckMillipore.com/emprove

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