european biopharmaceutical enterprises

EBE Concept Paper

Management and Control of Raw Materials Used in the Manufacture of Biological Medicinal Products and ATMPs

17 December 2018 Version 2

Executive Summary

Effective management and control of raw materials (RM) used in the manufacture of biological medicinal products including advanced therapy medicinal products (ATMPs) requires an appropriate framework to identify and focus on critical aspects that must be addressed from a quality, regulatory and business perspectives. There are currently no written industry guidelines available with detailed discussion on how to construct such a risk-based RM management approach and control strategy. The purpose of this concept paper is to provide such guidance by leveraging current practices and experiences of the EBE member companies.

This paper discusses background information related to RM regulatory requirements and industry challenges, and then highlights key principles to consider in setting up a risk-based RM management approach and control strategy. This paper then provides an example of how to translate those key principles into a detailed RM risk assessment methodology, and how to apply this methodology to specific raw materials. To better illustrate the diversity and nuance in applying a corresponding RM control strategy, a number of case studies with raw materials typically utilized in the manufacture of biological medicinal products including ATMPs are provided as well as discussion on phase-based mitigations.

The included examples of risk assessment methodology and model RM case studies are intended to demonstrate how an effective RM management and control plan could be structured. However, although the overall principles are considered key to all companies, alternative implementation approaches related to RM risk assessment methodology and RM control strategy may be equivalently applicable and more suitable for a particular individual company.

Table of Contents

Abbreviations

API	Active Pharmaceutical Ingredient[1]
ATMP	Advanced Therapy Medicinal Product
BSA	Bovine Serum Albumin
CoA	Certificate of analysis
CMA	Critical Material Attribute
CQA	Critical Quality Attribute
CTA	Clinical Trial Authorisation
CTD	Common Technical Document
DMSO	Dimethyl sulfoxide
DP	Drug Product
DS	Drug Substance[1]
EBE	European Biopharmaceutical Enterprises
FDA	Food and Drug Administration
FMEA	Failure Mode and Effect Analysis
GMP	Good Manufacturing Practices
HA	Health Authorities
ICH	International Council for Harmonisation
LCM	Life Cycle Management
MA	Marketing Authorisation
OOS	Out Of Specification
PDE	Permitted Daily Exposure
PQS	Pharmaceutical Quality System
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RM	Raw Material
SM	Starting Material
TTC	Threshold of Toxicological Concern
WHO	World Health Organisation

[1] In this document API and DS are used interchangeably where appropriate.

1. Objective and scope

The purpose of the present concept paper is to provide manufacturers of Biopharmaceutical and Advanced Therapy Medicinal Products (ATMPs) with a framework to guide and raise awareness on the critical aspects of the management of raw materials (RM) for biological medicinal products across the product lifecycle.

The goal of this document is to:

- Present some current practices from Industry.
- Raise awareness to raw material suppliers for biological medicinal products manufacturing on the criticality of RM and on the concerns Biopharmaceutical Industry has.
- Propose a methodology of risk assessment for the management of RM according to their level of criticality.

This document covers raw materials (e.g. chemicals, cell culture media, buffers, resins) and starting materials (SM) (e.g. cells) used for:

- The production of proteins, polypeptides and products of which they are components (e.g. conjugates). These proteins and polypeptides are produced using recombinant or non-recombinant cell culture/fermentation expression systems or isolated from tissues and body fluids.
- The production of viral vector-based vaccines and ATMPs.

In this document, the terminology starting materials will be considered only in the frame of ATMPs. Unless specifically mentioned, both starting materials and raw materials will be referred to as RM hereafter.

Even though excipients are not covered by the official definition of RM in this concept paper (See Definition in 2.1), the principles applied to RM can be applied to excipients as well.

This document covers the whole lifecycle of the product, i.e. clinical development and commercial use.

2. Background

Raw materials and starting materials are essential components of the manufacturing process for any medicinal product [1], [2]. In the Quality/CMC sections of regulatory submissions such as Clinical Trial Authorisation (CTA) applications and Marketing Authorisation (MA) Applications, RM and SM must be defined and demonstrated to be suitable for their intended use in the manufacturing process. Defining RM and SM requires that their role in the manufacturing process is contextualised and understood, where possible.

In this publication, the process for a biotechnological/biological medicinal product (recombinant proteins and ATMPs) is the manufacture of the Drug Substance from SM and RM.

2.1. Definition of raw material

Raw materials are defined as those materials entering in the manufacturing process but not intended to be part of the final product. RM would therefore be process inputs other than SM required to manufacture the Drug Substance.

Typical RM for a biotechnological/biological medicinal product and ATMPs would include cell culture medium and supplements, serum, serum replacements, enzymes, produced by rDNA technology or extracted from biological materials, recombinant proteins, cytokines. Components of buffer solutions and chromatographic resins would also be considered RM. Raw materials generally exclude materials such as consumables (plastics, tubes, bags)[2].

Excipients are pharmaceutically inactive components of the final formulation that are required to maintain the activity and stability of the active pharmaceutical ingredient and bring suitable functionalities of the defined dosage form. Excipients for biotechnological/biological medicinal products would typically include water-for-injections, simple buffer solutions and stabilisers such as sucrose, while ATMPs may include higher risk excipients such as human serum albumin and Dimethyl sulfoxide (DMSO). Although excipients do not fall in the scope of the RM definition, a similar management and control approach can be applied.

In summary, a perspective provided by the FDA [4] is that a RM can be "*any element or component used in the manufacture of a biotechnology product that comes in contact with the API or the API starting material. A raw material can be reactive or non-reactive with the API*".

2.2. Definition of starting material in the context of ATMPs

For biotechnological/biological medicinal products, the SM would be the recombinant cell line, tissue, body fluid or primary cells from which the desired molecule with the required therapeutic activity (i.e. the Drug Substance, sometimes also called the active substance or active pharmaceutical ingredient (API)) is expressed and/or purified.

For ATMPs, the definitions and differences between raw and starting materials are defined in Directive 2009/120/EC amending Part IV of 2001/83/EC, as those directly used in manufacture and intended to be part of the final product. However, due to the complexity and the heterogeneity of this class of products, SM are differently identified depending on whether the ATMP is a gene therapy, a cell therapy or a tissue engineered product.

As an example, in the EU, for gene therapy products consisting of viruses or viral vectors, the SM shall be the components from which the viral vector is obtained (e.g. the master virus vector). In the case of products consisting of plasmids or non-viral vectors, the SM shall be the components used to generate the producing cell (i.e. the plasmid), and in case of ex-vivo genetically modified cells the SM shall be the components used to obtain the genetically modified cells (i.e. the viral vector, the human cell substrate). However, some differences in terminology exists across the EU and US regulatory environment. In the US, viral vectors used for ex-vivo genetic modification of cells are defined as critical components. Despite these differences in terminology, regulatory expectations in terms of production, control and documentation

[2] Consumables are not considered in this document even though the same approach can be applied to consumables in contact with the API

are very similar as they shall be considered as active ingredient with the same level of control as drug substance and manufactured under appropriate GMP conditions. Starting materials can also be of non-biological origin as in the case of somatic cell therapy products or engineered cell and tissues combined with matrixes or scaffolds, medical or implantable devices which might or might not have a biological function.

ATMPs are still in their infancy on the forefront of science, therefore the space is subject to fast pace changes and the consolidated frame is often challenged by new technological advancements. For example, tools used in gene editing approaches (often referred to as genomic scissors) or siRNA can be hardly classified since borderline between raw and starting materials. From one hand, they are not intended to be part of the DP as long as they can be degraded by the intracellular systems, but on the other hand, they actively determine pharmacological properties of the end product inducing permanent genomic changes.

2.3 Regulatory perspective on raw and starting materials

Regulatory and quality standards for raw and starting materials are also different, consistently with the different roles and definition introduced by regulators.

2.3.1. General considerations for biotechnological/biological medicinal products

In line with the definition of raw materials provided above, EU Directive 2001/83/EC [3] states that "*Materials used during the manufacture of active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials*". Beyond this, specific regulations and guidance documents directly covering the selection, quality, management and control of RM do not exist. However, the content of certain guidance documents can be extrapolated to inform the management and control of RM.

When considering the applicability of regulatory guidance, it is important to first understand the risks posed by RM when used to manufacture a biotechnological/biological medicinal product. These potential risks also depend on whether a RM is of biological or non-biological origin. All raw materials pose a risk that they may contaminate a Drug Substance batch, because they are introduced into a manufacturing process and may remain in the Drug Substance (and therefore also Drug Product) as "process-related impurities". This concept is consistent with the statement above from EU Directive 2001/83/EC that RM are not intended to form part of the active substance. The exact nature of a process-related impurity will depend on the purity of a RM itself. This is particularly relevant to RM of biological origin, or any RM which uses animal-derived materials in its manufacturing process, because of the potential for contamination with human pathogens including bacteria, fungi, viruses and transmissible spongiform encephalopathy (TSE) agents. Several regulations and guidance documents on RM need to be considered [5], including those listed in Annex 1 (Table 1). Nonetheless, it is also important to understand the content/purity of non-biological RM to determine whether certain undesirable impurities (e.g. toxins) may also be present, and in this respect a specification and/or certificate of analysis (CoA) is important.

The specification of a RM is a key element that needs to be controlled and managed. RM could comply with a pharmacopoeial/compendial specification. However often the specification needs to be further developed to entail the specific material attributes

required by the manufacturing process. These material attributes should be carefully assessed during process development. Conformance with a compendial specification indicates that a RM is under a suitable quality assurance system for use in a medicinal product manufacturing process, provided its microbiological quality is commensurate to its point of use (microbiological contamination risk assessment). For example, compendial grades do not always meet requirements necessary for successful fermentation posing a risk of process failure, and conversely, including additional quality attributes testing and documentation that are not needed leads to unnecessarily high cost. Where pharmacopoeial specifications for certain RM are available in some territories but not in others (e.g. in the United States Pharmacopoeia but not in the European Pharmacopoeia), it may be possible to use the RM in territories where the specifications are not published only with limited testing.

For non-compendial RM, it is usually necessary to develop in-house specifications with specific acceptance criteria that must be met (e.g. purity, identity, bioburden) before a RM is used. Supplier audits and service level agreements are typically also needed to ensure that the material is manufactured in an appropriate manner (e.g. segregated from other product manufacturing lines and in the absence of animal-derived materials) and that potential supply issues or changes to specifications are communicated. These latter considerations are particularly important for critical RM because their unavailability would necessitate manufacturing process changes, and these changes would require amendments to CTAs and variations to MAs supported by comparability and validation studies.

The actual controls of process-related impurities in a Drug Substance, as well as considerations for RM and excipients specifications is discussed in the ICH Q6B guideline, “Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products”.

2.3.2. Specific considerations for ATMPs

For ATMPs, considering the critical role and the high potential impact played by SM on final product quality attributes, SM are expected to be produced and tested with the same standards adopted for an Active Pharmaceutical Ingredient (API). Consistently, the amount of data to be provided for each SM is the same as required for an Active Substance. Though process and testing methods knowledge may be considered according to the development stage, detailed information shall be provided on process manufacture, materials, characterisation, process development and validation as well SM control and stability (EMA/CAT/GTWP/671639/2008).

Because of the great heterogeneity of the ATMPs as a class of medicinal products, the diversity of therapeutic designs and of the manufacturing processes, SM are also very heterogenous, spanning from different classes of viruses genetically modified to control virulence and replication, primary cells at different stage of differentiation and procured from different sources, or from materials of non-biological origin used as scaffold or support for tissues engineered products.

As a consequence, requirements for SM can only be defined on a case by case basis, first starting from a sufficient understanding of the underlying biology and then tailored considering the respective role played in the manufacturing process, the source for procurement, the interaction among the different SM entering in process manufacture as well as the interaction between the final product and the receiving patient.

Beyond the known risks posed by RM of biological/animal origin as discussed in Section 2.3.1, SM are associated with additional risks as long as they are mostly constituted by living organisms like primary cells and viruses. The source of the cells is a key critical point as autologous and allogeneic cells are associated with different risk levels of both strong immune reactions in immunosuppressed patients and blood borne viruses transmission through contaminated material. For this reason, centers in charge for donor selection and cell procurement shall comply with requirements outlined in a bulk of EU directives (2004/23/EC, 2006/86/EC, 2015/566/EC), and FDA guidelines (Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)) and shall be granted for suitable quality standards for procurement and testing. The use of modified viruses as vectors to transfer genetic information into a target cell also entails specific risks which are of major considerations. Viruses used as vectors are generally extensively genetically modified to control replication thereby minimizing risk of spread and virulence. The residual viral load associated with the DP at the end of manufacture is therefore considered as a potential impurity and need to be estimated and characterized for off-target infectious properties and for replication. In particular, the assessment of replication properties and of any emergence or replicating virus from vectors designed as replication incompetent is asked at any production stage of both the SM and of the final product.

Beyond EU Directive 2001/83/EC, two documents specifically addressing requirements for RM used for ATMPs can be considered as major references for ATMPs developers. These are the USP <1043> (Ancillary Materials for Cell, Gene, and Tissue-Engineered Products) and the Ph.Eur.5.2.12 (Raw materials of biological origin for production of cell-based and gene therapy medicinal products). Both documents set quality standards in particular for RM of human/biological origin, considered as the highest risk class. It is acknowledged that quality of material can be related to the stage of the development of the cell-based or gene therapy product and therefore inherent to the evolution of the quality profile of the product during pharmaceutical and clinical development. On the other hand, ATMP developers need to set up an appropriate qualification strategy, risk assessment and minimization tools to ensure patient safety since the very early phase of clinical development.

Changes to RM are a frequent occurrence in ATMPs life cycle. Taken into consideration the high impact specific RM of biological origin might have on a cell-based or gene therapy medicinal product, changes need to be carefully evaluated and introduced after the evaluation of the impact on the end-product quality attributes by means of ad-hoc studies set up to assess comparability of the pre- and post-change materials.

All the other considerations discussed in Section 2.3.1 for biotechnological/biological medicinal products related to the followings are also applicable to ATMPs, namely:

- Material origin that may contaminate a Drug Substance batch
- Specifications.

2.3.3. *Examples of requirements expressed by Health Authorities during review of dossiers for clinical or commercial applications or during lifecycle management*

In the framework of CTA, MAA applications or post-marketing changes evaluation, the Industry has faced different requests from authorities regarding the information provided on the quality of RM. Table 1 below compiles typical requests received from authorities. It gives indications to pharmaceutical products manufacturers of which aspects to consider for the control and management of RM and SM.

Table 1: Examples for specific requirements from Health Authorities

Type of question	Description
Question related to the clearance of RM and SM	Assessment of process-related impurity clearance and/ or assessment of levels in the end product should be performed during all clinical phases, and cover impurities arising e.g. - from cell-culture RM/SM (e.g. antibiotics, media components, anti-foam residues, cytokines, immunomagnetic beads and growth factors), - from SM in ATMP (e.g. free residual vector particles, replication competent viruses, undesired side cell subpopulations) - from downstream processing RMs (e.g. processing reagents or column leachables).
Question related to the Quality of RM	A control strategy for well-known Critical Material Attributes (CMA) should be proposed (e.g. Polysorbate 80 can exhibit peroxide formation over time, which can lead to protein degradation through oxidation).
Questions related to extractable/ leachable of product contact materials.	The potential contaminants coming from physical RM put in contact with the product need to be considered. As development proceeds, data need to be gained on this aspect with a priority to single-use plastic materials and chromatography resins which present a higher risk by its nature to release impurities into the product.
In-house specifications developed by the company	When the RM plays a key role in the manufacturing process of the DS, and when no standard specification is established in pharmacopeias, Agencies are willing to obtain the results of the Quality Risk Assessment run by companies to establish in-house specifications commensurate to the RM use made in the specific process.
TSE/BSE Compliance Certificates for materials of animal origin.	In accordance with the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), the potential to bring prion proteins from RM of biological origin needs to be addressed and well-documented.

2.4. Challenges related to the management and control of raw materials

Despite the differences between biotechnological/biological and ATMPs products, the principles related to management and control of RM and SM are applicable to both. In consideration of all aspects discussed above, only raw materials that perform a specific role in a manufacturing process should be used, and in all cases, they should meet the quality standards required to guarantee acceptable final medicinal product quality (according to ICH Q6B), safety and efficacy.

Industry faces several challenges linked to the control and management of RM used for the production of biological medicinal products. The challenges are of varied origins such as the complex composition of some RM containing a large number of components, their complex supply chain and traceability, their lot-to-lot variability, the complexity of their testing. Table 2 summarizes some of these challenges.

Table 2: Challenges related to the management and control of RM

Challenge	Description
Large number and nature of components	Different nature: chemically defined, biological active complex ingredients, animal/plant-derived materials. Complex nature with high compositional variability (e.g. hydrolysates used in cell culture media).
Complex supply chain	Vendors are sometimes not the manufacturers but they release CoA, use brokers and sometimes multiple sub-suppliers. There can also be a large number of suppliers for a given RM. Traceability concerns with global sourcing with differences in quality practices between countries.
Variability/lot-to-lot consistency	Variability in source material: - Lot-to-lot variability - Variability in the RM quality and testing between different suppliers. Insufficient characterization or understanding of Critical Material Attributes hence impact of hidden variability on Critical Quality Attributes (CQAs) for the DS/DP.
Testing	Differences between pharmacopoeias e.g. Chinese Pharmacopeia requirements for PS-80 [6]. Different attributes needed in biological processes vs excipient grade (testing is often according to pharmacopeia “excipient grade”). No common understanding on how to deal with presence of trace foreign matter/particles. Defining tests and specifications for non-compendial RM. Compositional variability (e.g. media). Testing requirements: functional testing versus RM testing (e.g. scale down process testing of a specific part of the unit operation). Differences between development phases. Evaluation of clearance of some RM. Challenges linked to testing residual RM in final DP (e.g. when DP are cells).

Challenge	Description
Specification settings/quality	User requirements for raw materials not shared with the supplier (specification does not reflect CMA) Specification failure Chemical contaminants (e.g. trace metals) Visible and sub-visible particles [8] Adventitious agents Immunogenicity Some RM are only available as research grade and not yet fully commercialized, hence difficulty for RM manufacturers to apply quality management systems and e.g. provide necessary information to customers.
Animal derived source	Although adventitious agent contamination has not been linked to the transmission of infectious agents to a patient, cases of contamination arising during manufacture have been reported: - Contamination during manufacture has implicated mostly BSA (cache Valley virus, epizootic haemorrhagic disease virus (EHDV), bovine viral diarrhea virus (BVDV)). - Contamination by minute virus of mice (MVM) has also been reported but the source has not been clearly identified, although suspected of arriving through RM. - Porcine trypsin, antibody affinity columns and biological excipients should also be carefully evaluated.
Human derived	Potential risks in terms of adventitious agents. Examples: human platelet lysate, human AB serum, human serum albumin, human feeder cells of unknown origin.
Safety	Raw materials from biological origin. Lack of information from supplier to perform proper risk assessment (e.g. raw materials of secondary animal-origin, i.e. when a reagent of animal origin is used in the RM manufacturing process). Cross contamination when using same manufacturing equipment for non-animal and animal derived material. Viral risk of biological foreign matter (hair, insects etc.). Lack of toxicological safety level assessment, especially when added at the end of the process. Grade of material: research grade, higher-grade materials with documentation appropriate for use in GMP production.

An ideal RM for use in the manufacturing process of pharmaceutical products should be:

- Safe
- Of consistent quality (which includes stability) throughout the lifecycle of the biotechnological/biological medicinal product
- Well characterized/tested
- Well understood, especially its role in the manufacturing process and its interaction with active substance
- There should be a contractual agreement to ensure the RM is continuously and consistently supplied throughout its lifecycle (e.g. Quality Agreement with agreed specifications and test methods in place depending on outcome of risk assessment)
- Its supply chain should be transparent
- From a qualified manufacturer/vendor, and its manufacturing process should be well known and understood by the pharmaceutical manufacturer (e.g. audited) with appropriate notification of manufacturing process changes.

The criticality of a RM can be defined as its potential impact on the supply, quality and safety of a pharmaceutical product (see Section .3.1.). The criticality depends on those multiple parameters/challenges presented above.

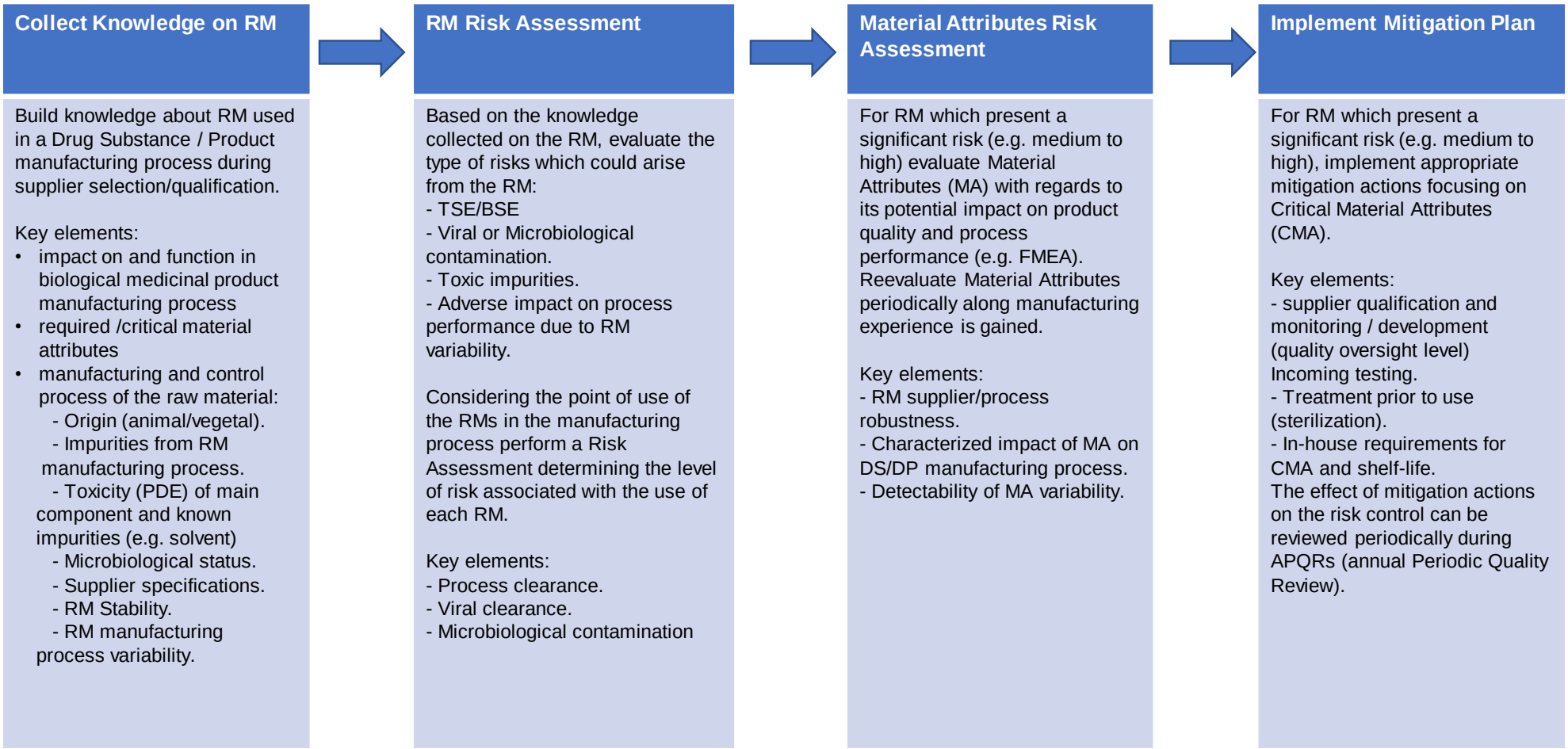
In accordance with ICH Q9, it is recommended to use a risk–based approach to define the criticality of the RM. In the following sections of this document, a risk assessment methodology for the management of RM is proposed and illustrated in several case studies from Industry.

3. Risk-based Approach

The level of control and quality management of RM must be commensurate to its criticality. The risk-based approach proposed here will help manufacturers prioritize activities for the quality oversight of RMs and must consider the phase of development of the pharmaceutical product.

An overview of the risk-based management process for RM detailed in this concept paper is provided in Figure 1.

Figure 1 Management of RM Process Overview



PDE: Permitted Daily Exposure
RM: Raw Material
APQR: Annual Product Quality Review (Integrated as part of Quality Risk Management System)

3.1. Definition of criticality

In order to define a proper control strategy for a RM, it is essential, where possible, to know the role of the RM in the manufacture of the DS, intermediate or DP in order to understand how it may interact with the active substance and final drug product. Where this is not known, the variability of the raw material needs to be controlled and kept at a minimum.

Based on the type, the source, production and control mode of the RM, and considering its potential impact on the supply, quality and safety of biological products including the risk of contamination with adventitious agents, RM used for production of biologics can be classified into different risk level categories from low (L) to high (H), following ICH Q9 and ICH Q11 principles.

The risks related to quality will drive the level of criticality in the risk assessment proposed here. Other risks, more business related, also exist but will not be further elaborated in this document, unless they also impact quality or availability of the Drug Product (e.g. consistent delivery of RMs). These risks are related to, for example, vendor failure, back-up source, understanding of supply chain, and evaluation in context of environmental regulation (REACH).

The risk factors that drive the levels of criticality with regards to quality are:

- The type of material and its origin (chemical, biological, complexity, animal/human origin).
- Where and how it is used in the process (cell bank, upstream (e.g. fermentation), downstream (e.g. purification, excipient)). Contact between RM and DS/DP as well as process time may also be relevant parameters to evaluate.
- What are the manufacturing process capabilities to reduce its amount to acceptable levels in DP?
- Its purity and how well it is characterized (including its stability).
- The level of understanding of its quality attributes on process and product interaction.
- The impact of its material quality attributes (CMA) on DP CQAs.
- Its variability in terms of quality under the standard manufacturing process used by suppliers.
- The quality agreement-audited quality systems, and change control notification.
- The storage conditions.
- The mode of use (use and re-use, e.g. resins).

3.2. Risk Management Approach

The Risk Management process can be described in six steps:

1. Collect the information on the RM:
    a. Identify the type (see below), the origin and supplier capabilities of all materials intentionally added and where they are used in the manufacturing process of the DS and/or DP as well as their intended function in the biotechnological/biological medicinal product manufacturing process step.
    b. What is known about the interaction of the RM and active substance? What type of RM contaminant can be present in relation of the RM manufacturing process (e.g. a virus can be part of a process, but in case of cell culture, a virus may multiply and become a safety issue)?

2. Evaluate the type of risk encountered:
    a. Potential quality impact on DS/DP linked to the interaction between the RM, the manufacturing process performance and the quality/safety of the active substance.
    b. Safety risk linked to this interaction or to the interaction with one RM contaminant. This can be done by determining the observed or predicted level/presence of the RM or one of its contaminants (e.g. virus, peroxide…) at the appropriate control point (unprocessed harvest, intermediate, DS and/or DP) in comparison with an established safety threshold (e.g. presence of adventitious agent, PDE, TTC…) when suitable.
    c. Potential risk of DP supply shortages caused by inconsistent quality (substance poorly characterized) and potential incompliance to applicable quality standards of RM.
3. Assess the level of the risk as described in section 3.3.
4. Assign a score for the criticality of the RM.
5. Deduce preventive/corrective actions related to control strategy, source strategy and supplier qualification. Identify if controls at receipt or built into the process are sufficient, or identify additional controls to be considered to limit the safety and quality risk on the drug substance and/or drug product related to RM. Develop appropriate source strategy and perform suitable supplier qualification to limit the risk of negative impact on supply (e.g. supply shortage) and quality of the biotechnological/biological medicinal product.
6. Evaluate residual risks upon implementation of mitigation action (optional).

Based on prior knowledge and past experience, companies may be able to reduce the risk and criticality as described in points 2 to 6 based on their understanding from cross-project platforms.

3.3. Risk Assessment

Based on the above, this paragraph aims to provide guidance on how to define the criticality of the RM depending on the risk factors defined in section 3.1. However, it is only an example illustrating general principles and can be adapted by companies according to their internal quality standards for risk assessment.

3.3.1. Proposed risk assessment methodology

The risk assessment methodology proposed here follows a simple risk ranking and filtering approach [7]. More elaborated risk analysis methodologies can also be implemented (e.g. FMEA) as illustrated in Annex 2.

Table 3 provides an example of questions to help assess the quality risks and typical examples. Practical examples are proposed in sections 3.3.2. to 3.3.5. and cover biological medicinal products (sections 3.3.2. to 3.3.4.) and ATMP (section 3.3.5.).

We do not propose a scoring methodology here. It is up to each company to set up the definition of the level of criticality and eventually a scoring approach with a threshold calculation, according to their needs.

Table 3: Example of questions to help assess the risks for RM

Question Driving the Quality Risk Assessment of RM	Example RM For Each Answer	
	Yes	No
Is the RM complex?	Cell culture media (multiple component mixture)	Simple buffer or salt (e.g. NaCl)
Is the RM well defined?	Simple buffer or salt (e.g. NaCl)	Soy peptone or hydrolysate
Is the material of animal/human origin?	Bovine Serum	Simple buffer or salt (e.g. NaCl)
Is the TSE/BSE assessment available?	Gamma-irradiated or certified country of origin	Salts obtained through chemical synthesis
Is the RM added in the late steps of the process?	Mannose (downstream, for final DS formulation)	Cell culture media (upstream)
Is there a need to demonstrate that the process will reduce the RM level to a safe residual level?	Antibiotic or insulin used in the cell culture media	NaCl
Is a relevant analytical method available to assess RM clearance?	Antibiotic or insulin used in the cell culture media	Simeticone
Is the level of quality of RM susceptible to impact product CQA?	Polysorbate	Sterile Water for Injection
Is the RM manufacturing process generating high variability in the RM quality attributes?	Soy peptone or hydrolysate	Amino acids obtained through chemical synthesis

3.3.2. Case Study 1: Risk Assessment and Mitigation Plan for Purification Buffers

The following examples are related to two "dummy" purification buffers used late in a drug substance manufacturing process. The assessment of its criticality is presented for two cases: one with no direct impact on CQA (Table 4) and a second one in which the product knowledge identified a link between the RM pH and the drug substance CQA (Table 5). For the second buffer, an example of a mitigation plan through modification of the RM incoming testing is illustrated.

Table 4 below represents an example of RM criticality assessment (based on Table 3) for a RM used in the purification process. As this RM is a biological buffer, a more complex and structured decision process was employed to determine the answer to question 6 than would be needed for a simple buffer (e.g. phosphate) or salt (e.g. NaCl). Overall, this RM was classified as Low risk with no specific mitigation implemented in the RM specification.

Table 4: Example of Risk Assessment for Biological Buffer Used in the Purification Process - Buffer with no Impact on Product CQAs

Assessment Question	Answer / Comments
Is the RM complex?	No, lower risk / Single component, well characterized.
Is the RM well defined?	Yes, lower risk / Single component
Is the material of animal/human origin?	No, lower risk.
Is the TSE/BSE assessment available?	Yes, lower risk / Supplier provides certification.
Is the RM added in the late steps of the process?	Yes, higher risk / RM used late in the purification process.
Is there a need to demonstrate that the process will reduce the RM level to a safe residual level?	Yes, medium risk / Based on the quantity added, additional assessment or controls are required to demonstrate acceptable residual RM levels in the DS/DP (subsequent calculations performed to confirm residual levels are below that of toxicological concern).
Is a relevant analytical method available to assess RM clearance?	No / Not considered a concern as process clearance not required to be demonstrated.
Is the level of quality of RM susceptible to impact product CQA?	No, lower risk (based on current process knowledge).
Is the RM manufacturing process generating high variability in the RM quality attributes?	No, lower risk (based on current process knowledge).

Table 5 below represents an example of RM criticality assessment (based on Table 3) for another buffer used in the purification process, but in this case with a known potential impact on a product CQA. Overall, this RM was classified as High risk because its pH impacted a critical process parameter linked to a product CQA.

Table 5: Example of Risk Assessment for Simple Buffer Used in the Purification Process - Buffer Impacting Product CQAs

Assessment Question	Answer / Comments
Is the RM complex?	No, lower risk / Single component, well characterized.
Is the RM well defined?	Yes, single component
Is the material of animal/human origin?	No, lower risk.
Is the TSE/BSE assessment available?	Yes, lower risk / Supplier provides certification.
Is the RM added in the late steps of the process?	Yes, higher risk / RM used late in the purification process.
Is there a need to demonstrate that the process will reduce the RM level to a safe residual level?	No, lower risk / No additional assessment or controls is required to demonstrate acceptable residual RM levels in the DS/DP (simple buffer with chemistry used throughout the industry).
Is a relevant analytical method available to assess RM clearance?	No / Not considered a concern as process clearance not required to be demonstrated.
Is the level of quality of RM susceptible to impact product CQA?	Yes, higher risk / RM used to make a formulated buffer (no pH adjustment) for which the pH in operational use is a critical process parameter. Variability in raw material pH within the compendial specification is a problem.**
Is the RM manufacturing process generating high variability in the RM quality attributes?	No, lower risk (based on current process knowledge).

**To address this, consider implementing a vendor specification on pH slightly narrower than the compendial range with an appropriate control strategy.

An example of RM specification established as a mitigation activity following the buffer criticality assessment in Table 5 is shown in Table 6.

In order to mitigate the risk of the buffer on the product quality, a vendor specification should be designed to control the quality risk upstream of the manufacturing process. Elements related to the fact the RM can impact a CQA (pH) and is used late in the purification process (bioburden/endotoxin, due to potential impact of contamination) are presented in bold. Additionally, as a High risk RM, supplier qualification and ongoing quality monitoring in particular for parameters impacting the pH value at the supplier (manufacturing parameters at the supplier determining the pH value and pH testing at the supplier) is more extensive than would be the case with a Low or Medium risk RM.

Table 6: Example of Internal Raw Material Specification Developed for Buffer Used Late in the Process (see Table 5) as Mitigation Activity

Example Specification	Vendor Test	Vendor Specification Range	Internal Specification / Test
Required Tests	Identification	Conforms to reference	Yes / Every lot to confirm GMP identity of RM
	Appearance (solution)	Clear and colorless	
Other tests, may utilize different strategies with respect to inclusion of internal testing	Assay	99.0 – 100.5 %	Yes / Depending on assessed RM risk and phase of development could either test for on every lot, or test periodically after vendor qualification, or simply accept vendor data;
	pH (solution)	**10.3 – 10.7 (narrower than the typical vendor range)**	
	Related substances	NMT 1.0 %	No / Depending on assessed RM risk and phase of development could either test for on every lot, or test periodically after vendor qualification, or simply accept vendor data;
	Heavy metals	NMT 10 ppm	
	Chlorides	NMT 10 ppm	
	Iron	NMT 10 ppm	
	Loss on drying	NMT 0.5 %	
	Sulfated ash	NMT 0.10 %	
Microbial testing	Bioburden	**NMT 100 CFU/g**	Yes, every lot to confirm vendor bioburden control of RM.
	Endotoxin	**NMT 500 EU/g**	
Vendor tests omitted from internal specification	Melting point		Omitted from internal specification based on evaluation that these material attributes either have no impact process performance or product quality, or that testing for these material attributes are redundant to all the specified testing.

3.3.3. Case Study 2: Risk Assessment and Mitigation Plan for Commercial Media

The following two examples are related to two “dummy” RM used in the cell culture production process as media, one being chemically defined (Table 7), the second containing undefined components (e.g. hydrolysates) (Table 8).
The tables represent an example assessment based on Table 3. As these RM are a mixture of many components, a more complex and structured decision process was employed to determine the answer to question 6 than would be needed for a simple singular component.

Overall the risk would likely be medium for the chemically defined media (Table 7) and high for a media containing undefined material (Table 8), for a company with no prior experience with this material, however prior knowledge/experience may reduce the risk related to this material.

Following the risk assessments, Table 9 and Table 10 present examples of specifications as mitigation strategy to demonstrate various options or strategies to handle vendor versus internal tests. The main difference between Table 9 and Table 10 resides in the identification test, using amino acid testing for the chemically defined medium and IR for the media containing undefined components. Additionally, as a High risk RM, supplier qualification and ongoing quality monitoring is more extensive than would be the case with a Low or Medium risk RM.

Table 7: Example of Risk Assessment and Mitigation Plan for Chemically Defined Commercial Media

Assessment Question	Answer / Comments
Is the RM complex?	No, medium risk / multiple components but chemically defined.
Is the RM well defined?	Yes, lower risk / chemically defined.
Is the material of animal/human origin?	No, lower risk.
Is the TSE/BSE assessment available?	Yes, lower risk / No animal derived components or supplier provides certification.
Is the RM added in the late steps of the process?	No, lower risk / opportunity for clearance.
Is there a need to demonstrate that the process will reduce the RM level to a safe residual level?	No, lower risk / Based on the component quantities added, no additional assessment or controls are required to demonstrate acceptable residual RM levels in the DS/DP.
Is a relevant analytical method available to assess RM clearance?	No / Not considered a concern as process clearance not required to be demonstrated.
Is the level of quality of RM susceptible to impact product CQA?	Yes, medium risk (based on current process knowledge).
Is the RM manufacturing process generating high variability in the RM quality attributes?	No, based on current process knowledge, low risk as vendor has sufficient controls on their manufacturing process.

Table 8: Example of Risk Assessment and Mitigation Plan for Commercial Media containing Undefined Components (e.g. hydrolysates)

Assessment Question	Answer / Comments
Is the RM complex?	Yes, high risk / multiple components and undefined components (e.g. hydrolysates).
Is the RM well defined?	No, higher risk due to undefined components
Is the material of animal/human origin?	No, lower risk.
Is the TSE/BSE assessment available?	Yes, lower risk / No animal derived components or supplier provides certification.
Is the RM added in the late steps of the process?	No, lower risk / opportunity for clearance.
Is there a need to demonstrate that the process will reduce the RM level to a safe residual level?	Yes, medium to high risk / Demonstrating removal of undefined components may be difficult and only sub-elements can be specifically addressed. Based on the component quantities added, additional assessment or controls may be required for at least one component to demonstrate acceptable residual RM levels in the DS/DP.
Is a relevant analytical method available to assess RM clearance?	No, medium to high risk / Not considered a concern for defined components as process clearance not required to be demonstrated. Undefined components may require assessment and testing to ensure clearance.
Is the level of quality of RM susceptible to impact product CQA?	Yes, high risk (based on current process knowledge).
Is the RM manufacturing process generating high variability in the RM quality attributes?	Yes, high risk as undefined components are present that have variability (based on current process knowledge).

Table 9: Example of Internal Raw Material Specification Developed for Chemically Defined Commercial Media (see Table 7) as Mitigation Activity.[1]

Example Specification	Vendor Test	Vendor Specification Range	Internal Specification /Test
Required Tests	Appearance	Beige to yellow powder	Yes / Every lot to confirm GMP Identity of RM
	Quantification by Amino Acid Testing	(g/L of prepared media solution) AA1: 4-6 AA2: 8-12 AA3: 0.2 – 0.4 AA4: 6-8	
Other Tests, may utilize different strategies with respect to inclusion of internal testing	Glucose	3.0 -5.0 g/L	Yes / Depending on assessed RM risk and phase of development could either test every lot or test periodically after vendor qualification, or simply accept vendor data.
	Osmolality	300 – 350 mOsm/kg	
	Solubility	Soluble at 20 g/L	
	pH	6.8 – 7.5	No / Depending on assessed RM risk and phase of development could either test every lot or test periodically after vendor qualification, or simply accept vendor data.
	Cell Culture Performance Assay	Passes Test	
Microbial testing	Bioburden	≤ 100 CFU/g	Yes / After qualification, confirm from vendor data on a specified frequency.
	Endotoxin	≤ 1.0 EU/mL	

[1] Note: These ranges are only illustrative examples and should not be taken as a recommendation for the establishment of specifications.

Table 10: Example of Internal Raw Material Specification Developed for Commercial Media Containing Undefined Components (e.g. hydrolysates) (See Table 8) as Mitigation Activity[1]

Example Specification	Vendor Test	Vendor Specification Range	Internal Specification /Test
Required Tests	Appearance	Beige to yellow powder	Yes / Every lot to confirm GMP Identity of RM
	Identification by IR Testing	Conforms to Reference	
Other Tests, may utilize different strategies with respect to inclusion of internal testing	Glucose	3.0 -5.0 g/L	Yes / Depending on assessed RM risk and phase of development could either test every lot or test periodically after vendor qualification, or simply accept vendor data.
	Osmolality	300 – 350 mOsm/kg	
	Solubility	Soluble at 20 g/L	
	Cell Culture Performance Assay	**Passes Test**	**Yes / After qualification, confirm from vendor data on a specified frequency.**
	pH	6.8 – 7.5	No / Depending on assessed RM risk and phase of development could either test every lot or test periodically after vendor qualification, or simply accept vendor data.
Microbial testing	Bioburden	≤ 100 CFU/g	Yes / After qualification, confirm from vendor data on a specified frequency.
	Endotoxin	≤ 1.0 EU/mL	

[1] Note: These ranges are only illustrative examples and should not be taken as a recommendation for the establishment of specifications

3.3.4. Case Study 3: Risk Assessment and Mitigation Plan for a "Dummy" Resin

The following example relates to a "dummy" resin used in the purification process.
Table 11 represents an example assessment based on Table 3.
Following the risk assessment, Table 12 presents an example of RM specifications as mitigation activity to demonstrate various options or strategies to handle vendor versus internal tests.

Table 11: Example of Risk Assessment and Mitigation Plan for a "Dummy" Resin

Assessment Question	Answer / Comments
Is the RM complex?	Yes, high risk / complex, often sole-sourced material required for process effectiveness.
Is the RM well defined?	Yes, low risk (based on both specific company and industry experience).
Is the material of animal/human origin?	No, lower risk.
Is the TSE/BSE assessment available?	Yes, lower risk / No animal derived components or supplier provides certification.
Is the RM added in the late steps of the process?	Yes, medium risk. May introduce process impurities of concern (resin leachables). May be some opportunity for clearance depending on placement in process train.
Is there a need to validate the process will reduce the RM level to a safe level?	Yes, low risk / Resin extractables and leachables assessment performed or testing included to ensure acceptable residual levels in the DS/DP.
Is a relevant analytical method available to assess RM clearance?	Yes, medium risk / Resin extractables and leachables identified components clearance must be demonstrated[1].
Is the level of quality of RM susceptible to impact product CQA?	Yes, high risk (based on current process knowledge).
Is the RM manufacturing process generating high variability in the RM quality attributes?	No, risk level based on vendor capability to limit variability.

[1]Note: As part of qualification or early development, specific evaluation of resin extractables and leachables may be performed on resins hence will not be further evaluated as part of routine testing.

Table 12: Example of Internal Raw Material Specifications Developed for a "Dummy" Resin as Mitigation Activity[1]

Example Specification	Vendor Test	Vendor Specification Range	Internal Specification /Test
Required Tests	Appearance	White suspension	Yes / Every lot to confirm GMP Identity of RM
	Identification by IR Testing	Conforms to Reference	
Microbial testing	Bioburden	≤ 100 CFU/g	Yes / After qualification, confirm from vendor data on a specified frequency.

[1] Note: These ranges are only illustrative examples and should not be taken as a recommendation for the establishment of specifications

3.3.5. Case study 4: Risk assessment and mitigation plan for a human derived raw material

Table 13 represents an example of RM criticality assessment (based on Table 3) for a human derived raw material used during the manufacturing process of a genetically modified cell. The RM is prepared from pooled donor blood and carries a risk not just limited to the transmission of communicable diseases from blood borne pathogens potentially propagated during manufacture, but also potential genomic changes to the target cell, as well as interference with components of the manufacturing process (e.g. viral vector).

Overall, this RM was classified as High risk. There are strict regulatory requirements to limit exposure to blood borne pathogens but these vary by country and undergo frequent changes and updates. Mitigations to minimize risk include documentation (evidence of medical questionnaire), donor screening, RM testing, pooling and processing (e.g. viral inactivation, irradiation, filtration). Following the risk assessment, Table 14 presents an example of RM specification as mitigation for the various risks.

Table 13: Example of Risk Assessment for a human derived raw material

Assessment Question	Answer/Comments
Is the RM complex?	Yes, high risk/biologically active, donor variability
Is the RM well defined?	No, high risk due to undefined components and donor variability
Is the material of animal/human origin?	Yes, high risk
Is the TSE/BSE assessment available?	Yes, low risk/medical screening by questionnaires
Is the RM added in the late steps of the process?	Yes, higher risk
Is there a need to demonstrate that the process will reduce the RM level to a safe residual level?	Process has no clearance steps other than washes, high risk
Is a relevant analytical method available to assess RM clearance?	No, high risk. Due to the type of product and limited availability of final product and lack of clearance process steps, testing is not feasible.
Is the level of quality of RM susceptible to impact product CQA?	Yes, high risk/donor variability
Is the RM manufacturing process generating high variability in the RM quality attributes?	Yes, high risk/Donor variability introduces high variability in the RM

Table 14: Example of specification developed for a human derived raw material

Example Specification	Individual Donor	Vendor Pool Donation	Vendor Pooled Serum	Vendor Specification	Internal Specification
Appearance			X		Yes/every lot
Identity					Yes/every lot
Hemoglobin			X	<30 mg/dL	Confirm results comply with vendor requirements
Endotoxin			X	≤10 EU/mL	Confirm results comply with vendor requirements
Mycoplasma			X	Negative	Confirm results comply with vendor requirements
Osmolality			X	260-350 mOsm/kg	Confirm results comply with vendor requirement
Sterility			X	Negative	Confirm results comply with vendor requirements
pH			X	7.0 to 9.0	Confirm results comply with vendor requirements
Calcium			X	<12 mg/dL	Confirm results comply with vendor requirements
Anti- HIV-1 and anti-HIV-2 antibodies with p24 antigen	X			Negative	Confirm results comply with vendor requirements
HIV-1 NAT		X		Negative	Confirm results comply with vendor requirements
Hepatitis C Virus: anti-HCV antibody	X			Negative	Confirm results comply with vendor requirements
HCV NAT		X		Negative	Confirm results comply with vendor requirements
Hepatitis B Virus (HBV): HBcAb	X			Negative	Confirm results comply with vendor requirements
Hepatitis B Virus (HBV): HBsAg	X			Negative	Confirm results comply with vendor requirements
HBV NAT		X		Negative	Confirm results comply with vendor requirements
anti-HTLV-1 and anti-HTLV-2 antibodies	X			Negative	Confirm results comply with vendor requirements
Syphilis	X			Negative	Confirm results comply with vendor requirements
Heat inactivation			X	56°C for a minimum of 30 min	Confirm results comply with vendor requirements
Gamma irradiation			X	30 to 50 KGy	Confirm results comply with vendor requirements
Functional evaluation				Pass	Yes/every lot

3.4 Elements of mitigation plans per phase of development

Following the assessment of the criticality of the RM used, mitigation plans need to be put in place. Depending on the phase of development of the product, these mitigation plans may be more or less important. Two mitigation plans will be discussed here (see Table 15):

- Supplier qualification. This example refers widely to the APIC guideline on supplier qualification [2]
- Raw material testing.

Table 15: Proposed mitigation plan per phase of development for supplier qualification [2] and for RM testing for a High-risk RM

Phase 1/2	Phase 3	Launch	Commercial
- check supplier CoA and ensure material meets supplier specification - ID and appearance testing at reception - safety tests (bioburden, endotoxins) - development of non-compendial methods e.g. purity testing/impurities, e.g. growth promotion test (cell culture medium). - consider trending of critical test for high critical material over time and batches (depending on the number of batches produced) - ensure traceability of manufacturer and supplier address	- Ensure the RM meets the specification defined by the customer confirmed by 1) sample evaluation (QC testing) and 2) by ensuring there is an evaluation of the quality systems in place designed to assure and control the manufacture, testing, release and distribution of the RM. - For critical RM including API starting materials the necessity to perform a due diligence can be based on risk assessment according to ICHQ9. - The level of quality assessment is based on risk assessment which will take into acount the level of in-house testing the customer intends to perform. If customer intends to implement reduced testing, a manufacturer's audit is recommended. - Audit will be done on a risk-based approach. For critical RM, evaluate variability of RM by testing different batches of RM from same supplier. - The quality assessment must be done as early as possible before production assessment. The customer cannot implement reduced testing until the manufacturer evaluation has been completed. - A quality/purchasing contract is required. This can be supplemented by a quality agreement. - recommendation to perform full testing of most critical material attributes - same tests as for phase 1/2 - compendial tests according to clinical trials countries - more characterisation including several lots - more knowledge drives additional testing/modified ranges	- RM are qualified ahead of Process Performance Qualification (PPQ) batches preferably - trending of critical tests for high critical material over time and batches (part of Continuous Process Verification) - supplier audited for PPQ batches	- provide multiple sources of RM. - Lifecycle Management: consider information from experience (process, deviations, scientific knowledge) that may cause you to revise your control strategy: the panel of tests and/or specification ranges

4. Conclusion

This paper has outlined some considerations for raw material control and provided examples of possible approaches for specific types of materials. Due to the constantly evolving regulatory and material quality and availability landscape, industry is encouraged to take a lifecycle approach to risk management and periodically review the raw material controls in light of the stage of the product, new raw material understanding, and regulatory changes as products move through the various stages of development and commercialization. Specifically, it is recommended to assess the risks after any material changes, introduction of new suppliers or supplier processes.

5. Authors

The main authors of this concept paper are:

- Annick GERVAIS, UCB
- Cindy RIGGINS, Novartis
- Nicole BLECKWENN, MedImmune
- Ralph QUADFLIEG, Roche
- Romain LE DEUN, Merck KGaA
- Sergio FRACCHIA, Novartis
- Stacey Masaaki KANESHIRO, Lilly

6. Acknowledgements

The paper was written in collaboration with experts in raw materials, reviewers and others from the EBE BioManufacturing group member companies that contributed and supported the preparation of this document.

A big thank to Lionel RANDON (Merck KGaA) who initiated this topic group.

7. References

[1]: ICHQ7
[2]: Active Pharmaceutical Ingredients Committee (APIC), Supplier qualification and management guideline, December 2009
[3]: EU Directive 2001/83/EC
[4]: R. Cordoba (2009) “Raw Materials in the Manufacture of Biotechnological Products: regulatory consideration”, CASSS CMC Strategy Forum.
[5]: P. J. Shadle (2004) “Qualification of Raw Materials for Biopharmaceutical Use”, BioPharm Intl.
[6]: Chinese Pharmacopeia 2015
[7]: T. Frank et al. (2008) “Quality risk management principles and industry case studies”, PQRI
[8]: Technically unavoidable particle profile, IPEC, 2015.
[9]: IEC 60812

Annex 1: Regulatory guidances for raw materials

Table 1: Excerpts from guidances related to GMP and quality of RM (non-exhaustive list)

Guideline References	Relevant content related to RM
ICH M4Q	Quality section of the Common Technical Document: Culture media and other additives (details provided in 3.2.S.2.3) The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3), information on the quality and control, information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation. (Details in 3.2.A.2 for both NCE and Biotech)
ICH Q3D	Guideline for elemental impurities
ICH Q5A(R1)	Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin. It is recommended that manufacturers develop programs for the ongoing assessment of adventitious viruses in production batches. The scope, extent and frequency of virus testing on the unprocessed bulk should be determined by taking several points into consideration including the nature of the cell lines used to produce the desired products, the results and extent of virus tests performed during the qualification of the cell lines, the cultivation method, raw material sources and results of viral clearance studies.
ICH Q5D	Guideline derivation and characterisation of cell substrates used for production of biotechnological/biological products
ICH Q7	Good manufacturing practice No (raw) material should be released or used before the satisfactory completion of evaluation by the quality unit(s)… The quality unit should establish a system to release or reject raw materials, intermediates, packaging and labeling materials. Specifications should be established and documented for raw materials….. Acceptance criteria should be established and documented for in-process controls. The (API) impurity profile should be compared….in order to detect changes to the API resulting from modifications in raw materials….
ICH Q9	Quality risk management. This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, including the use of raw materials. To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials.

Guideline References	Relevant content related to RM
ICH Q11	Development and manufacture of Drug Substance The manufacturing process development program should identify which material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be controlled. Risk assessment can help identify the material attributes and process parameters with the potential for having an effect on drug substance CQAs. Those material attributes and process parameters that are found to be important to drug substance quality should be addressed by the control strategy. The quality of each raw material used in the manufacturing process should be appropriate for its intended use. Raw materials used in operations near the end of the manufacturing process have a greater potential to introduce impurities into the drug substance than raw materials used upstream. Therefore, manufacturers should evaluate whether the quality of such materials should be more tightly controlled than similar materials used upstream.
9 CFR Part 113 sections 50, 52, 53	Requirements for ingredients of animal origin used for production of biologics 113.50 — Ingredients of biological products. 113.52 — Requirements for cell lines used for production of biologics. 113.53 — Requirements for ingredients of animal origin used for production of biologics.
21 CFR 610.15, 21 CFR 211 Subpart E and 21 CFR 211.110	21 CFR 610.15: constituents shall meet generally accepted standards of purity and quality 21 CFR 211 Subpart E: Control of components and drug product containers and closures; components are required to be controlled by a Quality Control to ensure appropriate management. Testing and monitoring of components…components should be tested for identity and for conformity for purity, strength and quality. 21CFR 211.110: In-process materials shall be tested for ID, strength, quality and purity as appropriate, and approved or rejected by the quality control unit…
USP<1043>	USP-NF General Chapter <1043> Ancillary materials for cell, gene and tissue-engineered products
USP<1074>	USP-NF General Chapter <1074> Excipient Biological Safety Evaluation Guidelines
ChPh 2015	Quality Control Procedures for Raw Materials and Excipients Used for Production of Biologics
Ph.Eur.5.2.12.	Raw Materials of Biological Origin for the Production of Cell-Based And Gene Therapy Medicinal Products
Ph. Eur. Monograph 2034	Substances for Pharmaceutical Use
EMA	EMEA/CHMP/410869/2006 Guideline on Human Cell-Based Medicinal Products

Guideline References	Relevant content related to RM
EMA	EMEA/CHMP/QWP/396951/2006 Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product
Directive 2009/120/EC	amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products
Eudralex Volume 4, Annex II	Good Manufacturing Practice (GMP) guidelines
EU guideline 2015/C 95/02	EU Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use
Other	PDA_Strategies for Controlling Raw Materials in Biologics Manufacturing by Annemarie Möritz, PhD, Novartis Pharma AG | Jan 05, 2015 https://www.pda.org/publications/pda-publications/pda-letter/latest-news/2015/01/05/strategies-for-controlling-raw-materials-in-biologics-manufacturing

Annex 2: Risk Assessment – Example for FMEA for Raw Materials

Introduction

This case study shows how a Failure Mode and Effect Analysis (FMEA) can be applied for raw material risk assessments. FMEA (see IEC 60812) provides an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding and methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.
FMEA as every quality risk assessment begins with a well-defined problem description or risk question. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong (hazard or harm)?

   For a raw material quality risk assessment, the hazard or harm could be a patient safety, product quality or product availability (supply continuity) issue caused by the failure of a raw material.

   Patient safety could be affected if for example the raw material failure would compromise the purity of a drug product e.g. when a raw material adulterates a drug product. Examples are toxic impurities in raw materials that could be present in the drug product.

   Product quality could be affected, when critical quality attributes for example the glycosylation pattern of a monoclonal antibody is affected because e.g. trace elements of a media are not appropriately controlled (for example not chemically defined media).

   An example for an effect on **supply continuity** could be a media component like a peptone that has a significant effect on yield of the fermentation of a drug substance process. When the peptone fails and yield is decreased significantly e.g. 30%, however, the product quality is not affected, the harm could be a potential supply issue.

   What could go wrong can be described with a **severity** of the issue caused by the raw material failure and its **probability of occurrence**. In an FMEA, a severity score is multiplied with a probability of occurrence score which results in a primary risk number (PRN) that can be used to quantify the magnitude of the risk. High severities and high probabilities of occurrence lead to a high risk whereas lower scores in severity and/or probability of occurrence lead to lower risks.

2. What is the likelihood (probability of occurrence) it will go wrong?

   In this case study, the probability of occurrence of the raw material failure is derived from the supplier's performance.

   The logic that is applied is that suppliers that show a high-quality performance with stable processes and a low variability of raw material quality, for example have
   - few to none open audit observations,
   - a high process capability,
   - few or no raw material related deviations in incoming control or in process in their history of raw material deliveries.

These suppliers have a lower probability of occurrence to deliver raw material with failures than suppliers that have:

- many open major or even critical audit observations and related gaps in their quality systems,
- a low process capability and a higher raw material variability,
- a high number of raw material related deviations in incoming control or in process in their quality history.

Monitoring the performance of raw material suppliers and defining a model to calculate a supplier risk score e.g. with the above-mentioned performance indicators could be used to derive the probability of occurrence score per supplier. Re-evaluation of the supplier's performance could be used to adjust the supplier risk and the probability of occurrence score accordingly.

3. What could be ratings for the severity of a raw material failure?

The severity of what could go wrong (the harm) can be divided e.g. as follows:

- **negligible**: where the raw material failure causes negligible handling errors only,
- **minor**: where the raw material failure results in process deviations or minor defects e.g. significant but low decrease in yield without affecting supply continuity,
- **major**: where the raw material failure disturbs the manufacturing process e.g. increased production lead time or decreased yield affecting delivery performance with risk of supply delays,
- **critical**: where the raw material failure adulterates the drug product or affects delivery performance with risk of supply interruption or drug product batch recall,
- **catastrophic**: where the raw material failure could cause serious adverse health consequences, permanent disability or death of patients.

Typical severity and probability of occurrence scores as well vary between 2 (low) to 10 (high):

Severity of raw material/component failure				
Direct Material failure cause serious adverse health consequences, permanent disability or death of patients	raw material failure adulterates product or affects delivery performance with risk of supply interruption or product batch recall	raw material failure disturbs manufacturing process (production lead time or yield) affecting delivery performance with risk of supply delays	raw material failure that may result in the opening of discrepancies, or to minor defects e.g. unwanted cosmetic defects	raw material failure does not affect product quality parameters or delivery performance but could cause negligible handling issues
Associated severity score				
10	8	6	4	2

Performing a raw material FMEA

Performing an FMEA for the risk of raw materials/components' failures should be done by a cross functional team that can identify raw material failures, and assess the severity as well as the probability of occurrence of a harm. The assigned severity scores are strongly dependent on the individual manufacturing process of a pharmaceutical product, its critical control points and robustness, in particular with regards to raw material variability.

The examples given in that case study are fictional and should illustrate the application of the concept rather then taken over for real conditions.

To guide the process of severity score assessments for raw materials, it may be helpful to walk through different areas of the raw material usage for a particular process or process type. Typical areas that can be assessed are **where in the process (1)** the raw material is used and if there are process steps later in the process that eliminate the harm of a raw material failure (e.g. chemical, physical or biological purification steps like recrystallization, filtration or bioburden reduction steps).
For example, a single use technology system used in the aseptic filling of a drug product into its final container closure system has a higher risk to adulterate product than a single use technology system that is used for media preparation upstream. Chemicals used in fermentation have a lower severity when adulterating the process than excipients added to the Drug Substance at the very end of its manufacturing process for example.

Other raw material failures could arise from the Raw Material's **origin (2)** (animal, human, plant, synthetic etc.), where a raw material of animal origin for example could bear the risk to contaminate the product with prions (TSE) which would be a high severity.

The **composition (3)** of a raw material (chemically defined versus an undefined mixture), its **complexity (4)** (a chromatography resin is typically more complex than an inorganic salt) could lead to risks of different severities.
The **function** of the raw material **in the manufacturing process (5)** of the drug product can also contribute to risks with a different severity, for example a shear protection agent in the fermenter typically has a more important function than a vent filter and its failure to function as expected could lead to decrease in yield and dependent on the process and product might lead to severe supply issues.

Every raw material or raw material group could be assessed for severity of its failure according to the above mentioned **five** areas following the definitions of the different severity levels discussed before and the final severity score for the raw material can be assigned.

Final Severity score assessment

In this example, a raw material or raw material group of similar raw materials gets a severity score assigned that can be associated to every of the **five** areas discussed earlier. The raw material used as an example is a peptone used in the fermentation of a monoclonal antibody, which does not have a significant effect on fermentation yield, it is of bovine origin and chemically not defined. Its composition is not fully known but it is not deemed to be a complex raw material. Its function in the manufacturing process is to support the fermentation only without major impact on quality or yield of the product.
The final severity score corresponds to the highest severity score for each assessed area and is used for the FMEA.

Example 1 for severity score assessment for a raw material – Peptone

If a cross functional team assesses the above-mentioned peptone, it could walk through the five areas:

1. **Where used**: upstream in fermentation with potential to disturb the manufacturing process (production lead time or yield) affecting delivery performance with risk of supply delay.
   Severity of harm: **raw material failure does not affect product quality parameters but could cause negligible handling issues -> *severity score 2,*** see table above
2. **Origin**: animal origin, could transmit TSE.
   Severity of harm: ***raw material failure adulterates product with risk of batch recall -> severity score 8,*** see table above
3. **Composition**: not complex composition, hard to analyze and to predict its performance.
   Severity of harm: ***raw material failure does not affect delivery performance -> severity score 2,*** see table above
4. **Complexity**: undefined peptone mixture of various chemicals, one could transmit TSE.
   Severity of harm: ***raw material failure adulterates product with risk of product batch recall -> severity score 8,*** see table above
5. **Function in the manufacturing process**: fermentation agent, no impact on product quality or patient safety.
   Severity of harm: ***raw material failure does not affect delivery performance -> severity score 2,*** see table above

In this example, the highest severity of harms is the risk to adulterate the product with TSE because of the bovine origin.

Severity scores	Process step	Material Origin	Material Composition	Material Complexity	Material Function	***Final score***
Peptone	upstream in fermentation with potential to disturb the manufacturing process (production lead time or yield) affecting delivery performance with risk of supply delay	animal origin, could transmit SE	complex composition, hard to analyze and to predict its performance	undefined peptone mixture of various chemicals	fermentation agent, no impact on product quality or patient safety	
	Direct Material failure does not affect product quality parameters but could cause negligible handling issues -> *severity score 2*	raw material failure adulterates product with risk of batch recall ***-> severity score 8***	raw material failure does not affect delivery performance -> *severity score 2*	raw material failure adulterates product with risk of product batch recall (risk of TSE) -> ***severity score 8***	raw material failure does not affect delivery performance -> *severity score 2*	***8***

Example 2 for severity score assessment for a raw material – Poloxamer

The second example is Poloxamer which is widely used as shear protectant in mammalian cell culture. In this example, Poloxamer has a significant effect on the yield of the assessed fermentation process, is of chemical origin, its composition is well understood and can be analyzed, its complexity is low and its function in the fermentation is important for the supply continuity. The severity score assignment for the five areas would look as follows:

Severity scores	Process step	Material Origin	Material Composition	Material Complexity	Material Function	***Final score***
Poloxamer	upstream in fermentation, does not affect product quality parameters -> *severity score 2*	Chemical origin, (e.g. excipient grade) with potential to open discrepancies, or to see minor defects -> *severity score 4*	Composition well understood, analytical methods available to predict its performance, potential to open discrepancy, or to see minor defects -> *severity score 4*	Complexity is low though a mixture of different polymers, potential to open discrepancy, or to see minor defects -> *severity score 4*	Shear protectant in cell culture with high impact on product yield and supply continuity, with potential to affect delivery performance with risk of supply interruption -> ***severity score 8***	***8***

Example 3 for severity score assessment for a raw material – Polysorbate

The third example is Polysorbate which is often used as excipient in biotechnology products formulations.

Severity scores	Process step	Material Origin	Material Composition	Material Complexity	Material Function	***Final score***
Polysorbate	Excipient in final drug product, could affect product quality parameters -> ***severity score 8***	Chemical origin, (e.g. excipient grade) with potential to open discrepancies, or to see minor defects -> *severity score 4*	Composition not well understood, no analytical methods available to predict its performance, potential to adulterate product with risk of batch recall ***-> severity score 8***	Complexity is low potential to open discrepancy, or to see minor defects -> *severity score 4*	Excipient to stabilize the protein solubility over the shelf life with potential to adulterate product with risk of batch recall ***-> severity score 8***	***8***

Probability of Occurrence

As mentioned earlier the probability of occurrence of the failure is derived from the supplier's performance. Performance data can be raw material failures detected in (A) incoming control (OOS) or (B) in production incl. foreign matter contamination e.g. during the last 12 months and (C) open major audit observations. Other information like the responsiveness to complaints (supplier lead time), the number of re-occurring deviations (CAPA effectiveness) etc. can be included in the supplier performance assessment. Weighing factors can be used to balance between the different elements of the performance assessment of the suppliers.

An example of a formula could look like:

$$A + 2B + 5C = Supplier\ Risk\ Score$$

In this example, the in-process raw material failures are weighed higher than the incoming raw material failures. Open major audit observations are weighed higher than raw material failures. The following table gives an indication how to classify Supplier Risk Scores calculated from the supplier information into overall supplier risk and probability of occurrence scores:

Supplier Risk Score	Supplier Risk	Probability of Occurrence Score
>25 (e.g. A>3, B>3, C>5)	High	10
10-25	Medium-high	8
2-9	Medium	6
0-2	Low	4

Primary Risk Number (PRN)

The multiplication of the severity score times the probability of occurrence score gives the **primary risk numbers (PRN)** between 8 and 100 in that example. The PRN can be used as a simplified measure for raw material risk. A risk-based application of quality oversight (like on-site audit interval) can be applied and adjusted, when the supplier risk assessment is repeated e.g. every half a year. In this case, the severity is a more static parameter whereas the supplier risk and the probability of occurrence is dynamic.

An example of a matrix of raw material risk and on-site audit interval could look like the following:

	Material Risk (Severity Score)					
		2	4	6	8	10
Supplier Risk (Probability of Occurrence Score)	2	4	8	12	16	20
	4	8	16	24	32	40
	6	12	24	36	48	60
	8	16	32	48	64	80
	10	20	40	60	80	100

In this case, red could correspond to a 2 year, yellow to a 5 year on-site audit frequency and green to no on-site audit but for example sending out a questionnaire only.

Suppliers can float between the different PRNs and further tools for quality oversight can be tied to either raw material risk (severity score), supplier risk (probability of occurrence) or PRN.
In other FMEAs, a probability of detection score (2 – 10) is assigned as well and multiplied with the PRN to get the Risk Priority Number (RPN). In cases of raw materials, the probability of detection can be neglected to keep it simple. A good rationale could be that e.g. all raw materials are controlled in QC and released for production before use.

European Biopharmaceutical Enterprises
Rue du Trône 108
Leopold Plaza Building
B-1050 Brussels, Belgium
T: +32 2 626 25 55
www.ebe-biopharma.eu

Follow EBE on Twitter @EBE_EU

Follow us on Linkedin