EBE Concept Paper

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

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Executive Summary

Effective management and control of raw materials (RM) used in the manufacture of biological medicinal products requires an appropriate framework to identify and focus on critical aspects that must be addressed from a quality, regulatory and business perspective. 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 have been included as well as discussion on phase-based mitigations.

The included example risk assessment methodology and model RM case studies are intended to demonstrate how 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.

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Abbreviations

API	Active Pharmaceutical Ingredient
ATMP	Advanced Therapy Medicinal Product
CTA	Clinical Trial Authorisation
CTD	Common Technical Document
EBE	European Biopharmaceutical Enterprises
EC	Established Conditions
FDA	Food and Drug Administration
HA	Health Authorities
ICH	International Conference on Harmonisation
LCM	Life Cycle Management
MA	Marketing Authorisation
Non EC	Non Established Conditions
PDE	Permitted Daily Exposure
PQS	Pharmaceutical Quality System
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RM	Raw Material
TTC	Threshold of Toxicological Concern
WHO	World Health Organisation

1. Objective and scope

The purpose of the present concept paper is to provide a framework to facilitate, guide and raise awareness to manufacturers of pharmaceutical products on the critical aspects of the management of raw materials (RM) across the product lifecycle.

The goal of this document is to:

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

This document covers raw materials (e.g. chemicals, cell culture media, buffers, resins) 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.

And in a second version of this document, the discussion will cover the following scope:

- The production of viral vector-based vaccines and advanced therapy medicinal products.

Even though excipients are not covered by the official definition of raw materials (See Definition in 3.1), the principles applied to RM can be applied to excipients as well.

This document will cover all development phases of the product, i.e. clinical development, commercialization and lifecycle management.

2. Background

2.1. Definition of raw material

Raw 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, raw materials must be defined and demonstrated to be suitable for their intended use in the manufacturing process. Defining raw materials requires that their role in the manufacturing process is contextualised and understood, where possible. In this respect, the manufacturing process for a biotechnological/biological medicinal product (typically recombinant proteins or monoclonal antibodies) can be considered to involve, first, the manufacture of the Drug Substance from starting materials and raw materials, and secondly, the manufacture of the Drug Product from the Drug Substance and raw materials and/or excipients.

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

Raw materials would therefore be process inputs other than starting materials required to manufacture the Drug Substance. Typical raw materials for a biotechnological/biological medicinal product would include cell culture medium and supplements, enzymes, the components of buffer solutions, and chromatographic resins. Once the Drug Substance has been isolated, the next step is to manufacture the Drug Product, which can be considered to be the Drug Substance in its final formulation.

In this Drug Product step, inputs other than the Drug Substance would typically be excipients rather than raw materials. 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. Typical excipients for biotechnological/biological medicinal products would include water-for-injections, simple buffer solutions and stabilisers such as sucrose. In summary, a perspective provided by the FDA [4] is that a raw material 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 Regulatory perspective on raw materials

2.2.1. General considerations

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 raw materials do not exist. However, the content of certain guidance documents can be extrapolated to inform the management and control of raw materials.

When considering the applicability of regulatory guidance, it is important to first understand the risks posed by raw materials when used to manufacture a biotechnological/biological medicinal product. These potential risks also depend on whether a raw material 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 raw materials 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 raw material itself. This is particularly relevant to raw materials of biological origin, or any raw material 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 raw materials 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 raw materials 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 raw material is a key element that needs to be controlled and managed. For this reason, raw materials that comply with a pharmacopoeial/compendial specification should be used, when possible. Conformance with a compendial specification indicates that a raw material can be considered suitable for use in a medicinal product manufacturing process, provided its microbiological quality is commensurate to its point of use (microbiological contamination risk assessment). Where pharmacopoeial specifications for certain raw materials are available in some territories but not others (e.g. in the United States Pharmacopoeia but not the European Pharmacopoeia), it may be possible to use the raw materials in territories where the specifications are not published with only limited testing. For non-compendial raw materials, it is usually necessary to develop in-house specifications with specific acceptance criteria that must be met (e.g. purity, identity, bioburden) before a raw material 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 raw materials because their unavailability would necessitate manufacturing process changes, and these changes would require amendments to CTAs and variations to MAs through comparability and validation studies.

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

2.2.2. 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 applications, 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.

Table 1: Examples for specific requirements from Health Authorities

Type of question	Description
Question related to the clearance of RM	Assessment of process-related impurity clearance should be performed during all clinical phases, and cover impurities arising from cell-culture RMs (i.e. antibiotics, media components, anti-foam residues) and downstream processing RMs (i.e. 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.

2.3 Challenges related to the management and control of raw materials

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 be of the highest quality

available to ensure the quality (according to ICH Q6B), safety and efficacy of the final medicinal product.

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 sometimes the complex composition of RM with a large number of components in the same RM, 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 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 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).

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

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) Foreign matter Adventitious agents Immunogenicity Particles 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 be also be carefully evaluated.
Human derived	Potential risks in terms of adventitious agents. Examples: human platelet lysate, human AB serum, 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 its life-cycle
- Well characterized/tested
- Well understood, especially its role in the manufacturing process and its interaction with active substance
- Compliant to global regulatory/compendial requirements
- 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 quality and safety of a pharmaceutical product (see Section 4.1.). The criticality depends on those multiple parameters/challenges presented above.

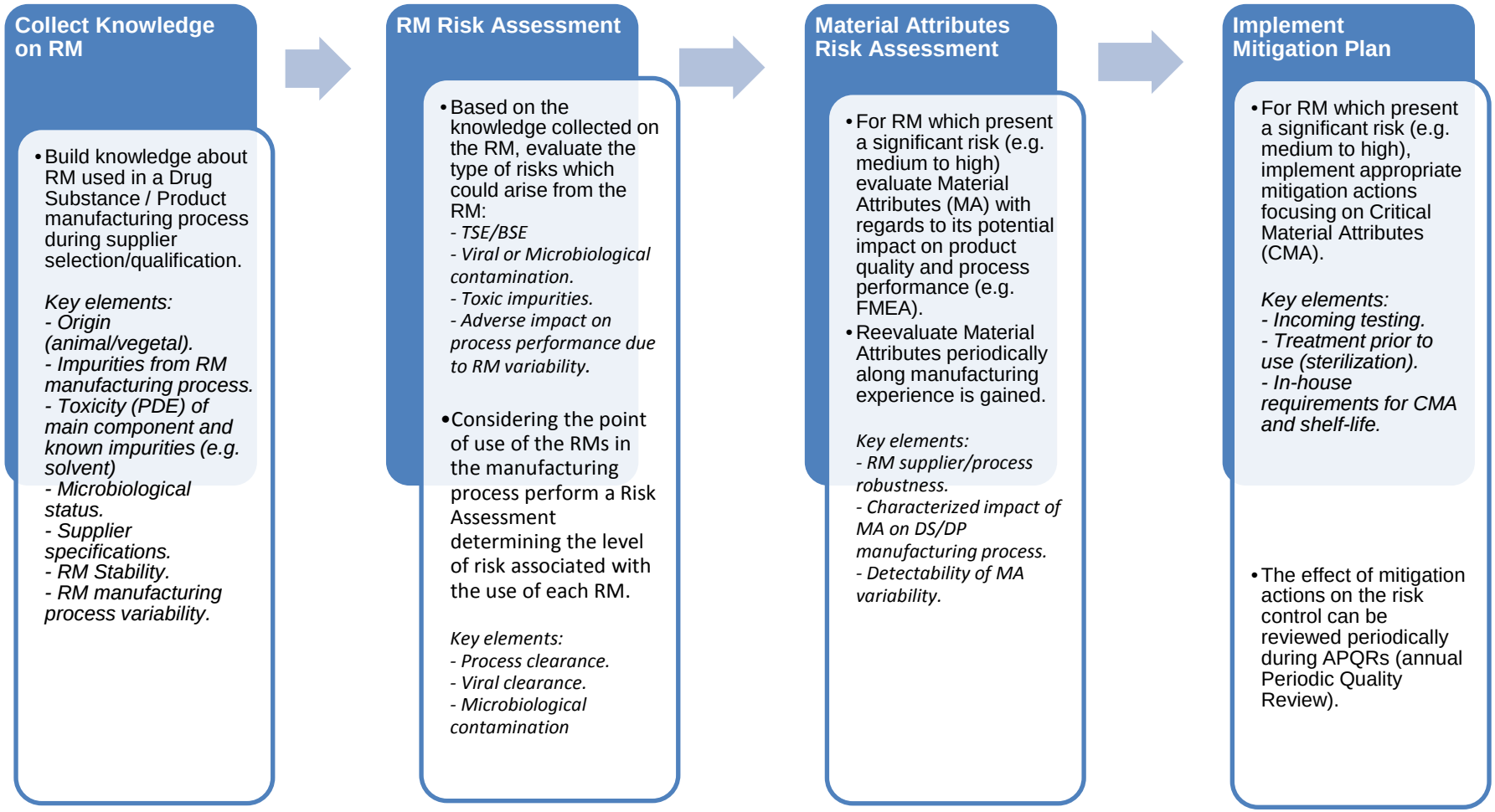
In accordance with ICH Q9, it is recommended to use a risk–based approach to define the criticality of the RM. In the following sections of this document, a risk assessment methodology for the management of RM is proposed and illustrated in several case studies from Industry.

3. Risk-based Approach

The level of control and quality management of RMs 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 and production mode of the RM, and considering its potential impact on the quality and toxicity of biological products as well as 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.
- How well it is characterized (including stability) and the level of understanding of its quality attributes on process and product interaction and related quality impact (material quality attribute (CMA) and relationship with 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 condition, 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 role.
    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 GMP incompliance 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 supply shortage.
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 cross-project platform understanding.

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 proposed risk assessment methodology follows a simple risk ranking and filtering approach [7]. More elaborated risk analysis methodologies could be implemented (e.g. FMEA). Table 3 provides an example of questions to help assess the quality risks and typical examples. Practical examples are proposed in section 3.3.2. to 3.3.4.

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	NaCl
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	Salts 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
1. Is the RM complex?	No, lower risk / Single component, well characterized.
2. Is the RM well defined?	Yes, lower risk / Single component.
3. Is the material of animal/human origin?	No, lower risk.
4. Is the TSE/BSE assessment available?	Yes, lower risk / Supplier provides certification.
5. Is the RM added in the late steps of the process?	Yes, higher risk / RM used late in the purification process.
6. 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).
7. Is a relevant analytical method available to assess its clearance?	No / Not considered a concern as process clearance not required to be demonstrated.
8. Is the level of quality of RM susceptible to impact product CQA?	No, lower risk (based on current process knowledge).
9. Is the production process of the RM 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.

Assessment Question	Answer / Comments
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 its 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 production process of the RM 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 internal release testing on every received lot.

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, an internal specification could 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 is more extensive than would be the case with a Low or Medium risk RM.

Table 6: Example of Internal 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.

These types of RM are not available as compendial materials, although many of their individual components may be. 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 platform 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
1. Is the RM complex?	No, medium risk / multiple components but chemically defined.
2. Is the RM well defined?	Yes, lower risk / chemically defined.
3. Is the material of animal/human origin?	No, lower risk.
4. Is the TSE/BSE assessment available?	Yes, lower risk / No animal derived components or supplier provides certification.
5. Is the RM added in the late steps of the process?	No, lower risk / opportunity for clearance.
6. 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.
7. Is a relevant analytical method available to assess its clearance?	No / Not considered a concern as process clearance not required to be demonstrated.
8. Is the level of quality of RM susceptible to impact product CQA?	Yes, medium risk (based on current process knowledge).
9. Is the production process of the RM generating high variability in the RM quality attributes	No, lower risk as vendor has tight controls on their manufacturing process (based on current process knowledge).

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

Assessment Question	Answer / Comments
1. Is the RM complex?	Yes, high risk / multiple components and undefined components (e.g. hydrolysates).
2. Is the RM well defined?	No, higher risk due to undefined components.
3. Is the material of animal/human origin?	No, lower risk.
4. Is the TSE/BSE assessment available?	Yes, lower risk / No animal derived components or supplier provides certification.
5. Is the RM added in the late steps of the process?	No, lower risk / opportunity for clearance.
6. 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.
7. Is a relevant analytical method available to assess its 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.
8. Is the level of quality of RM susceptible to impact product CQA?	Yes, high risk (based on current process knowledge).
9. Is the production process of the RM 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 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
	Identification 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 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. These types of RM are not available as compendial materials.

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
1. Is the RM complex?	Yes, high risk / complex, often sole-sourced material required for process effectiveness.
2. Is the RM well defined?	No, Low risk (based on both specific company and industry experience).
3. Is the material of animal/human origin?	No, lower risk.
4. Is the TSE/BSE assessment available?	Yes, lower risk / No animal derived components or supplier provides certification.
5. 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.
6. 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.
7. Is a relevant analytical method available to assess its clearance?	Yes, medium risk / Resin extractables and leachables identified components clearance must be demonstrated[1].
8. Is the level of quality of RM susceptible to impact product CQA?	Yes, high risk (based on current process knowledge).
9. Is the production process of the RM 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 Specification Developed for a "Dummy" Resin as Mitigation Activity1

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

3.4 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 13):

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

Table 13: 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	Marketing	Post marketing
- 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 PPQ batches preferably - trending of critical tests for high critical material over time and batches (part of CPV) - supplier audited for PPQ batches	- provide multiple sources of RM. - LCM: 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. Concepts regarding ICHQ12 will be considered along with ATMP products in a second version of this paper as those guidance documents and concepts continue to evolve.

5. Authors

The main authors of this concept paper are:

- Annick GERVAIS, UCB
- Nicole BLECKWENN, MedImmune
- Romain LE DEUN, Merck Serono
- Stacey Masaaki KANESHIRO, Lilly

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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

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

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

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