



RAW MATERIAL RISK ASSESSMENTS

**A HOLISTIC APPROACH TO
RAW MATERIAL RISK ASSESSMENTS
THROUGH INDUSTRY COLLABORATION**

**CONNECT
COLLABORATE
ACCELERATE™**

Contents

1.	Introduction	5
2.	Objective	7
3.	Definitions	8
4.	Scope	10
5.	Goals of raw material risk assessment	11
6.	Raw material attributes to consider when assessing risk	11
7.	How to differentiate risk – recommended factors and examples to consider	14
8.	A tool for quantitative risk assessment	20
	8.1 Quality functional deployment (QFD)	20
	8.2 Risk criteria	21
	8.3 Weighted score	23
	8.4 Total risk score	25
9.	Outcomes/deliverables	27
10.	Which functions/subject matter experts should participate?	28
11.	When to perform/frequency of review	29
12.	Data Management	31
13.	Other considerations	33
	13.1 Compliance/regulatory impact	33
	13.2 Risk management	33
14.	Case studies	35
15.	Acronyms	39

Contributors

The Raw Material Risk Assessments effort was co-led by Chiali Liu and Kara S. Quinn.

The document was assembled and written by Kara S. Quinn with contributions from the following member companies:

Ajinomoto Biotechnology Corp

Zackary Paulakovich

Alexion Pharmaceuticals, Inc.

Susan Neenan

Biogen Inc.

Aaron Mack, Patrick Moebius

Bristol Myers Squibb

Mitchell Bennett

Catalent Biologics

Claudia Berdugo-Davis

GlaxoSmithKline, Plc.

Ann Ly

Janssen Pharmaceutical

Chiali Liu (Co-lead)

Merck & Co., Inc.

Laura K. Bentley

Ewelina K. Flamm

Kara S. Quinn (Co-lead and Author)

Pfizer Inc.

Dan Lasko

BioPhorum

Julian Goy

This BioPhorum Operations Group Guidance Document on Raw Material Risk Assessments represents the combined work of the Raw Material Risk Management team within the Drug Substance Phorum Raw Material Variability workstream.

The team would like to acknowledge our facilitator, Julian Goy, particularly for knowing when to stop facilitating. Thank you for giving us the time and focus to align our efforts and work through the debate.

The team would also like to thank Duncan Low of Claymore Biopharm LLC., for his invaluable expertise and mentorship on the complex topic of raw material use in biopharmaceutical manufacturing and associated risks. Table 2: Raw material risk categories, published in *Managing Raw Materials in the QbD Paradigm*, Part 1: Understanding Risks article, co-authored by Duncan Low in *BioPharm International* Volume 23, Issue 11, was a foundational inspiration for the development of the qualification categories.

About BioPhorum

The BioPhorum Operations Group's (BioPhorum's) mission is to create environments where the global biopharmaceutical industry can collaborate and accelerate its rate of progress, for the benefit of all. Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum now comprises 53 manufacturers and suppliers deploying their top 2,800 leaders and subject matter experts to work in seven focused Phorums, articulating the industry's technology roadmap, defining the supply partner practices of the future, and developing and adopting best practices in drug substance, fill finish, process development and manufacturing IT. In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

1.0

Introduction

Regulations for current Good Manufacturing Practices (cGMPs) dictate the development of a system within the biopharmaceutical industry for the selection, qualification, and approval of raw materials and their suppliers, both initially and periodically. In addition to testing and acceptance programs, raw material and supplier management systems set the standards by which companies ensure that materials procured from appropriate supply chains meet the technical, regulatory, and supply needs for the designated use and function, referred to as 'fit-for-use' or 'fit-for-function'. When identifying risks associated with raw materials, any potential for misalignment in the fit-for-function status should be assessed.

However, raw materials within the biopharmaceutical industry are not defined by a single set of regulatory/compliance/quality criteria, since one set cannot practically serve all possible fits and functions. Even a common standard ingredient (e.g. salt or sugar) can have a wide range of designated functions with differing criteria for fit. Similarly, compendia monographs (e.g. United States Pharmacopeia (USP)-National Formulary (NF), Pharmacopeia Europe (Ph. Eur.), Japanese Pharmacopeia (JP), etc.) are limited to the standardization of raw material identification and characteristics as they are used in multiple medicinal industries, not just biopharmaceuticals. As such, monographs do not comprehensively address the unique quality and safety attributes necessary for use in biopharmaceuticals¹. Instead, regulatory guidance asserts that it is in fact the medicinal product manufacturer's responsibility to decipher the level of supervision required to establish and maintain the qualified status of a procured raw material, as well as the stringency with which GMPs are to be applied². The guiding principle, it seems, is that oversight should be proportionate to the risks posed by the specific material to its unique designated function and purpose, as developed by the medicinal product manufacturer, accounting for material origin, derivation and supply chain complexity, etc.³

¹ U.S. Department of Health and Human Services, Food and Drug Administration, CDER / CBER, *Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005)

² ICH Q7, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, Section 1.3, Scope

³ EU (2015/C 95/02), *Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use*, Chapter 2.3

International Conference on Harmonisation (ICH) Q7A *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (APIs) introduces the concept that the rigor with which GMP standards are applied should increase as the medicinal manufacturing process proceeds from early drug substance manufacture to the final stages. This concept of escalating application of GMPs aligns precisely with the transition of scopes from ICH Q7A Drug Substance to EudraLex Volume 4 and 21CFR200 Drug Product standards. Although notably excluded from ICH Q7A as out of scope, raw material manufacturing in support of biopharmaceutical development is likely more of a 'runway' to the GMP continuum, with the application requiring reasonable interpretation in the context of proportionate risk to GMP 'lift-off'.

The delegation of GMP standard oversight and the allowance for 'reasonable interpretation' and 'proportionate risk' likely enables arbitrary differences in raw material management, qualification, and requalification within the biopharmaceutical industry. When the applied definition of cGMP is flexible to individual circumstances, it is typically the inherent 'risk cultures' (i.e., tolerance or aversion to risk-based decision-making) within each company that more strongly influences the application of GMP standards, often independent of the unique fit-for-function considerations. Currently, raw material suppliers face diverse, sometimes conflicting customer requirements; the result of varying interpretations of the same regulations and GMPs. There is a significant opportunity within the biopharmaceutical industry for alignment on a common set of raw material attributes to consider when discussing risk, for broader agreement on the perspectives of high versus low risk; and for a shared methodology to assist in determining the proportionality of risk.

However, standardization in an industry that is operating to meet a broad spectrum of deliverables is a significant task. What is considered fit-for-function can change significantly depending on the product and customer. A list of the considerations is outlined below, for example:

- clinical product/process development versus commercial supply
- Good Clinical Practices (GCPs) versus GMPs
- country-specific versus global regulations
- sterile injectable versus oral dosage forms
- prophylactic versus therapeutic versus compassionate indications
- healthy patients versus vulnerable, immunocompromised, or near-death patients
- chemically-synthesized and pure versus undefined naturally-derived materials
- materials with a long history of established safety in humans versus novel materials
- commercially available off-the-shelf versus sole-sourced or proprietary materials
- non-compedia assay development versus multi-compedia harmonization.

Subject matter experts (SMEs) from a variety of disciplines and functions within the biopharmaceutical industry committed to a process of developing a common language with full appreciation that both the 'fit' and 'function' could be highly variable and proprietary. As the BioPhorum Raw Material Variability team embarked on standardization, some key principles were developed:

- the methodology must be reproducible within a variety of contexts and not restricted to product-specific scenarios
- the rigor of the analysis must be adaptable to organizations of all sizes
- the quantitative tool used to distribute proportional risk must allow for flexibility and differing scales of risk tolerance.

2.0

Objective

The objective of this document is to provide an aligned industry perspective on the risks associated with raw material qualification within biopharmaceutical manufacturing and a step-by-step adaptable method to assess raw material risk. The deliverable is a comprehensive, practical working tool that does not demand exhaustive resources to prioritize proportionate risk effectively. The methodology is not intended to be prescriptive or one size fits all but offers flexible options so that the impact of ‘risk realization’ is measured consistently but in terms that are most meaningful to the assessor.

Often the topic of assessing raw material risk quickly, perhaps prematurely, eliminates entire categories of raw materials from further in-depth assessment based solely on one-dimensional attributes (e.g. non-excipient use, non-animal origin, or low-risk region of manufacture). This document sets out to provide:

- a holistic approach to the assessment of all raw materials used in biopharmaceutical manufacturing, identifying common attributes to consider (Table 6.1)
- shared examples of high, medium, and low risks (Tables 7.1, 7.2, 7.3)
- criteria for determining misalignment in fit-for-function (Section 8.2)
- methods for quantitative/comparative analysis (Sections 8.3, 8.4)
- outcomes and deliverables (Section 9)
- recommended functional representation (Section 10)
- suggested timing and frequency of assessment (Section 11)
- a worksheet for knowledge management (Section 12)
- case studies (Section 14).

3.0

Definitions

Table 3.1: Material definitions

Term	Definition
Ancillary raw materials	Raw materials used during the drug substance processing that are not intended to be a part of the final product formulation. Commonly: solvents, inorganic salts/buffers, defoaming agents, carbohydrates/energy sources, amino acids, trace elements, vitamins, growth media, etc.
Biologic starting materials	Biotechnological cell constructs, substrates, banks, seeds, etc. as defined by EMA/CHMP/BWP/429241/2013.
Excipients	Raw materials intentionally added to create the final drug product formulation in quantifiable amounts intended to perform a specific function. Commonly: stabilizers, buffers, diluents, preservatives, adjuvants, etc.
GMP support materials	Procured materials supporting GMP manufacturing without direct product contact. Commonly: Clean-In-Place (CIP), cleaning agents/disinfectants, aseptic gowning materials, process equipment gaskets, process simulation media, etc.
Laboratory reagents	Used as part of analytical testing either in-line/in-process or offline, with no contact with the process stream.
Primary packaging components	Container closure systems and device components directly responsible for the delivery of the final drug product. Commonly: vials, stoppers, syringes, caps, needles, plungers, etc.
Process aids	Materials used to facilitate the manufacturing process that are not consumed during processing and may or may not be multi-use. Commonly: resins, chromatography columns, process filters, intermediate containers, etc.
Process gases	Procured compressed gases directly added to the process stream to perform physical, chemical, or biochemical reactions and are consumed during processing. Commonly: overlays / sparged gasses in bioreactors or fermenters, pressure sources, drying agents, freezing agents, etc.
Raw materials	A general term used to describe manufacturing ingredients consumed in the process that may or may not be present in the final drug product.
Single-use components	Components directly contacting the process stream for a single purpose and discarded. Commonly: bio-process bags, tubing, hoses, filters, connectors, gaskets, o-rings, microcarriers, etc.
Other	Other procured materials that do not meet the definitions provided above.

Table 3.2: Risk definitions

Term	Definition
Fit-for-use / Fit-for-function	The qualified state of procured raw materials used in commercial human medicinal product manufacturing through the active verification that the supply chain is capable of providing the necessary material attributes to meet the designated user requirements.
Qualification category	Fit-for-use or fit-for-function qualification requires alignment between three categories of assessment: user requirements, material attributes, and supply chain.
Risk attributes	A common set of features or factors within each qualification category. User requirements, material attributes, and supply chain are used as a guide to establish the type of information necessary to assess fit.
Score	A quantitative measure of the 'likelihood to occur' or the likelihood for a risk to be present for a given raw material risk attribute.
Scale	A qualitative distribution of scores or weights intended to differentiate a continuum of high to low.
Risk criteria	The alignment of topic-relevant risk attributes between the qualification categories for the purpose of determining fit. The degree to which the relevant attributes do not align is risk.
Adjusted score	A quantitative measure of the risk criteria indicating misalignment in fit-for-function attributes and severity.
Weight	A quantitative factor designed to differentiate risk instances based on the perceived impact of risk realization. It defines what is impacted and to what degree, or tolerance, to an organization.
Risk profile	The qualitative scales defining 'what' is impacted and the severity of the impact within a unique risk assessment.
Weighted score	Raw material risk criteria adjusted score multiplied by risk criteria weight.
Total risk score	The sum of weighted scores for each risk criteria for a specific raw material.
Proportionate risk	A list of raw materials for which the quantified risk to fit-for-function are prioritized by those for whom risk-realization outcomes are least tolerable or higher priority for mitigation.

4.0

Scope

This guidance applies to procured raw materials, used in the production of biopharmaceutical intermediates, drug substance, and drug product that have not been excluded below (Table 4.1).

Table 4.1: Scope

In:	There are two distinct categories of procured raw materials within the scope of this document:
	<ul style="list-style-type: none">• ancillary raw materials• excipients.
Optional:	Additional categories of procured raw materials that may benefit from the same or a similar analysis include:
	<ul style="list-style-type: none">• resins• process gases.
Out:	The following procured materials are not within the scope of this document:
	<ul style="list-style-type: none">• procured biologic starting materials and/or intermediates• procured product contact materials used to facilitate the manufacturing process and/or store the product intermediate or final dosage, to include: single-use components, primary packaging components, intermediate containers, process filters, CIP / cleaning agents• procured raw materials with no direct contact with the drug substance or product manufacturing stream, to include: GMP support materials, laboratory reagents, other.

The methodology developed within this document relies on the comparative analysis of like risk attributes. The risk attribute definitions must apply to all of the material types within the scope of the assessment in order to deliver a meaningful analysis of proportionate risk. Thus ancillary raw materials and excipients were chosen to demonstrate the Raw Material Risk Assessment. However, the BioPhorum team would like to emphasize that the tools and methodology provided are readily adaptable and encourage relevant subject matter experts to adjust the risk attribute definitions and scales to align to the unique considerations of the other material types.

5.0

Goals of raw material risk assessment

- To identify risks proactively that could contribute to interruption of raw material sourcing, material performance, and material qualification essential to the supply of safe, efficacious, biopharmaceutical drug products.
- To prioritize resources in the pursuit of risk mitigation/resolution proportionate to the potential for impact on patient safety and public health as a result of interruption of supply.

6.0

Raw material attributes to consider when assessing risk

Qualification of raw materials used within biopharmaceutical product manufacturing, must consider three fundamental questions:

- What function is the raw material designated to perform?
- What material attributes are essential to the designated function versus what might have unintended consequences?
- Are there reliable supply chains available within the marketplace to assist in addressing the first two questions by providing materials of reasonable quality, both initially and in an ongoing capacity?

Answering these questions gives a simple example of how to select procured raw materials for fit-for-function. However, for those tasked with executing raw material qualification in the biopharmaceutical industry, it is only a surface scratch to the substance of the three fit-for-use qualification categories:

- **User requirements:** the designated function of the chosen raw material; for example, at what phase of production the raw material is introduced to the process, whether the raw material will be delivered in the final drug product; the process needs for sterility assurance, compendia grade, or custom packaging, etc.

- **Material attributes:** the unique characteristics of the raw material must be well understood; is it growth-promoting, pure, stable, well-characterized (i.e., compendia monograph), flammable, or hazardous in other ways?
- **Supply chain:** is the selected supplier capable of producing materials of reasonable quality? Are quantities available to fill the demand? Does the marketplace offer multiple sources of equivalent material that meet pharmacopeia needs with sufficient technical and regulatory support despite quantities purchased and expectations for high customer support?

Specific attributes were defined within each qualification category to develop a comprehensive list of the necessary types of information commonly considered to assess fit. For the purposes of this risk assessment methodology, the listed items are termed risk attributes.

The recommended risk attributes for consideration are given in Tables 6.1, 6.2 and 6.3, together with example questions to prompt thorough assessment.

Table 6.1: User requirements risk attributes

USER REQUIREMENTS (UR)		
Patient exposure	Impact to product quality	Impact to process
<ul style="list-style-type: none"> Will the RM function as an excipient intentionally added for delivery? Is the RM a known residual? Is the RM removed upstream? 	<p>Always assuming the RM is in fact added to the process as intended:</p> <ul style="list-style-type: none"> will the RM individually and/or specifically result in OOS of a CQA, KPA, or other process attribute necessary for product acceptance? 	<p>Always assuming the RM is in fact added to the process as intended:</p> <ul style="list-style-type: none"> will the RM individually and/or specifically disrupt a CPP, KPP, or other process parameter deemed indicative or necessary for process control?
Microbial restrictions	Regulatory/compendia requirements	Material acceptance requirements
<ul style="list-style-type: none"> Will the RM be added to the product/process upstream or downstream of the sterile envelope? Will the RM undergo further processing to modify microbial content? 	<p>Does the function of the RM dictate:</p> <ul style="list-style-type: none"> novel excipient approval? adherence to compendia grade? reporting of detailed acceptance criteria in the dossier? 100% ID testing? 	<p>Does the RM container design need to account for:</p> <ul style="list-style-type: none"> single-use or multi-use quantities? sterility assurance? 100% ID testing? unique sampling or handling conditions necessary to meet functional requirements?

Table 6.2: Material risk attributes

MATERIAL ATTRIBUTES (MA)		
Microbial characteristics	Origin, composition, structural complexity	Material shelf life and stability
<ul style="list-style-type: none"> Is the RM non-sterile, bioburden-reduced, or sterile? Is the RM growth-promoting, bacteriostatic, or bacteriocidal? Does the RM require container closure integrity to maintain acceptable microbial characteristics? 	<ul style="list-style-type: none"> Is the RM derived from chemical, mineral, microbial, plant, or animal origin? Is the RM pure or a composition? Does the RM have a defined chemical formula, defined structure, or is undefined? Is the origin/composition inherently at risk for adventitious agents or other naturally occurring impurities (e.g., metals, toxins)? 	<ul style="list-style-type: none"> Is the RM stable? Is there data to support stability? Does the RM require adherence to specific handling controls to maintain acceptance criteria throughout shelf-life; temperature (e.g., controlled room temp, refrigerated, frozen), humidity, light exposure, oxygen/nitrogen overlay, etc.?
Manufacturing complexity and impurities	Analytical complexity/compendia status	Material handling requirements
<ul style="list-style-type: none"> Is the RM produced by chemical-synthesis, biosynthesis, bioconversion, or refinement of natural substances? Does the RM manufacturing process introduce, eliminate, concentrate potential impurities? Is the manufacturing process robust or highly variable? 	<ul style="list-style-type: none"> Does the RM have an existing pharmacopeia compendia monograph for standardized identification and characterization? Is the RM non-compendia? Is the RM complex and proprietary requiring significant method development to effectively identify and characterize (e.g., high molecular weight contaminant; Poloxamar)? 	<ul style="list-style-type: none"> Does the RM require unique, particular, or complicated shipping or storage conditions in order to maintain the qualified shelf life?

Table 6.3: Supply chain risk attributes

SUPPLY CHAIN (SC)		
Supplier quality system performance	Continuity of supply	Supplier technical capability
<ul style="list-style-type: none"> • Does the supplier adhere to certified or regulated quality system standards (e.g., ISO, IPEC, GMP, etc.)? • Has the supplier met the requirements of quality assessment? • Does the supplier effectively implement CAPAs? 	<ul style="list-style-type: none"> • Is the supplier the only manufacturer of the material (e.g., sole-source)? • Do other suppliers offer the material? • Are alternate suppliers approved for dual sourcing? • Is the supplier constrained by sourcing? • Are lead times long? • Is shelf-life short? • Is safety stock maintained? 	<ul style="list-style-type: none"> • Is the supplier considered an expert in their field? • Is the supplier familiar with the challenges of biopharmaceutical manufacturing standards? • Is the supplier the expert in the analytical characterization and method performance for the material? • Does the supplier assist in investigating deviations? • Is the supplier shelf life supported by data?
Supplier relationship	Supplier material grade	
<ul style="list-style-type: none"> • Is the supplier established or new? • Is biopharma considered a nuisance customer? • Is the RM proprietary to the supplier or custom manufacture on behalf of biopharma? • Is the supplier forthcoming and transparent with information exchange? • Is the full supply chain visible? • Does the supplier effectively provide prior notification of changes? • Does the supplier effectively manage third-party suppliers? 	<ul style="list-style-type: none"> • Does the supplier offer compendia-grade or technical-grade material? • Does the supplier offer multi-compendia or compendia of specific interest? • Does the supplier certify compendia grade or test to meet compendia specifications? 	

7.0

How to differentiate risk – recommended factors and examples to consider

For each risk attribute listed in Table 6.1, 6.2, 6.3, specific examples are developed in Tables 7.1, 7.2, and 7.3. The examples are differentiated by the 'likelihood to occur', or the likelihood of a potential risk being present. The examples in Tables 7.1, 7.2, and 7.3 are not exclusive. They demonstrate variations in risk and give a shared industry perspective on scale. For simplification and adaptability, the tool in this document uses a qualitative scale: high, medium and low. However, in order to quantitatively distribute risk in a cumulative manner, the scales should be differentiated by numbers, or scores. The actual numerical value assigned to each scale can be determined by the user, but consideration should be given to avoiding diminishing granularity by having too many scales or by assigning numbers that are too close together (e.g. 1, 2, 3, etc.). For the purposes of the case studies provided in this document, scores are assigned as follows: high = 9, medium = 3, and low = 1.

Table 7.1: Examples of risk scales for user requirement attributes

User requirement attributes	Score	Examples may include:
Patient exposure	Low	Ancillary raw materials; low potential that raw material would be delivered to the patient at administration (e.g. downstream purification); low potential to impact patient safety, efficacy, etc.
<ul style="list-style-type: none"> Will the RM function as an excipient intentionally added for delivery? Is the RM a known residual? Is the RM removed upstream? 	Medium	Ancillary raw materials that serve specifically to aid the process in the removal of measurable or label-specified drug product impurities (e.g., benzonase>DNA; nuclease>allergenic proteins; etc.), ancillary raw materials likely to be present in residual or trace amounts (i.e., often mentioned on label); acids or bases used to pH the final drug product formulation
	High	Excipients; high potential to be delivered to the patient; exist in measurable quantities in the drug product to serve a specific function in the delivery
Impact to product quality	Low	Low likelihood to impact in-process or off-line quality attributes, lot disposition, CQAs, etc.
Always assuming the RM is in fact added to the process as intended: <ul style="list-style-type: none"> Will the RM individually and/or specifically result in OOS of a CQA, KPA, or other process attribute necessary for product acceptance? 	Medium	Medium likelihood to impact in-process or off-line quality attributes, lot disposition, CQAs, etc.
	High	High likelihood to impact in-process or off-line quality attributes, lot disposition, CQAs, etc.
Impact to process	Low	Low likelihood to impact in-process parameters (i.e., CPP, KPP, KOPs, yields, titers, cell count, etc.)
Always assuming the RM is in fact added to the process as intended: <ul style="list-style-type: none"> Will the RM individually and/or specifically disrupt a CPP, KPP, or other process parameter deemed indicative or necessary for process control? 	Medium	Medium likelihood to impact in-process parameters (i.e., CPP, KPP, KOPs, yields, titers, cell count, etc.)
	High	High likelihood to impact in-process parameters (i.e., CPP, KPP, KOPs, yields, titers, cell count, etc.)
Microbial restrictions	Low	Product is non-sterile; process is non-aseptic; does not require sterile, bioburden-reduced, or micro-Limits characterized raw materials
<ul style="list-style-type: none"> Will the RM be added to the product/process upstream or downstream of the sterile envelope? Will the RM undergo further processing to modify microbial content? 	Medium	Product is sterile or bioburden-controlled; process is bioburden-controlled; warrants bioburden-reduced or micro-limits characterized raw materials
	High	Product is sterile; process is aseptic; requires sterile raw materials
Regulatory/compendia requirements	Low	Ancillary raw materials, no requirement to meet compendia grade; or excipients, fully compliant to compendia; or no regulatory impact as the dossier does not require, or have details of, the raw material
Does the function of the RM dictate: <ul style="list-style-type: none"> novel excipient approval? adherence to compendia grade? reporting of detailed acceptance criteria in the dossier? 100% ID testing? 	Medium	Excipient is non-compendia, no compendia exists; biomanufacturer responsible for defining critical tests and specifications; or raw material details are required or present within the dossier triggering notification; or use of a standard/technical grade excipient that is tested to meet compendia
	High	Change to existing dossier excipient; or novel excipient; or raw material details are required or present within the dossier triggering prior approval
Material acceptance requirements	Low	Typical lot identity testing upon receipt
Does the RM container design need to account for: <ul style="list-style-type: none"> single-use or multi-use quantities? sterility assurance? 100% ID testing? unique sampling or handling conditions necessary to meet functional requirements? 	Medium	100% container identity testing upon receipt; or retention samples required; or beginning/middle/end or top/middle/bottom sampling required; or sterility testing required; or tailgate sample risk assessment required; or reduced testing risk assessment required
	High	100% container identity required of a sterile raw material; or pre-acceptance testing required; or single-use container sampling; or point-of-use release; or tailgate sampling without acceptable risk analysis

Table 7.2: Examples of risk scales for material attributes

Material attributes	Score	Examples may include:
Microbial characteristics	Low	Raw material is bacteriocidal; or a non-sterile dry powder; or a non-sterile liquid with bioburden criteria or micro-limits
<ul style="list-style-type: none"> Is the RM non-sterile, bioburden-reduced, or sterile? Is the RM growth-promoting, bacteriostatic, or bacteriocidal? Does the RM require container closure integrity to maintain acceptable microbial characteristics? 	Medium	Raw material is bacteriostatic with no lot assessment of microbial content; or a non-sterile liquid with no assessment of microbial content; or growth promoting with lot sterility testing and container closure integrity
	High	Raw material is growth promoting without confirmatory sterility testing, it may or may not be sterile-filtered or have CCI
Origin, composition, structural complexity	Low	Raw material is chemically-defined, may or may not have a defined purity/assay specification, and has no exposure to materials of animal origin (i.e., ACDF, single-use/ disposable, dedicated, cleaning validation, etc.)
<ul style="list-style-type: none"> Is the RM derived from chemical, mineral, microbial, plant, or animal origin? Is the RM pure or a composite? Does the RM have a defined chemical formula, defined structure, or is undefined? Is the origin/composition inherently at risk for adventitious agents or other naturally occurring impurities (e.g., metals, toxins)? 	Medium	Raw material is a chemically-defined composite (i.e., many different ingredients of defined materials); or raw material is intentionally exposed to materials of animal origin during manufacture (i.e., tertiary origin/exposure); raw material is of defined plant origin with potential exposure to inherent impurities; or raw material is well-defined or structurally-defined without chemical purity (i.e., PEG, starches, HEPEs)
	High	Raw material is of primary animal origin; or the composite contains an ingredient of primary animal origin (i.e., secondary origin/exposure); or of undefined plant origin; or of undefined composition (i.e., proprietary formulations); or has exposure to these materials through shared equipment
Material shelf life and stability	Low	Raw material has an established stability profile based on relevant stability data to support shelf life
<ul style="list-style-type: none"> Is the RM stable? Is there data to support stability? Does the RM require adherence to specific handling controls to maintain acceptance criteria throughout shelf-life; temperature (e.g., controlled room temp, refrigerated, frozen), humidity, light exposure, oxygen/nitrogen overlay, etc.? 	Medium	Raw material is known to be stable but no data exists (i.e., technical literature to support); or raw material is known to be unstable but adequate packaging controls are in place
	High	Raw Material is of unknown stability, no stability data is available, and there is no technical literature to support shelf life
Manufacturing complexity and impurities	Low	Raw material is manufactured through synthesis (i.e., chemical, biologic); or manufacturing process is known to be highly reproducible and consistent; or there is low likelihood or experience confirming low variability Manufacturing process limits or removes impurities (i.e., metal catalysts, residual solvents); raw material manufacturing or composition is not susceptible to counterfeiting or falsification; low likelihood of impurities
<ul style="list-style-type: none"> Is the RM produced by chemical-synthesis, biosynthesis, bioconversion, or refinement of natural substances? Does the RM manufacturing process introduce, eliminate, concentrate potential impurities? Is the manufacturing process robust or highly variable? 	Medium	Raw material is of unknown variability with limited experience Raw material has impurity analysis either because it is naturally-derived with refinement or manufacturing conditions are known to introduce or concentrate potential impurities (i.e., high temperatures, extreme pH, extreme humidity, high pressure, high-speed moving parts, gram-negative bacterial fermentation)
	High	Raw material is known to be of variable composition, analytically inconsistent, or perform with variable results Raw material lacks impurity analysis despite being naturally-derived with refinement or manufacturing conditions are known to introduce or concentrate potential impurities (i.e., high temperatures, extreme pH, extreme humidity, high pressure, high-speed moving parts, gram-negative bacterial fermentation); or raw material composition or analytical methods are susceptible to falsification or counterfeiting

Table 7.2 continued: Examples of risk scales for material attributes

Material attributes	Score	Examples may include:
Analytical complexity/compendia status <ul style="list-style-type: none"> Does the RM have an existing pharmacopeia compendia monograph for standardized identification and characterization? Is the RM non-compendia? Is the RM complex and proprietary requiring significant method development to effectively identify and characterize (e.g., high molecular weight contaminant; Poloxamar)? 	Low	Raw material can be adequately characterized using standard assays; or a compendia exists
	Medium	Raw material characterization is dependent on an assay that is technique dependent (i.e., activity assays)
	High	Existing analytical methods used to determine raw material acceptance are not reproducible, non-robust/low reliability, low validity rate, invalid system suitability, or not developed or readily accessible
Material handling requirements <ul style="list-style-type: none"> Does the RM require unique, particular, or complicated shipping or storage conditions in order to maintain the qualified shelf life? 	Low	Standard material handling requirements (i.e., room temp, ambient, etc.)
	Medium	Requires temperature controlled shipping and storage; or is hygroscopic, or light sensitive, etc.
	High	Requires nitrogen overlay after sampling or dispensing; or temperature monitoring (TOR) during shipping and storage; or specific packaging configurations or environmental conditions during shipping (i.e., do not use dry ice, do not airfreight)

Table 7.3: Examples of risk scales for supply chain attributes

Supply chain attributes	Score	Examples may include:
Supplier quality system performance	Low	The supplier has been approved through quality assessment (i.e., approved and active); or the supplier is a GMP manufacturer, serving the biopharmaceutical industry; or the supplier is a health authority inspected manufacturer; or a supplier quality agreement is in place
<ul style="list-style-type: none"> Does the supplier adhere to certified or regulated quality system standards (e.g., ISO, IPEC, GMP, etc.)? Has the supplier met the requirements of quality assessment? Does the supplier effectively implement CAPAs? 	Medium	The supplier has been categorized as preliminary or conditionally approved until further quality assessment; or the supplier has been approved historically but is currently inactive; or the supplier is non-GMP, but has established quality system standards; or the supplier is approved and active but recent health authority action (i.e., warning letter) requires surveillance; or the supplier refuses to sign a full quality agreement, opting for subject specific agreements
	High	The supplier has not been approved through quality assessment (i.e., not approved or not assessed); or the supplier has refused to allow assessment of quality systems (i.e., qualified based on sample performance)
Continuity of supply	Low	There are multiple qualifiable source manufactures available in the marketplace; or the item is off-the-shelf routinely manufactured year-round; or the item can be ordered with short lead time; or the item does not require safety stock contingencies
<ul style="list-style-type: none"> Is the supplier the only manufacturer of the material (e.g., sole-source)? Do other suppliers offer the material? Are alternate suppliers approved for dual sourcing? Is the supplier constrained by sourcing? Are lead times long? Is shelf-life short? Is safety stock maintained? 	Medium	The item is single-sourced from one manufacturer but, the supplier manufactures from multiple available sites; or the IP is transferrable; or the item is a custom product tied to supply agreement; or a safety stock program is possible/in place
	High	The supplier is a sole-source manufacturer, there is no other manufacturer in the world; or the item requires a long lead time for manufacturing and receipt; or market availability is reliant on unassociated markets (i.e., veal consumption); or the market is subject to geo-political issues; or a safety stock program is not an option
Supplier technical capability	Low	The supplier is also the manufacturer; or the supplier specializes in purveying the type of materials or the method of manufacture for the materials; or the item is a custom material collaboration; or the item is a proprietary material for which the supplier is fully willing to partner on data queries and investigations, etc.; or the item comes with comprehensive COA testing indicative of fit-for-use; or the supplier is qualified to test on behalf with specifications tighter than acceptance criteria
<ul style="list-style-type: none"> Is the supplier considered an expert in their field? Is the supplier familiar with the challenges of biopharmaceutical manufacturing standards? Is the supplier the expert in the analytical characterization and method performance for the material? Does the supplier assist in investigating deviations? Is the supplier shelf life supported by data? 	Medium	The supplier does not manufacture but performs re-package/re-test/re-label without detailed knowledge of the manufacturing process or the material; or the supplier only provides characterization testing of the material or uses different assay methodologies or reports specifications misaligned to acceptance criteria
	High	The supplier is solely the distributor (i.e., no re-pack, re-test, etc.); or the supplier does not provide technical assistance or additional insight to proprietary material; or the supplier provides limited pertinent characterization testing or specifications outside of acceptance criteria

Table 7.3 continued: Examples of risk scales for supply chain attributes

Supply chain attributes	Score	Examples may include:
Supplier relationship	Low	Each supply chain node is fully known back to the source manufacturer with effective change notification in place for both process and location, on-site audits are allowed and performed; or the supplier audit program is qualified in place of biopharma audit program; or there is an established working relationship to mutually resolve concerns, the supplier is attentive to biopharmaceutical customer needs and provide open dialogue for a mutual understanding of risks/benefits within biopharma
<ul style="list-style-type: none"> • Is the supplier established or new? • Is biopharmaceutical considered a nuisance customer? • Is the RM proprietary to the supplier or custom manufacture on behalf of biopharmaceutical? • Is the supplier forthcoming and transparent with information exchange? • Is the full supply chain visible? • Does the supplier effectively provide prior notification of changes? • Does the supplier effectively manage third-party suppliers? 	Medium	The source manufacturer is known or available by code sufficient to enable quality assessment; or there is limited change notification in place; or the supplier has been approved through quality assessment but the supplier is new or unknown in terms of routine business
	High	The source manufacturer is unknown and not disclosed for proprietary reasons, neither on-site audits or quality assessment is granted, change notification of source manufacturer or process-related changes are not granted; or the supplier provides commodity items for which the biopharm industry is not the intended customer (i.e., food industry, etc.), and biopharmaceutical regulatory standards are not recognized
Supplier material grade	Low	Suppliers readily offer multi-compedia or pharmacopeial-specific grade materials manufactured by GMPs; or the material does not have an existing compedia monograph
<ul style="list-style-type: none"> • Does the supplier offer compedia-grade or technical-grade material? • Does the supplier offer multi-compedia or compedia of specific interest? • Does the supplier certify compedia grade or test to meet compedia specifications? 	Medium	The supplier offers compedia grade but not from the desired pharmacopeia; or the material is purchased ACS/reagent; or the material is tested to meet compedia but is not manufactured by GMPs
	High	The supplier offers technical/standard grade materials (i.e., compedia exists but material is not manufactured to meet it)

8.0

A tool for quantitative risk assessment

8.1 Quality functional deployment (QFD)

The goal for assessing risk is to identify any raw materials that warrant mitigating actions at the earliest possible stage to prevent or reduce the impact of risk realization. Any disruption in the qualified fit-for-function status of a raw material has the potential to disrupt the supply of the medicinal product. However, most biopharmaceutical companies have limited resources to address all perceived risks. Effective prioritization of the most impactful raw material risks is one means to nimbly safeguard medicinal product availability and supply. But consensus, even in a biopharmaceutical organization on the 'right' prioritization and the 'most impactful' risk is not likely to occur without a structured method for measurable differentiation. An adaptable quantitative tool provides the structure necessary to create measurable differentiation but must be applied in the context that is most meaningful to each unique risk assessment project team.

A version of QFD methodology is recommended for quantifying and proportioning risk. The QFD concept takes qualitative attributes defined by a team with shared deliverables (e.g. user demands) and transforms them

into quantitative parameters for comparative analysis. Applied to raw material risk assessments, with the ability to identify both the presence of risk as well as the impact of realization quantitatively, QFD is a powerful means by which to differentiate risk and align prioritization of mitigation resources.

Figure 8.1 is a summary of all associated raw materials (i.e. ancillary and excipients) within the end-to-end manufacture of an example drug product using the methodology presented in this document (i.e. the data does not correlate to the case studies). Each data point represents a unique raw material from a specific supply chain and its cumulative risk score (i.e. higher score = greater potential for impact). Visually, it becomes clear that in the context of risk realization and impact, all raw material risks are not equal. The qualitative risks are translated into meaningful quantitative terms to facilitate differentiation of proportionate risk consistent with the assessment team's user demands. The result is a prioritized list of at-risk materials and an aligned strategy on which to resource first.

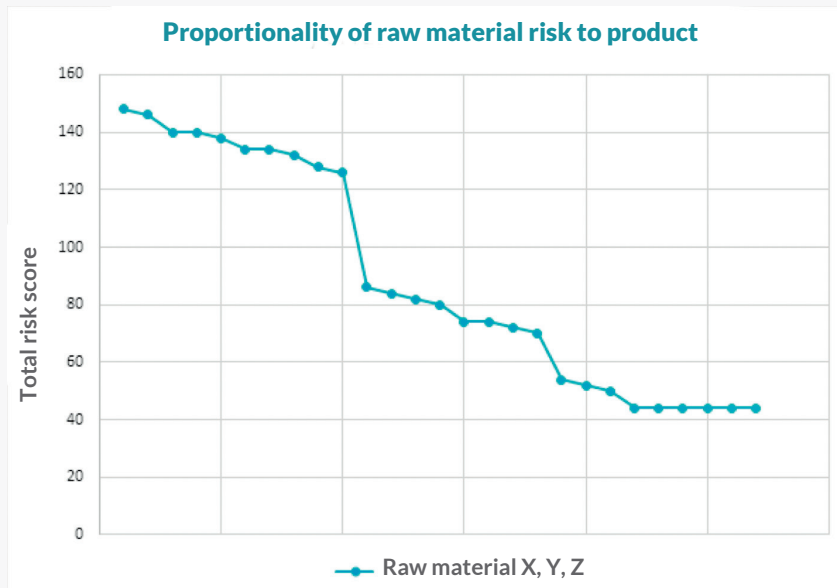


Figure 8.1: Proportionality of raw material risk to product

8.2 Risk criteria

A standard set of risk attributes has been defined and a cursory assessment performed on the likelihood or potential for risk to be present, based on independent user requirements, material attributes, and supply chain considerations. If the assessment were to end at this point, the team would have a long list of potential risks for each raw material without the actual fit-for-function analysis. For example, a raw material of animal origin might score 'high' in origin, composition and structural complexity, but if the biopharmaceutical development has already eliminated synthetic alternatives as an option, that risk remains high unless further fit-for-function analyses identify alternate risk attributes that have the ability to mitigate.

The risk attributes detailed in Tables 7.1, 7.2 and 7.3 are therefore independent data points for consideration within each of the three separate qualification categories. Risk criteria are introduced to provide a comparative analysis between unique risk attributes when alignment has the ability to indicate a fit, but misalignment can equate to risk. Therefore, relevant risk attributes that share common aspects of fit-for-use determination are directly compared as risk criteria. To demonstrate, if the user requirements dictate that the raw material meet compendia grade, and the material attributes correspond to an existing compendia monograph, identifying a supply chain that offers the compendia-grade material is considered a fit. Alternatively, if in this instance a corresponding compendia monograph simply doesn't exist, fit-for-function is not automatically dismissed. There is still opportunity for a reasonable conclusion of fit. However, by changing the circumstances to one where a corresponding compendia monograph does exist and the marketplace offers certified compendia-grade material, but a biopharmaceutical manufacturer chooses to purchase standard or technical grade, misalignment to fit-for-function equates to risk.

Risk criteria pose the question, 'do I have fit-for-function?' However, misalignment between multiple relevant risk attributes presents risk to a varying level of degree, therefore an adjusted score is assigned. Scores assigned to individual risk attributes represent a measure of the potential for risk introduction, but the adjusted score provides an indication of the presence of misalignment in fit-for-function as well as the severity. For example, the raw material of animal-origin discussed earlier might be assigned a risk attribute score of 'high', but through the evaluation of the risk criterion (i.e. origin and impurities), the manufacturing complexity and impurities attribute could provide additional relevant context that improves the overall risk profile. For instance, if the original animal-derived material undergoes subsequent synthetic processing culminating in a chemically-defined end material tested to meet high purity standards, the adjusted score can reasonably reflect less risk.

Similar to scores assigned to risk attributes, the actual number value assigned to each adjusted score can be determined by the user, but consideration should be given to avoid diminishing granularity by either having too many scales or by assigning numbers that are too close together (e.g. 1, 2, 3, etc.). For the purposes of the case studies in this document, adjusted scores were assigned as follows: high = 9, medium = 3, and low = 1.

The risk criteria are identified in Table 8.1 and Figure 12.1. The 'Source for assessment' column in the worksheet tool identifies the specific risk attributes suggested for comparison to evaluate fit or misalignment (i.e. UR, MA, or SC). It should be emphasized however, that the assessment of fit-for-function is highly dependent on all of the unique risk attribute circumstances relevant to the requirements of the final medicinal product (e.g. route of administration, dosage, patient population, etc.), and can and should be adapted as appropriate.

Table 8.1: List of suggested risk criteria

Criteria [Section 8.2]	Source for assessment [UR Table 7.1, MA Table 7.2, SC Table 7.3]
Patient exposure	UR
	UR - Impact to product quality
Process robustness	UR - Impact to process
	MA - Manufacturing complexity and impurities
RM variability/complexity	MA - Origin, composition, structural complexity
	MA - Manufacturing complexity and impurities
Origin and impurities	MA - Origin, composition, structural complexity
	MA - Manufacturing complexity and impurities
Regulatory impact/compedia compliance	UR - Regulatory/compedia requirements
	MA - Origin, composition, structural complexity
	MA - Analytical complexity/compedia status
	SC - Supplier material grade
Microbial restrictions/characteristics	UR - Microbial restrictions
	MA - Microbial characteristics
Material shelf life and stability	MA - Material shelf life and stability
	SC - Supplier technical capability
Material acceptance	UR - Material acceptance requirements
	MA - Analytical complexity/compedia status
	SC - Supplier technical capability
Supply chain	SC - Supplier quality system performance
	SC - Continuity of supply
	SC - Supplier relationship
	SC - Supplier technical capability
Inventory management	MA - Material handling requirements
	SC - Continuity of supply
Total risk score [Section 8.4]	

8.3 Weighted score

Risk criteria are also assigned a weight. Weights differ from scores in that they are assigned to each of the risk criteria and remain constant within the scope of a risk assessment independent of the specific raw material being evaluated. The weight is a multiplication factor used to differentiate perceived risks by assigning a scale for impact in the event of risk realization. The scales for weight not only identify what is to be impacted but also to what degree of tolerance to an organization (Figure 8.2). In general terms, a weight assigned a low number would be an acceptable or tolerable risk (i.e. 1 or 3) versus the less tolerable risks (i.e. 7 or 9). Quantitatively, the same considerations discussed regarding scores apply to weights. The actual number assigned to each qualitative scale is flexible, but consideration should be given to avoid diminishing granularity.

One of the key principles in the development of this industry risk assessment methodology is that the tool must provide allowances for the specific needs of unique products/processes and flexibility to adjust to differing scales of risk tolerance. Each step of the assessment process has the ability to be customized to some degree, but it is in the definition of weights and their assigned value to the risk criteria that firmly establishes the tailored objectives and priorities of the risk assessment. Identifying what is impacted and differentiating the degrees to which the risk assessment team would tolerate realization of that risk, is the function of assigned weights. As an example, the methodology within this document assesses the impact of risk realization to the potential disruption of medicinal product supply due to varying scales of raw material fit-for-function misalignment (Figure 8.3).

Figure 8.3 shows that the least tolerable misalignment in raw material fit-for-function qualification would be any risk that has the potential to impact the final drug product quality or lead to patient exposure. A weight of 9 is then applied to any risk criterion for which the risk assessment team believes could contribute to that outcome. The remaining scales within the categorization of weight for this example decrease in numeric value as the impact is contained to process performance, followed by regulatory or compendia status, and finally the handling or release of the raw material itself. The assignment of weights to risk criteria in this document reflect consensus of the risk assessment design team, but are open to further interpretation as the members, objectives, experiences, and tolerance of a risk assessment team change.

Categorizing weight of impact

Flexible to risk tolerance or unique product/program needs

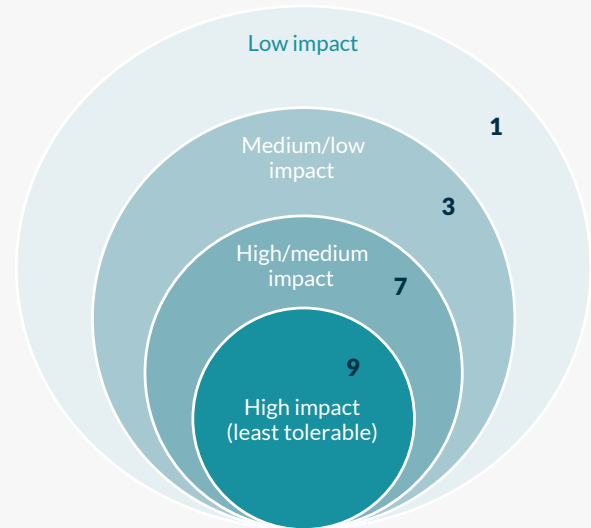


Figure 8.2: Impact to product/program needs

Categorizing weight of impact

Impact to product/patient

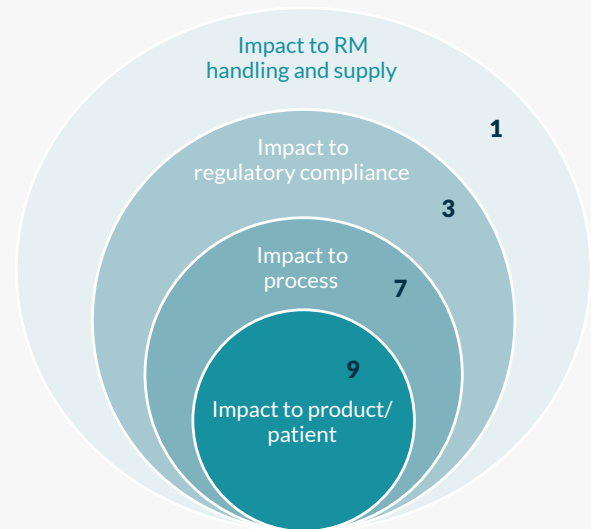


Figure 8.3: Impact to product/patient

Table 8.2: List of risk criteria with assigned weights for impact to product/patient

Criteria [Section 8.2]	Source for assessment [UR Table 7.1, MA Table 7.2, SC Table 7.3]	Weight [Section 8.3]
Patient exposure	UR	9
Process robustness	UR - Impact to product quality	7
	UR - Impact to process	
RM variability/complexity	MA - Manufacturing complexity and impurities	7
	MA - Origin, composition, structural complexity	
Origin and impurities	MA - Manufacturing complexity and impurities	3
	MA - Origin, composition, structural complexity	
Regulatory impact/compendia compliance	UR - Regulatory/compendia requirements	3
	MA - Origin, composition, structural complexity	
	MA - Analytical complexity/compendia status	
Microbial restrictions/characteristics	SC - Supplier material grade	3
	UR - Microbial restrictions	
Material shelf life and stability	MA - Microbial characteristics	3
	MA - Material shelf life and stability	
Material acceptance	SC - Supplier technical capability	3
	UR - Material acceptance requirements	
Supply chain	MA - Analytical complexity/compendia status	1
	SC - Supplier technical capability	
	SC - Supplier quality system performance	
	SC - Continuity of supply	
Inventory management	SC - Supplier relationship	1
	SC - Supplier technical capability	
Inventory management	MA - Material handling requirements	1
	SC - Continuity of supply	
Total risk score [Section 8.4]		

Other ways in which the categorization of weight impact can be structured are provided as examples in Figures 8.4 and 8.5. The flexibility inherent in the tool enables various organizations, with differing responsibilities in the raw material qualification continuum, to prioritize risks in the context of their specific functional expertise.

Categorizing weight of impact
Impact to regulatory compliance

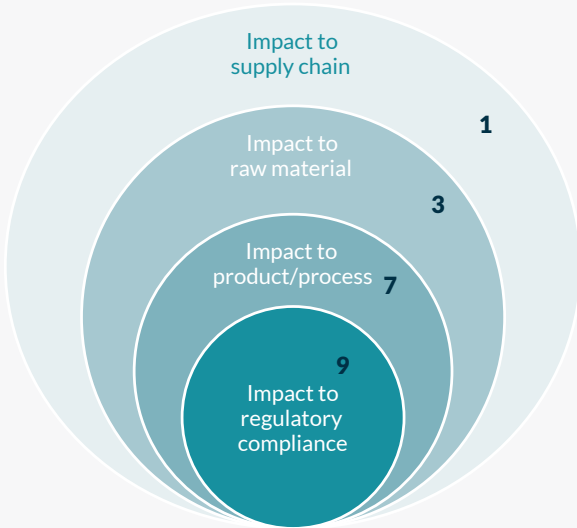


Figure 8.4: Impact to regulatory compliance

Categorizing weight of impact
Impact to supply

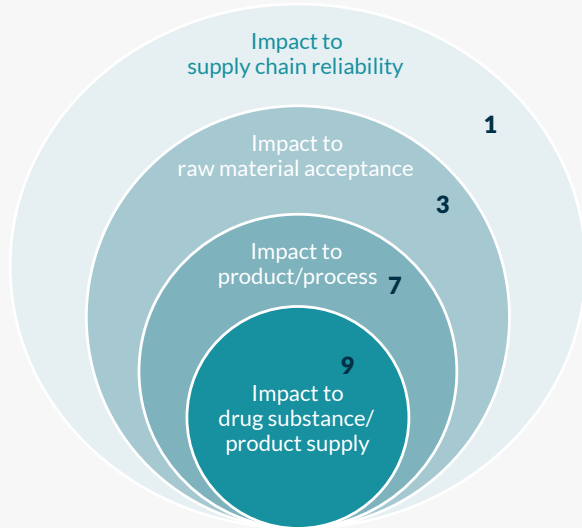


Figure 8.5: Impact to supply

The adjusted score assigned to each raw material risk criterion is then multiplied by the pre-assigned risk criterion weight resulting in a weighted score. It is the weighted score that readily differentiates the least tolerable risks as defined by the objectives set by the risk assessment team.

8.4 Total risk score

Finally, the weighted scores for each risk criterion of a given raw material are summed to deliver one total risk score. The highest total risk scores represent those raw materials for which the perceived fit-for-function misalignment is considered the least tolerable to the risk assessment team and therefore require mitigating actions (Figure 8.6).

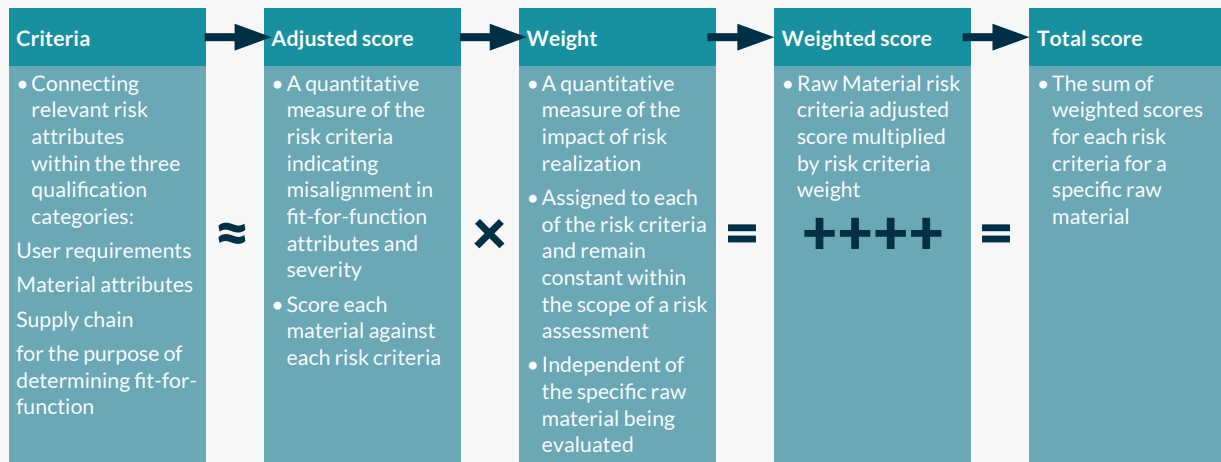


Figure 8.6: QFD Calculation

Three case studies have been provided in Section 14 (Sucrose, Ferrous sulfate, and Poloxamer). Each case study includes direct comparisons of alternate supply chains. An example of the cumulative ranking of total risk scores is provided in Figure 8.7 and incorporates the adjusted scores taken from the case studies and the various supply chains.

EXAMPLE of adjusted scores		Weight										Risk criteria														
Item name	Function	Catalog # (s)	Supplier / Manufacturer	A	B	C	D	E	F	G	H	I	J	K	Patient exposure	RM variability/complexity	Regulatory impact/compendia compliance	Microbial restrictions/characteristics	Material shelf life and stability	Material acceptance	Supply chain	Inventory management	Total risk score			
4 Sucrose	Excipient	12345	Re-packer/Source manufacturer 2	9	3	3	3	9	3	1	9	9	3	210	9	3	3	9	3	1	3	3	3	1	178	
5 Sucrose	Excipient	ABCDE	Re-packer/Source manufacturer 1	9	3	3	9	1	1	3	3	3	3	178	1	9	1	1	1	1	1	3	1	104		
6 Ferrous sulfate	Ancillary	54321	Re-packer/Source manufacturer 1	1	9	1	3	1	1	1	1	3	1	104	1	9	9	3	1	1	3	1	3	1	166	
7 Ferrous sulfate	Ancillary	EDCBA	Re-packer/Source manufacturer 2	1	9	9	3	1	1	1	1	9	9	3	166	1	9	9	1	1	1	1	3	9	1	124
8 Poloxamer	Ancillary	Technical grade	Sole manufacturer	1	9	9	3	1	1	1	1	3	9	1	124	1	1	1	1	1	1	1	1	1	1	40
9 Poloxamer	Ancillary	BioPharma grade	Sole manufacturer	1	9	3	1	1	1	1	1	1	1	40	1	1	1	1	1	1	1	1	1	1	58	
10 NaCl	Ancillary	XYZ		1	1	1	1	1	1	1	1	1	1	40	3	1	1	1	1	1	1	1	1	1	58	
11 NaOH pellets	pH adjuster	MNOP	optional adjustment at final formulation	3	1	1	1	1	1	1	1	1	1	58	1	1	1	1	1	1	1	1	1	1	40	
12 Alcohol	Ancillary	BPOG		1	1	1	1	1	1	1	1	1	1	40												

Step 1: each risk criterion is assigned a weight (row 2)

Step 2: for each unique raw material supply chain an adjusted score (i.e. rows 4-9 by columns A-J) is assigned

Step 3: the adjusted score for sucrose catalog #12345, patient exposure (9, row 4, column A) is multiplied by the corresponding weight for the patient exposure risk criterion (9, row 2, column A), producing a weighted score (81, A4 x A2) that is not visible in the Figure 8.7.

Step 4: the weighted score for sucrose catalogue #12345 patient exposure (81) is summed with the sucrose catalogue #12345 weighted scores for process robustness (21, B4 x B2), RM variability/complexity (21, C4 x C2), origin and impurities (9, D4 x D2), regulatory impact/compendia compliance (27, E4 x E2), microbial restrictions/characteristics (9, F4 x F2), material shelf life and stability (3, G4 x G2), material acceptance (27, H4 x H2), supply chain (9, I4 x I2), and inventory management (3, J4 x J2) to deliver one total risk score (210, K4).

Step 5: the total risk score for sucrose catalog #12345 (210, K4) provides a quick quantitative estimate of risk to either an alternate supply chain under consideration (i.e. narrow scope) or to the remainder of the other raw materials used within the product manufacturing process to provide a broader end-to-end perspective of the raw material's risk status to the product.

Figure 8.7: Cumulative ranking of case study total risk scores for a theoretical product

9.0

Outcomes/deliverables

The raw material risk assessment methodology is a business tool used to align available resources at a common starting point for the systematic mitigation of risks deemed most impactful to the risk assessment team. The tool promotes organized alignment to achieve the greatest benefit by addressing the greatest risks first. With that in mind, it is essential to recognize that the application of a QFD tool means that there is no such thing as a zero or 'no risk' endpoint. The goal is not to eliminate the concept of risk, but to standardize the method used to interpret risks proportional to impact.

As the team deploys mitigation strategies, the risk scoring for an individual raw material can be adjusted to reflect a decrease in the likelihood or misalignment in fit-for-function; the team then moves on to the next highest raw material at risk. When the team determines that the total risk score for a particular raw material cannot be mitigated further, the tool provides the necessary history and context to drive alignment on the acceptance of remaining risk.

The methodology presented is not designed to prescribe standard mitigation techniques. Mitigation strategies cannot be prescriptive just as regulations cannot prescribe all instances of standard fit-for-function. It is important that the teams performing raw material risk assessments have the flexibility to identify actions as unique and tailored to the risk circumstances as necessary. Mitigating actions could include any measures taken on a continuum from simply monitoring the circumstances to full discontinuation or replacement of the procured material or supply chain.

In summary, what is delivered uniquely in this document as part of this recommended methodology is the following:

- industry alignment on the necessary considerations when qualifying raw materials for fit-for-function (Table 6.1, 6.2, 6.3, risk attributes)
- a shared industry perspective on practical examples for when raw material attributes have a high, medium, or low potential to introduce risk (Tables 7.1, 7.2, 7.3)
- a specific example for how misalignment in fit-for-function attributes might be assessed (Table 8.1)
- the importance of weight as a mechanism to provide meaningful context to the impact of risk realization and its role in the adaptability of the methodology to meet alternate objectives (Figures 8.2, 8.3, 8.4, 8.5)
- a quantitative means to compare the potential for risk introduction, the severity of fit-for-function misalignment, and the tolerability of impact in the event of risk realization (Figure 8.7) that lends itself well to visual communication (Figure 8.1)
- a worksheet template for the execution of the methodology and knowledge management (Figure 12.1)

10.0

Which functions/subject matter experts should participate?

The effectiveness of the risk analysis is dependent upon subject matter experts (SMEs) with current input and experience pertaining to the three key raw material qualification categories: user requirements, material attributes, and supply chain. As such, unique organizational design will influence the actual functional roles assigned to the assessment process, but in general terms the following expertise are recommended for consultation:

User requirements

- process SMEs
- process engineers
- process development experts
- dossier scientists, etc.

Material attributes

- material scientists
- raw material experts
- origin and adventitious agent experts, etc.

Supply chain

- procurement
- quality auditors
- incoming quality release
- supplier management experts, etc.

11.0

When to perform/frequency of review

Initiation, frequency, and deliverables will vary depending on the needs of the biopharmaceutical manufacturer. The raw material risk assessment methodology developed in this document is designed to apply flexibly to the broad range of product and process development stages, final dosage forms, medicinal product indications, and dosing regimens.

Organizations involved in clinical product development may choose to initiate the process after confirmation of safety and prior to dosing/efficacy. Application of the assessment at this stage could be used to inform the design of experiments to assess performance variability or correlation of raw material characteristics to process specifications.

Initiating the process prior to fit-for-use qualification provides a thorough punch list of actions to select optimal supply chains, to ensure compliance to regulatory expectations prior to filing and to establish thorough meaningful supplier contracts.

Finally, biopharmaceutical companies focused on commercial product manufacture can mitigate risks to market supply or product/process quality by identifying those raw materials that require additional oversight or intervention. Possessing a central location for SME analysis of the raw material functions, origin, and supply requirements can aid in the proper prioritization and impact analysis of unplanned supplier change notifications or planned process improvement projects (Figure 11.1).

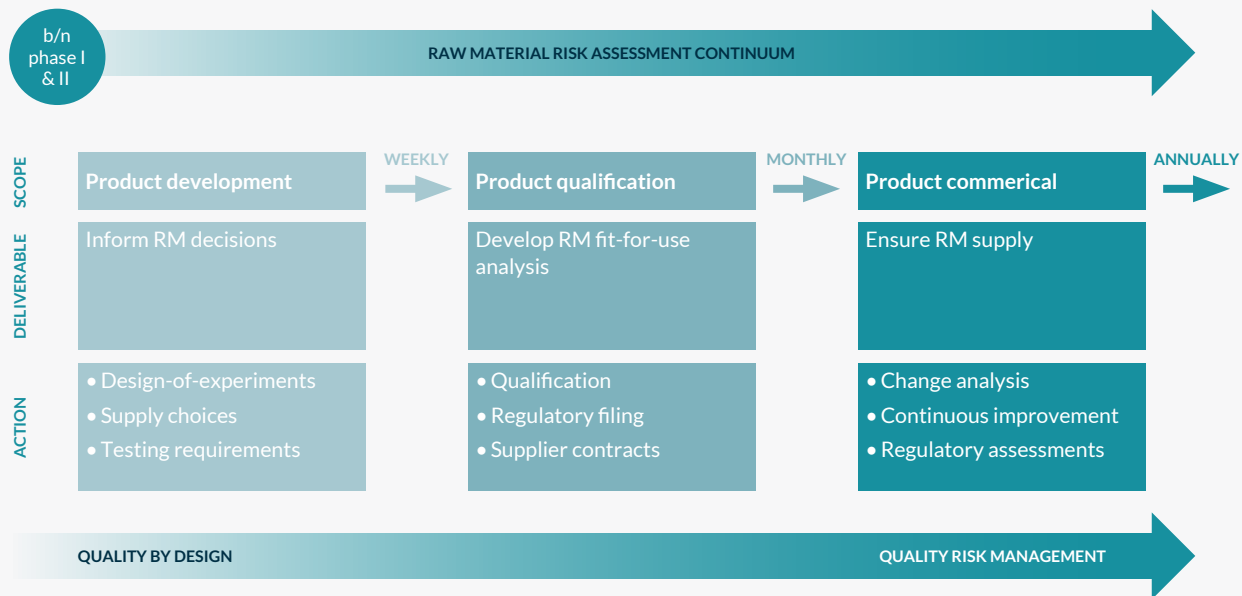


Figure 11.1: Raw material risk assessment lifecycle

As the intended deliverables of the risk assessment effort change concurrent with the lifecycle of the product or in alignment with the limited scope of biopharmaceutical manufacturing, the frequency of risk ranking refresh can be adjusted. Pre-determined refresh may occur more frequently during the stages of product/process development when different raw materials and supply chains are still being finalized. Conversely, once a biopharmaceutical product has been licensed to market, significant changes to overall risk status, might be less likely due to historic process performance/experience or regulatory hurdles.

Regardless of when initiated or how frequently refreshed, the risk assessment analysis of raw materials is intended to be a continuous exercise. As resources are deployed to mitigate the higher-ranking risks or changes are inevitably introduced by the supplier or the process, the cumulative score should be recalculated to highlight the next priority opportunities.

12.0

Data management

Material name:		SAP #		Considerations and actions: elemental impurities, filing strategies, quality agreement and change control agreement, filing decisions (CMO versus internal)	
CAS #	Legacy #	Item name	Raw material	Raw material	
Ancillary or Excipient	Catalog #	Supplier	Typically re-packer	Typically re-packer	
Manufacturer Location		Supplier	Source manufacturer 1	Source manufacturer 2	
Criteria [Section 8.2]		Disposition	Scoring (1,3,9)	Selected Source	Scoring (1,3,9)
Source for assessment [UR Table 7.1, MA Table 7.2, SC Table 7.3]		Weight [Section 8.3]	Sources for score	Potential Source	Sources for score
Patient exposure	UR - Impact to product quality	9			
Process robustness	UR - Impact to process	7			
RM variability/complexity	MA - Manufacturing complexity and impurities	7			
	MA - Origin, composition, structural complexity				
Origin and impurities	MA - Manufacturing complexity and impurities	3			
	MA - Origin, composition, structural complexity				
Regulatory impact/compendia compliance	UR - Regulatory/compendia requirements	3			
	MA - Origin, composition, structural complexity				
	MA - Analytical complexity/compendia status				
Microbial restrictions/characteristics	SC - Supplier material grade	3			
	UR - Microbial restrictions				
Material shelf life and stability	MA - Microbial characteristics	3			
	MA - Material shelf life and stability				
Material acceptance	SC - Supplier technical capability	3			
	UR - Material acceptance requirements				
	MA - Analytical complexity/compendia status				
Supply chain	SC - Supplier quality system performance	1			
	SC - Continuity of supply				
	SC - Supplier relationship				
	SC - Supplier technical capability				
Inventory management	MA - Material handling requirements	1			
	SC - Continuity of supply				
Total risk score [Section 8.4]			0	0	0

Figure 12.1: Data management worksheet

13.0

Other considerations

13.1 Compliance/regulatory impact

The raw material risk assessment is a living tool, as the circumstances which create risk are continually changing. Routinely updating the business tool to reflect current state also serves as a valuable record for knowledge management of nuanced process experience, temporary supply chain risks that might warrant additional oversight, or preliminary concepts for dual sourcing strategies, for example. It is recommended that the tool serves a function similar to confidential self-audit, in that the identification of potential risks and opportunities is unrestrained.

13.2 Risk management

Within the broader context of risk management, risk assessments are the very first step of the quality risk management process described in Figure 13.1. Risk assessments, to include risk identification, analysis, and evaluation, facilitate an enhanced understanding of risk differentiation in terms of the likelihood to occur and the ultimate impact. A thorough perspective on the proportionality of risk is essential to inform effective risk control and reduction strategies during the latter stages of risk management

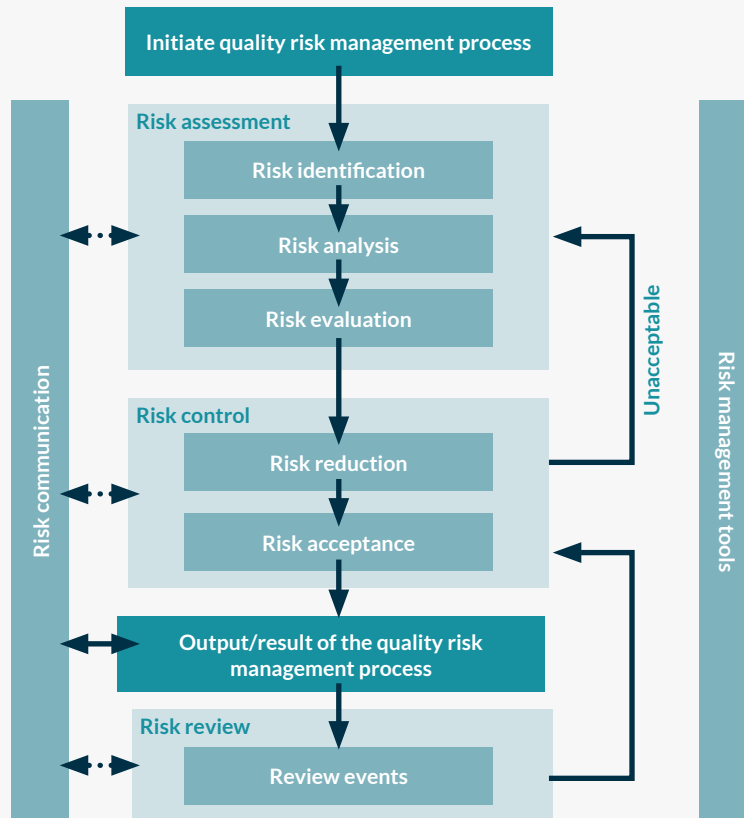


Figure 13.1: ICH Q9 Overview of a typical quality risk management process

For this reason, the European Biopharmaceutical Enterprises (EBE) published a concept paper entitled *Management and Control of Raw Materials Used in the Manufacturer of Biological Medicinal Products and ATPMs*. It outlines the importance, regulatory basis, and challenges of managing and controlling raw material risks, using case studies as examples of risk assessment with related mitigation strategies. Although similar in lifecycle approach and with a shared emphasis on the power of risk assessments, this BioPhorum document was written to deliver a specific, structured, reproducible, yet flexible tool for the quantitative differentiation of identified risks in a consistent manner. And while this BioPhorum document does not specifically address risk mitigation techniques, the concept paper provides recommendations for risk mitigation strategies that are suitable and appropriate for all raw material risks (Figure 13.2). The concept paper also provides a comprehensive list of raw material regulatory guidance and is a practical and valuable reference for raw material risk management principles alongside this document.

Phase 1/2	Phase 3	Marketing	Post marketing
<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - 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 account 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 	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - 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

Figure 13.2: Proposed mitigation plan per phase of development for supplier qualification and for RM testing for a high-risk RM (from EBE Concept Paper)

14.0

Case studies

Examples of using the risk assessment method and worksheet template are presented in Figures 14.1, 14.2, 14.3. Three different raw materials, Sucrose, Ferrous sulfate heptahydrate, and Poloxamer 188, were used to demonstrate how this method could facilitate evaluation of risks on different raw materials as well as different sources of a raw material.

Material name: Sucrose		SAP #		Considerations and actions: elemental impurities, filing strategies, quality agreement, filing decisions (CMO versus internal)			
CAS # 57-50-1		Legacy #		Sucrose			
Excipient		Item name		Sucrose			
		Catalog #		Typically re-packer			
		Supplier		Source manufacturer 2			
		Manufacturer		Source manufacturer 1			
		Location		Selected Source			
		Disposition		Potential Source			
Criteria	Source for assessment	Scoring (1,3,9)	Weight	Sources for score	Scoring (1,3,9)	Sources for score	Mitigation plans
Patient exposure	UR	9	9	Excipient	9	Excipient	Subject to EU excipient risk assessment
Process robustness	UR - Impact to product quality						
	UR - Impact to process		7	Stabilizer, important to drug product quality, potential degradants	3	Stabilizer, important to drug product quality, potential degradants	
	MA - Manufacturing complexity and impurities						
	MA - Origin, composition, structural complexity		7	Chemically-defined, not pure, naturally-derived, some variability between different manufacturers	3	Chemically-defined, not pure, naturally-derived, some variability between different manufacturers	
RM variability/complexity	MA - Manufacturing complexity and impurities						
Origin and impurities	MA - Origin, composition, structural complexity			Cane sugar, exposure to bone char requiring regulatory notification and change notification, animal attractant requiring container, storage, and pest control considerations, endotoxin not measured or controlled	9	Beet sugar, vegan but animal attractant requiring container, storage, and pest control considerations, endotoxin measured and controlled	Must consider endotoxin, elemental impurities, and residual solvents
	MA - Manufacturing complexity and impurities		3				
Regulatory impact/compendia compliance	UR - Regulatory/compendia requirements						
	MA - Origin, composition, structural complexity		3	Compendia exist, compendia grade purchased, compendia match all intended markets	9	Compendia exist, standard/technical grade purchased and up-tested prior to acceptance	
	MA - Analytical complexity/compendia status						
Microbial restrictions/characteristics	SC - Supplier material grade						
	UR - Microbial restrictions		3	Not required to be sterile; non-sterile, bioburden measured, reported, and limited to within acceptance testing	3	Not required to be sterile; non-sterile, bioburden not tested by supplier, bioburden performed as part of incoming acceptance testing	
Material shelf life and stability	MA - Microbial characteristics						
	MA - Material shelf life and stability		3	5 year shelf life from DOM, no data on file to support	1	48 months shelf life from date of release, data on file to support	Supply chain 1: Set expiry to 5 years, with re-test every 1 year
Material acceptance	SC - Supplier technical capability						
	UR - Material acceptance requirements		3	100% ID testing per container, acceptance testing per compendia methods and specifications	9	100% ID testing per container, supplier is not testing for quality or material characteristics; therefore potential for batch failure is high	
	MA - Analytical complexity/compendia status						
Supply chain	SC - Supplier technical capability						
	SC - Supplier quality system performance		1	Approved and active, but recent audit refusal and pharma industry not the targeted industry; limited support provided to "nuisance" customers	9	Unevaluated, don't know	
	SC - Continuity of supply						
	SC - Supplier relationship						
Inventory management	SC - Supplier technical capability						
	MA - Material handling requirements		1	Ambient/room temperature storage, off-the-shelf, no significant lead time	3	Ambient/room temperature storage, supplier requires development of custom material to meet compendia standards and long lead time	
	SC - Continuity of supply						

Figure 14.1:
Sucrose case study

Material name: Ferrous sulfate heptahydrate CAS # 7782-63-0 Ancillary	SAP # Legacy # Item name Catalog # Supplier Manufacturer Location Disposition	Source for assessment	Weight	Scoring (1,3,9)		Sources for score	Sources for score	Mitigation plans
				Scoring (1,3,9)	Scoring (1,3,9)			
Patient exposure	UR - Impact to product quality	UR	9	1	1	Ancillary raw material	Ancillary raw material	
	UR - Impact to process		7	9	9	Key role in antibody production, glycation, and trace element introduction.	Key role in antibody production, glycation, and trace element introduction.	
	MA - Manufacturing complexity and impurities		7	1	1	Chemically-defined, full panel of trace elements known and controlled	Chemically-defined, unknown trace elements	
Process robustness	MA - Origin, composition, structural complexity		7	1	1	Chemically-defined, full panel of trace elements known and controlled	Chemically-defined, unknown trace elements	
	MA - Manufacturing complexity and impurities		3	3	3	Mineral, composite	Mineral, composite	
	MA - Origin, composition, structural complexity		3	3	3	Mineral, composite	Mineral, composite	
RM variability/complexity	MA - Manufacturing complexity and impurities		3	3	3	Mineral, composite	Mineral, composite	
	MA - Origin, composition, structural complexity		3	3	3	Mineral, composite	Mineral, composite	
	MA - Manufacturing complexity and impurities		3	3	3	Mineral, composite	Mineral, composite	
Origin and impurities	MA - Manufacturing complexity and impurities		3	3	3	Mineral, composite	Mineral, composite	
	MA - Origin, composition, structural complexity		3	3	3	Mineral, composite	Mineral, composite	
	MA - Manufacturing complexity and impurities		3	3	3	Mineral, composite	Mineral, composite	
Regulatory impact/compendia compliance	UR - Regulatory/compendia requirements		3	1	1	Compendia exists; compendia is purchased	Compendia exists; compendia is purchased	
	MA - Origin, composition, structural complexity		3	1	1	Compendia exists; compendia is purchased	Compendia exists; compendia is purchased	
	MA - Analytical complexity/compendia status		3	1	1	Compendia exists; compendia is purchased	Compendia exists; compendia is purchased	
Microbial restrictions/characteristics	SC - Supplier material grade		3	1	1	Non-sterile, but not required to be sterile	Non-sterile, but not required to be sterile	
	UR - Microbial restrictions		3	1	1	Non-sterile, but not required to be sterile	Non-sterile, but not required to be sterile	
	MA - Microbial characteristics		3	1	1	Non-sterile, but not required to be sterile	Non-sterile, but not required to be sterile	
Material shelf life and stability	MA - Material shelf life and stability		3	1	1	Stable, data on file	Stable, supplier does not have data	
	SC - Supplier technical capability		3	1	1	Stable, data on file	Stable, supplier does not have data	
	UR - Material acceptance requirements		3	1	1	Compendia testing	Compendia testing	
Material acceptance	MA - Analytical complexity/compendia status		3	1	1	Compendia testing	Compendia testing	
	SC - Supplier technical capability		3	1	1	Compendia testing	Compendia testing	
	UR - Material acceptance requirements		3	1	1	Compendia testing	Compendia testing	
Supply chain	SC - Supplier quality system performance		1	3	3	Source manufacturers are not accessible; biopharma not intended customer	Source manufacturers are not accessible; biopharma not intended customer	
	SC - Continuity of supply		1	3	3	Source manufacturers are not accessible; biopharma not intended customer	Source manufacturers are not accessible; biopharma not intended customer	
	SC - Supplier relationship		1	3	3	Source manufacturers are not accessible; biopharma not intended customer	Source manufacturers are not accessible; biopharma not intended customer	
Inventory management	SC - Supplier technical capability		1	1	1	Off-the-shelf, no long lead time, no safety stock, ambient storage	Off-the-shelf, no long lead time, no safety stock, ambient storage	
	MA - Material handling requirements		1	1	1	Off-the-shelf, no long lead time, no safety stock, ambient storage	Off-the-shelf, no long lead time, no safety stock, ambient storage	
	SC - Continuity of supply		1	1	1	Off-the-shelf, no long lead time, no safety stock, ambient storage	Off-the-shelf, no long lead time, no safety stock, ambient storage	
Total risk score			104				166	

Figure 14.2:
Ferrous sulfate heptahydrate case study

Material name: Poloxamer 188		SAP #		Considerations and actions: elemental impurities, filing strategies, quality agreement, and change control (CMO versus internal)		
CAS # 9003-11-6	Legacy #	Poloxamer 188		Poloxamer 188		
Ancillary	Item name	Poloxamer 188		Poloxamer 188		
	Catalog #	Typically re-packager		Typically re-packager		
	Supplier	Source manufacturer 1		Source manufacturer 2		
	Manufacturer					
	Location					
	Disposition					
Criteria	Source for assessment	Scoring (1, 3, 9)	Selected Source	Scoring (1, 3, 9)	Selected Source	Mitigation plans
Patient exposure	UR - Impact to product quality	1	Ancillary raw material	1	Ancillary raw material	
	UR - Impact to process	9	Sheer protectant	9	Sheer protectant	
	MA - Manufacturing complexity and impurities	7	Technical-grade: manufacturing process introduces impurities due to carry-over on multi-use equipment; lot-to-lot variability	3	Enhanced-grade: manufacturing process modified to limit impurities, no performance issues since	
RM variability/complexity	MA - Origin, composition, structural complexity	7	Chemically-synthesized	1	Chemically-synthesized	
	MA - Manufacturing complexity and impurities	3	Compendia exists, material tested to USP, not required to be purchased compendia grade	1	Compendia exists, material tested to USP, not required to be purchased compendia grade	
Origin and impurities	MA - Origin, composition, structural complexity	3	Non-sterile, not required to be sterile	1	Non-sterile, not required to be sterile	
	UR - Regulatory/compendia requirements	3	Stable	1	Stable	
Regulatory impact/compendia compliance	MA - Origin, composition, structural complexity	3	Specific cell line testing appropriate as an early indicator of performance	9	High molecular weight testing very important indicator, but not reported on COA	
	MA - Analytical complexity/compendia status	3	Sole sourced, not a good history of open communication	9	Sole sourced, not a good history of open communication	
	SC - Supplier material grade	1	Variable performance has led to keeping more lots	3	Room temperature / ambient	
Microbial restrictions/characteristics	UR - Microbial restrictions	3				
	MA - Microbial characteristics	3				
Material shelf life and stability	MA - Material shelf life and stability	3				
	SC - Supplier technical capability	3				
Material acceptance	UR - Material acceptance requirements	3				
	MA - Analytical complexity/compendia status	3				
	SC - Supplier technical capability	3				
Supply chain	SC - Supplier quality system performance	1				
	SC - Continuity of supply	1				
	SC - Supplier relationship	1				
	SC - Supplier technical capability	1				
Inventory management	MA - Material handling requirements	1				
	SC - Continuity of supply	1				
Total risk score		186		124		

Figure 14.3:
Poloxamer 188 case study

15.0

Acronyms

ACDF	animal component derived free
ACS	American Chemical Society
CAPA	corrective actions/preventative actions
CAS	Chemical Abstracts Service of the American Chemical Society
CCI	container closure integrity
CIP	clean-in-place
CMO	contract manufacturing organization
COA	certificate of analysis
CPP	critical process parameter
CQA	critical quality attribute
DOM	date of manufacture
EP or Ph. Eur.	European Pharmacopeia
EU	European Union
GMP	good manufacturing practices
ID	identity
IP	intellectual property
IPEC	International Pharmaceutical Excipients Council
ISO	International Organization for Standardization
JP	Japanese Pharmacopeia
KOP	key operating parameters
KPP	key process parameter
KQA	key quality attribute
MA	material attributes
NF	national formulary
OOS	out of specification
PEG	polyethylene glycol
PPQ	process performance qualification
QC	quality control
QFD	quality function deployment
RM	raw material
RT	room temperature
SC	supply chain
TOR	time out of refrigeration
UR	user requirements
USP	United States Pharmacopeia

Permission to use

The contents of this report may be used unaltered as long as the copyright is acknowledged appropriately with correct source citation, as follows "Entity, Author(s), Editor, Title, Location: Year"

Disclaimer

This document represents a consensus view, and as such it does not represent fully the internal policies of the contributing companies.

Neither BioPhorum nor any of the contributing companies accept any liability to any person arising from their use of this document.

The views and opinions contained herein are that of the individual authors and should not be attributed to the authors' employers.

