Review paper
UDC 615.076.7

RISK ASSESSMENT IN PHARMACEUTICAL MICROBIOLOGY

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Abstract

Risk management in pharmaceutical microbiology is considered as supportive tool in defining and documenting process of evaluation, analysis and control of assessed risks in terms of establishing control of the microbiological quality of raw materials incorporated in finished drug products.

The respective paper provides an overview of the established concept for microbiological control of raw materials in pharmaceutical industry and is considered applicable for measuring risk significance in microbiological control of raw materials as well as providing science-based evidence for the conclusions drawn in setting microbiological parameters and appropriate specification limits. The risk assessment for microbiological quality of raw materials in the presented work is based on evaluation of general and critical control points (GCP and CCP) related to substance manufacturer, manufacturing / synthesis process of raw material and manufacturing process of finished product. Additionally, every risk level is connected to appropriate measures for mitigation or elimination of the identified risk and appropriate control of possible residual risk.

Risk characterization results are provided in form of risk estimates and detailed risk descriptions in terms of microbiological quality of raw materials. Due to existing critical control points in microbiological assessment of raw materials, hazard analysis for each step of the assessment process were identified.

***Key words**: Risk management, Microbiology, Raw materials, Microbiological control, Microbiological parameters.*

1. Introduction

Risk management principles are effectively used in many areas of industries. In pharmaceutical industry the holder of manufacturing authorization must ensure that the all his medicinal products comply with the requirements of the marketing authorization so that the patient is not exposed to risk in terms of safety, quality or efficacy of drug product. It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.

Formal risk management process is based on four concepts: risk assessment, risk control, risk review and risk communication. Risk assessment comprises principles of: risk identification, risk analysis and risk evaluation, while risk control is performed through implementation of: risk reduction and risk acceptance. The respective principles of risk management process have been described in the ICH Q9 Guideline for Quality Risk Management (QRM) [1]. The principles of quality risk management are:

- Evaluation of risk to quality should be scientifically knowledge-based and should be linked to protection of the patient and
- Level of effort, formality and documentation of the quality risk management process should be proportional to the risk level.

Risk assessment in pharmaceutical industry has become an expectation of regulatory authorities. Risk assessment tools and techniques are applicable in every aspect of pharmaceutical processing. Common regulatory accepted risk methodologies are referenced in ICH Q9:

- Failure Mode Effects Analysis [FMEA];
- Failure Mode, Effects and Criticality Analysis [FMECA];
- Fault Tree Analysis [FTA];
- Hazard Analysis and Critical Control Points [HACCP];
- Hazard Operability Analysis [HAZOP];
- Preliminary Hazard Analysis [PHA];

- Basic risk management facilitation methods (flow charts, check sheets etc.);
- Risk ranking and Filtering, and
- Supporting statistical tools.

In respect of referenced guideline selection of particular risk methodology should be supportive to pertaining drug substance and drug product quality (Table 1).

Numerous literature references define risk management strategies in pharmaceutical industry [2, 3, and 4].

2. Microbiological risk assessment in pharmaceutical industry

Microbiological risk assessment is performed for sterile and nonsterile manufacturing activities to establish the microbial risks and their impact on the quality of the medicinal products [5]. Also, the risk management in pharmaceutical microbiology is considered as supportive tool for establishing control of the microbiological quality of raw materials incorporated in finished drug products. Risk characterization results are provided in form of risk estimates and detailed risk descriptions in terms of microbiological quality of raw materials.

Microbiological quality for raw materials is one of the necessary requirements to fulfil the Good Manufacturing Practices in the pharmaceutical Industry [6]. Raw materials are rarely sterile, and some must have special treatment to be microbiological acceptable for use. These materials can be from natural, synthetic or semisynthetic origin which is one of the crucial elements for likelihood of microbiological contamination with high bioburden or with presence of objectionable microorganisms [6]. Due to existing critical control points in microbiological assessment of raw materials, hazard analysis for each step of the assessment process were identified.

Microbiological control is a regulatory requirement. The parameter 'microbiological quality' should be continuously monitored and revised with regards to the interaction of science and applied technology with products, processes, materials, equipment and personnel entering the manufacturing areas. Sufficient microbiological control should be defined upon understanding the risks for the microbial contamination of the manufacturing process and identification of possible types of contaminants. The results obtained from such risk assessment strategies are also used during facility and equipment design as well as for establishing equipment and personnel flow patterns [7].

WHO emphasizes the fact that variety of tools can be used for the purposes of QRM. It is important to note that no single tool or combination of tools is applicable to each QRM procedure. As stated in WHO guideline [8] - examples of tools are listed in regulatory guidance. The important criterion for acceptability is that amended tools are used effectively to support the key attributes of a good risk assessment.

The overview of the one typical risk management process described as per ICH Q9 guideline is presented as follows:

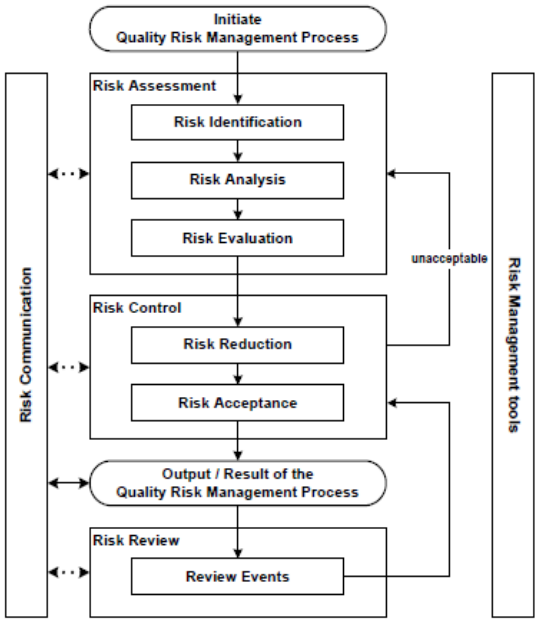

Figure 1. Phases in the QRM process

Table 1. Advantages and disadvantages of common risk assessment approaches (adopted from Sandle, [4])

Focus	Methods	Fault Tree Analysis (FTA)	Failure Mode and Effects Analysis (FMEA)	Hazard Analysis and Critical Control Points (HACCP)	Statistical Methods
Risk assessment	Risk identification	+	o	o	+
	Risk analysis	o	+	o	+
	Risk evaluation	-	+	o	+
Controlling risks	Risk reduction	-	+	+	-
	Risk acceptance	-	+	+	-
	Risk review	A single method may or may not be ideal; sometimes different approaches need to be combined			
	Risk communication				

Legend: + = very suitable; o = limited suitability; - = not suitable.

Risk management processes are defined as per ICH Q9 (Table 2).

Table 2. Definitions of risk management processes

Risk management process	Explanation of the process (ICH Q9)
Risk identification	Systemic use of information to identify hazards referring to the risk question or problem description
Risk analysis	Estimation of risks associated with identified hazards
Risk evaluation	Comparison of the identified and analyzed risk against given risk criteria
Risk reduction	Process for mitigation or avoidance of quality risk when it exceeds an acceptable level
Risk acceptance	Decision to accept risk
Risk communication	Sharing information about risk and risk management between the decision makers and other stakeholders
Risk review	Monitoring the output/results of the risk management process considering new knowledge and experience about the risk

Hazard Analysis Critical Control Points (HACCP) has traditionally been considered as food safety management system [8] and was first developed to prevent food borne infection in astronauts by NASA, the food company Pillsbury, and US Army Natick Center [9]. Nowadays HACCP has been accepted as a management system in which product or process safety can be addressed through the analysis and control of biological, chemical and physical hazards from raw material production to manufacturing, distribution and use of the finished product. Despite the fact that HACCP was developed by the food industry, it is also widely used in the pharmaceutical industry. HACCP is considered as systematic, proactive and preventive tool for assurance of quality, reliability and safety of the product [8].

HACCP methodology was chosen for assessing risks of inappropriate microbiological control of raw materials. The reasons for choosing HACCP instead of other available methodologies are:

- Provides systematic and science-based approach;
- Successfully assesses hazard points and emphasizes the impact of critical factors, which facilitates prevention (properly assessing microbiological bioburden);
- HACCP plans are focused on hazards which are overall objective to ensure that established criteria are suitable for control of the microbiological quality of the respective incoming raw materials.

The main principles of the HACCP system are defined as follows:

1. Conducting a hazard analysis;
2. Determining the Critical Control Points (CCP);
3. Establishing the critical limits;
4. Establishing effective system to monitor control of CCP;
5. Establishing corrective actions to be taken when monitoring indicates that a particular CCP is not under control;
6. Establish procedures for verification to confirm that the HACCP system is working effectively;
7. Establishing documentation concerning all procedures and records appropriate to these principles and their application.

2.1 Risk assessment process for microbiological quality of raw materials

The procedure for defining suitable microbiological quality of the incoming raw materials is essential element in production of medicinal products. Crucial part of the risk management process is establishing of an appropriate risk scenario. The following risk scenarios will be defined upon the assessment procedure:

- Including the parameter microbiological quality in finished product manufacturer's specification (FPM SP);
- Establishing the microbiological specification for incoming raw materials;
- Defining the microbiological method for examining the microbiological quality of incoming raw materials.

The process is defined in accordance with the procedure and protocol for risk management, adopted from the corporate procedure of risk management. Risk management process is defined as systemic process with exceptional dynamics, and therefore it is necessary that all phases are proactively and regularly updated. The process is intended to be applied proactively as well as retrospectively, whichever is accordingly justified.

Due to existing critical points with significant impact on the process of establishing proper microbiological parameters and appropriate limit, HACCP has been chosen as appropriate risk assessment methodology applied.

The corporate procedure is defined according to ICH Q9 guideline for risk management. From the available methodologies presented HACCP methodology was selected as most appropriate to existing multiple control parameters within the process. The control parameters are separated into critical control points (CCP)

and general control points (GCP). CCP have significant impact on the cumulative risk for microbiological quality unlike the GCP. According to the predefined impact of these control points several criticality levels are established (numerated from 1 to 3 and 4 for GCP and CCP, respectively). The parameters evaluated are divided according to their relation with different parts of the assessment process (Figure 2):

- Parameters for evaluation of the supplier / manufacturer;
- Parameters for evaluating the raw material;
- Parameters for evaluating the finished product.

The procedure of risk assessment is defined in accordance with the protocol for the risk management defined in the corporate risk management procedure. The risk assessment process is defined as systemic process with exceptional dynamics. Therefore, it is especially necessary the process to be adopted proactively as well as subsequently upon raw material's evaluation.

The procedure for defining the microbiological quality of incoming raw materials is crucial, apparently in cases when the supplier/manufacturer does not include the microbiological quality as parameter in CoA (Certificate of Analysis). The conclusion is provided for adopting the following strategies:

- Including (setting) the parameter microbiological quality in specification (SP) for new incoming raw materials by the Finished Product Manufacturer (FPM);
- Defining the SP for the microbiological quality of new incoming raw materials and
- Defining appropriate and suitable microbiological method for analysis of the microbiological quality of new incoming raw materials.

Risk assessment methodology is defined in accordance with the following phases:

- Risk identification;
- Risk analysis and evaluation;
- Risk control and risk management.

Identification of risk is the initial estimate of the necessity for performing risk analysis. Risk identification is initiated with evaluation of available documentation, European Pharmacopoeia (Ph. Eur.) monography as well as available literature and experience-based findings for the bioburden of the respective raw material. By adopting the decision generated from the decision trees (Figures 3 and 4 - DT#1 and DT#2) the necessity for including the microbiological quality in the specification and developing proper microbiological method is defined.

The activities defining the phase of risk analysis are presented by evaluation of selected parameters conditioning the microbiological quality of raw material(s). These activities include selection of physical, chemical, biological and pharmacological parameters for assessing their impact on the microbiological quality of the substance. Furthermore, objectives of the assessment are also the synthesis processes of drug substance and formulation aspects of finished product, which might have influence the microbiological quality.

Risk evaluation is defined with predetermined criteria for parameters with significant impact on the cumulative risk.

The risk assessment process is defined in accordance with the risk matrices presented in the respective risk assessment form. As previously presented, the parameters are divided according to their impact on the cumulative risk into critical (CCP) and general control points (GCP). The risk assessment process is divided into several risk categories presented in literature and pharmaceutical quality guidelines: low, middle (moderate), high and critical risk. Risk categorization is performed not only by the cumulative risk but also by the number of critical control points with higher risk level assessed.

Risk control amends activities for mitigation, elimination and/or risk acceptance.

Appropriate measures for risk control are defined in terms of risk mitigation or risk elimination, as well as control of residual risks.

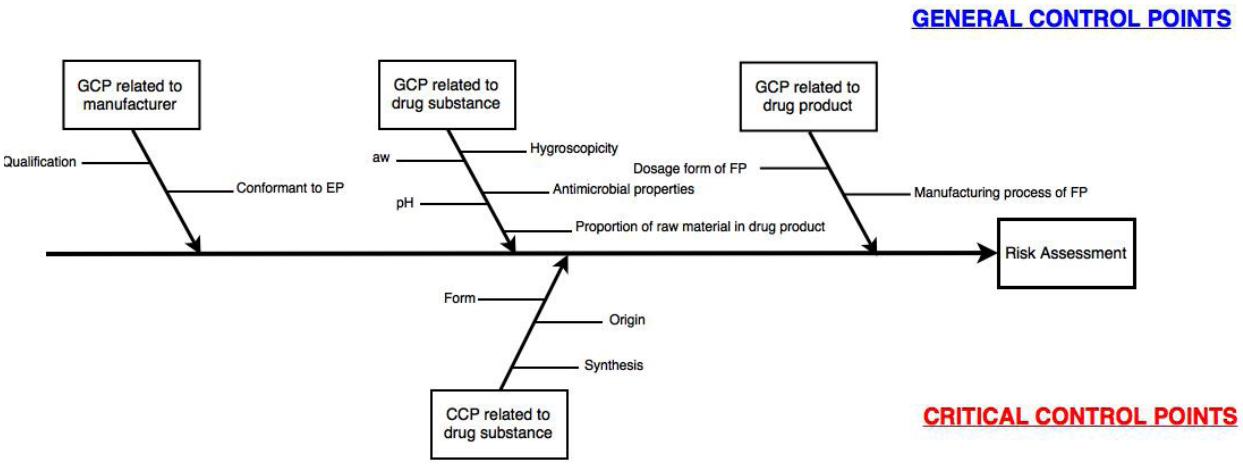

Figure 2. Ishikawa diagram of the control points with the impact on the cumulative risk

2.2 Risk assessment process

Risk assessment process is initiated by literature evaluation of available documentation from the manufacturer/supplier. The process flow is defined as per the selected decision from the decision trees DT#1 and DT#2 (Figures 3 and 4).

Acceptance criteria are generally established in line with recommendations given in Ph. Eur. chapter 5.1.4 - Table 2 (Figure 5):

The criticality of decision making is recognized by setting appropriate microbiological control in accordance with the bioburden of the substance. Literature evaluation and evaluation of available documentation obtained from manufacturer/supplier was performed.

Risks are identified regarding the fact that the material's origin, its synthesis processes, the proportion of raw material in finished product as well as the finished product properties (type of dosage form and manufacturing process). For suitable assessment of general and critical control points the following risk assessment form is filled for each substance (Figure 6).

HACCP methodology for proper assessment and evaluation of possible risks due to absence of microbiological parameters in the CoA or insufficient microbiological parameters is adopted.

In case of high or critical risk recommendations from Ph. Eur. chapter 5.1.4. (Table 1) are considered whereas the administration route of the dosage form is considered prior establishing proper microbiological control.

Cumulative risk, as mathematically calculated points is presented. Furthermore, overall risk level is evaluated by merging the conclusions from the number of general control points (GCP) assessed with highest risk level (3) and critical control points (CCP) assessed with highest risk level (4). According to the evaluation presented – the following risk assessment measures are been proposed:

Table 3. Proposed risk assessment measures

Risk clasiification	Risk evaluation		Risk control
	Cumulative risk	Rules	
Critical risks	33	Ttwo CCP report risk level 4	Immediate risk communication with relevant authorities in order to minimize risks as soon as possible. Consider reviewing process of existing SP/MM in order to stringent microbiological limits and/or add additional microbiological tests
High risks	30 - 32	One CCP report risk level 4	Setting stringent limits for defined microbiological parameters is considered necessary
Medium risks	17 - 29	One CCP report risk level 3 and NMT three GCP report risk level NMT 3	Reevaluate critical control points and reevaluate cumulative risk. Additional justification of defined MM and/or SP is considered appropriate
Low risks	10 - 16	CCP report risk level NMT 2 and GCP report risk level NMT 3	Risks are considered insignificant; proposed defining MM and/or SP is acceptable unless otherwise justified

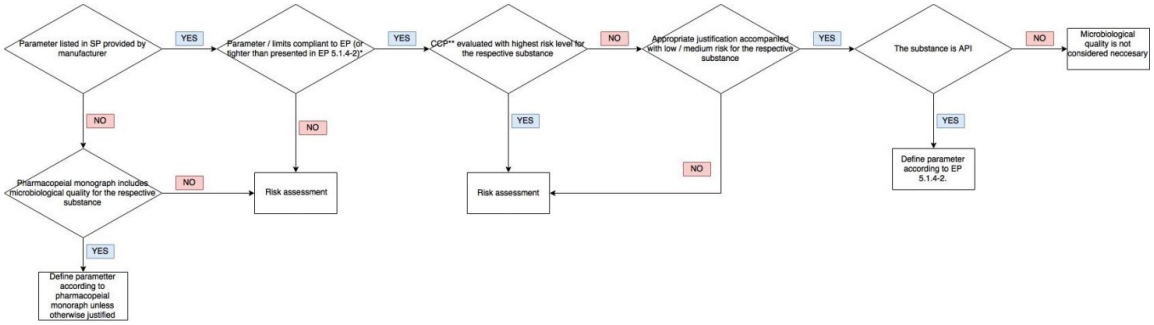

Figure 3. Decision tree #1 - Risk assessment for defining the microbiological quality parameters in specification for incoming raw materials

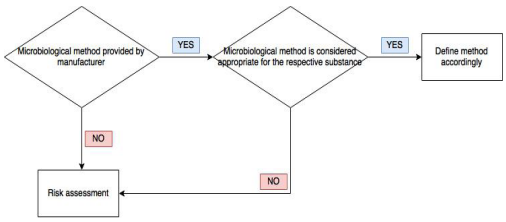

Figure 4. Decision tree #2 - Risk assessment in defining the microbiological method for control parameters in specification for incoming raw materials

Table 5.1.4.-2. – *Acceptance criteria for microbiological quality of non-sterile substances for pharmaceutical use*

	TAMC (CFU/g or CFU/mL)	TYMC (CFU/g or CFU/mL)
Substances for pharmaceutical use	10^3	10^2

♦*Recommended acceptance criteria for microbiological quality of herbal medicinal products for oral use are given in general chapter 5.1.8.*♦

Figure 5. Acceptance criteria for microbiological quality of non-sterile substances for pharmaceutical use

	6. Risk evaluation			
1	Qualification of supplier/manufacturer	Riskscenario 1 or 2	Riskscenario 3	General control points related to manufacturer
	Proven supplier/manufacturer with perspective collaboration	1	1	
	New supplier	2	2	
	Poor collaboration	3	3	
2	The manufacturer has CEP/COS			
	Yes (no microbiological quality declared or the microbiological parameter is included as additional test)	1	1	
	Yes (microbiological quality included in respective CEP/COS)	2	2	
	No	3	3	
3	Origin and form of the substance*			Critical control points
	Solid / synthetic	1	1	
	Semi-solid / synthetic	2	2	
	Solid / natural	3	3	
	Liquid / natural or Unknown	4	4	
4	Synthesis of substance*			
	Antimicrobial treatment / Organic solvents	1	1	
	Combined organic solvents	2	2	
	Aqueous solvents	3	3	
	Water extraction / Water used as final isolation solvent / Enzymatic (fermentation) processes or Unknown	4	4	
5	Dosage form / Manufacturing process of FP*			
	Solid dosage forms / dry blending / direct compression / dry milling / slugging	1	1	
	Solid and semi-solid dosage forms (process including organic solvents) / wet blending / wet granulation / wet milling	2	2	
	Solid and semi-solid dosage forms (process including aqueous solutions) / wet blending / wet granulation / wet milling or Solid with unknown pharmaceutical process	3	3	
	Liquid dosage forms: sterilization / preservative utilization / liquid separation or Liquid form with unknown pharmaceutical	4	4	
6	Water activity of the substance			General control points related to substance
	≤ 0.60%	1	1	
	0.60% - 0.75%	2	2	
	0.75% - 1.0% or Unknown	3	3	
7	Hygroscopic nature of the substance			
	No	1	1	
	Medium hygroscopic	2	2	
	Highly hygroscopic	3	3	
8	pH of the substance			
	1-3 / 8-14	1	3	
	3-6	2	2	
	6-8 or Unknown	3	1	
7	Antimicrobial properties of the substance			
	None	3	1	
	Non-specific agens	2	2	
	Yes	1	3	
10	Proportion of raw material in FP			
	0-25%	1	1	
	25-50%	2	2	
	50-100% or Unknown	3	3	
	Cumulative risk	72	72	
	N° CCP with level 4	3	3	
	N° CCP with level 3	3	3	

Figure 6. Risk assessment form for evaluating the impact of the predefined parameters on the microbiological bioburden of raw material

Appropriate risk control measures are adopted in favor of achieving risk mitigation. The risk assessment process and risk mitigation measures are concluded upon careful evaluation of control points previously described. The overall process and further action points are defined as per case-by-case basis and unified pattern for decision making is not considered applicable. Nevertheless, if the MB quality is considered as critical parameter it is compulsory for the MB quality to be regularly controlled by raw material's manufacturer as well as by finished product manufacturer. For the respective cases - stringent MB specification and specification limits should be defined (including specific microorganisms in specification).

Upon adopting proper control measures - risk mitigation is expected to be achieved.

3. Conclusions

- Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.

- The application of risk assessment and risk management is a key part of the manufacture and quality control of pharmaceuticals. Managing the risk to quality of pharmaceuticals should be considered of prime importance to protect the patient.

- Risk management is a regulatory requirement and can provide regulators with greater assurance of a company's ability to deal with potential risks.

- In undertaking risk assessment, it is important to attempt risk mitigation and to attempt to lower the risk until the risk can be lowered no further. This involves identifying actions to reduce the probability of event and to reduce the severity of event.

- Risk assuming actions should be periodically re-assessed.

- Hazard Analysis Critical Control Point (HACCP) methodology is successfully applied by pharmaceutical companies to reduce risk of microbial contamination through identifying areas in the process and types of raw materials and equipment that are at high risk of being contaminated with microorganisms.

- Assessment of the critical control points and the ability to consistently monitor them for any process makes it better for preventive applications than reactive.

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