Q9(R1) QUALITY RISK MANAGEMENT

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FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

QUALITY RISK MANAGEMENT
Q9(R1)

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At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

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ICH HARMONISED GUIDELINE

QUALITY RISK MANAGEMENT

Q9(R1)

ICH Consensus Guideline

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1. INTRODUCTION

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. In the pharmaceutical sector, the principles and framework of ICH Q9, coupled with the official ICH training material that supports this guideline, are instrumental in enhancing the application of effective quality risk management by industry and regulators. The importance of *quality systems* has been recognized in the pharmaceutical industry, and it is evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In addition, subjectivity can directly impact the effectiveness of risk management activities and the decisions made. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality and availability, when availability risks arise from quality/manufacturing issues, should be considered of prime importance.

The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* is assured based on appropriate risk-based decision-making throughout the *product lifecycle,* such that the attributes that are important to the quality of the drug product are maintained and the product remains safe and effective.

An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. A proactive approach to quality risk management facilitates continual improvement and is of strategic importance in achieving an effective pharmaceutical quality system. Additionally, use of quality risk management can improve the decision making if a quality problem arises. In the development phase, quality risk management is part of building knowledge and understanding risk

scenarios, so that appropriate risk control can be decided upon during technology transfer, for use during the commercial manufacturing phase. In this context, knowledge is used to make informed risk-based decisions, trigger re-evaluations and stimulate continual improvements. Effective and proactive quality risk management can facilitate better, more informed and timely decisions throughout the lifecycle. This can provide regulators with greater assurance of a company's ability to deal with potential risks and avert problems, and can beneficially affect the extent and level of direct regulatory oversight.

The application of digitalization and emerging technologies in the manufacture and control of medicinal products can present certain challenges. The application of quality risk management to the design, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerized systems is important.

The purpose of this document is to offer a systematic approach to quality risk management for better, more informed, and timely decisions. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

An understanding of formality in quality risk management (see Section 5 below) may lead to resources being used more efficiently, where lower risk issues are dealt with via less formal means, freeing up resources for managing higher risk issues and more complex problems that may require increased levels of rigor and effort. An understanding of formality can also support risk-based decision-making, where the level of formality that is applied reflects the degree of importance of the decision, as well as the level of uncertainty, complexity and criticality which may be present.

Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators. Quality risk management should not be used in a manner where decisions are made that justify a practice that would otherwise, in

accordance with legal requirements, be deemed unacceptable.

2. SCOPE

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug products, biological and biotechnological products).

3. PRINCIPLES OF QUALITY RISK MANAGEMENT

Two primary principles of quality risk management are:

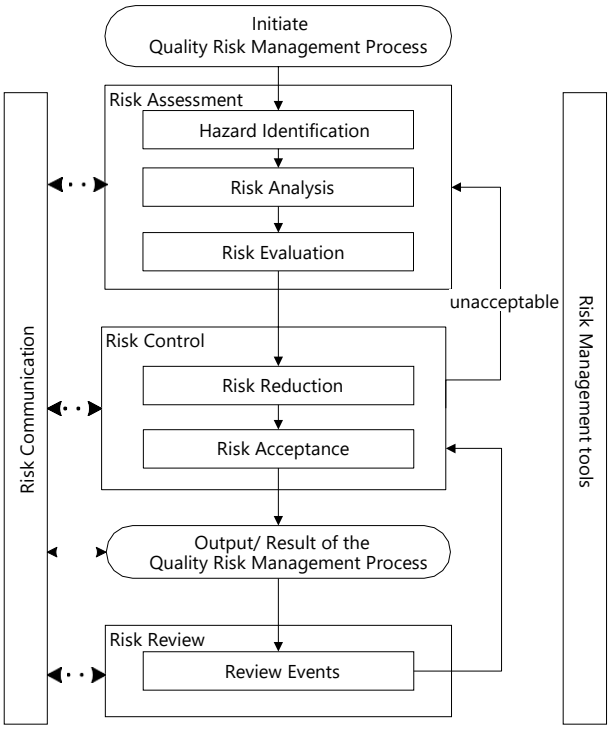
- The evaluations of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient. (Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm.)
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4. GENERAL QUALITY RISK MANAGEMENT PROCESS

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.

A model for quality risk management is outlined in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical quality risk management process



Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: "unacceptable" in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also to indicate that the risk assessment process should be revisited.

4.1 Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, supply chain, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Subjectivity can impact every stage of a quality risk management process, especially the identification of hazards and estimates of their probabilities of occurrence, the estimation of risk reduction and the effectiveness of decisions made from quality risk management activities. Subjectivity can be introduced in quality risk management through differences in how risks are assessed and in how hazards, harms and risks are perceived by different stakeholders.

Subjectivity can also be introduced through the use of tools with poorly designed risk scoring scales. While subjectivity cannot be completely eliminated from quality risk management activities, it can be controlled by addressing bias, the proper use of quality risk management tools and maximizing the use of relevant data and sources of knowledge (see ICH Q10, Section II.E.1).

All participants involved with quality risk management activities should acknowledge, anticipate, and address the potential for subjectivity.

Decision makers should

- take responsibility for coordinating quality risk management across various functions and departments of their organization; and
- assure that a quality risk management process is defined, deployed and reviewed and that adequate resources and knowledge are available;
- assure that subjectivity in quality risk management activities is controlled and minimized, to facilitate scientifically robust risk-based decision making.

4.2 Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

4.3 Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in Section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?

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

3. What are the consequences (severity)?

Hazard identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Hazard identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

4.4 Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

4.5 Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

4.6 Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).

5. RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1 and chapter 8):

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

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality. Quality risk management methods and the supporting

statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.

5.1 Formality in Quality Risk Management

Formality in quality risk management is not a binary concept (i.e. formal/informal); varying degrees of formality can be applied during quality risk management activities, including when making risk-based decisions. In this way, formality can be considered a continuum (or spectrum), ranging from low to high.

When determining how much formality to apply to a given quality risk management activity, certain factors can be considered. These can include, for example, the following:

- **Uncertainty:** The term "uncertainty" in quality risk management means lack of knowledge about risks. The level of uncertainty that is associated with the area being risk assessed informs how much formality may be required to manage potential risks. Systematic approaches for acquiring, analyzing, storing and disseminating scientific information are essential for generating knowledge, which in turn informs all quality risk management activities. Uncertainty may be reduced via effective knowledge management, which enables accumulated and new information (both internal and external) to be used to support risk-based decisions throughout the lifecycle.

- **Importance**: The more important a risk-based decision is, the higher the level of formality that should be applied, and the greater the need to reduce the level of uncertainty associated with it.

- **Complexity:** The more complex a process or subject area is to a quality risk management activity, the higher the level of formality that should be applied to assure product quality.

In general, higher levels of uncertainty, importance or complexity require more formal quality risk management approaches to manage potential risks and to support effective risk-based decision making.

The overall approach for determining how much formality to apply during quality risk

management activities should be described within the quality system. Resource constraints should not be used to justify the use of lower levels of formality in the quality risk management process. Regardless of how much formality is applied, the robust management of risk is the goal of the process. This should be based on evidence, science and knowledge, where risk scores, ratings or assessments are supported by data or by an appropriate justification or rationale.

The following may be characteristics of higher levels of formality:

- All parts of the quality risk management process (Risk Assessment, Risk Control, Risk Review and Risk Communication) are explicitly performed, and stand-alone quality risk management reports (or related documents) which address all aspects of the process may be generated and are documented (e.g., within the quality system).

- Recognized or other quality risk management tools are used in some or all parts of the process.

- A cross-functional team is assembled for the quality risk management activity. Use of a trained quality risk management facilitator may be integral to a higher formality process.

The following may be characteristics of lower levels of formality:

- One or more parts of the quality risk management process are not performed as stand-alone activities but are addressed within other elements of the quality system which may have risk assessment and risk control activities embedded within them.

- Recognized or other quality risk management tools might not be used in some or all parts of the process. A cross functional team might not be necessary.

- Stand-alone quality risk management reports might not be generated. The outcome of the quality risk management process is usually documented in the relevant parts of the quality system.

Note: Degrees of formality between the above higher and lower levels also exist and can be used.

5.2 Risk-based Decision Making

Risk-based decision making is inherent in all quality risk management activities; it provides an essential foundation for decision makers in an organization. Effective risk-based decision

making begins with determining the level of effort, formality and documentation that should be applied during the quality risk management process. The outputs of quality risk management activities include decisions in relation to what hazards exist, the risks associated with those hazards, the risk controls required, the acceptability of the residual risk after risk controls, the communication and review of quality risk management activities and outputs.

Approaches to risk-based decision-making are beneficial, because they address uncertainty through the use of knowledge, facilitating informed decisions by regulators and the pharmaceutical industry in a multitude of areas, including when allocating resources. They also help recognize where uncertainty remains, so that appropriate risk controls (including improved detectability) can be identified to enhance understanding of those variables and further reduce the level of uncertainty.

As all decision making relies on the use of knowledge, see ICH Q10 for guidance in relation to Knowledge Management. It is important also to ensure the integrity of the data that are used for risk-based decision making.

Approaches to risk-based decision-making:

There are different processes that can be used to make risk-based decisions; these are directly related to the level of formality that is applied during the quality risk management process. (See Section 5.1 above for guidance on what constitutes formality in quality risk management.) In general, higher levels of formality in quality risk management call for higher levels of structure in relation to risk-based decision making. There can be varying degrees of structure with regard to approaches for risk-based decision making. These degrees of structure can be considered to be on a continuum (or spectrum). Below are descriptions for highly structured vs. less structured processes, and for rule-based processes when making risk-based decisions:

- Some risk-based decision making processes are highly structured and can involve a formal analysis of the available options that exist before making a decision. They involve an in-depth consideration of relevant factors associated with the available options. Such processes might be used when there is a high degree of importance associated with the decision, and when the level of uncertainty and/or complexity is high.

- Other risk-based decision making processes are less structured; here, simpler approaches are used to arrive at decisions, and they primarily make use of existing knowledge to support an assessment of hazards, risks and any required risk controls. Such processes might still be used when there is a high degree of importance associated with the decision, but the degree of uncertainty and/or complexity is lower.

- Decisions might also be made using rule-based (or standardized) approaches, which do not require a new risk assessment to make such decisions. This is where there are SOPs, policies or well understood requirements in place which determine what decisions must be made. Here, rules (or limits) may be in place which govern such decisions; these can be based on a previously obtained understanding of the relevant risks and they usually lead to predetermined actions or expected outcomes.

6. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. While manufacturing and supply chain diversity can be enablers of product availability, increasingly complex supply chains lead to interdependencies that can introduce systemic quality/manufacturing risks impacting supply chain robustness. Application of quality risk management can proactively mitigate these risks. Preventive measures supporting product availability may be identified through quality risk management activities.

Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for industry and regulatory operations (see Annex II):

- Quality management.

Examples for industry operations and activities (see Annex II):

- Development;
- Facility, equipment and utilities;
- Materials management;
- Production;
- Laboratory control and stability testing;
- Packaging and labeling;
- Supply Chain Control.

Examples for regulatory operations (see Annex II):

- Inspection and assessment activities.

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

The role of Quality Risk Management in addressing Product Availability Risks

Quality/manufacturing issues, including non-compliance with Good Manufacturing Practice (GMP), are a frequent cause of product availability issues (e.g., product shortages). The interests of patients are served by risk-based drug shortage prevention and mitigation activities that help to proactively manage supply chain complexities and ensure availability of needed medicines. An effective pharmaceutical quality system drives both supply chain robustness and sustainable GMP compliance. It also uses quality risk management and knowledge management to provide an early warning system that supports effective oversight and response to evolving quality/manufacturing risks from the pharmaceutical company or its external partners. The level of formality applied to risk-based drug shortage prevention and mitigation activities may vary (see Chapter 5). Factors that can affect supply reliability, and hence product availability, include the following:

Manufacturing Process Variation and State of Control (internal and external):

Processes that exhibit excessive variability (e.g., process drift, non-uniformity) have capability gaps that can result in unpredictable outputs and may adversely impact quality, timeliness, yield, and consequently product availability. Quality risk management can help design monitoring systems that are capable of detecting departures from a state of control and deficiencies in manufacturing processes, so they can be investigated to address root causes.

Manufacturing Facilities:

A robust facility infrastructure can facilitate reliable supply; it includes suitable equipment and well-designed facilities for manufacturing and packaging. Robustness can be affected by multiple factors, such as an aging facility, insufficient maintenance or an operational design that is vulnerable to human error. Risks to supply can be reduced by addressing these factors, as well as through use of modern technology, such as digitalization, automation, isolation technology, amongst others.

Oversight of Outsourced Activities and Suppliers:

Quality system governance includes assuring the acceptability of supply chain partners over the product lifecycle. Approval and oversight of outsourced activities and material suppliers is informed by risk assessments, effective knowledge management, and an effective monitoring

strategy for supply chain partner performance. A successful manufacturing partnership is strengthened by appropriate communication and collaboration mechanisms. When substantial variability is identified in the quality and safety of supplied materials or in the services provided, enhanced review and monitoring activities are justified (See Section 2.7 of ICH Q10). In some cases, it may be necessary to identify a new supply chain entity (e.g. a pre-qualified backup option) to perform a function.

7. DEFINITIONS

Decision Maker(s):

Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.

Detectability:

The ability to discover or determine the existence, presence, or fact of a hazard.

Harm:

Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard:

The potential source of harm (ISO/IEC Guide 51).

Hazard Identification:

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Product Lifecycle:

All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Quality:

The degree to which a set of inherent properties of a product, system or process fulfills requirements (see ICH Q6A definition specifically for "quality" of drug substance and drug (medicinal) products.)

Quality Risk Management:

A systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.

Quality System:

The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements:

The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health care professionals, regulators and legislators). In this document, “requirements” refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk:

The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Acceptance:

The decision to accept risk (ISO Guide 73).

Risk Analysis:

The estimation of the risk associated with the identified hazards.

Risk Assessment:

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk-based Decision Making:

An approach or process that considers knowledge about risks relevant to the decision and whether risks are at an acceptable level.

Risk Communication:

The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control:

Actions implementing risk management decisions (ISO Guide 73).

Risk Evaluation:

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Management:

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

Risk Reduction:

Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Review:

Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Severity:

A measure of the possible consequences of a hazard.

Stakeholder:

Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

Trend:

A statistical term referring to the direction or rate of change of a variable(s).

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ANNEX I: QUALITY RISK MANAGEMENT METHODS AND TOOLS

The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

It is neither always appropriate nor always necessary to use highly formal quality risk management methods and tools. The use of less formal quality risk management methods and tools can also be considered acceptable. See Chapter 5 for guidance on what constitutes formality in quality risk management.

I.1 Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

- Flowcharts;
- Check Sheets;
- Process Mapping;
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

I.2 Failure Mode Effects Analysis (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Potential Areas of Use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). FTA is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual

representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

(1) conduct a hazard analysis and identify preventive measures for each step of the process;

(2) determine the critical control points;

(3) establish critical limits;

(4) establish a system to monitor the critical control points;

(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;

(6) establish system to verify that the HACCP system is working effectively;

(7) establish a record-keeping system.

Potential Areas of Use(s)

HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

I.6 Hazard Operability Analysis (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result, 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures.

Potential Areas of Use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

I.9 Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

- Control Charts, for example:
  - Acceptance Control Charts (see ISO 7966);
  - Control Charts with Arithmetic Average and Warning Limits (see ISO 7873);
  - Cumulative Sum Charts (see ISO 7871);
  - Shewhart Control Charts (see ISO 8258);
  - Weighted Moving Average.
- Design of Experiments (DOE);

- Histograms;
- Pareto Charts;
- Process Capability Analysis.

ANNEX II: QUALITY RISK MANAGEMENT AS PART OF INTEGRATED QUALITY MANAGEMENT

This Annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality Risk Management as Part of Integrated Quality Management

Documentation

To review current interpretations and application of regulatory expectations;

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness);

To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.

Quality defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc;

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

Auditing/Inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements;
- Overall compliance status and history of the company or facility;
- Robustness of a company's quality risk management activities;
- Complexity of the site;
- Complexity of the manufacturing process;
- Complexity of the product and its therapeutic significance;
- Number and significance of quality defects (e.g., recall);
- Results of previous audits/inspections;
- Major changes of building, equipment, processes, key personnel;
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches);
- Test results of official control laboratories.

Periodic review

To select, evaluate and interpret trend results of data within the product quality review;

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).

Change management / change control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing;

To evaluate the impact of the changes on the availability of the final product;

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers;

To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators.

Continual improvement

To facilitate continual improvement in processes throughout the product lifecycle.

II.2 Quality Risk Management as Part of Regulatory Operations

Inspection and assessment activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" Section in Annex II.1);

To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings;

To determine the appropriateness and type of post-inspection regulatory follow-up;

To evaluate information submitted by industry including pharmaceutical development information;

To evaluate impact of proposed variations or changes;

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

II.3 Quality Risk Management as Part of development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8(R2));

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials;

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);

To decrease variability of quality attributes:

- reduce product and material defects;
- reduce manufacturing defects.

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer;

To make use of the "design space" concept (see ICH Q8(R2)).

II.4 Quality Risk Management for Facilities, Equipment and Utilities

Design of facility / equipment

To determine appropriate zones when designing buildings and facilities, e.g.,

- flow of material and personnel;
- minimize contamination;
- pest control measures;
- prevention of mix-ups;
- open versus closed equipment;
- clean rooms versus isolator technologies;

- dedicated or segregated facilities / equipment.

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants);

To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water);

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts).

Hygiene aspects in facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns);

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured.

Qualification of facility/equipment/utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods).

Cleaning of equipment and environmental control

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production);

To determine acceptable (specified) cleaning validation limits.

Calibration/preventive maintenance

To set appropriate calibration and maintenance schedules.

Computer systems and computer controlled equipment

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance);

To determine the extent of validation, e.g.,

- identification of critical performance parameters;

- selection of the requirements and design;
- code review;
- the extent of testing and test methods;
- reliability of electronic records and signatures.

II.5 Quality Risk Management as Part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

Starting material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing);

To determine appropriateness of reprocessing, reworking, use of returned goods.

Storage, logistics and distribution conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design);

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines;

To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance);

To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6 Quality Risk Management as Part of Production

Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods);

To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation);

To distinguish between critical and non-critical process steps to facilitate design of a validation study.

In-process sampling & testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control);

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

Production planning

To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results.

Retest period / expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials.

II.8 Quality Risk Management as Part of Packaging and Labelling

Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

Selection of container closure system

To determine the critical parameters of the container closure system.

Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

II.9 Quality Risk Management as Part of Supply Chain Control

With regard to product availability risks related to quality/manufacturing issues, lifecycle oversight of the supply chain includes maintaining current knowledge of quality/manufacturing hazards and prioritizing efforts to manage such risks. Understanding hazards to quality/manufacturing is critical to maintaining supply predictability. When risks are well understood and minimized, a higher confidence in product availability can be attained.

Manufacturing Process Variation and State of Control

To decrease variability in the manufacturing process (e.g., process drift, non-uniformity) and associated capability gaps that can result in unpredictable outputs, adversely impact quality and consequently timeliness, yield and product availability;

To design monitoring systems that are capable of detecting departures from a state of control and deficiencies in manufacturing processes, so they can be appropriately investigated to determine root causes and any required risk mitigations.

Manufacturing Facilities

To ensure that facility infrastructure and equipment are suitable and well-designed for manufacturing and packaging;

To establish equipment and facility maintenance programs that assure reliable facility and equipment performance;

To ensure that the operational design of equipment is not vulnerable to human error;

To obtain efficiency gains (e.g. speed, throughput, supply timeliness, etc.) from investing in quality through the utilization of digitalization, automation, isolation technology, and other innovations.

Supplier Oversight and Relationships

To enhance review and monitoring activities (see Section 2.7 of ICH Q10) when substantial variability is identified in the quality and safety of supplied materials or in the services provided.

To manage external product availability risks relating to quality/manufacturing, (e.g. from raw material suppliers, contracted organizations, service providers, etc.)