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1 Introduction

Risk management principles have been effectively utilized in many areas of business and government including finance, insurance, medical, safety, product design and agencies regulating other industries (references to be added). Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. The importance of *quality systems* has been recognized in the pharmaceutical industry and it is becoming evident that 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. Achieving a shared understanding of the application of risk management among diverse *stakeholders* is very difficult because each stakeholder may identify different potential harms, place different probability on each harm occurring and characterize different severities of the harm. These concepts are especially important in relation to pharmaceuticals due to the variety of stakeholders, including patients and medical practitioners as well as government and industry.

The use of a drug (medicinal) product necessarily entails some degree of risk. It is important to understand that the need is to maintain product *quality*, such that the risk to the patient is not significantly different than that observed in the clinical program. An effective risk management approach can further ensure the high quality of the drug product to the patient in providing a proactive means to identify and mitigate potential quality issues with the product at the earliest stages of product development (i.e. as described in ICH Q8 – Pharmaceutical Development) and manufacturing. Additionally, use of risk management techniques can also improve the decision making if a quality problem arises. Effective risk management can facilitate better and more informed decisions and may provide regulators with greater assurance of a company's ability to deal with potential risks and may affect the extent and level of direct regulatory oversight.

The purpose of this document is to provide guidance on the principles and the tools of risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substance/product across the *product lifecycle*. This guideline also supports and compliments existing quality practices, requirements, standards, and guidelines.

Although a systematic approach to risk management is generally preferred, it may not always be appropriate or necessary to use a formal risk management process. Even if risk management is utilized appropriately, it does not obviate industry's regulatory requirements and does not replace the necessary communications between industry and regulator.

2 Scope

This guideline provides a framework that may be applied to all aspects of pharmaceutical quality including GMP and submission/review processes throughout the lifecycle of drug substances (API) and drug (medicinal) products, biological and vaccine products, and the use of excipients and packaging materials.

This guideline is not intended to apply to risk management used in a pharmacovigilance setting involving safety and efficacy.

3 Principles of Quality Risk Management

Risk is a concept that has different meanings to different people and organizations. Therefore, before implementing risk management approaches, it is important to articulate a common definition of risk, including explicit identification of the harm (e.g., reduction in the quality of medicinal products) that is to be addressed. At a fundamental level, definitions of risk capture the likelihood of harm or loss from exposure to a source of harm (*hazard*). Risk definitions for a specific context usually specify what are "at risk" (e.g., drug quality, health, property, quality of life) given exposures to the hazard (the property of a substance or event that can cause harm, e.g., contaminant), and call for an estimate of likelihood that harm (e.g., illness) will occur from the exposure.

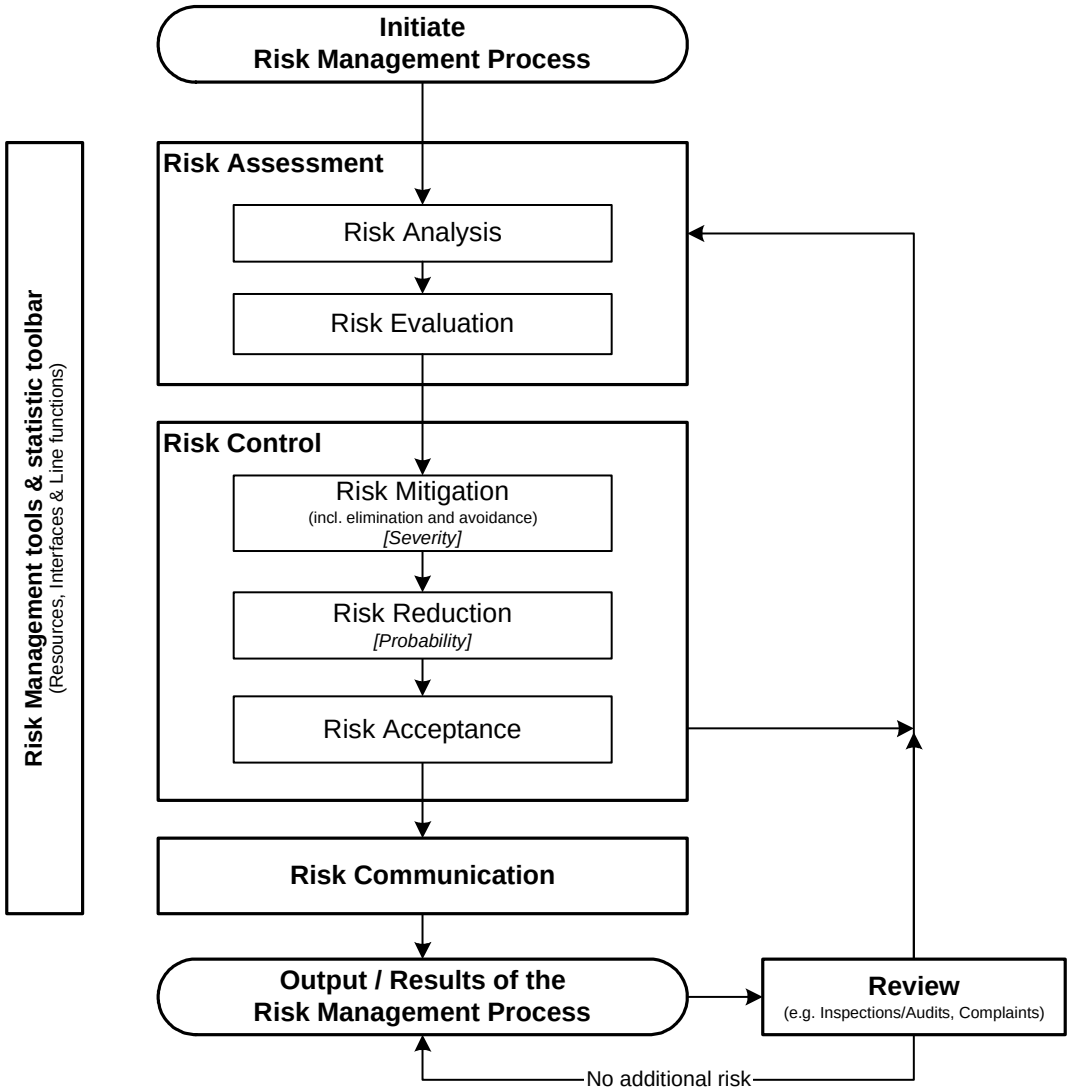
Risk may be measured using a quantitative or qualitative approach depending on the circumstance and criteria established in specific fields of analysis. Risk definitions intending to span a broad and diverse range of hazards and harms generally incorporate the concept of severity. The definition of risk used here is broadly inclusive of diverse harms and hazards eliciting those harms: risk is a combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51). Below are essential principles for the use of quality risk management:

- The evaluation of the risk should ultimately link back to the potential risk to the patient.
- The extent of the risk management process should be commensurate with the level of risk associated with the decision.
- A more robust the data set will lead to lower uncertainty.
- It is essential to have a clear delineation of the risk question.
- Risk management should be a *dynamic / iterative* process.
- People who apply risk management should have the appropriate training, skills and experience.
- The risk management process should be appropriately documented and verifiable.

4 General Quality Risk Management Process

Risk management is a systematic process for the identification, assessment and control of risks to the quality of pharmaceuticals across the product lifecycle. The level of effort, formality and documentation of the risk management process should be commensurate with the level of risk.

Risk management for pharmaceutical quality generally includes systematic processes for the identification, assessment, control and communication of risks to the quality of pharmaceuticals across the product lifecycle. The application of the risk management process developed in this document focuses on risk assessment, risk control, risk communication and review with the understanding that a separate process for problem (hazard) identification may be used by industry and/or regulators.



4.1 Responsibilities

Risk management activities are usually, but not necessarily, undertaken by interdisciplinary teams dedicated to the task. Teams formed for specific risk management activities should include expertise from the technical areas involved in addition to individuals who are knowledgeable of the risk management process.

Decision makers may use different processes for controlling risks including risk management, benefit-cost analysis and decision analysis. Risk management decisions inevitably involve allocation of resources to manage risk.

Quality risk management is a joint responsibility among decision makers from various functions and departments (e.g., product development, production, quality control, quality assurance, engineering, and logistics). Management is responsible for ensuring that the risk management process is applied appropriately. The decision taken about a particular risk may be to expend resources either to mitigate, avoid or eliminate the risk, or to accept the risk.

4.2 Initiate Risk Management Process

Possible steps used by decision makers to initiate and plan a risk management process may include:

- Defining specifically the risk management problem or question, including the assumptions leading to the question.
- Assembling background information and data on the hazard, harm or human health impact relevant to the assessment.
- Defining how the assessment information and conclusions will be used by the decision makers.
- Identifying the necessary resources, members of the team who have the appropriate expertise, with the leader clearly identified.
- Asking the right risk assessment question(s)
- Stating clearly the assumptions in the risk assessment
- Assessing the quality and sufficiency of relevant data
- Specifying a timeline and deliverables for the risk assessment

4.3 Risk Assessment

Confusion often arises over the distinction between risk assessment and risk management. Risk assessment is *a systematic process of organizing information to support a risk decision* to be made by a risk management process. Risk assessments characterize the sources of harm (hazards), events, severities, consequences and probability.

Quality risk assessments begin with a well-defined *risk question*. If the risk in question is well defined, the appropriate tools needed to answer the question are more readily identifiable.

Risk assessment can be thought of as asking three simple questions (after Y. Haimes, 1998) to address the probability of occurrence of harm and the severity of the harm:

- What can go wrong?
- What is the likelihood (probability) it would go wrong?
- What are the consequences?

Risk assessment consists of risk analysis and risk evaluation.

Risk analysis is a systematic use of information to identify specific sources of harm (hazards) and to estimate the risk. This provides a basis for risk evaluation, risk control and risk communication. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. To estimate risk, a qualitative or quantitative process might be used to assign the probability and severity of a risk. Risk analysis can consider quality, cost, benefits, the concerns of stakeholders, and other variables, as appropriate for risk evaluation.

Risk evaluation compares the estimated risk against given risk criteria using a quantitative or qualitative scale to determine the significance of the risk. Quantitative scales are usually based on probability (0 to 100% likely) whereas qualitative scales use descriptive terms, such as “high”, “medium” or “low.” Sources of uncertainty are included the overall evaluation. Typical sources of uncertainty includes gaps in knowledge about the data, sources of harm, probability of detection or the model linking the quality issue (e.g., critical variables), with the risk-benefit to the patient are evaluated as a part of the overall risk evaluation.

4.4 Risk control

Risk control describes the actions of implementing risk management decisions. It includes risk mitigation, risk reduction and risk acceptance. Normally, risk mitigation and risk reduction are performed in parallel. The purpose of risk control is to minimize the risk. The efforts used for risk control is related to the significance of the risk.

In contrast to risk assessment, risk control is a decision-making activity focused on controlling risks and addresses the following questions:

- What can be done to mitigate and reduce risks?
- What options for controlling risks are available?

- What are the impacts of current risk management decisions on future options for risk management?

Risk mitigation focuses on a reduction of severity of harm; it does not necessarily remove the probability of harm entirely. It limits any negative consequences of a particular event. Examples of mitigating risk include elimination and avoidance.

Risk reduction focuses on the reduction of probabilities of occurrence of harm and detection of harm.

Risk acceptance is a decision to accept risk, i.e., no additional risk control activities are necessary. Risk acceptance has to be supported by the decision maker(s). The decision to accept risk includes acceptance of risks that have not been identified.

4.5 Risk communication

Risk communication is the exchange or sharing of information about risk and risk management between the decision maker and other stakeholders. The information can relate to the existence, nature, form, probability, severity, acceptability, treatment, detectability or other aspects of risks to quality.

The communication between industry and its stakeholders concerning quality risk management decisions can be made through existing channels.

4.6 The Review Phase

All risk management processes are iterative. New information at any stage of the risk management process may lead to a new risk assessment or new components of the risk management process, any of which facilitate continuous improvement. Quality risk management when applied should benefit from new knowledge at each cycle and use it to enhance future decisions. Once a risk management process has been initiated, that process will continue to be utilized for events that may impact the original risk management decision whether it be planned (e.g. results of annual product review, inspections, audits, change control) or unplanned (e.g. recall, complaints, deviations).

5 Risk Management Tools

Risk management tools support a scientific approach for decision-making by providing documented, transparent and reproducible methods to accomplish steps of the risk management process (Chapter 4).

A variety of risk management tools have been developed and others will potentially be developed in the future. For use in specific areas, such as pharmaceuticals, these tools may need to be adapted. It is also possible to combine the tools or their components to address particular risk management questions. The variations of tools allow supporting the risk management process.

Below are some of the primary tools used today in the field of risk management together with short, purely illustrative, examples of how they may be used in pharmaceutical quality.

5.1 Process Mapping

Process mapping is a prerequisite for the use of some of the tools described in this section. The purpose of a process map is to provide a clear and simple visual representation of the steps involved in the process and to show how they are interrelated. Process mapping can be used to facilitate understanding, explaining and systematically analyzing complex processes and associated risks.

5.2 Preliminary Hazard Analysis (PHA)

PHA is an inductive method of analysis whose objective is to identify the hazards, hazardous situations and events that can cause harm for a given activity, facility or system.
A PHA formulates a list of hazards and generic hazardous situations by considering characteristics such as:

- materials used or produced and their reactivity;
- equipment employed;
- operating environment;
- layout;
- interfaces among system components, etc.

The method is completed with the identification of the possibilities that the risk event happens, the qualitative evaluation of the extent of possible injury or damage to health that could result and the identification of possible remedial measures. PHA should be updated during the phases of design, construction and testing to detect any new hazards and make corrections, if necessary. The results obtained can be presented in different ways such as tables and trees.

It is most commonly carried out early in the development of a project when there is little information on design details or operating procedures and can often be a precursor to further studies. It can be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used.

Example:

It can be used for product, process and facility design. It can be used for example to evaluate the types of hazards for the general product type, then the product class and finally the specific product. Once hazards are identified a plan is put together on how to control them (e.g. by design, by protective measures and/or by labeling).

5.3 Hazard Analysis of Critical Control Points (HACCP)

It is a systematic, proactive, and preventive method for assuring product quality, reliability, and safety. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or the adverse consequence(s) of hazard(s) due to the design, development, production, and use of products. An effective HACCP system when properly applied and implemented may improve product reliability and safety, and reduce cost of poor quality.

HACCP consists of the following seven steps:

1. Conduct hazard analysis and identify preventive measures
2. Determine critical control points
3. Establish critical limits
4. Monitor each critical control point
5. Establish corrective action to be taken when deviation occurs
6. Establish verification procedures
7. Establish record-keeping system

It is most useful when process understanding is sufficiently comprehensive to support identification of all critical control points.

Example:

In the context of a risk management system, it can be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination).

5.4 Hazard Operability Analysis (HAZOP)

HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic technique for identifying hazards. This bottom up method is based on systematic brainstorming using so-called “guide-words”. “Guide-words” (e.g., No, More, Other Than, Non, Part of, etc.) are used to help identify potential deviations from normal use or design intentions.

In the pharmaceutical area, the objectives of the technique are:

- To produce a full description of a pharmaceutical and its quality attributes.
- To systematically review every part of the process to discover how deviations from the normal operating conditions and the intended process design can occur.
- To identify the consequences of such deviations and to decide whether these consequences can lead to hazards.

It uses a team of people with expertise covering the design of process or product and its application.

A HAZOP generally can be applied to formulation processes used in the manufacture of a pharmaceutical product or the manufacture of drug substances (API, excipients, sterilization, etc). It has also been used in the pharmaceutical industry for evaluating process safety hazards.

Example:

Applied to pH adjustment in product formulation to determine the effects of adding more or less acid/ base.

ADD—ACID—to TANK.

5.5 Fault tree analysis (FTA)

The FTA method (see IEC 61025) is based on a top down approach and assumes failure of the functionality of a product or process. In a systematic and deductive manner, starting with the fault, the possible causes are identified. The method may be used to establish the pathway to the root cause of the failure. This method evaluates system (or subsystem) failures one at a time but can combine multiple causes by working on 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.).

One limitation of this method is that the outputs are only as good as the inputs. It is a team exercise and relies on process understanding of the experts to identify causal factors. The use of FTA may be applied to managing complaints 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).

Example:

An example is a complaint where the customer could not open the container. Starting with the top-level event, e.g., container, could not be opened identify potential causes until the root cause is identified. In this example, one might determine the cap required too much force for the customer; the cause of that problem was too much force and over torquing or is a result of original designed. If over torquing was a problem, it could be caused by calibration or maintenance, etc.

5.6 Failure Mode Effects Analysis (FMEA)

FMEA identifies functional failure as a result of process step or component failure using an inductive (bottom up), non-quantitative approach. It is an evaluation and documentation of potential failure modes for processes and the likely effect on process outcomes and/or product performance. Once failure modes are established mitigation is then used to eliminate, reduce or control the potential failures. It relies on process understanding. It is methodical and breaks large

complex products or processes into manageable steps. As a bottom up approach, it complements the Fault Tree Analysis (FTA). It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures. It is possible to use FMEA to prioritize risk, and monitor the effectiveness of risk mitigation activities.

Example:

This method may be used to identify potential sources of risk associated with a new facility or process and their potential impact on product quality. FMEA can be used to analyze a production process to identify high risks steps or critical control points. FMEA can be applied to assess particle contamination to identify the step with the highest risk to introduce particles in the finished product. FMEA is also useful in establishing a corrective action plan (CAPA).).

5.7 Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA can be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence and their detectability, and can become a Failure Mode Effect and Criticality Analysis (FMECA). In order to perform such an analysis, the product or process specifications should be established in detail. FME(C)A application in the pharmaceutical industry will mostly be focused on failures and risks associated with manufacturing processes. FME(C)A can identify places where additional preventive actions may be necessary to minimize risks. Once established, a FME(C)A analysis should be updated as new information becomes available.

For example:

- Successful production without deviations may positively impact the original estimation of the probability of occurrence.
- Future deviations, rejects and complaints may provide additional information to refine the original analysis, either the detection capability or the occurrence estimation.

5.8 Risk Ranking and Filtering

Risk ranking is a tool to compare and prioritize risks. Risk ranking of complex systems typically requires 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 risk score that can then be compared, prioritized and ranked. The key steps to building a risk ranking framework and a robust model for risk-based prioritization of a portfolio of risks can be characterized as:

1. Identify top-level components of the risks in question
2. Identify the attributes of the risks to be considered in the ranking
3. Identify mid-level categories for risk attributes (to facilitate model organization and communication of the model)
4. Categorize risk attributes under the mid-level categories
5. Develop questions for the individual risk attributes under each mid-level categories and develop or identify qualitative or quantitative metrics for the risk attributes
6. Describe the relationship between the individual risk attributes, the categories of the risks, and subsequent impact of the individual risks and categories of risks on the overall risk ranking, i.e. define the mathematical algorithm for aggregating component risk scores into an overall risk score.
7. Prioritize the risks based on the overall rankings

Sources of specific risk information for risk ranking might include, not only the results of separate FMEA, FTA, or other analysis, but also the elicitation of expert opinion in instances where there are data gaps and large uncertainties.

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. The strengths of risk ranking and filtering include the obvious benefit of organizing the

organization's risk management activities on a risk basis. Risk ranking is useful when management needs to evaluate both quantitatively and qualitatively assessed risks within the same organizational framework.

Example: Prioritizing manufacturing sites for inspection/audit by regulators or industry. In contrast, FMEA, Fault Tree Analysis, and other risk tools are appropriate for assessment of *specific* risks to drug quality.

5.9 Informal Risk Management

By definition, any decision-making activity about risks involves a risk management process. The pharmaceutical industry and pharmaceutical regulators have traditionally assessed and managed risk in a variety of more empirical ways, based on for example compilation of observations, trends and other information. Such approaches continue to provide useful information that can support, for example handling of complaints, quality defects, allocation of resources to inspection oversight and aspects of more formalized risk management.

5.10 Supporting Statistical Tools

There are numerous tools that may be used to support quality risk management processes, including the risk identification step. In order to aid understanding, some commonly used statistical tools deserve special mention. These tools may be helpful to support risk assessments to enable effective data assessment when making decisions for risk mitigation (reduction of severity/consequences) and to reduce probability. They may also aid in determining the significance of the data set(s) and/or the identification of interactions and interconnection.

Design of experiments (DOE)

This approach is used to design experiments and analyze data to determine e.g. establish key parameters and/or process variables and explore potential interactions. It is mainly used in the research and development area and also for retrospective evaluation of established parameters (Proven Acceptable Ranges).

Process Capability Analysis

A useful tool for both regulator and industry to monitor/measure process variability this statistical tool can be used to analyze data retrospectively (e.g. Annual Product Review) and determine the relationship between process variability and specification... The process capability metrics are process specific data and are used to estimate the potential percent of defective product.

Control charts

These tools are used for monitoring "variables". A control chart **(ISO 7870:1993)** shows statistically determined upper and lower control lines drawn on either side of the process average. The control chart provides information to determine if a process is in control.

Using acceptance control charts (see ISO 7966:1993) during regular batch manufacturing can give guidance for determining sample size, action limits and decision criteria. Ongoing improvements under process robustness/six sigma program can be initiated.

Shewart control charts (see ISO 8258:1991) are used for the statistical control of the process. They use warning limits and analysis trend patterns.

Cumulative sum charts **(ISO 7871:1997)** can be used to analyze process parameters or analytical results. They allow the detection of slight discrepancies in a process before a trend is visible using other control charts.

5.11 General Guide on the Application of a Combination of Tools

(NOTE to Reviewers: This section may become part of the Appendix)

The risk assessment method described here is an integration of a process FMEA with HAACP decision making to identify the Critical Control Points (CCP's). The process FMEA is used to define, identify potential (and known) failures. The hazard is assigned a ranking for severity and the failure mode is assigned a ranking for probability of occurrence and the ability to detect the failure before the next step. Evaluation rules are applied to the rankings to determine whether the step is a CCP. The CCP approach is presented rather than the straight mathematical approach of calculating a Risk Probability Number (RPN), as in a traditional FMEA, because it places the emphasis on failure modes connected to end user safety. Since the primary objective is to control product risk to the patient, hazards with a low severity rating are not considered CCPs. Control points where the severity is high are considered CCPs and further analyzed for the Key Characteristics/Attributes necessary to minimize patient risk.

Here are two approaches that illustrate the flexible application of a combination of tools in a structured way:

- *Mapping the process* that encompasses the subject, issues, processes and/or the system being managed.
- Create the *table for severity, probability and detection*. This step may include a flexible ranking and filtering step developed between a company and the corresponding regulatory body (e.g. an Example of severity, Probability and Detection chart) (for an example see Annex x2).
- Create a table of *Essential User Requirements*. This may include: technical, medical, product insert claims and other implied requirements (for an example see Annex x3)
- Create a table and *Identify hazards* using step (1) to provide structure to the analysis. Each step is evaluated for potential failure modes and impact on the product. This step combines the universal aspects of Hazard Analysis Critical Control Points (HACCP) and Failure Modes and Effects Analysis (FMEA) and is best implemented through a multidisciplinary team comprised of skills to enrich the subject and a risk management expert to exercise the tool (for an example see Annex x4).
- *Decision Tree*. This step is a unifying step that is intended to allow consistency of expectations and outcomes. This step may include a flexible ranking and filtering step developed between a company and the corresponding regulatory body (for an example see Annex x5).
- Add the Critical Control Points (CCP'S) to the table created in step 4 (for an example see Annex x6)
- Create a *plan* using all feasible organizational capabilities *to control risk* at the Critical Control Points (CCP'S). This table is intended to be the list of subjects that have met the criteria to be a CCP and it is used to focus resources on mitigation. Associate CCP with the plan by incorporating specific capability information. (Map each Key Characteristic to the plan table) (for an example see Annex x7).
- Create an *action plan* if appropriate to include the roles and responsibilities that would include the original team and the communication with the relevant regulatory body (for an example see Annex x8)
- *Maintenance* of the plan to implement continuous/dynamic risk management. There are a variety of project management tools that can be used to prioritize and follow up. (for an example see Annex x9).

I. Define the scope of an analysis and collect all relevant data surrounding the system and subject to determine the need for additional information.
II. Describe the desired and controlled conditions of the process.
III. Using a structured approach identify the risk by reviewing the direct and indirect causal areas.
IV. Using assessment tools (e.g. statistical) assess the hazard.

6 Integration of Quality Risk Management Process into Current Operations

Risk management is a key concept that provides the foundation for science-based decisions when integrated into quality management systems and other business processes. The degree of rigor

and formality of the risk management should be linked to the complexity and/or criticality of the issue to be addressed; i.e., for simple, less critical changes, deviations, etc. a less formal approach is usually sufficient. For major changes, new facility designs and other more complex or critical situations a more formal approach, using one of the recognized tools (as described in section 5) to conduct and document the risk management, may be beneficial.

The aim of this section is to provide examples of where conducting a risk management may provide information regarding critical parameters that can then be used in a variety of pharmaceutical operations, some of which are given below. These examples are intended to be purely illustrative and they should not be considered a definitive or exhaustive list.

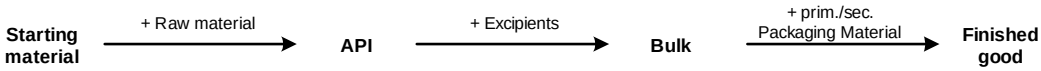
As outlined in the introduction, appropriate use of risk management does not obviate industry's regulatory requirements but may facilitate better and more informed decisions.

6.1 Risk Management as part of Development

To support selection of most appropriate dosage form (e.g. parenteral concentrates vs. pre-mix) or process selection (e.g. terminal sterilization vs. aseptic process).

Specification Setting and Test Method Selection
To assess the criticality of variables and attributes of raw materials, API's, excipients, or packaging materials in order to select appropriate specifications and/or analytical methods to be used for either in-process control or release analysis (following the guidance given in ICH Q8) to ensure product quality.

To continue to assess the critical variables and attributes. These variables and attributes may change as the product and process move through its lifecycle from research, to development and production phase. These critical variables and attributes, as well as associated specifications, have to be re-evaluated during product lifecycle and might change. All ingredients and processes along the synthesis and processing might have an influence on critical variables and attributes:



Risk management may help decision making by identifying the critical variables and attributes of each step and phase.

R&D/commercial operations interface
To support technology transfer and scale-up by assessing the need for additional supportive studies; e.g., bioequivalence, stability, etc.

6.2 Risk Management as as Tool for Better Quality Management

Auditing and Self-Inspection
To define frequency of audits (both internal or external) and regulatory inspections taking into account assessment of relevant factors, such as compliance status, criticality of material or product and previous history. In the case of regulatory inspections, issues such as the complexity of the site, product(s) and/or manufacturing process (es), compliance history, number of quality defects and recalls etc. may provide additional useful information.

Training and Education
To determine the need and repetition of training sessions based on education, experience and working habits of staff as well as on a periodic assessment of previous training.

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

Deviations/Discrepancies, Complaints & Recall Management

To assess deviations/discrepancies and complaints, to provide the basis for evaluation and communication of the potential quality impact (documented in a deviation or investigation report). This will enable science-based decisions about potential actions (e.g., recall) in conjunction with regulatory authorities.

Change Management/Change Control
To evaluate the impact of the changes to the quality of the final product.
To evaluate of the equivalence of changes of facility, equipment, manufacturing process and technical transfers.

To assess the impact of changing specifications and/or methods of analysis (including analytical method transfer) of raw materials, API's, excipients, drug product or packaging material testing used either for in-process control or release analysis. Determination of appropriate actions, e.g., notification of authorities, revalidation, additional stability testing and additional tests.

Product Quality Complaints
To Be Determined

6.3 Risk Management as part of Facilities, Equipment and Utilities

Design of Building/Facility
To determine appropriate zones, considering the flow of material and personal, microbiological aspects, the need to minimize contamination, pest control measures, prevention of mix-ups, open versus closed equipment, etc.

Hygiene Aspects in Facilities
To support the approach to the control of exposure to hazardous substances including the choice of clothing and gowning, smoking & eating policy setting, response to infections of personnel, etc

Facility/Equipment/Utility Qualification
To determine the scope and extent of qualification of facilities, buildings, production equipment and/or laboratory instruments including proper calibration and the selection of critical measuring devices.

To determine appropriate product contact materials on equipment and containers; e.g. selection of food grade lubricant.

To determine appropriate quality of utilities such as steam, gases, compressed air, heating ventilation and air conditioning (HVAC), water etc., including preventive maintenance for associated equipment

Cleaning of Equipment and Environmental Control
To differentiate efforts based on the intended use; i.e., multipurpose, mono or continuous production, and determine acceptable levels of residual contamination using science based decisions

Preventive Maintenance
To set appropriate calibration and maintenance schedules.

Computer Systems and Computer Controlled Equipment.
To select the design (modular, structured), the extent of testing and test methods, as well as identification of critical performance parameters, including reliability of electronic records and electronic signatures.

6.4 Risk Management as part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers
To provide a comprehensive evaluation of suppliers including regulatory /quality, commercial, physical and technical risks.

Starting Material
To assess differences and possible risks associated with early versus late stage starting materials

Release of Materials
To determine if it is appropriate to release material under quarantine (e.g., for shipping) providing an appropriate risk mitigation strategy is in place.

Re-use of Materials
To support and enable science-based decisions for reprocessing, reworking, use of returned goods etc.

Storage and Distribution Conditions
To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions.

Logistics
To Be Determined

6.5 Risk Management as part of Production

Validation
To identify the extent of validation activities required for analytical methods, processes and cleaning methods and the need for follow-up activities such as sampling, monitoring and re-validation.

In-process Sampling & Testing
To evaluate the frequency and extent of in-process control (IPC) testing. This could be used to justify using results from IPC testing or the application of process analytical technologies (PAT) as the results for release (‘real-time’ release).

To analyze data and supplier or process performance to justify reduced testing under conditions of proven control.

Reporting and Trending
To select, evaluate and interpret of trend results within the Product Quality Review (e.g. annual product review) or to interpret monitoring data to support an assessment of the need for revalidation, changes of sampling points, etc.

6.6 Risk Management as part of Laboratory and Stability Testing

Stability
To make science-based decisions about a stability study, including the need for additional studies, assessing frequencies of testing, explain effects on quality by discrepancies in storage or transport conditions (e.g. cool-chain management) in conjunction with other ICH guidelines.

To rationalize existing stability programs in relation to different regulations for humidity and temperature ranges in different regions and to focus programs on attributes that are truly critical to product performance.

Out of specification results
To identify potential failure modes during the investigation of out of specification results.

Retest / Expiration Date Setting
To challenge results of use tests, stress tests rationalizing decisions for extensions and use of material, including widely used excipients where equivalent data is not available.

6.7 Risk Management as part of Packaging and labelling

Selection of container closure system
To determine the "critical to quality attributes" that have to be maintained by the container/closure system.

Label controls
To design label control procedures based on risk of mixing up different product labels and different versions of the same label.

6.8 Risk Management As Part of Regulatory Activities

To Be Determined

7 Definitions

Decision Maker - process owner of risk management process

Dynamic / Iterative Process - TBD

Harm – Damage to health, including the damage that can occur from loss of product efficacy, safety, quality or availability

Hazard - the source of harm. Can be a chemical, biological or physical substance, or an event that can cause harm.

Product Lifecycle – All phases in the life of a product covering both the inherent characteristics of the product and how these may change over time. The lifecycle is from the initial development through pre- and post-approval until the product's discontinuation and includes the associated regulatory processes.

Quality – Degree to which a set of inherent characteristics of a product, system or process fulfills requirements

Quality System – A formalized system that documents the structure, responsibilities and procedures required to achieve effective quality management.

Requirements – Needs or expectations that are stated, generally implied or obligatory by the patients or their surrogates (e.g. health care professionals, regulators and legislators)

Risk – Combination of the probability of occurrence of harm and the severity of that harm (from ISO/IEC Guide 51)

Risk Management – Systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling and communicating risk

Severity – Measure of possible consequence of a potential source of harm

Stakeholder - Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. The decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, authority, regulator, industry, business, customer.

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