1. Purpose

To establish a standardized process detailing requirements and responsibilities for the application of Risk Management to the design, development, manufacture, and lifecycle management of Macro Biologics’ products in accordance with ICH Q9(R1) and/or ISO 14971:2019 as applicable to the regulations set forth in 21 CFR 820/ISO 13485:2016 and EU 2017/745 MDR. This document also establishes the Risk Management policy and details the process to analyze, evaluate, control, accept or reject, communicate, and monitor risk throughout the entire product lifecycle.

1. Scope
   1. In Scope

This standard operating procedure (SOP) applies to investigational and commercial products, i.e., the combination product and its constituent parts and associated manufacturing processes that are designed, developed, manufactured, or distributed by or for Macro Biologics under current good manufacturing practice (cGMP). Risk Management is applicable throughout the product’s entire lifecycle.

This procedure establishes and defines processes for identifying and managing quality risks, safety risks, or hazards that can potentially lead to harm. This procedure does not define the threshold for acceptable risk or risk index, as this is dependent on the intended use and expected benefit of using the product (defined in the Risk Management Plan).

Where Macro Biologics is the product applicant, Macro Biologics is responsible for ensuring appropriate Risk Management processes are applied by design partners and contract manufacturers. Macro Biologics is responsible for combination product Risk Management. Partners, consultants, contract manufacturers or suppliers performing cGMP activities are evaluated and approved in accordance with SOP-007 Purchasing Controls.

* 1. Out of Scope

This procedure excludes:

* Decisions on the use of a product for any particular clinical procedure
* Business risk management (ISO 31000)

1. Responsibilities

Risk Management requires cross-functional teams to contribute their expertise to Risk Management activities within a program. Needs for a specific program help determine the lead responsible for Risk Management for a particular product. The appropriate experience, training, certification, and education records are retained in accordance with SOP-003 Training and SOP-001 Document control.

Macro Biologics has overall responsibility for the effective execution and oversight of the Risk Management process, including both internal and external organizations’ scope of work.

The responsibilities listed below are functional requirements that may be overseen by a single individual within Macro Biologics. Functions may be conducted by an external party; the external party is evaluated and approved in accordance with SOP-007 Purchasing Controls.

| **Function** | **Responsibility** |
| --- | --- |
| Top Management / Management with Executive Responsibility | * Ensures adequate level of management oversight and review of significant risks associated with business strategies, processes, and activities * Ensures adequacy, availability, and competency of resources for compliant execution of Risk Management * Reviews the suitability of the Risk Management process at planned intervals to ensure continuing effectiveness * Defines and documents a policy for establishing risk acceptability along with establishing period review of the process |
| Product Development | * Executes and oversees Risk Management activities * Approves Risk Management documentation * Reviews data from post-market reports and provides input into updates to Risk Management deliverables based on proposed updates and engineering solutions |
| Quality | * Responsible for the Risk Management process (establishing, implementing, maintaining, and reviewing the effectiveness of the process) * Creates and maintains the Risk Management File * Ensures Risk Management File complies with this SOP and documented quality systems * Approves and monitors Risk Management deliverables, activities, or efforts * Defines evaluation criteria for quality risks * Publishes the Risk Management Report and maintains it once a product is on the market |
| Regulatory Affairs | * Evaluates Risk Management activities for compliance with applicable national or regional regulations, relevant international standards, and guidelines for the product * Reviews and approves the Benefit-Risk Analysis report |
| Medical Representative | * Reviews and approves the final product risk assessment * Establishes applicable harms * Establishes the severity associated with the harm * Establishes the likelihood of a hazardous situation leading to harm (P2, see 6.5.3 and Appendix 5), if applicable * Creates Benefit-Risk Analysis report |

1. Applicable Documents

| **Document #** | **Document Title** |
| --- | --- |
| SOP-001 | Document control |
| SOP-003 | Training |
| SOP-004 | Design Controls |
| SOP-006 | Human Factors Engineering |
| SOP-007 | Purchasing Controls |
| TMP-005 | Risk Management Plan |
| TMP-006 | Risk Management Report |
| TMP-007 | Hazard Analysis |
| ICH Q9(R1) | Quality Risk Management |
| EN ISO 14971:2019 | Medical devices – Application of risk management to medical devices |
| ISO/TR 24971:2020 | Medical devices - Guidance on the application of ISO 14971 |
| AAMI/TIR105:2020 | Risk Management Guidance for Combination Products |

1. Definitions and Acronyms

| **Term/Acronym** | **Definition** |
| --- | --- |
| Applicant | The entity that holds the marketing authorization for a medical device or combination product (regardless of whether that entity is directly engaged in manufacture of the product). Responsible for ensuring Design Controls are correctly applied to the medical device or combination product. Applicant is the manufacturer of record |
| Accompanying documentation | Materials accompanying a medical device or combination product containing information for the user or those accountable for the installation, use, maintenance, decommissioning, and/or disposal of the medical device, particularly regarding safe use |
| Benefit | Positive impact or desirable outcome of use of the medical device or combination product on the health of an individual or the public, or on patient management. |
| cGMP | Current Good Manufacturing Practice |
| Critical Material Attribute (CMA) | A physical, chemical, biological, or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material |
| Critical Process Parameter (CPP) | A process parameter whose variability impacts a CQA or CtQ and therefore should be monitored or controlled |
| Critical Quality Attribute (CQA) | A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (e.g., identity, strength/potency, purity, and safety) |
| Critical to Quality (CtQ) | Essential characteristic of a product, process, or service that is vital to the performance/functionality/usability of a product; A given CtQ should be within an appropriate limit, range, or distribution to ensure the desired product quality (e.g., dose accuracy) |
| Combination product | Product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product |
| Design and Development File / Design History File (DHF) | A compilation of records that describes the design history of a finished device |
| Detectability | The ability to discover or determine the existence, presence, or fact of a hazard. Detectability is only used for process risk analyses |
| Failure Modes and Effects Analysis (FMEA) | A systematic bottom-up technique for evaluating processes to identify where and how they might fail, and for assessing the relative impact of different failures |
| Fault Tree Analysis (FTA) | A systematic top-down method for identifying and analyzing the potential failure modes of a system |
| Harm | Injury or damage to the health of people, or damage to property or the environment |
| Hazard | Potential source of harm |
| Hazard identification | The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description |
| Hazardous situation | Circumstance in which people, property, or the environment is/are exposed to one or more hazards |
| Intended use / Intended purpose | Use for which a product, process, or service is intended according to the specifications, instructions, and information provided by the manufacturer |
| Lifecycle | Series of all phases of a product’s existence, from the initial conception to final decommissioning and disposal |
| Objective evidence | Data supporting the existence or verity of something |
| Preliminary Hazard Analysis (PHA) | Technique used early in the development process that identifies and evaluates the hazards, hazardous situations, and resulting harms associated with a product |
| P | Probability of occurrence of harm |
| P1 | Probability of a hazardous situation occurring |
| P2 | Likelihood of a hazardous situation leading to harm |
| Post-production | Part of a product’s lifecycle: after the design has been completed and the product has been manufactured |
| Process | Set of interrelated or interacting activities that use inputs to deliver an intended result |
|  |  |
| Reasonably foreseeable misuse | Use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable human behavior |
| Residual risk | Risk remaining after risk control measures have been implemented |
| Risk | The combination of the probability of occurrence of harm (P) and the severity of that harm |
| Risk analysis | Systematic use of available information to identify hazards and estimate risks. Risk analysis may utilize various risk analysis/assessment tools or methodologies |
| Risk assessment | Overall process comprising a risk analysis and a risk evaluation  Systematic process of organizing information to support a risk decision to be made within a Risk Management process. It consists of hazard identification and the analysis and evaluation of risks associated with exposure to those hazards (risk analysis/risk evaluation) |
| Risk communication | The sharing of information about risk and Risk Management between the decision maker(s) and other stakeholders |
| Risk control | Process in which decisions are made and measures implemented to reduce or maintain risk within specified levels |
| Risk estimation | Process used to assign values to the probability of occurrence of harm and the severity of that harm (estimated risk) |
| Risk evaluation | The comparison of the estimated risk to given risk criteria, using a quantitative or qualitative scale to determine the acceptability of the risk. Outputs provide the basis for risk reduction and/or risk acceptance decisions |
| Risk Management (also “Quality Risk Management” (QRM)) | Systemic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk |
| Risk Management File (RMF) | Set of records and other documents that are produced by Risk Management |
| Risk Management Plan (RMP) | Iterative guide to Risk Management activities throughout the entire lifecycle of a given product or family of products |
| Risk reduction | Actions taken to lessen the probability of occurrence of harm and/or the severity of that harm |
| Risk review | Review or monitoring of output/results of the RM process |
| Safety | Freedom from unacceptable risk |
| Severity | A measure of the possible consequences of a hazard |
| State of the art | Developed stage of technical capability at a given time as regards products, processes, and services, based on the relevant consolidated findings of science, technology, and experience |
| Top management | Person or group of people who directs and controls a manufacturer at the highest level |
| Use environment | Actual conditions and setting in which users interact with the product |
| Use error | User action or lack of user action while using the product that leads to a different result than intended by the manufacturer or expected by the user |
| User | A person who interacts with (i.e., operates or handles) the product |
| Use-related risk analysis (URRA) | A risk analysis tool used to identify use-related hazards  associated with medical product use and the measures implemented to reduce associated risks |
| Validation | Confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled |
| Verification | Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled |

1. Procedure
   1. Overview

Risk Management is a systematic, evidenced-based approach to support risk-based decision making around a product and its manufacture, with the aim of reducing subjectivity. The process helps to ensure quality is maintained throughout a product’s lifecycle and the critical quality attributes (CQAs)/critical to quality (CtQs) are consistently controlled through the establishment of critical process parameters (CPPs), critical material attributes (CMAs), and other control strategies as appropriate.

Risk Management is integrated within the Design Control process, reference SOP-004 Design Controls. During development, Risk Management is intended to proactively identify and eliminate or minimize potential hazards, hazardous situations, and harms before manufacture. The goal is to reduce risks to an acceptable level so that when a product is placed on the market, its continued safe and effective performance is ensured. Once the product is on the market, Risk Management activities shift to continuous improvement efforts and ensuring manufacturing controls are in place and remain effective. Post-market surveillance helps to monitor the safety and effectiveness of the product, verifying that the residual risk remains acceptable.

An overview of the Risk Management process is shown in Figure 1 below. For each step, the constituent part and the combination product as a whole are considered.

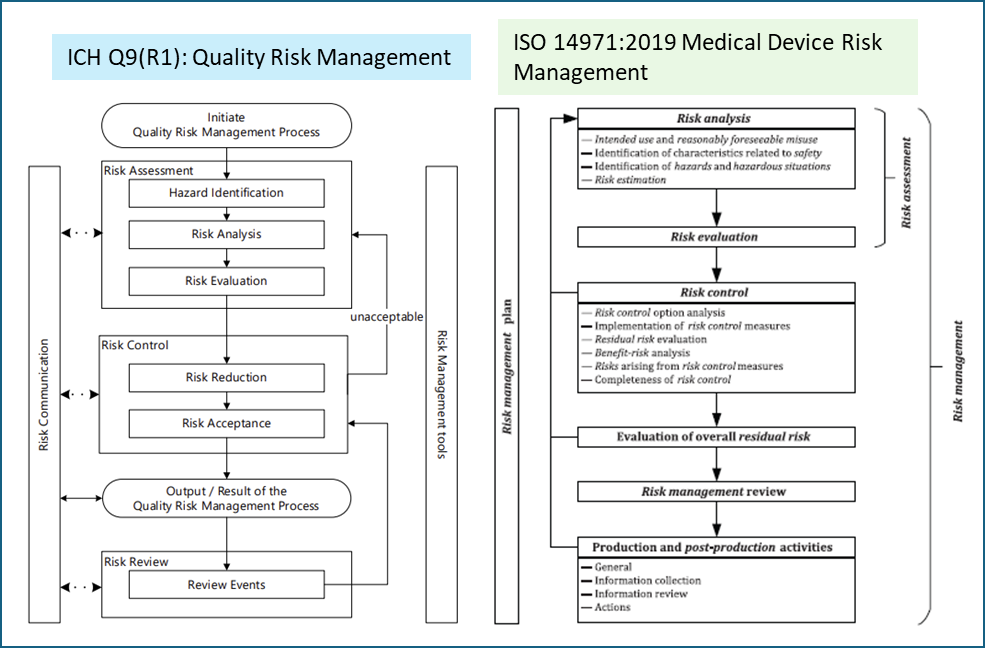


Figure 1. Schematic representations of the frameworks for Risk Management

It is important that the Risk Management team acknowledges their subjectivity and aims to minimize their bias through the use of relevant data and sources of knowledge.

* 1. Risk Management policy

Macro Biologics’ policy for Risk Management provides guidance for establishing the criteria for risk acceptability used for the evaluation of residual risks. The Risk Management policy applies to a product throughout its entire lifecycle. The policy for a product applies to all personnel involved in Risk Management activities and explicitly to those who are responsible for the risk acceptability matrix as defined in the Risk Management Plan (RMP, section 6.3).

Macro Biologics ensures that intended and approved products are only placed or kept on the market when the clinical benefit outweighs the residual risks. The RMP outlines the specific criteria for risk acceptability for a product or family of products. The following considerations will be made when establishing the risk acceptability criteria:

* Regulatory requirements for regions where the product is intended to be marketed
* Relevant international standards for the product, including standards for testing specific properties with approval/rejection limits
* Generally acknowledged state of the art, best practices in technology, and publications/guidelines published by authorities
* Stakeholder concerns obtained through communication with users, clinics, patients, and/or regulatory bodies

The risk control strategy for a given product or family of products is defined within the RMP as certain regulations within the intended market region could require specific methods for managing risk. The preferred strategy is to reduce risk as far as possible (AFAP) without having an adverse impact on the benefit-risk ratio.

Approval of this document provides approval of the Risk Management policy. Review of the policy is in accordance with the periodic review defined in SOP-001 Document control. Management reviews also address the Risk Management policy. The effectiveness of the Risk Management process is evaluated as a part of internal quality system audits. Management reviews assess the effectiveness and suitability of the process based on summaries of production and post-production information.

* 1. Risk Management Plan (RMP)

Risk Management activities for a product or family of products will be planned. The RMP will establish and document activities in accordance with this process. TMP-005 Risk Management Plan may be used. Risk Management planning will identify all the necessary activities, associated deliverables, and responsibilities for the combination product.

At a minimum, the RMP will include or reference the following information:

* List of intended products to which the plan applies along with a description of the product(s)
* Scope of the planned Risk Management activities, identifying and describing the product and the lifecycle phases for which each element of the plan is applicable
  + Inclusive of external activities if applicable
* Identification of the Risk Management team including assignment of responsibilities and authorities
  + Inclusive of external team if applicable
* As applicable, consideration for the integration of information from CMOs or third-party suppliers
* Supply chain risks – consideration for the loss of product quality, supply availability, changes to components sourcing and distribution concerns may be included, as phase appropriate
* Milestones for Risk Management activities
* Requirements for review(s) of Risk Management activities
* Criteria for risk acceptability, based on the Risk Management policy for determining acceptable risk, including when the probability of occurrence of harm cannot be estimated
* Risk control strategy
* Method to evaluate individual residual risk and criteria for acceptability of the overall residual risk based on the Risk Management policy
* Activities for verification of the implementation and effectiveness of risk control measures
* Activities related to collection and review of relevant production and post-production information

The RMP will be reviewed, approved, controlled, maintained, and updated as design and development progresses. The RMP and its revision(s) will be maintained in the Risk Management File (RMF); all information may not be known at its initial creation and will be defined in later revisions. Changes to the RMP will be maintained in the RMF.

* 1. Risk Management File

The RMF will contain all Risk Management records or pointers to Risk Management records for a product. The RMF will provide traceability for each hazard to the risk analysis, evaluation, implementation, and verification of the risk control measures, along with the evaluation of residual risks. This file can be a standalone file or incorporated in the Design and Development File.

The RMF will contain the following minimum records:

* Risk Management Plan
* Risk analysis and/or evaluation records (e.g., preliminary hazard analysis, use related risk analysis (URRA), failure modes and effects analysis (FMEA), or other acceptable risk analysis tools)
* Risk assessment
* Benefit-Risk analysis report
* Risk Management Report
* Post-market surveillance plan / post-market surveillance review reports / post-market risk review reports

Each deliverable will document the team involved with the Risk Management activity and the approval date in accordance with SOP-001 Document control.

* 1. Risk assessment

Risk assessment involves risk identification, analysis, and evaluation based on the intended use of the product by the intended users in the intended use environments. This process helps to identify which factors (e.g., material, process) can have a potential impact on CQAs/CtQs. Including CQAs, CtQs, CMAs, or CPPs when performing risk analyses can help the team to understand the impact on product quality, safety, effectiveness, functionality, and usability along with the harm(s) each is associated with thus leading to the identification of appropriate risk controls.

In the case of the development of combination products it is critical to consider the risks of each constituent part of the product and the interactions between those constituents. The interactions may lead to adverse effects on other constituents, or they could serve as a risk control. Appendix 1 outlines questions to ask during the risk assessment process.

* + 1. Hazard / risk identification

Hazard / risk identification aims to define the hazards associated with the product’s use and possible consequences. Understanding the product, its characteristics, and underlying factors helps in the identification of sequence(s) of events that could lead to hazardous situations. Reference Appendix 2 for possible hazard categories.

During preliminary hazard identification the following sources can be helpful for identification of hazards and hazardous situations:

* Clinical trials
* Predicate devices
* Regulations, standards, and guidance
* Human factors evaluations
* Task analysis
* Management review
* Adverse event reporting
* Product recalls
* Scientific literature

Hazard/risk identification will be documented, for example in a preliminary hazard analysis (PHA), reference Appendix 3.

* + 1. Risk analysis

The RMP will outline the risk analysis activities. The risk analyses that are conducted will identify and describe the product being analyzed, identify the team and organization(s) who conducted the risk analyses, and include the scope and date of the analysis. If there is a modification to a product already on the market, an existing risk analysis may be updated if applicable, rather than creating a new analysis.

There are various risk analysis techniques that can be utilized. Techniques such as FMEA do not address all requirements to be compliant with ISO 14971:2019 and may only provide supporting information.

Prior to or concurrent with the initiation of risk analysis activities, external and internal sources of data should be reviewed as they can provide useful inputs to the risk analysis. This data is often useful for preliminary identification of failure modes, hazards, hazardous situations, and harms.

The risk analysis(es) will identify and document:

* Intended use of the product taking into consideration the intended medical indication, patient population, part of the body or type of tissue interacted with, user profile, use environment, and operating principle (for example within an intended use document or User Requirements Specification). Reference SOP-004 Design Control and SOP-006 Human Factors Engineering
* Reasonably foreseeable misuse (for example within a task analysis or use related risk analysis). Reference SOP-006 Human Factors Engineering
* Qualitative and/or quantitative characteristics related to safety and where appropriate the defined limits, may be documented in the PHA
* Known and foreseeable hazards associated with the product based on the intended use, reasonably foreseeable misuse, and the characteristics related to safety in both normal and fault conditions (for example within a preliminary hazard analysis)
* Reasonably foreseeable sequences or combination of events that can result in a hazardous situation and the resulting harm to the user from the hazardous situation (for example within a URRA, FMEA, FTA). Reference Appendix 4 for a URRA example.
  + 1. Risk estimation

Risk will be estimated based on available information or data for both severity of harm and probability of occurrence of harm.

Severity is a qualitative measure of the consequence of the harm and will be assigned based on Table 1. Note the severity associated with each harm will be assigned by a medical professional or determined from literature (reference to source will be documented).

Table 1. Severity of harm ranking

|  |  |  |
| --- | --- | --- |
| **Severity Rating** | **Severity Term** | **Severity of Harm Description** |
| 5 | Catastrophic | Results in death |
| 4 | Critical | Results in permanent impairment or irreversible injury |
| 3 | Serious | Results in injury or impairment requiring medical or surgical intervention |
| 2 | Minor | Results in temporary injury or impairment not requiring medical or surgical intervention |
| 1 | Negligible | Results in inconvenience or temporary discomfort |

Establishing a master harms list is recommended. The master harms list will map the harms applicable to the intended use(s) to the corresponding severity level(s). The list can also determine the severity of harm(s) that impact surrounding property and environment based on the intended use environment.

The probability of occurrence of harm can be qualitative and/or quantitative. During development, a qualitative or semi-quantitative approach may be taken, as high confidence data is often not available to assess probability quantitatively. The RMP will detail the probability limits if quantitative probabilities are assigned. The probability of occurrence of harm (P) for each potential hazardous situation will be assessed based on Table 2 below.

Table 2. Probability of occurrence of harm (P) Levels

|  |  |  |  |
| --- | --- | --- | --- |
| **Occurrence Rating** | **Qualitative description** | **Description** | **Probability Limit Example** |
| 5 | Frequent | Harm is almost inevitable | ≥1:1000 |
| 4 | Probable | Harm is likely and will occur in most circumstances and has been repeatedly observed | <1:1000 to 1:10,000 |
| 3 | Occasional | Harm is probable at some time and has been observed | <1:10,000 to 1:100,000 |
| 2 | Remote | Harm could occur at some time and isolated incidents have been observed | <1:100,000 to 1:1,000,000 |
| 1 | Improbable | Harm is extremely unlikely and has not been observed | <1:1,000,000 |

Probability of occurrence of harm will be estimated as a single probability or as the combination of two probabilities (P1xP2) where:

* P1 is the probability of a hazardous situation occurring (this requires input from technical experts)
* P2 is the likelihood of a hazardous situation leading to harm (this requires the input of a medical professional)

The RMP will document the approach to probability rankings, if a single probability is used the team scoring must include input from a medical professional and technical subject matter experts. In cases where the probability cannot be estimated, a worst-case probability of one (1) will be used. Using the P1xP2 approach may reduce the estimated risk as a hazardous situation may not always result in harm. Reference Appendix 5 for additional information, and for an example of the P1xP2 approach.

To support risk estimation, valid sources of information or data can be referenced and include, but are not limited to:

* Published standards
* Scientific or technical investigations (e.g., performance, reliability, biocompatibility, stability testing)
* Field data from similarly marketed products
* Publicly available reports of incidents (e.g., FAERs, MDR)
* Usability studies (e.g., formative and summative studies)
* Clinical evidence
* Results of relevant investigations or simulations (e.g., tolerance stacks, finite element analysis, design of experiments)
* Expert opinion
* Peer-reviewed journals or published texts

If the scoring for risk estimation (severity or probability) differs from that in this procedure it will be documented in the RMP with a rationale justifying its use.

* + 1. Product risk assessment / system level risk assessment

The product risk assessment or risk traceability matrix will tie all the risks associated with the product (including components, constituents, combination product) back to each hazard and provide a summary of the risks of concern. This will also reference the source of the information. A hazard analysis may be used to meet this requirement, reference TMP-007 Hazard Analysis.

* + 1. Risk evaluation

Risk evaluation is the process of comparing the estimated risks against the criteria for risk acceptability as defined in the RMP.

For each individual risk, a risk index will be determined based on probability and severity. The acceptability of each individual risk will then be evaluated. An example of risk categories and a risk acceptability matrix are shown in Table 3 and Table 4 below, respectively. The RMP will detail the risk category and risk acceptability matrix.

Table 3. Risk categorization example

|  |  |
| --- | --- |
| **Risk** | **Effect / Magnitude of Risk (Residual Risk)** |
| Low | The magnitude of risk is so small that it can be regarded as insignificant or negligible. The risk acceptability criteria defined in the RMP directs whether risk control efforts are required. |
| Medium | The magnitude of risk is between two states and may be conditionally acceptable. Risks require investigation to determine if risk control measures are feasible or practicable.  Medium Risks are acceptable if the overall Benefit-Risk Analysis is acceptable. |
| High | The magnitude of risk exceeds the criteria for risk acceptability. Risks require risk control measures to reduce risk to an acceptable level or have been accepted upon a Benefit-Risk Analysis for the individual high risk. |

Table 4. Risk acceptability matrix example

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **Severity** | | | | |
| Negligible (1) | Minor  (2) | Serious  (3) | Critical  (4) | Catastrophic (5) |
| **Probability of Occurrence of Harm (P)** | Frequent  (5) | Medium | Medium | High | High | High |
| Probable  (4) | Low | Medium | Medium | High | High |
| Occasional (3) | Low | Low | Medium | Medium | High |
| Remote  (2) | Low | Low | Low | Medium | Medium |
| Improbable (1) | Low | Low | Low | Low | Medium |

If risk reduction is not required, then the estimated risk will be treated as residual risk. If the risk is not acceptable then risk control activities will ensue; see 6.6 Risk control.

* 1. Risk control

The goal of risk control is to reduce risks to an acceptable level. When risk control activities are performed for a given risk, all efforts will be made to remove the risk, if possible.

* + 1. Risk control option analysis

The following process will be used for implementing risk control options based on the order listed:

* Inherent safety by design and manufacture
* Protective measures in the product itself or in the manufacturing process
* Information for safety and, where appropriate, training to users
* Compliance with relevant international standards as they can be applied
* For drug products, risk controls may rely on testing to help support the benefit-risk profile. Specifications and process controls are used to control and mitigate the drug not meeting CQAs
* For the drug product, risk control may rely on product labeling (e.g., boxed warning) as a risk mitigation

*Note that one option or a combination of options can be applied to reduce a risk.* Where risk reduction is not practicable the risk will be treated as residual risk and will be a part of the Benefit-Risk Analysis.

* + 1. Implementation and verification of risk control measures

Once risk control measures have been identified they will be implemented and subsequently verified. The verification will be included as a part of the RMF. Verification is often performed through design validation and can be a part of design verification and process qualification if the relationship between the effectiveness in risk reduction and the result of those activities is known.

* + 1. Residual risk evaluation

After risk controls are implemented and verified, re-evaluation of the risk will be performed by updating the occurrence and/or severity rankings, if applicable, and determining the residual risk index. The residual risk will then be evaluated based on the criteria for risk acceptability as defined in the RMP.

Residual risks that are acceptable do not require additional mitigation. If the residual risk is still unacceptable, additional mitigations will be investigated. If additional mitigations are not available or feasible a rationale will be provided. A Benefit-Risk Analysis will be performed for residual risk that is not acceptable to determine if the expected benefit of the intended use of the product outweighs the residual risk.

* + 1. Benefit-Risk Analysis

A Benefit-Risk Analysis will be performed on residual risks and the overall residual risk of the combination product. This analysis is a matter of judgment and performed by experienced, knowledgeable, and competent professionals that are responsible for understanding and considering the technical, clinical, and regulatory context of the Risk Management decision.

For a specific residual risk, if the risk is deemed unacceptable based on the criteria established in the RMP and further risk control is not practicable, a Benefit-Risk Analysis will be performed for this individual risk.

The Benefit-Risk Analysis will be performed by a direct comparison of the benefits of the intended use of the product against the residual risk using available clinical data, literature, generally acknowledged state of the art, and clinical/medical expert opinion. The evaluation will include a detailed review of the accompanying information to determine if the risks are articulated.

Benefits arising from the intended product and its intended use are related to the likelihood and extent of improvement of health expected from its use. Benefits will be estimated based on the following factors:

* Type of expected benefit (e.g., lifesaving treatment, essential in a given medical scenario or improves the quality of life of the patient)
* Magnitude of expected benefits (e.g., degree to which the patient will experience therapeutic benefit)
* Probability that the patient will experience the expected benefit (therapeutic efficacy)
* Duration of the expected effects
* Medical necessity if the product addresses unmet needs by other therapies

Interviews may be held with intended users or other parties that help to provide insight into the clinical usefulness of the product, component, or process. When relevant, the benefit risk analysis can be compared to similar products to see if there are alternative solutions without the same level of risk available. When there are significant risks and the benefit of the intended use is uncertain, the anticipated performance or effectiveness will be verified through a simulated use study or clinical investigation.

Results of the Benefit-Risk Analysis will be documented in a Benefit-Risk Analysis summary document and approved per the RMP. If the results of the analysis do not support that the medical benefits outweigh the residual risk, additional risk control measures and/or modification of the design and its intended use will be required to reduce risk to an acceptable level. Further modifications that can be made include:

* Changes to user interface
* Improvement in usability
* Design changes to improve functionality, reliability, robustness, or constituent interactions
* Incorporation of safety features in the design
* Process changes including equipment updates
* Improvements in detection during process
* Updates to improve process capability
  + 1. Risks arising from risk control measures

The effects of risk control measures will be reviewed to determine if:

* New hazards or hazardous situations have been introduced
* Estimated risks for previously identified hazardous situations have been altered by the introduction of risk control measures

Additional hazards that are generated will be assessed, evaluated, and if required, controlled. The appropriate documentation will be updated to record these activities so that the review is documented and incorporated in the RMF.

* + 1. Completeness of risk control

Risk control activities will be reviewed to ensure that the risks from all identified hazardous situations are considered, and risk control activities are completed. During development, these reviews may be conducted concurrently with Design Control phase reviews. Risk controls and their implementation, verification, and re-evaluation can be added as columns to the product risk assessment/hazard analysis to properly document activities and results.

Results of the review will be recorded in the RMF.

* 1. Evaluation of overall residual risk

After all risk control measures are implemented and verified, evaluation of the overall residual risk will be performed. The method for determining overall residual risk will be documented in the RMP. This evaluation will consider contributions from all residual risks in relation to benefits of the intended use based on the criteria of acceptability defined in the RMP.

If the outcome of the evaluation of overall residual risk is judged acceptable, any significant residual risks will be disclosed to the user in accompanying documentation. If the outcome is judged unacceptable, additional risk control measures or modification of the intended use will be required. The evaluation and its results will be included in the RMF as an overall residual risk evaluation report.

* 1. Risk Management review and report

Execution of the RMP will be evaluated for completeness prior to release for commercial production. The review will ensure the following, at a minimum:

* Risk Management Plan has been appropriately executed
* Risk Management process has been appropriately implemented in accordance with this procedure
* Overall residual risk acceptability and overall benefit risk analysis have been determined and meet risk acceptability criteria
* Appropriate methods to collect and review information in the production and post-production phases have been determined and are in place
* Requirements for disclosure of overall and individual residual risks through product labeling and other forms of user communication have been determined

The review and its results will be documented as a report that consists of the executed RMP and all associated records or reference to those as outlined in the plan. Reference TMP-006 Risk Management Report. Upon review and approval, the report will be maintained as a part of the RMF. This report will be shared with management and will document the original risk management decision.

* 1. Product availability (supply chain risks)

As the loss of product availability can lead to patient harm, it is important to understand risks associated with the supply chain. Understanding the supply chain and manufacturing process can allow for proactive implementation of preventive measures to help mitigate these risks. Main areas to evaluate include:

1. Manufacturing process

Processes with high variability can result in unpredictable outputs, potentially compromising quality, yield, or production time, which can impact product availability. Statistical process control and monitoring systems can help identify issues with a process to find a root cause and investigate improvements.

1. Manufacturing facilities and equipment

Aging facilities, inadequate maintenance, and process designs with vulnerability to human error can lead to issues with product availability. Robust facilities, procedures, and equipment can help reduce these errors (e.g., automation, isolation technology, digitization).

1. Suppliers (outsourced activities)

Supplier oversight is critical to maintain product availability. Reference SOP-007 Purchasing Controls for details on supplier management. Risk-based supplier management aims to minimize issues with suppliers by implementing appropriate controls and systems for adding controls to mitigate quality and supply issues if needed. Identification of alternate supply chain partners is prudent to limit supply chain issues.

* 1. Risk communication

Risk communication serves as a mechanism for sharing information about risk between various stakeholders. The level and formality of communication will depend on what is being communicated and between which stakeholders.

Communication during development occurs when conducting Risk Management activities. Conversations during these activities will often lead to improvements in the design and removal of risks early on. Outputs of the Risk Management process will be formally documented and communicated through records and reviews, reference SOP-004 Design Controls for details on design reviews.

Communication of risk to external stakeholders will include:

* Risk communication between Macro Biologics and its suppliers, which is essential for appropriate evaluation of risk
* Communication to regulatory authorities dictated by defined channels and mechanisms
* Communication to users and/or patients, often through packaging and labeling along with other marketing material, to help inform a user on proper use and disposal of the product
  1. Production and post-production activities

The RMP will identify the system for collecting and reviewing information (monitoring) related to the product for production and post-production. Information will be actively collected and reviewed in the production and post-production phases by quality.

Outputs of the Risk Management process will be reviewed and take into account new information or experience from sources such as:

* Production information and data from monitoring
* Non-conformances
* Complaints
* Adverse events
* Risk Management
* Clinical activities
* Market/patient surveys
* Scientific literature
* Media sources
* Regulatory body notifications
* Information related to the generally acknowledged state of the art
* Information generated by the supply chain
* Publicly available information about similar products on the market
* As applicable, information generated by those accountable for the installation, use, and maintenance of the product

The appropriate teams will review information to determine if it is relevant to product safety and if so, what actions should be taken. The following questions will be considered when reviewing information:

* Are there new hazards or hazardous situations present?
  + If yes, the RMF is updated to include an assessment of new risks. New risks that are deemed unacceptable may result in a product recall or advisory notice.
* Is the estimated risk arising from a hazardous situation no longer acceptable?
  + If yes, the previously implemented risk control measures are evaluated and, if necessary, modified. Risk control efforts may lead to a design change, manufacturing process change, or modification to the intended use of the product to ensure the risk is acceptable.
* Is the overall residual risk no longer acceptable in relation to the benefits of the intended use?
  + If yes, the previously implemented risk control measures are evaluated and if necessary, modified. Risk control efforts may lead to a design change, manufacturing process change, or modification to the intended use of the product to ensure the risk is acceptable.
* Has the generally acknowledged state of the art changed?
  + If yes, the RMF is reviewed to determine the impact of the change and if reassessment of risks is necessary.

In general, if the information is determined to be relevant to safety, the following actions should be taken:

* Review the RMF to determine if reassessment of risks and/or assessment of new risks is necessary
* If a residual risk is no longer acceptable, the impact on previously implemented risk control measures is evaluated and considered as an input for modification of the product
* Determine if there is a need for an action to address potential concerns with product on the market
* Evaluate the impact on previously implemented Risk Management activities
* Provide the results of the evaluation as an input for review of suitability of the Risk Management process by top management

If changes are made to the Risk Management process, an evaluation of the impact on previously implemented Risk Management activities will be conducted. This information will be used as input for a review of the updated Risk Management process’s suitability by management.

The Risk Management process applies to all changes made during production and post-production prior to implementation. Any change may result in additional testing or implementation of risk control measures. Regulatory agencies may need to be informed of any proposed changes prior to implementation.

All reviews, decisions, and actions as a result of this process will be documented and maintained in the RMF.

* 1. Periodic reviews

As part of post-market surveillance, the quality team will be responsible, with assistance from relevant departments, for reviewing and updating the RMF, as necessary. A planned review will take place approximately once per year (9-15 months) unless the RMP specifies a different review frequency, with justification if it extends beyond 15 months. The frequency of review for mature products may be reduced by updating the RMP. This will require changing the RMP in accordance with SOP-001 Document control. *Note: there is an expectation for active monitoring of product performance, in which case more frequent reviews may be needed based on information gathered.*

* 1. Summary

Risk Management is integrated with the Design Control process as a part of product realization, reference SOP-004 Design Controls. The Risk Management process is iterative; deliverables will be reviewed and updated, as necessary, throughout the product’s lifecycle, especially if design changes are made. Table 5 below summarizes possible deliverables associated with the Risk Management process. SOP-004 Design Controls describes the corresponding Design Control stage in which initial control of the document occurs, however, planning documents (i.e., DDP/RMP) will detail the specific timing for these deliverables for a given program. Outputs from the Risk Management process may be inputs to other quality processes.

Table 5. Potential Risk Management deliverables associated with the Risk Management process

| **Risk Management Topic** | **Deliverable(s)** |
| --- | --- |
| Risk planning | Risk Management Plan |
| Hazard identification / Risk analysis | Intended use (can be contained in User Requirements Specification) |
| Task analysis |
| Master harms list |
| Characteristics related to safety |
| Preliminary Hazard Analysis |
| Risk analysis / evaluation / control | Use risk analysis / Use-related risk analysis |
| Design risk analyses (e.g., dFMEA, FTA) |
| Process risk analyses (e.g., pFMEA) |
| Risk analysis / evaluation / control / evaluation of overall residual risk | Product risk assessment (e.g., Risk Traceability Matrix / Hazard Analysis) |
| Risk control | Benefit-Risk Analysis / Summary report |
| Evaluation of overall residual risk | Overall residual risk evaluation report |
| Risk Management review | Risk Management Report |
| Production and post-production / Risk review | Post-market surveillance plan |
| Post-market surveillance review reports |
| Post-market risk review reports |
| Risk communication | Risk Management Plan (outlines key development / commercial stakeholder interactions) |
| Design reviews |
| Product labeling (communication with user / patient) |

1. Approvals

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Approvals** | **Name** | **Title** | **Signature** | **Date** |
| **Prepared by:** |  |  |  |  |
| **Approved by:** |  |  |  |  |

1. Version History

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Effective Date** | **Author** | **Change Description** |
| 1 |  |  | New SOP |

1. Appendices

Appendix 1. Recommended quality Risk Management questions

| **QRM Process Step** | **Recommended Questions** |
| --- | --- |
| Risk/hazard identification | 1. What might go wrong? (possible risks) 2. How do we know that it might go wrong? (evidence, assumptions) 3. Are there any new hazards that could arise from combined use of the constituent parts? 4. Are there any new hazardous situations that could arise from the combined use of the constituent parts? 5. Are there any new harms that arise due to the interactions of the constituent parts? |
| Risk analysis | 1. What is the likelihood it will go wrong? (probability of risk) 2. What are the consequences if it goes wrong? (severity) 3. Is there increased severity of harm from the combined use of the constituent parts? 4. What is the ability to know if it goes wrong? (detectability) **only for process FMEA** |
| Risk evaluation  *(dependent on tools used)* | 1. Is information used for risk evaluation robust? 2. Are there uncertainties in the data set? How do those impact the risk evaluation? 3. What is the risk index (probability x severity? (qualitative score) 4. What is the combination of severity, probability, and detectability? **Only for process FMEA** 5. What is the range of risk? (qualitative score) |
| Risk reduction | 1. Is the current risk above an acceptable level? 2. What can be done to reduce or eliminate the risk? 3. What can be done to reduce or eliminate the hazard associated with the risk? 4. What can be done to enhance detectability of the risk or associated hazard? **Only for processes / process FMEA** 5. Are new risks introduced as a result of the identified risk being controlled? |

Appendix 2. Hazard Categories

| **Device** | **Drug** | **Production** | **Interactions** |
| --- | --- | --- | --- |
| Electrical | Purity | Incapable processes | Drug formulation / device material interactions |
| Mechanical | Excipients | Inaccurate procedures | Container closure integrity |
| Thermal | Content uniformity | Operator non-compliance | Device functionality and reliability |
| Biocompatibility | Sterilization | Poor training | Ease of use |
| Usability | Stability | Cleaning | Particles/Contaminants |
| Electromechanical | Biological | Labeling |  |
| Software | Pyrogenic | Test methods |  |
| Device not compatible with users’ ability |  | Particles/contaminants |  |
| Moving Parts |  | Caustic, corrosive |  |

Appendix 3.Preliminary Hazard Analysis Template

| **Hazard** | **Hazardous Situation** | **Harm** | **Severity of Harm** |
| --- | --- | --- | --- |
| <Add the hazard being evaluated> | <Describe the circumstance that would result in exposure to the hazard> | <Add the potential resulting harm> | <Describe the circumstance that would result in exposure to the hazard> |
| <Ex. Contaminants / Particulate Matter – Chemical and Biological Hazards> | <Ex. Solution containing particulates administered> | <Ex. Skin Irritation> | <Ex. Moderate> |

Appendix 4. Example use-related risk analysis (minimum expected columns from FDA)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Task No.** | **User Task** | **Potential Use Error** | **Hazard** | **Hazardous Situation** | **Harm** | **Severity** | **Critical Task (Y/N)** | **Risk control measures** | **Evaluation Method** |
|  |  |  |  |  |  |  |  |  |  |

*Adapted from: Draft Guidance: Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products Guidance for Industry and FDA Staff*

Appendix 5. Determination of P if using P1xP2

Below is an example outlining the process for determining P by the combination of P1 and P2. The RMP will detail the specific approach.

Table 6. Probability of Occurrence of Hazardous Situation (P1)

|  |  |  |  |
| --- | --- | --- | --- |
| **Occurrence Rating** | **Qualitative description** | **Probability Limit Example** | **Description** |
| 5 | Frequent | ≥1:1000 | Occurring often; happening repeatedly at frequent intervals |
| 4 | Probable | <1:1000 to 1:10,000 | Likely to occur, can reasonably but not certainly be expected to occur |
| 3 | Occasional | <1:10,000 to 1:100,000 | An irregular occurrence, infrequently occurring |
| 2 | Remote | <1:100,000 to 1:1,000,000 | Slight, faint, a remote chance of occurring |
| 1 | Improbable | <1:1,000,000 | Not probable, unlikely to ever occur |

Table 7. Likelihood of occurrence of hazardous situation leading to harm (P2)

|  |  |  |  |
| --- | --- | --- | --- |
| **Occurrence Rating** | **Qualitative description** | **Probability Limit Example** | **Description** |
| 5 | Frequent | >50% | Harm is expected to occur; the Patient or User is expected to experience the Harm |
| 4 | Probable | > 10% - 50% | Harm is likely to occur; some Patients or Users are likely to experience the Harm |
| 3 | Occasional | > 1% - 10% | Harm is possible to occur; some Patients or Users may experience the Harm occasionally |
| 2 | Remote | > 0.1 – 1% | Harm is unlikely to occur; a few Patients or Users may experience the Harm in rare circumstances |
| 1 | Improbable | <0.1% | Harm is not expected to occur; very few Patients or Users are expected to experience Harm |

In the cases where probabilities are determined qualitatively or semi-quantitatively for P1 and P2, Table 8 can be used to determine P. P is calculated per section C.1 of ISO 14971:2019 as shown in Figure 2. In the case where there are quantitative probabilities P is calculated by multiplying P1 x P2.

Table 8. Semi-quantitative determination of P

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Probability of Hazardous Situation Leading to Harm (P2)** | Frequent  (5) | Improbable | Remote | Occasional | Probable | Frequent |
| Probable  (4) | Improbable | Remote | Occasional | Probable | Probable |
| Occasional (3) | Improbable | Improbable | Remote | Occasional | Probable |
| Remote  (2) | Improbable | Improbable | Improbable | Remote | Occasional |
| Improbable (1) | Improbable | Improbable | Improbable | Improbable | Remote |
|  | | Improbable (1) | Remote  (2) | Occasional  (3) | Probable  (4) | Frequent  (5) |
| **Probability of Occurrence of Hazardous Situation (P1)** | | | | |

****

Figure 2. Schematic of risk relationship showing calculation of P, figure from ISO 14971:2019