1. PURPOSE

This procedure defines the risk management process required for the development and commercialization of medical device combination products.

1. SCOPE

This procedure applies to all medical device combination products, for which [company name] is the legal manufacturer. The entire lifecycle of the product is within scope. This procedure is intended to meet the requirements of ISO 14971:2019 Medical Devices – Application of risk management to medical devices.

Risks solely related to the drug product are out of scope, but risks associated with interaction of the drug product, device, and product packaging are within scope.

[If applicable: Risk management for medical device software is addressed in TBD]

1. DEFINITIONS

Failure Mode and Effects Analysis (FMEA) - systematic, step-by-step risk analysis approach to identify and prioritize possible failures

Harm – injury or damage to the health of people, or damage to property or the environment

Hazard – potential source of harm

Hazardous situation – circumstance in which people, property, or the environment is/are exposed one or more hazards

Residual risk – risk remaining after risk control measures have been implemented

Risk – combination of the probability of occurrence of harm and the severity of that harm

Risk analysis – systematic use of available information to identify hazards and estimate the risk

Risk assessment – overall process comprising a risk analysis and a risk evaluation

Risk control – process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

Risk estimation – process used to assign values to the probability of occurrence of harm and the severity of that harm

Risk evaluation – process of comparing the estimated risk against specified criteria to determine the acceptability of the risk

Risk management – systematic application of policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk

Safety – freedom from unacceptable risk

Severity – measure of the possible consequences of a hazard

State of the art – what is currently and generally accepted as good practice in technology and medicine (not necessarily the most technologically advanced solution).

1. ROLES AND RESPONSIBILITIES

[Company name] is responsible for risk management of the finished product and oversight of any risk management activities performed by external parties.

Persons performing risk management tasks shall be competent on the basis of education, training, skills, and experience appropriate to the tasks assigned to them. Roles and responsibilities shall be performed as defined below unless otherwise specified in the Risk Management Plan.

[Customize roles below based on organization]

[Top management / Senior management] shall ensure sufficient resources and competent personnel are provided to perform risk management activities and shall review the suitability of the risk management process at planned intervals per [reference Quality Management Review or other applicable SOP].

[Device Quality / Risk Management] shall have overall responsibility for risk management activities, review and approve all risk management documentation, and ensure compliance with this procedure.

[Device Development / Human Factors Engineering] shall be responsible for identifying use hazards and analyzing use risks.

[Device Development] shall be responsible for identifying design hazards and analyzing design risks.

[Manufacturing] shall be responsible for identifying manufacturing hazards and analyzing manufacturing risks.

[Clinical/medical officer] shall be responsible for reviewing and approving severity rankings for all harms, probability of occurrence of harm rankings (P2) if used, overall Benefit-Risk Analyses, and Risk Management Reports.

[Regulatory Affairs] shall be responsible for ensuring the risk management file meets current regulatory requirements, and for reviewing and approving Risk Management Plans, overall Benefit-Risk Analyses, and Risk Management Reports.

[Supplier Quality / Legal] shall be responsible for executing Quality Agreements which define any risk management responsibilities for external parties.

[If applicable: TBD shall be responsible for identifying and analyzing Software Hazards]

1. RISK POLICY [or reference external document if applicable]

All identified risks shall be reduced as far as possible without affecting the benefit-risk analysis in order to comply with the requirements of ISO 14971 and Regulation (EU) 2017/745. Acceptability of risks shall be evaluated based on the associated severity and probability of occurrence of harm. Overall acceptability of risk shall be evaluated based on the benefits and risks of the product in comparison to similar products available on the market and the generally accepted state of the art.

1. RISK MANAGEMENT PROCESS
   1. General

[Company name] shall establish, implement, document, and maintain an ongoing process for medical device risk management which shall apply throughout the lifecycle of the product. The process shall include risk analysis, risk evaluation, risk control, and production and post-production activities.

A Risk Management File (RMF) containing all required risk management documentation shall be created for the finished combination product. The RMF is a subset of the product Design History File.

Any risk management activities / documentation performed by external parties according to an applicable Quality Agreement shall be considered as inputs into the finished combination product Risk Management File.

* 1. Risk Estimation and Evaluation

Risks shall be estimated by assigning values from 1 to 5 for severity of harm (S) and probability of occurrence of harm (O).

The severity of harm shall be assigned a value according to the table below by persons with appropriate medical expertise.

|  |  |
| --- | --- |
| **Severity Ranking** | **Description of Harm** |
| 5 | Results in death |
| 4 | Results in permanent impairment or irreversible injury |
| 3 | Results in injury or impairment requiring medical or surgical intervention |
| 2 | Results in temporary injury or impairment not requiring medical or surgical intervention |
| 1 | Results in inconvenience or temporary discomfort |

Occurrence of harm may be estimated as a single probability or as the combination of 2 probabilities (P1xP2) where P1 is the probability of a hazardous situation occurring and P2 is the probability of the hazardous situation causing harm. The Risk Management Plan shall specify the approach to be used for ranking occurrence (single probability or P1xP2).

Occurrence of harm as a single probability estimates the probability of a hazardous situation/failure mode and takes a conservative approach which assumes the failure always leads to harm.

The use of P1xP2 is more complex but may provide a more realistic estimate by taking into account that a hazardous situation/failure mode may not always result in harm.

The occurrence of harm shall be assigned a value according to the table below by persons with appropriate technical and/or medical expertise. If a single probability is used, the occurrence ranking shall be determined by the technical team and persons with appropriate medical expertise. If the P1xP2 approach is used, P1 shall be ranked by the technical team, and P2 shall be ranked by persons with appropriate medical expertise.

|  |  |  |
| --- | --- | --- |
| **Occurrence Ranking** | **Qualitative Description** | **Quantitative Description** |
| 5 | Very probable | p ≥ 0.1% (higher than 1 in 1000) |
| 4 | Probable | p < 0.1% (less than 1 in 1000) |
| 3 | Occasional | p < 0.01% (less than 1 in 10,000) |
| 2 | Improbable | p < 0.001% (less than 1 in 100,000) |
| 1 | Very improbable | p < 0.0001% (less than 1 in 1,000,000) |

After severity and occurrence rankings have been assigned, acceptability of each individual risk is evaluated using the Risk Matrix below.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Severity | | | | |
|  |  | 1 | 2 | 3 | 4 | 5 |
| Occurrence of Harm | 5 | Medium | High | High | High | High |
| 4 | Low | Medium | High | High | High |
| 3 | Low | Medium | High | High | High |
| 2 | Low | Low | Medium | High | High |
| 1 | Low | Low | Low | Medium | Medium |

Green / Low Risk: Acceptable/insignificant risk

Yellow / Medium Risk: Investigate further risk control

Red / High Risk: Unacceptable risk

* 1. Risk Management Deliverables
     1. Risk Management Plan

A Risk Management Plan shall document the scope of planned risk management activities for the medical device. The plan shall include or reference the location of the following information:

* Identify and describe the medical device
* Scope of planned risk management activities and the lifecycle phases for which each element of the plan is applicable. In all cases the Risk Management Plan shall be completed in the [Design Planning phase] and the Risk Management Report shall be completed prior to release of clinical or commercial product. Identify activities to be performed for clinical vs. commercial release if applicable.
* Roles and responsibilities for risk management activities, including activities performed by external parties
* Requirements for review of risk management activities
* Approach to be used for ranking occurrence of harm (single probability or P1xP2)
* Criteria for individual risk acceptability and overall residual risk acceptability (refer to this procedure)
* Activities for verification of implementation and effectiveness of risk control measures
* Activities related to collection and review of relevant production and post-production information

Requirements for the above activities shall at a minimum include the requirements of this procedure, but additional details may be included in the risk management plan as needed. If information for all activities is not known at a particular phase, parts of the plan may be developed over time.

* + 1. Hazard Analysis

A Hazard Analysis (HA) shall be created to identify known and foreseeable hazards and hazardous situations for the product based on the intended use, reasonably foreseeable misuse, and both normal and fault conditions. For each hazard, the reasonably foreseeable sequences or combinations of events that can result in a hazardous situation shall be considered.

The harms associated with each hazard / hazardous situation shall be identified and ranked in the HA as described in 6.2.

If the RMP specifies that the P1xP2 approach is to be used, P2 for each harm shall be ranked in the HA as described in 6.2. If P1xP2 if not used, occurrence rankings are not included in the HA.

* + 1. Failure Modes and Effects Analysis (FMEA)

FMEA shall be the approach used to document risk estimation, risk evaluation, and risk controls unless otherwise specified in the RMP.

Three FMEAs shall be created to address risk in the following areas:

* Use FMEA (UFMEA) / Use-related risk analysis (URRA) to assess use risks
* Design FMEA (DFMEA) to assess product design risks
* Process FMEA (PFMEA) to assess product manufacturing process risks

FMEA shall assess risks of the entire finished product including unit packaging and labeling. Subsystem FMEAs may be created for specific elements of the product as needed. FMEAs created by external parties shall be used as inputs to the applicable finished product FMEA.

FMEA shall identify and evaluate potential failure modes associated with the product. The failure modes shall be traced to the hazards and hazardous situations identified in the HA. All hazards and hazardous situations identified in the HA shall be traceable to failure modes in the FMEA (hazards may be divided among the UFMEA, DFMEA, and PFMEA).

* + 1. Risk Estimation

For each hazardous situation, the corresponding harms, severity rankings, and P2 occurrence rankings (if applicable) established in the HA shall be used in the FMEA. All failure modes resulting in severity of 3 or higher are considered characteristics related to safety.

The occurrence of harm shall be estimated according to the RMP either as a single probability or by estimating P1 and then combining it with P2 from the HA. If no data exist to estimate the probability of harm, a conservative estimate shall be made based on the team’s expertise and experience.

* + - 1. Risk Evaluation

Acceptability of each risk shall then be evaluated as High, Medium, or Low based on the severity and occurrence rankings per the risk matrix in 6.2.

* + - 1. Risk Control

Risk controls required to reduce risks to an acceptable level shall be implemented, taking account of the generally acknowledged state of the art. Potential risk controls shall be prioritized in the order below:

* Inherently safe design and manufacture
* Protective measures in the device itself or in the manufacturing process
* Information for safety and training to users where appropriate

All Medium and High risks identified per section 6.2 shall be investigated to determine if additional risk controls are practicable, considering the current state of the art. FMEA shall document verification of implementation of all risk controls as well as verification of effectiveness of all risk controls. New risks or impact to other existing risks arising from risk control measures shall be considered. After verification of risk controls, the residual risk will be evaluated by updating the severity and/or occurrence rankings if applicable and re-evaluating the risk level.

Significant residual risks shall be disclosed to the user in the product labeling and confirmed in the FMEA as a risk control.

If the residual risk is not judged acceptable and further risk control is not practicable, data and literature may be reviewed to determine if the benefits of the intended use outweigh the residual risk.

FMEA shall document that risks from all applicable identified hazardous situations have been considered and that all applicable risk control activities are completed.

* + - 1. Use-Related Risk Analysis (URRA)

For products submitted for FDA approval, the UFMEA shall be provided in a URRA format per applicable FDA guidance.

* + 1. Risk Management Review

Review of risk management activities shall be documented in a Risk Management Report (RMR) prior to release of the product for clinical use or commercial distribution. The RMR shall document at a minimum:

* The Risk Management Plan has been appropriately implemented
* The overall residual risk is acceptable
* Appropriate methods are in place to actively collect and review information in the production and post-production phases
  + - 1. Evaluation of Overall Risk

After all risk control measures have been implemented and verified, acceptability of the overall residual risk shall be evaluated by persons with appropriate medical expertise taking into account all individual residual risks in relation to the benefits of the intended use. The benefit-risk analysis shall consider a comparison of the benefits and risks of the product compared to similar products or other drug presentations on the market. The level of acceptable risk may be different for clinical release compared to commercial release.

If the overall residual risk is not judged acceptable, additional risk control measures, changes to the device, or changes to the intended use may be considered.

The overall benefit-risk analysis shall be included or referenced in the RMR. The benefit-risk analysis shall be approved by senior management.

* + 1. Production and Post-Production Activities

Information from the production and post-production phases shall be actively collected and reviewed, including periodic/planned reviews of the data sources below as well as unplanned reviews arising from unexpected events:

* Manufacturing / quality data
* Product complaints, user feedback, etc.
* Information from those responsible for installation or maintenance of the product, if applicable
* Supplier information
* Publicly available information (may include information on similar products)
* Information related to the generally acknowledged state of the art
* Changes to the device, drug product, or associated manufacturing processes

The information shall be reviewed at least annually [or other review period] for potential impact to safety, impact to the Risk Management File, or impact to the Risk Management process.

**REVISION HISTORY**

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| --- | --- |
| **REV.** | **CHANGES** |
| 1 | Initial release |