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## 1. Purpose

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


## 2. Scope

This procedure applies to all medical device combination products, for which Bluejay is the legal manufacturer. This procedure is intended to meet the requirements of ISO 14971:2019 Medical Devices – Application of risk management to medical devices and ICH Q9, Quality Risk Management.


## 3. Responsibilities

<b>Role/Department</b>	<b>Responsibilities</b>
Senior Management	<ul style="list-style-type: none"> <li>Shall ensure sufficient resources and competent personnel are provided to perform risk management activities</li> <li>Shall review the suitability of the risk management process at planned intervals as a part of Quality Management Review per SOP-QA-011, Management Responsibility.</li> </ul>
Quality Assurance	<ul style="list-style-type: none"> <li>Shall have overall responsibility for risk management activities, review and approve all risk management documentation, and ensure compliance with this procedure</li> </ul>
Device Development / Human Factors Engineering	<ul style="list-style-type: none"> <li>Shall be responsible for identifying use hazards and analyzing use risks of devices</li> </ul>
Device Development	<ul style="list-style-type: none"> <li>Shall be responsible for identifying design hazards and analyzing design risks of devices.</li> </ul>
Manufacturing	<ul style="list-style-type: none"> <li>Shall be responsible for identifying manufacturing hazards and analyzing manufacturing risks.</li> </ul>
Clinical Affairs / Medical Officer	<ul style="list-style-type: none"> <li>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.</li> </ul>
Regulatory Affairs	<ul style="list-style-type: none"> <li>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</li> </ul>
Supplier Quality / Legal	<ul style="list-style-type: none"> <li>Shall be responsible for executing Quality Agreements which define any risk management responsibilities for external parties.</li> </ul>

## 4. Definitions

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<b>Term</b>	<b>Definition</b>
Combination Product	Any 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 Failure Mode and Effects Analysis (DFMEA)	Systematic, step-by-step risk analysis approach to identify and prioritize possible failures associated with design deficiencies
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
Process Failure Mode and Effects Analysis (PFMEA)	Systematic, step-by-step risk analysis approach to identify and prioritize possible failures associated with process/manufacturing deficiencies
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
Use Failure Mode and Effects Analysis	Systematic, step-by-step risk analysis approach to identify and prioritize possible failures associated with the use and reasonable misuse of a product or process
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).

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## 5. General

### 5.1. Risk Policy:

5.1.1. 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 and/or ICH Q9, as applicable. 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.

5.2. Bluejay 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
- Evaluation of overall residual risk
- Risk management review (report)
- Production and post-production activities

5.3. Bluejay is responsible for risk management of the finished product and oversight of any risk management activities performed by external parties.

5.4. 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 in this procedure unless otherwise specified in the Risk Management Plan.


## 6. Risk Management Process

### 6.1. Risk Management File

6.1.1. 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.

6.1.2. The Risk Management File shall contain all records and associated documents produced by risk management activities or may be in the form of an index that contains references to the records and associated documents. The Risk Management File consists of the following items, at a minimum:

- Risk Management Plan
- Hazard Analysis
- Risk Analyses (FMEA or other method)
- Risk Management Report(s) with Benefit-Risk Analysis
- Post-production Risk Management Report(s) (when appropriate)
- Any supporting or referenced documents or records of activities required by the risk management plan

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6.1.3. 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.

## 6.2. Hazard Analysis

6.2.1. 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.

6.2.2. Hazard / hazardous situation identification methods may include the following:

- Review of the same or similar medical devices (internally or externally), adverse event (AE) databases, publications and other sources.
- Task Analysis identifying the steps that shall be performed by the user to meet intended use
- Consideration of hazard categories (ref. ISO 14971) such as:
- Energy hazards: acoustic energy, electric energy, mechanical energy, potential (stored) energy, radiation energy, thermal energy
- Biological and chemical hazards: biological agents, chemical agents, immunological agents
- Performance-related hazards: drug delivery, functionality, data, diagnostic information

6.2.3. For each identified hazard, possible hazardous situations shall be identified where people, property or the environment are exposed to one or more hazard(s) that could cause or lead to harm.

6.2.4. Identification of hazards, hazardous situations, and resulting harms shall be documented in a Hazard Analysis.


6.2.5. The harms associated with each hazard / hazardous situation shall be identified and ranked in the HA as described in this procedure (Risk Estimation and Evaluation).

6.2.6. 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 this procedure (Risk Estimation and Evaluation). If P1xP2 is not used, occurrence rankings are not included in the HA.

## 6.3. Risk Estimation and Evaluation

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

6.3.2. The severity of harm (S) shall be assigned a value according to Table 1 below by persons with appropriate medical expertise. All failure modes resulting in severity of 3 or higher are considered characteristics related to safety.

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- 6.3.2.1. Different definitions and categories for severity may be used, as appropriate, but shall be documented and justified in the program RMP.

**Table 1: Severity Rankings**

<b>Severity Ranking</b>	<b>Description of Harm</b>
5	Results in death or permanent impairment without warning
4	Results in permanent impairment with warning 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 minor inconvenience or temporary discomfort, or no effect

- 6.3.3. Occurrence of harm (O) 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
  - P2 is the probability of the hazardous situation causing harm
  - Overall occurrence is calculated by  $O = (P1 \times P2)$
- 6.3.4. The Risk Management Plan shall specify the approach to be used for ranking occurrence (single probability or P1xP2).
- 6.3.4.1. 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.
- 6.3.4.2. 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.
- 6.3.5. The occurrence of harm shall be assigned a value according to the table below by persons with appropriate technical and/or medical expertise.
- 6.3.5.1. If a single probability is used, the occurrence ranking shall be determined by the technical team and persons with appropriate medical expertise.
- 6.3.5.2. 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.

**Table 2: Occurrence Rankings (for P1, P2, and  $O = P1 \times P2$ )**

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<b>Occurrence Ranking</b>	<b>Qualitative Description</b>	<b>Quantitative Description</b>
5	Very probable	$p \geq 0.1\%$ (greater 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)

6.3.6. Methods for estimating occurrence may include the following:

- Review of the same or similar medical devices (internally or externally), adverse event (AE) databases, publications and other sources. (Similar medical devices may include shared subsystems, software code or intended use(s).)
- Use of bench data (laboratory) or simulations
- Use of data from clinical trials
- Use of expert judgement

6.3.7. When the occurrence of harm cannot be estimated, the risk acceptance criteria should be developed based on the following:

- Whenever possible, the occurrence of harm should be estimated.
- Consider the occurrence for similar products.
- If it is not possible to estimate overall occurrence of harm O, P1, or P2, a worst-case probability of 100% may be used. If this assumption results in an unacceptable risk, conduct a benefit-risk analysis to determine if the potential risk is acceptable based on the potential benefit of the product.

6.3.8. Occurrence ranges and values that differ from Table 2 shall be documented and justified in the program Risk Management Plan (RMP).

6.3.8.1. Process failure mode and effect analysis (PFMEA) may also include a Detectability factor, to assess the ability of the process to detect the hazard. However, detection is not utilized in design FMEA's (DFMEA) in order to maintain the focus on risk reduction activities that ensure the product is safe by design and/or include protective measures.


6.4. Failure Modes and Effects Analysis (FMEA)

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

6.4.2. 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

6.4.2.2. Other risk analyses tools may utilized, as appropriate, and shall be documented and justified in the program RMP. Execution and requirements of the risk assessments shall be defined in the program Design and Develop Plan (DDP) and RMP.

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6.4.3. FMEA shall assess risks of the entire finished product including unit packaging and labeling.

6.4.3.1. Subsystem FMEAs may be created for specific elements of the product as needed.

6.4.3.2. FMEAs created by external parties shall be used as inputs to the applicable finished product FMEA.

6.4.4. FMEA shall identify and evaluate potential failure modes associated with the product.

6.4.4.1. The failure modes shall be traced to the hazards and hazardous situations identified in the HA.

6.4.4.2. 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).

#### 6.5. Risk Control

6.5.1. All risks shall be reduced as far as possible, taking account of the generally acknowledged state of the art.

6.5.2. 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

6.5.3. All Medium and High risks identified per Table 3: Risk Level Matrix shall be investigated to determine if additional risk controls are practicable, considering the current state of the art.

6.5.4. The FMEA shall document verification of implementation of all risk controls as well as verification of effectiveness of all risk controls.

6.5.5. New risks or impacts to other existing risks arising from risk control measures shall be considered.


6.5.6. 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.

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

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

#### 6.6. Evaluation of Overall Residual Risk

6.6.1. After all risk control measures have been implemented and verified, acceptability of the overall residual risk shall be evaluated by persons with appropriate medical

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expertise taking into account all individual residual risks in relation to the benefits of the intended use.

6.6.2. If the residual risk is not judged acceptable and further risk control is not practicable, a benefit-risk analysis of the residual risk shall be conducted. Data and literature may be reviewed to determine if the benefits of the intended use outweigh the residual risk.

6.6.3. 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.

6.6.3.1. The level of acceptable risk may be different for clinical release compared to commercial release.

6.6.4. 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.

6.6.5. The overall benefit-risk analysis shall be included or referenced in the Risk Management Report (RMR). The benefit-risk analysis shall be approved by senior management.

#### 6.7. Risk Management Review (Report)

6.7.1. 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.


6.7.2. 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

#### 6.8. Production and Post-Production Activities

6.8.1. 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

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## 7. Attachments/Appendices


Appendix	Title

## 8. References

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####	Management Responsibility
####	Design Controls
ICH Q9	Quality Risk Management
21 CFR 820	21 CFR 820 Quality System Regulation
EN ISO 14971:2019 +A11:2021	EN ISO 14971:2019 +A11:2021, "Medical devices – Application of risk management to medical devices"
ISO/TR 24971:2020	ISO/TR 24971:2020, "Medical devices - Guidance on the application of ISO 14971"

## 9. Revision History

VERSION #	Author	DESCRIPTION OF CHANGES
01	XXXX	Initial

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## Appendix A: First Appendix