Document Number: QAP013.01	Title: **RISK MANAGEMENT PROGRAM**	Effective Date: 26Jun2024
Section: Quality Assurance		Supersedes Date: N/A
Subsection: Procedures	***CONFIDENTIAL INFORMATION*** **VIKING THERAPEUTICS, INC.**	Page: 1 of 1

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1. Purpose

1.1. The purpose of this Standard Operating Procedure (SOP) is to establish, implement, document and maintain an ongoing process for risk management at Viking Therapeutics for combination products, including identifying hazards associated with a combination product, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls in accordance with applicable subclauses of ISO 13485:2016, ISO 14971:2019, and taking into consideration the guidelines provided by ISO/TR 24971:2020.

Scope

1.2. This SOP applies to the commercial and investigational (clinical) combination products designed, manufactured, and distributed under Current Good Manufacturing Practice (cGMP) conditions throughout the product lifecycle phases, including product development, technology and design transfer, manufacturing, product surveillance and product discontinuation. This SOP applies to all sites and/or functions supporting and/or executing cGMP activities.

1.3. This SOP establishes and defines processes for identifying and managing quality risks, safety risks or hazards that can potentially lead to harm. This SOP does not define the threshold for acceptable risk (or risk index) since this threshold will change based on the intended use and expected benefit of using the combination product.

1.4. Where Viking Therapeutics is the product applicant, Viking Therapeutics is responsible for ensuring appropriate risk management processes are applied by design partners and contract manufacturers. Partners, consultants, contract manufacturers or suppliers performing cGMP activities shall be evaluated and approved in accordance with XX-XXX, *Supplier Qualification and Management.*

1.5. Risk management related to drug substance and drug product is out of scope of this SOP.

2. Responsibilities

2.1. Viking Therapeutics Product Development and Quality Assurance (QA) are responsible for ensuring compliance with this SOP. All functional leads/managers are responsible for ensuring compliance with the applicable segments of this procedure that are within their areas of responsibility.

Role	Responsibility
Functional Area Management (Product Development, Clinical Development, Regulatory Affairs and Quality Assurance Management)	• Responsible for ensuring that the risk management process is followed within area of responsibility • Provides subject matter expertise, as appropriate, to risk management activities • Ensures execution of risk reduction activities • Creates and maintains risk management documentation • Assures adequate resources and support to carry out this process. • Defines and documents criteria for risk acceptability in the Risk Management Procedure. This provides a framework that ensures that criteria are based upon applicable national or regional regulations and relevant International Standards and considers available information such as the general acknowledged state of the art and known stakeholder concerns. • Ensures risk management policies are established and followed • Ensures provision of adequate resources and assignment of competent personnel for risk management • Reviews suitability of the risk management process at planned intervals to ensure continuing effectiveness of the risk management process and documents any decisions and actions taken
Clinical Development	• Defines applicable harms • Assigns severity rating to harms • Participates in benefit risk analysis activity in accordance with this procedure
Quality Assurance Management	• Overall responsibility for effective execution and oversight of risk management process, including both internal and external organizations' scope of work. • Overall responsibility for the Quality Management System (QMS), including the risk management process • Responsible for the implementation and maintenance of a quality system which enables the organization to provide safe and effective combination products that meet customer and regulatory requirements • Overall responsibility for establishing, implementing, maintaining, and reviewing the effectiveness of the risk management process

Role	Responsibility
Quality Assurance	In accordance with this procedure: • Provides oversight of a compliant risk management process • Approves and monitors risk management activities • Approves risk management documents and risk reduction activities • Defines evaluation criteria for quality risks • Completes all required training and qualification activities prior to conducting formal risk analysis • Conducts formal Risk Management in accordance with this procedure • Defines and documents criteria for risk acceptability in the Risk Management Plan according to the process established in this SOP.
Regulatory Affairs	• Provides regulatory input based on relevant regulatory guidelines • Approves design control documents, activities, and/or efforts

3. References

- 21CFR820.30
- ISO 14971: 2019
- ISO 12971: 2020
- Viking QAP012 Design Control
- ISO 62366: 2005

4. Definitions

4.1. **Accompanying Documentation:** Materials accompanying a combination product and containing information for the user or those accountable for the installation, use, maintenance, decommissioning and disposal of the combination product, particularly regarding safe use.

4.2. **Applicant:** The entity that holds the marketing authorization for a combination product (regardless of whether that entity is directly engaged in the manufacture of the product). Responsible for ensuring the risk management process is correctly applied to the combination product. Applicant is the manufacturer of record.

4.3. **Benefit:** The positive impact or desirable outcome of the use of a combination product on the health of an individual, or a positive impact on patient management or public health.

4.4. **cGMP:** Current Good Manufacturing Practice; That part of quality which ensures that products are consistently produced and controlled to the quality standards appropriate to the intended use and as required by the marketing authorization and product specification. The GMPs are a description of standardized, acceptable methods, controls, and production facilities.

4.5. **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.

4.6. **Harm:** Injury or damage to the health of people, or damage to property or the environment.[1]

4.7. **Hazard:** Potential source of harm.[1]

[1] EN ISO 14971:2019/A11:2021

4.8. **Hazardous Situation:** Circumstance in which people, property, or the environment is/are exposed to one or more hazards.[1]

4.9. **Intended Use/Intended Purpose:** Use for which a product, process or service is intended according to the specification, instructions and information provided by the Applicant/manufacturer.[1]

4.10. **Lifecycle:** Series of all phases in the life of a combination product, from the initial conception to final decommissioning and disposal.[1]

4.11. **Medical Device:** An instrument, apparatus, implement, machine, contrivance, implant, reagent for in vitro use, software, material, or other similar or related article, intended by the Applicant/manufacturer to be used, alone or in combination, for human beings for one or more of the specific medical purpose(s) of: [1,2]

4.11.1. diagnosis, prevention, monitoring, treatment, or alleviation of disease,

4.11.2. diagnosis, monitoring, treatment, alleviation of or compensation for an injury,

4.11.3. investigation, replacement, modification, or support of the anatomy or of a physiological process,

4.11.4. supporting or sustaining life,

4.11.5. control of conception,

4.11.6. disinfection of combination products,

4.11.7. providing information for medical purposes by means of in vitro examination of specimens derived from the human body,

4.11.8. and which does not achieve its primary intended action in or on the human body by pharmacological immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

4.12. **Objective Evidence:** Data supporting the existence or verity of something, which can be obtained through observation, measurement, test or by other means.[1]

4.13. **Post-production:** Part of the lifecycle of the combination product after the design has been completed and the combination product has been manufactured.[3]

4.14. **Process:** Set of interrelated of interacting activities that use inputs to deliver an intended result.

4.15. **Reasonable Foreseeable Misuse:** Use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable behavior.

4.16. **Residual Risk:** Risk remaining after risk control measures have been implemented.[3]

4.17. **Risk:** Combination of the probability of occurrence of harm and the severity of that harm.[3]

4.18. **Risk Analysis:** Systematic use of available information to identify hazards and to estimate the risk.[3]

4.19. **Risk Assessment:** Overall process comprising a risk analysis and a risk evaluation.[3]

4.20. **Risk Control:** Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels.[3]

4.21. **Risk Estimation:** Process used to assign values to the probability of occurrence of harm and the severity of that harm.[3]

4.22. **Risk Evaluation:** Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk.[3]

4.23. **Risk Management:** Systemic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk.[3]

4.24. **Risk Management File:** Set of records and other documents that are produced by risk management.[3]

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[2] ISO 13485:2016

[3] EN ISO 14971:2019/A11:2021

4.25. Safety: Freedom from unacceptable risk.[3]

4.26. Severity: Measure of the possible consequences of a hazard.[3]

4.27. State of the Art: Developed stage of technical capacity at a given time as regards products, processes, and services, based on the relevant consolidated findings of science, technology, and experience.

4.28. Top Management: A person or group of people who directs and controls an organization at the highest level, having the power to delegate authority and provide resources within the organization.

4.29. User Error: User action or lack of user action while using the combination product that leads to a different result than that intended by the manufacturer or expected by the user.[4]

4.30. Validation: Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled.

4.31. Verification: Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.[4]

5. Procedure

5.1. Background

5.1.1. Risk management is a process to identify, assess and control risks that affect the quality or safety of a combination product. The risk management process is intended to identify and manage quality risks or hazards that can potentially lead to patient or user harm. Outputs from this process may be inputs to other quality processes.

5.1.2. Risk management is integrated within *QAP012*, *Design Control* as part of product realization. The Risk Management File and related activities shall be reviewed when design changes are implemented to assure any new risks or changes to existing risks are identified and evaluated.

5.1.3. Elements of this procedure may be used for combination products in early clinical development to ensure risks to user/patient safety have been evaluated.

5.1.4. The risk management process includes the following elements throughout the product life cycle:

5.1.4.1. Identifying hazards and hazardous situations associated with the combination product

5.1.4.2. Estimating and evaluating the associated risks

5.1.4.3. Controlling risk and monitoring the effectiveness of the risk control measures

5.1.4.4. Monitoring the effectiveness of the risk control measures

5.1.4.5. Risk reviews driven by new information

5.1.4.6. Periodic review of identified risks

5.1.5. Figure 1 illustrates the systemic representation of the risk management process. Depending on the specific product lifecycle phase, individual elements of risk management can have varying emphasis, but always governed by a risk management plan (RMP). In addition, risk management activities can be performed iteratively or in multiple steps as appropriate to the combination product.

5.1.6. As a check on the effectiveness of the risk management processes defined, management shall regularly review the outputs of processes, products, services, and the quality system, and make improvements as needed, in accordance with the Management Review Process specified in *XX-YYY, Management Responsibility.*

5.1.7. Documented records, including evidence of decisions and actions taken, shall be maintained to ensure and demonstrate the effective planning, operation, and control of this

[4] EN ISO 14971:2019/A11:2021

process.

5.1.8. Persons performing risk management tasks have the knowledge and experience appropriate to the tasks assigned to them. These shall include, where appropriate, knowledge and experience of the particular combination product (or similar products) and its use, the technologies involved, or the risk management techniques. Appropriate competence and training program requirements are described in *QAP011*, *GMP Training Program*.

5.1.9. Risk management tasks may be performed by representatives of several functions, each contributing their specialist knowledge.

5.1.10. Risk management activities shall be communicated during the product development phases as part of the design review process, and as part of the production and post-production process during the commercialization phase.

5.1.11. Major risks shall be communicated to Senior Product Development and Quality Assurance Management.

5.1.12. A risk profile for the combination product shall be established and reviewed periodically.

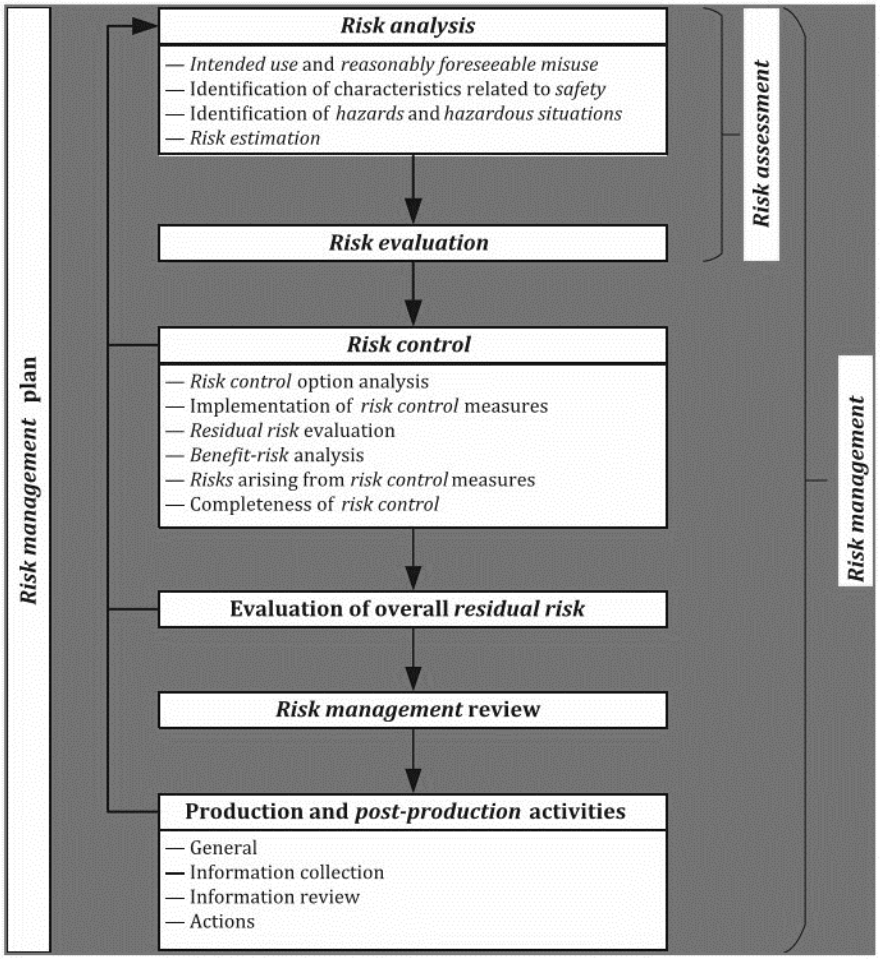

Figure 1. Risk Management Overview

5.2. Risk Management Plan

5.2.1. Planning involves specifying processes and associated resources to meet specific objectives. Factors to consider during the planning phase should align with the organization's overall business planning and, at a minimum, the type of combination product being manufactured, intended markets and users, and regulatory requirements.

5.2.2. Risk management activities shall be planned.

5.2.3. For the particular combination product (or product family) being considered, a risk management plan shall be documented and shall include the following, at a minimum:

5.2.3.1. The ***scope*** of the planned risk management activities, identifying and describing the combination product (or product family), intended use, interfaces with external systems or processes, and the lifecycle phases for which each element of the plan is applicable

5.2.3.2. Assignment of ***responsibilities and authorities*** for the execution of specific risk management activities throughout the product lifecycle shall include:

5.2.3.2.1. Identification by function or area of expertise the necessary reviewers, contributors, and personnel responsible for risk management execution throughout the product lifecycle

5.2.3.2.2. Top management of Product Development, Clinical Development, Regulatory Affairs and Quality Assurance establish acceptable thresholds for residual risk acceptance within this procedure.

5.2.3.2.3. When a product exceeds risk acceptability thresholds, but still has clinical benefit as designed, a benefit risk analysis is required to justify acceptance of risk.

5.2.3.2.4. Risk management responsibilities may be shared with design partners, consultants, contract manufacturers or suppliers, if applicable. The risk management plan shall identify the shared risk management activities, responsible party(ies), controlling procedure(s) and controlling location(s)/documentation system(s).

5.2.4. Requirements for review of risk management activities throughout the product lifecycle.

5.2.4.1. The design and development plan should detail when risk reviews will occur for the specific combination product. The requirements for the review of risk management are contained in *QAP012, Design Control*.

5.2.5. Categories of risk and criteria for risk acceptability, in accordance with this procedure, including criteria for accepting risks when the probability of occurrence of harm cannot be estimated. The risk acceptance criteria are based on the following decisions:

5.2.5.1. The risk presented by the current standard of care

5.2.5.2. The potential health benefits of using the combination product

5.2.5.3. The generally acknowledged state of the art defined in recognized consensus standards

5.2.6. The evaluation method and criteria for acceptability for the overall residual risk, considering all the impact of all risks together, shall be clearly defined and documented in the risk management plan.

5.2.7. Verification and/or validation activities required to verify effectiveness of risk control measures.

5.2.7.1. At a minimum, data from design verification and design validation activities shall be used as part of the residual risk analysis.

5.2.7.2. Other potential sources of verification/validation information include, but are not limited to scientifically valid characterization studies

5.2.8. Method(s) for obtaining and reviewing relevant product-specific production and post-production information, including requirements for documentation of decisions, based on a risk analysis, with regard to post-market surveillance activities appropriate for the product.

5.2.8.1. At a minimum, data from the complaint handling process, if applicable, shall be used as part of the residual risk analysis. Potential sources of post-production information may include, but are not limited to:

5.2.8.1.1. Commercial & Clinical complaints (if applicable)

5.2.8.1.2. Manufacturing and process performance data

5.2.9. The risk management plan should include documentation of decisions, based on risk analysis, about what sort of post-market surveillance is appropriate for the combination product. For example, whether reactive surveillance is adequate or whether proactive studies are needed.

5.2.10. The risk management plan may be developed for a specific product or for a family of similar products, as appropriate.

5.2.11. Unplanned risk management activities (ad hoc) may be required during the product lifecycle. These unplanned activities shall comply with this procedure and shall be included in the risk management file.

5.2.12. The risk management plan shall be reviewed periodically at specified time intervals. The review shall be conducted to ensure the plan content is accurate, current, and compliant with requirements in this procedure, and that the risk management plan has been implemented appropriately.

5.2.13. During product development, the risk management plan review requirements shall be specified in the design and development plan. After the product is released to market, the risk management file shall be reviewed.

5.2.14. The risk management plan shall be included as part of the risk management file. If the plan changes during the product lifecycle, a record of the changes shall be maintained in the risk management file.

5.3. Risk Management File

5.3.1. For the combination product being considered, a risk management file shall be established and maintained throughout the product lifecycle.

5.3.2. All risk management activities executed throughout the product lifecycle shall be included in the risk management file.

5.3.3. The risk management file shall provide traceability to each identified hazard to the following:

5.3.3.1. Risk analysis

5.3.3.2. Risk evaluation

5.3.3.3. Implementation and verification of the risk control measures

5.3.3.4. Results of the evaluation of residual risks

5.3.4. The risk management file may physically 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 deliverables, at a minimum:

5.3.4.1. Hazard Analysis

5.3.4.2. Risk Management Plan

5.3.4.3. Risk Analyses (internal and external)

5.3.4.4. Benefit Risk Analysis (when applicable)

5.3.4.5. Risk Management Report(s)

5.3.4.6. Post-production Risk Management Report(s) (when appropriate)

5.3.4.7. Any supporting or referenced documents or records of activities required by the risk management plan

5.3.5. The contents of the risk management file (documents, records, trace items, etc.) shall be controlled and maintained in the document management system in accordance with *QAP001*, *Format, Content, Approval and Issuance of Controlled Documents*.

5.3.6. The risk management file shall be maintained in the associated combination product design history file (DHF).

5.4. Hazard Analysis

5.4.1. This document provides a list of potential hazards, harms, the associated severities, and the probability of harm occurring given the hazard has occurred (P_2) for the combination product. This document shall serve as the source for harms, associated severities, and associated probabilities of harm (P_2) for all risk management activities performed on the combination product. The risk management plan may identify or plan for the development of a Hazard Analysis that maps specific hazards related to the intended use of the combination product (or product family) into severity levels based on the potential health and environmental consequences defined in this procedure. When the risk management plan directs the development of the Hazard Analysis, it shall specify the approval requirements for the list. Clinical Development shall be involved in the development, review, and approval of the Hazard Analysis.

5.5. Criteria for Verification of Risk Controls

5.5.1. Verification that a risk control has been implemented into the design is conducted in accordance with the Design Verification procedure. Refer to *QAP012*, *Design Control* for more information.

5.5.2. The mechanism to develop the risk-based acceptance criteria for design verification shall be defined in the risk management plan. The risk management plan shall associate each risk index with a specified level of reliability (also known as the probability content) and statistical confidence.

5.5.3. Verification that the risk control is effective is conducted in accordance with QAP012*, Design Control*.

5.5.4. Verification that the risk control remains effective is conducted per Section 5.13, Periodic Reviews of this procedure.

5.6. Risk Analysis

5.6.1.**Risk Analysis Process**

5.6.1.1. The purpose of the risk analysis is as follows.

5.6.1.1.1. Identify all reasonably foreseeable and/or known hazards, hazardous situations, causes, foreseeable sequences of events and associated harms (reference ISO/TR 24971:2020 Annex A for examples)

5.6.1.1.2. Estimate the probability of the occurrence and severity of the harms in order to estimate risk

5.6.1.1.3. Identify the risk controls necessary to mitigate and control risk

5.6.1.1.4. Estimate the reduction or elimination of the probability of occurrence due to the implementation of the risk controls.

5.6.1.2. The risk analysis shall take into consideration the intended use, the user(s) and the use environment for the combination product.

5.6.1.3. If a risk analysis, or other relevant information, is available for a similar combination product, that analysis or information may be used as a starting point for a new analysis. The degree of relevance depends on the differences between the devices and whether these introduce new hazards or significant differences in outputs, characteristics, performance, or results. The extent of use of an existing analysis is also based on the systematic evaluation of the effects the changes have on the development of hazardous situations.

5.6.1.4. At a minimum, a usability risk analysis and a system risk analysis are required. The risk management plan may specify additional risk analysis (e.g., process) as appropriate.

5.6.1.4.1. The usability risk analysis is used to analyze the risk of the use of the combination product.

5.6.1.4.2. The system risk analysis is used to analyze the risk of the design and/or

manufacture of the combination product (as specified in the scope of the risk management plan).

5.6.1.4.3. The usability and system risk analyses utilize the same basic structure and methods of risk estimation.

5.6.1.5. Risk analyses shall be conducted with the support of a team composed of subject matter experts with expertise on the subject being analyzed. Expertise provided by each team member shall be documented.

5.6.1.6. Severity, likelihood and (optionally) detection ratings shall be defined in applicable risk management work instructions or procedures based on the scope of the risk analysis (i.e., usability, system, process). Use of alternate definitions from those established in the associated procedures may be acceptable with proper justification and approval from Quality Assurance. Any alternative definitions shall be documented in the Risk Management Plan.

5.6.2. **Intended Use, Reasonably Foreseeable Misuse, and Identification of Characteristics Related to the Safety of the Combination Product**

5.6.2.1. For the combination product being considered, the Applicant shall document the intended use and reasonably foreseeable misuse. The intended use should consider information such as the intended medical indication, patient population, part of the body or type of tissue interacted with, user profile, use environment, and operating principle. Intended use and reasonably foreseeable misuse are documented in the Hazards Analysis and the Failure Mode and Effects Analyses (FMEAs).

5.6.2.2. The Applicant shall identify and document those qualitative and quantitative characteristics that could affect the safety of the combination product. Where appropriate, the limits of those characteristics shall be defined. These characteristics are documented in the Hazards Analysis and FMEAs.

5.6.2.3. Annex A of ISO 24971:2020 contains identification of hazards and characteristics for safety such as those relating to use that can serve as a guide in identifying combination product characteristics that could have an impact on safety. Considerations for Safety are listed in Appendix A. Examples of Hazards from ISO 14971:2019, Annex C are listed in Appendix B. Both appendices have been modified, removing items that are not relevant to Viking Therapeutics devices.

5.6.2.4. Documentation collected during this phase of the risk management process shall be maintained in the risk management file.

5.6.3. **Identification of Hazards**

5.6.3.1. The risk analysis shall identify and document the known and foreseeable hazards associated with the combination product based on the intended use, reasonably foreseeable misuse and the characteristics related to safety in both normal and fault conditions.

5.6.3.2. Hazards resulting from interfaces with external (to the combination product) systems and processes shall be considered.

5.6.3.3. For each identified hazard, the reasonably foreseeable sequences or combinations of events that can result in hazardous situations shall be considered and the hazardous situations shall be identified and documented in the hazards analysis and FMEAs. Hazard identification methods may include the following:

5.6.3.3.1. Review of the same or similar combination products (internally or externally), adverse event (AE) databases, publications, and other sources. (Similar combination products may include shared subsystems, software code or intended use(s).)

5.6.3.3.2. Usability flow chart identifying the steps that shall be performed by the user and the combination product to meet intended use.

5.6.3.3.3. Known interfaces with external (to the combination product) systems and processes (may be documented in the risk management plan).

5.6.4. **Identification of Hazardous Situations**

5.6.4.1. A hazardous situation is a circumstance in which people, property or the environment are exposed to one or more hazard(s) that could cause or lead to harm. The risk analysis shall identify and document the hazardous situations based on the intended use resulting from reasonably foreseeable sequences of events or cause(s) for each hazard.

5.6.4.2. The hazardous situation identification documentation shall be maintained in the risk management file. Hazardous situation identification methods may include the following:

5.6.4.2.1. Review of the same or similar combination products (internally or externally), adverse event (AE) databases, publications, and other sources. (Similar combination products may include shared subsystems, software code or intended use(s).)

5.6.5. **Identification of Harms**

5.6.5.1. A harm is a physical injury or damage to the health of people, property, or the environment. The risk analysis shall identify and document the harm(s) resulting from the identified hazardous situation(s).

5.6.5.2. The harm identification documentation shall be maintained in the risk management file. Harm identification methods may include the following:

5.6.5.2.1. Review of the same or similar combination products (internally or externally), adverse event (AE) databases, publications, and other sources. (Similar combination products may include shared subsystems, software code or intended use(s).)

5.6.5.2.2. Review of identified hazards and hazardous situations

5.6.5.2.3. Expert medical opinion (as applicable)

5.6.6. **Reasonably Foreseeable Sequence of Events or Cause(s)**

5.6.6.1. A reasonably foreseeable sequence of events or cause(s) is the process that results in a hazardous situation (exposure to a hazard). The risk analysis shall identify and document sequences of events or cause(s) for each hazard that could result in a hazardous situation. Sequences of events are documented in the Hazards Analysis and the FMEAs.

5.6.6.2. Reasonably Foreseeable sequence of events or cause(s) may include the following:

5.6.6.2.1. Faults during use (documented in the Usability Risk Analysis), use faults related to misuse, and intentional misuse shall be considered.

5.6.6.2.2. Faults in design (or manufacturing as applicable) or interactions with external systems and processes (documented in the System Risk Analysis)

5.6.6.2.3. Hazardous situations may result from no-fault conditions (documented in the System Risk Analysis)

NOTE: Sequences of events or cause(s) that relate to both usability and design may be documented in either the usability or system risk analysis, depending on the primary cause(s) of the hazard (Use or System).

5.7. Risk Estimation

5.7.1. Reasonably foreseeable sequences or combinations of events that can result in a hazardous situation shall be considered and the resulting hazardous situation(s) shall be recorded in the hazards analysis and the FMEAs.

5.7.2. For each identified hazardous situation, the associated risk(s) shall be estimated using available information or data. For hazardous situations for which the probability of the occurrence of harm cannot be estimated, the possible consequences shall be listed for

use in risk evaluation and risk control. The results of these activities shall be recorded in hazards analysis and the FMEAs.

5.7.3. Risk estimation may be quantitative or qualitative. Information or data for estimating risks may be obtained from the following sources:

5.7.3.1. Published standards

5.7.3.2. Scientific or technical investigations

5.7.3.3. Field data from similar combination products already in use, including publicly available reports of incidents

5.7.3.4. Usability tests employing typical users

5.7.3.5. Clinical evidence

5.7.3.6. Results of relevant investigations or simulations

5.7.3.7. Expert opinion

5.7.3.8. External quality assessment schemes

5.7.4. Risk has two (2) components, which are the probability of occurrence of harm and the severity of harm. To estimate risk, the occurrence and severity shall first be estimated.

5.7.4.1. Occurrence is estimated by first estimating two (2) probabilities referred to as P_1 and P_2.

5.7.4.1.1. P_1 is the probability that the hazardous situation will occur.

5.7.4.1.2. P_2 is the probability that the hazardous situation will result in harm.

5.7.4.1.3. The overall occurrence is $P = P_1 \times P_2$.

5.7.4.2. Methods for estimating occurrence may include the following:

5.7.4.2.1. Review of the same or similar combination products (internally or externally), adverse event (AE) databases, publications, and other sources. (Similar combination products may include shared subsystems, software code or intended use(s).)

5.7.4.2.2. Use of fault tree analysis (FTA) to decompose the probability estimation

5.7.4.2.3. Use of bench data (laboratory) or simulations

5.7.4.2.4. Use of data from clinical trials

5.7.4.2.5. Use of expert judgement

5.7.4.3. Whenever possible, the probability of occurrence of harm should be estimated. When the probability of occurrence of harm cannot be estimated, the risk acceptance criteria should be developed based on the following:

5.7.4.3.1. If it is not possible to estimate P_1, assume that the P_1 probability is equal to 1. If it is not possible to estimate P_2, assume that the P_2 probability is equal to 1. If these assumptions result in an unacceptable risk, conduct a benefit risk analysis to determine if the potential risk is acceptable based on the potential benefit of the combination product.

5.7.4.4. Unless otherwise prescribed by the Risk Management Plan, the probability of the hazardous situation occurring (P_1) shall be interpreted from Table 1.

Table 1. Probabilities of Hazardous Situations Occurring (P_1)

Term	Quantitative Ranges		
	Percentage / Rate	**Defects per Opportunities**	**Qualitative Description**
Very High	$P \geq 1\%$	$P \geq 1/100$	Occurrence is near certain
High	$1\% < P \leq 0.1\%$	$1/100 < P \leq 1/1{,}000$	Frequent & repeated occurrence
Moderate	$0.1\% < P \leq 0.01\%$	$1/1{,}000 < P \leq 1/10{,}000$	Occasional occurrence
Low	$0.01\% < P \leq 0.001\%$	$1/10{,}000 < P \leq 1/100{,}000$	Relatively few occurrences
Very Low	$0.001\% < P \leq 0.0001\%$	$1/100{,}000 < P$	Occurrence is unlikely
No Rating	N/A		

5.7.4.5. Unless otherwise prescribed by the Risk Management Plan, the probability of harm occurring, given that the hazardous situation has occurred (P_2) shall be interpreted from Table 2

Table 2. Probability of Harm, Given the Hazardous Situation has Occurred (P_2)

Term	Quantitative Ranges	
	Frequency	**Percentage / Rate**
Very High	Occurs in 1 or more patients out of 100 patients	$P \geq 1\%$
High	Occurs in up to 1 out of 1,000 patients	$0.1\% < P \leq 1\%$
Moderate	Occurs in up to 1 out of 10,000 patients	$0.01\% < P \leq 0.1\%$
Low	Occurs in up to 1 out of 10,000 patients	$0.001\% < P \leq 0.01\%$
Very Low	Occurs in up to 1 out of 100,000 patients	$0.0001\% < P \leq 0.001\%$
No Rating	N/A	

5.7.4.6. Unless otherwise specified in the Risk Management Plan, the overall probability of harm (P) shall be interpreted from Table 3.

Table 3. Overall Probability of Harm (P)

		P2 Probability					
		Very High	**High**	**Moderate**	**Low**	**Very Low**	**No Rating**
P1 Probability	**Very High**	Very High	High	Moderate	Low	Very Low	No Rating
	High	High	Moderate	Low	Very Low	Very Low	No Rating
	Moderate	Moderate	Low	Very Low	Very Low	Very Low	No Rating
	Low	Low	Very Low	Very Low	Very Low	Very Low	No Rating
	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	No Rating
	No Rating	No Rating	No Rating	No Rating	No Rating	No Rating	No Rating

5.7.4.7. Severity is a measure of the consequence(s) of the harm. Reference Table 4.

5.7.4.7.1. In general, severity should be assigned based on expert medical judgement or literature review.

Table 4. Severity

Harm Rating	Description
S5	Life Threatening - Results in death or life-threatening injury
S4	Serious - Results in permanent impairment or irreversible injury
S3	Moderate - Results in injury or impairment requiring professional medical intervention
S2	Minor - Results in temporary impairment or injury not requiring professional intervention
S1	No Safety Impact - Results in inconvenience or temporary discomfort
S0	No resulting harm to the end user

5.7.4.8. The Risk Index is assigned based on the estimated overall probability of harm and severity. Unless otherwise specified by the Risk Management Plan, the Risk Index value shall be determined using Table 5.

Table 5. Risk Index

		Severity (S)					
		S0	**S1**	**S2**	S3	**S4**	**S5**
Overall Probability of Harm (P)	**S5**	N/A	Yellow	Red	Red	Red	Red
	S4	N/A	Green	Yellow	Red	Red	Red
	S3	N/A	Green	Green	Yellow	Red	Red
	S2	N/A	Green	Green	Green	Yellow	Red
	S1	N/A	Green	Green	Green	Yellow	Yellow
	S0	N/A	N/A	N/A	N/A	N/A	N/A

5.7.5. Any system used for qualitative or quantitative categorization of probability of occurrence of harm or severity of harm shall be recorded in the risk management file.

5.8. Risk Evaluation

5.8.1. For each identified hazardous situation, the applicant shall evaluate estimated risks to determine whether the risk is acceptable, using criteria for risk acceptability defined in the risk management plan. If risk reduction is not required, the only risk control activities that shall be performed are those provided in Section 5.9.6, and the estimated risk shall be treated as residual risk.

5.9. Risk Control

5.9.1. Risk Reduction

5.9.1.1. When risk reduction is required, risk control activities, as described in Sections 5.9.2 to 5.9.7 shall be performed.

5.9.1.2. Risk reduction shall be achieved by any combination of designing for inherent safety

and/or implementation of protective measures.

5.9.1.3. Information for safety, intended for residual risk disclosure, provided to users and patients is not considered a mechanism for reducing risk.

5.9.1.4. All foreseeable and/or known risk controls shall be identified and included in the applicable risk analysis.

5.9.1.5. Risk reduction measures shall be defined, when possible, to reduce identified risks. Risk reduction and/or risk control measures shall be documented in the hazard analysis and FMEA documents.

5.9.1.6. Risks shall be reviewed after risk reduction actions are implemented, or following sufficient monitoring time to accumulate required data, to confirm that the desired risk reduction was achieved.

5.9.1.7. After all risk control measures have been implemented and the effectiveness of the risk control has been verified, each risk shall be reviewed to establish the residual risk and the overall residual risk of the combination product.

5.9.2. **Risk Control Option Analysis**

5.9.2.1. The applicant shall identify risk control measure(s) that are appropriate for reducing the risk(s) to an acceptable level.

5.9.2.2. The applicant shall use one or more of the following risk control options in the priority listed:

5.9.2.2.1. Inherent safety by design

5.9.2.2.2. Protective measures in the combination product itself or in the manufacturing process

5.9.2.2.3. Information for safety

5.9.2.3. If implementing protective measures or information for safety above, reasonably practicable control measures to reduce risk should be evaluated to determine if the reduced risk is acceptable.

5.9.2.4. If, during risk control option analysis, the applicant determines that required risk reduction is not practicable, a benefit-risk analysis of the residual risk shall be conducted.

5.9.2.5. The risk control measure(s) selected shall be recorded in the Hazards Analysis and/or the FMEAs.

5.9.3. **Implementation of Risk Control Measures**

5.9.3.1. The applicant shall ensure implementation of the risk control measures selected from the risk control option analysis.

5.9.3.2. Implementation of each risk control measure(s) shall be verified, and the results shall be recorded in the hazards analysis and/or the FMEAs. The verification of effectiveness may include validation activities.

5.9.4. **Residual Risk Evaluation**

5.9.4.1. After the risk control measures are implemented, the applicant shall evaluate the residual risk using the criteria for risk acceptability defined in the risk management plan. The results of this evaluation shall be recorded in the Hazards Analysis and/or the FMEAs.

5.9.4.2. If a residual risk is deemed unacceptable using these criteria, further risk control measures shall be applied in accordance with Section 5.9.2.

5.9.4.3. The actions required, based on the residual risk evaluation, are defined in Table 6. The specific action(s) taken will depend on the nature of the risk analysis and the acknowledged industry state-of-the-art technological limitations.

Table 6. Required Action Based on Residual Risk Evaluation

Risk Index	Required Actions
Red	• Benefit-risk analysis specifically addressing the risk • Technical analysis detailing the barriers to additional risk reduction • Residual risk disclosure within product labeling
Yellow	• Investigate further risk controls • Benefit-risk analysis specifically addressing the risk
Green	• Overall benefit-risk analysis within the Risk Management Report

5.9.4.4. Based on the strength of the risk control(s) and verification results, the estimation of risk may be reduced; however, information for safety (e.g., labeling) intended for residual risk disclosure, provided to users, shall not be considered a mechanism to reduce risk.

5.9.5. **Benefit-Risk Analysis**

5.9.5.1. A benefit-risk analysis shall be performed to determine the acceptability of each individual risk and the overall residual risk of the combination product.

5.9.5.2. If a residual risk is deemed unacceptable using the criteria established in the risk management plan and further risk control is not practicable, the Applicant may gather and review data and literature to determine if the benefits of the intended use outweigh this residual risk.

5.9.5.3. If this evidence does not support the conclusion that the benefits outweigh the residual risk, then the Applicant must modify the combination product or its intended use.

5.9.5.4. The results of the benefit-risk analysis shall be recorded in the Risk Management Report.

5.9.6. **Risks Arising from Risk Control Measure(s)**

5.9.6.1. The effects of risk control measures shall be reviewed with regard to the following:

5.9.6.1.1. If new hazards or hazardous situations are introduced

5.9.6.1.2. If the estimated risks for previously identified hazardous situations are affected by the introduction of risk control measures.

5.9.6.2. Any new or increased risks shall be managed in accordance with this procedure.

5.9.6.3. The results of this review shall be recorded in the risk management file.

5.9.7. **Completeness of Risk Control**

5.9.7.1. The applicant shall review the risk control activities to ensure that the risks from all identified hazardous situations have been considered. Traceability is necessary to demonstrate that the risk management process has been applied and all risk control activities have been completed with respect to each identified hazard. The details required in Section 5.6.1, for documentation of the conduct and results of a risk analysis, form the basic minimum data set for ensuring traceability and verification of risk control completeness.

5.9.7.2. The results of this activity shall be recorded in the risk management report.

5.10. Evaluation of Residual Risk

5.10.1. After all risk control measures have been implemented and verified, the Applicant shall evaluate the overall residual risk posed by the combination product, taking into account the contributions of all residual risks, in relation to the benefits of the intended use, using the method and the criteria for acceptability of the overall residual risk defined in the risk management plan.

5.10.2. If the overall residual risk is judged acceptable, the Applicant shall inform users of significant residual risks and shall include the necessary information in the accompanying documentation in order to disclose those residual risks.

5.10.3. If the overall residual risk is deemed unacceptable in relation to the benefits of the intended use, the applicant must implement additional risk control measures or modify the combination product or its intended use.

5.10.4. The results of the overall residual risk evaluation shall be recorded in the risk management report.

5.11. Risk Management Report

5.11.1. Prior to release for clinical usage or commercial production of the combination product, the applicant shall review the execution of the risk management plan. This review shall ensure the following, at a minimum:

5.11.1.1. The risk management plan has been appropriately implemented.

5.11.1.2. The risk management process has been appropriately implemented in accordance with this procedure.

5.11.1.3. The overall residual risk acceptability and overall benefit risk analysis have been determined.

5.11.1.4. Appropriate methods to collect and review the information in the production and post-production phases have been determined and are in place.

5.11.1.5. Requirements for disclosure of overall and individual residual risks through product labeling and other forms of user communication have been determined.

5.11.1.6. Top management of Product Development, Clinical Development, Regulatory Affairs, and QA must approve the risk management report if the benefit risk assessment is needed to justify release of the product according to established risk thresholds.

5.11.2. The results of this review shall be documented and maintained in the Risk Management Report and included in the risk management file.

5.12. Production and Post-Production Activities

5.12.1. Information relevant to the combination product shall be actively collected and reviewed in the production and post-production phases to comply with post market surveillance regulations as well as to use the data to provide input to the risk management file for the device being marketed. This information is collected in the Post Market Surveillance and Complaint Handling Process.

5.12.2. Information collected and reviewed about the combination product shall entail the following considerations, at a minimum:

5.12.2.1. Information generated during production and monitoring of the production process

5.12.2.2. Information generated by the user

5.12.2.3. Information generated by those accountable for the installation, use and maintenance of the combination product (as applicable)

5.12.2.4. Information generated by the supply chain

5.12.2.5. Publicly available information

5.12.2.6. Information related to the generally acknowledged state of the art.

5.12.3. The information collected shall be reviewed for possible relevance to safety, especially with respect to the following:

5.12.3.1. Previously unrecognized hazards or hazardous situations are present

5.12.3.2. An estimated risk arising from a hazardous situation is present

5.12.3.3. The overall residual risk is no longer acceptable in relation to the benefits of the intended use

5.12.3.4. The generally acknowledged state of the art has changed

5.12.4. If any of these conditions occur, the following activities shall be performed:

5.12.4.1. The risk management file shall be reviewed to determine if reassessment of risks and/or assessment of new risks is necessary.

5.12.4.2. If a residual risk is no longer acceptable, the impact on previous implemented risk control measures shall be evaluated and should be considered as an input for modification of the combination product

5.12.4.3. Consider the need for actions regarding combination products on the market

5.12.4.4. Evaluate the impact on previously implemented risk management activities

5.12.4.5. Provide the results of the evaluation as an input for the review of suitability of the risk management process by top management, as noted in Section 5.13.3.

5.12.5. The results of any production and post-production evaluation(s) shall be recorded in the affected documents in the risk management file which include the risk management plan, hazards analysis, FMEAs, and risk management report.

5.13. Periodic Reviews

5.13.1. Periodic reviews of risk management documentation shall be conducted as a post market activity on an annual basis or as specified by the team and documented in the risk management plan or when events that may impact the original risk management decision occur. Consider the sales volume or product age when determining the review cycle. These events may be planned (i.e., results of product review, inspections, audits, change control, design reviews, human factors studies, production, and post-production information review) or unplanned (i.e., root cause from failure investigations, product recall).

5.13.2. Periodic review of risk management reports shall be conducted, when elements in the risk management file change, to assess the acceptability of residual risks and the overall residual risk of the combination product.

5.13.3. The risk management process shall be reviewed as part of the management review following requirements in *XX-YYY, Management Responsibility*. At a minimum, the review shall include the following:

5.13.3.1. Risk management process

5.13.3.2. Summaries of responses for critical and high risks

5.13.3.3. Risk profile(s)

6. Appendices, Forms and Templates

6.1. Appendix A: Characteristics Related to Safety

6.2. Appendix B: Examples of Hazards

7. Revision History

REV	Change Summary
A	New Document

Appendix A: Characteristics Related to Safety
What is the intended use of the device? Consider: What is the combination product's role relative to: • diagnosis, prevention, monitoring, treatment or alleviation of disease • diagnosis, monitoring, treatment or alleviation of or compensation for an injury • investigation, replacement, modification or support of anatomy or a physiological process, or control of conception What are the indications for use (e.g., patient population, user profile, use environment)? What are the contra-indications? Does the combination product sustain or support life? Is special intervention necessary in the case of failure of the *combination product*?
Is the combination product intended to be in contact with the patient or other persons? Factors that should be considered include the nature of the intended contact, i.e., surface contact, invasive contact, or implantation and, for each, the period and frequency of contact.
What materials or components are utilized in the combination product or are used with, or are in contact with, the combination product? Factors that should be considered include: • compatibility with relevant substances • compatibility with tissues or body fluids • whether characteristics relevant to safety are known • whether the combination product is manufactured utilizing materials of animal origin **NOTE**: See Annex B of ISO 10993-1:2018 and also the ISO 22442 series of standards.
Are substances delivered to or extracted from the patient? Factors that should be considered include: • whether the substance is delivered or extracted • whether it is a single substance or range of substances • the maximum and minimum transfer rates • control of the transfer rates
Is the combination product supplied sterile or intended to be sterilized by the user, or are other microbiological controls applicable? Factors that should be considered include: • whether the combination product is intended for single use or reuse packaging • shelf-life issues • method of product sterilization

Appendix A: Characteristics Related to Safety
Is the combination product modified by the patient environment? Factors that should be considered include: • temperature • humidity • atmospheric gas composition • pressure • light
Is the combination product intended for use in conjunction with other medical devices, combination products, medicines or other medical technologies? Factors that should be considered include: • identifying any other medical device, combination products, medicines or other medical technologies that can be involved • the potential problems associated with interactions (such as the combination product impacting the performance of other medical devices or combination products) • whether the patient follows the instructions for the therapy
Are there unwanted outputs of energy or substances? Energy-related factors that should be considered include noise and vibration, heat, radiation (including ionizing, non-ionizing, and ultraviolet/visible/infrared radiation), contact temperatures, leakage currents, and electric or magnetic fields. Substance-related factors that should be considered include substances used in manufacturing, cleaning, or testing having unwanted physiological effects if they remain in the product. Other substance-related factors that should be considered include discharge of chemicals, waste products, and body fluids.
Is the combination product susceptible to environmental influences? Factors that should be considered include the operational, transport and storage environments. These include light, temperature, humidity, vibrations, spillage, susceptibility to variations in power and cooling supplies, and electromagnetic interference.
Does the combination product influence the environment? Factors that should be considered include: • the effects on power and cooling supplies • emission of toxic materials • the generation of electromagnetic disturbance
Does the combination device have a restricted shelf life? Factors that should be considered include whether the combination product can deteriorate over time, the impact of storage conditions and primary packaging, the communication of the expiry date (by labelling or an indicator), possibility of use after the expiry date, and the disposal of expired combination products.

Appendix A: Characteristics Related to Safety
Are there any delayed or long-term use effects? Factors that should be considered include ergonomic and cumulative effects. Examples could include pumps for saline that corrode over time, mechanical fatigue, loosening of straps and attachments, vibration effects, labels that wear or fall off, and long-term material degradation.
To what mechanical forces will the combination product be subjected? Factors that should be considered include whether the forces to which the combination product will be subjected are under the control of the user or controlled by interaction with other persons.
What determines the lifetime of the combination device? Factors that should be considered include battery depletion, deterioration of materials and failure of components due to aging, wear, fatigue or repeated use. The availability of spare parts should be considered as well.
Is the combination product intended for single use? Factors that should be considered include: • whether the combination device self-destructs after use • whether it is obvious to the user that the combination device has been used
Is safe decommissioning or disposal of the combination product necessary? Factors that should be considered include the waste products that are generated during the disposal of the combination device itself, and the proper sanitization (removal) of all sensitive data on the combination product. For example, does it contain hazardous material (e.g., toxic chemical or biological agent), or is the material recyclable?
Does installation or use of the combination device require special training or special skills? Factors that should be considered include the complexity and novelty of the combination product and the knowledge, skills and ability of the persons installing, maintaining, or using the combination product. This can include training, education, competence assessment, certification, or qualification.
How will information for safety be provided?
Are new manufacturing processes established or introduced? Factors that should be considered include the application of new or innovative technology and changes in the scale of production. This can also involve changes in contract manufacturing, suppliers and vendors.

Appendix A: Characteristics Related to Safety
Is successful application of the combination product dependent on the usability of the user interface? Factors that should be considered include: control and indicators, symbols used, ergonomic features, physical design and layout, hierarchy of operation, visibility of warnings, audibility of alarms, standardization of color coding. See IEC 62366-1 for additional information on usability.
Is the combination product used in an environment where distractions can cause use error? Factors that should be considered include: • the consequence of use error • whether the distractions are commonplace • whether the user can be disturbed by an infrequent distraction • whether repetitive stress can reduce the user's awareness or attention
Does the combination product have connecting parts or accessories? Factors that should be considered include the possibility of wrong connections, similarity to other products' connections, connection force, feedback on connection integrity, and over- and under-tightening.
Is the successful use of the combination product dependent on a user's knowledge, skills and abilities? Factors that should be considered include: • the (intended) users, their mental and physical abilities, skill and training • the use environment, ergonomic aspects, installation requirements • the capability of intended users to control or influence the use of the combination product • the personal characteristics of intended users that can affect their ability to successfully interact with the combination product. See IEC TR 62366-2
Will the combination product be used by persons with specific needs? Factors that should be considered include: • users with special characteristics, such as disabled persons, the elderly, and children, who might need assistance by another person to enable the use of a combination product • users having wide-ranging skill levels and differing cultural backgrounds and expectations that could lead to differences in what is considered appropriate application of the combination product.
In what ways might the combination product be misused (deliberately or not)? Factors that should be considered are incorrect use of connectors, disabling safety features, or neglect of manufacturer's recommended instruction.

Appendix A: Characteristics Related to Safety
Is the combination product intended to be mobile or portable? Factors that should be considered are the need for grips, handles, wheels or brakes, and the need for mechanical stability and durability.
Does the use of the combination product depend on essential performance? Factors that should be considered are, for example, the characteristics of the output of life supporting combination products or the operation of an alarm. See IEC 60601-1 for a discussion of essential performance of medical electrical equipment and medical electrical systems.
Does the combination product have a degree of autonomy? Factors that should be considered include: • awareness of the user when the combination product with a degree of autonomy generates an error, alarm or failure • awareness of the user when intervention in an autonomously performed action is required • the ability of the user to intervene in or to abort an action that is performed autonomously • the ability of the user to select and perform proper corrective actions. See IEC TR 60601-4-1for further guidance on combination products with a degree of autonomy
Does the combination product produce an output that is used as an input in determining clinical action? Factors that should be considered include whether incorrect or delayed outputs can result in direct or indirect risks to patients, e.g., an incorrect diagnosis resulting in delayed or omitted therapy for a patient.

Appendix B: Examples of Hazards		
Energy hazards	**Biological and chemical hazards**	**Performance-related hazards**
Electric energy — Static discharge Mechanical energy Kinetic energy — falling objects — high pressure fluid injection — moving parts — vibrating parts Potential (stored) energy — bending — compression — cutting, shearing — gravitational pull — suspended mass — tension — torsion	Biological agents Bacteria, fungi, parasites, prions, toxins, viruses Chemical agents Carcinogenic, mutagenic, reproductive Caustic, corrosive — acidic — alkaline — oxidants Flammable, combustible, explosive fumes, vapors Osmotic Particles (including micro- and nano-particles) Pyrogenic Solvents Toxic — asbestos — heavy metals — inorganic toxicants — organic toxicants — silica Immunological agents Allergenic — antiseptic substances — latex Immunosuppressive Irritants — cleaning residues Sensitizing	Data — access — availability — confidentiality — transfer — integrity Delivery — quantity — rate Functionality — critical performance