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Title:	Risk Management Procedure for Combination Products			

APPROVAL PAGE

Prepared By:

Print Name and Title	Signature	Date
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1.0 Purpose

The purpose of this procedure is to establish, implement, document and maintain an ongoing process for risk management at Altimmune 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 [1], ISO 14971:2019, and taking into consideration the guidelines provided by ISO/TR 24971:2020.

Commented [LS1]: Is it desired to use the terms medical devices and combination products throughout the procedure? There are cases where both terms are used and cases where just medical devices are used. Since Altimmune is just working with a combination product, what is most appropriate?

2.0 Scope

This procedure 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 procedure applies to all sites and/or functions supporting and/or executing cGMP activities.

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

Where Altimmune is the product applicant, Altimmune 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 QA-008, *Supplier Qualification and Management* [6].

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

3.0 Responsibilities

- 3.1 Altimmune Product Development and Quality Assurance are responsible for ensuring compliance with this procedure. All functional leads/managers are responsible for ensuring compliance with the applicable segments of this procedure that are within their areas of responsibility.



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Role	Responsibility
Functional Area Management (Product Development, Clinical Development, Regulatory Affairs and Quality Assurance Management)	<ul style="list-style-type: none">Responsible for ensuring that the risk management process is followed within area of responsibilityProvides subject matter expertise, as appropriate, to risk management activitiesEnsures execution of risk reduction activitiesCreates and maintains risk management documentationAssure 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 consider available information such as the general acknowledged state of the art and known stakeholder concerns.Ensures risk management policies are established and followedEnsures provision of adequate resources and assignment of competent personnel for risk managementReviews 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	<ul style="list-style-type: none">Defines applicable harmsAssigns severity rating to harmsParticipates in benefit risk analysis activity in accordance with this procedure

Commented [LS2]: The roles need discussion. We need to be able to assign clear responsibility so that we can determine who should train on this SOP.

Commented [JAH3R2]: Given current division of responsibilities and the way this is managed at other companies, I would recommend **Quality Assurance** be the overall owner of the RM process at Altimmune. Agree that this should be made clear within this section.

Commented [LS4]: Which departments would this apply to? Product Development? Others?

Commented [SR5R4]: Product Development Manufacturing and Quality at a minimum. It is a good idea to include Human Factors, Clinical and Regulatory as well.

Commented [JAH6R4]: This would likely be Quality Management if this is assigned to QA.

Commented [LS7]: Please clarify where the policy would be located

Commented [SR8R7]: Removed reference to the policy. It is embedded in this document.

Commented [LS9]: Is this document being created as part of Phase 1? Or is this referring to the current procedure?

Commented [JAH10R9]: This appears to be a requirement related to a deliverable (likely the RM Plan) - Sandra, please move to the relevant section - and this would be something included in that document as a part of Phase 2.

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Role	Responsibility
Quality Assurance Management	<ul style="list-style-type: none">• Overall responsibility for effective execution and oversight of risk management process, including both internal and external organizations' scope of work.• Overall responsibility for the 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
Quality Assurance	<p>In accordance with this procedure:</p> <ul style="list-style-type: none">• 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 policy as established in the Risk Management Procedure.
Regulatory Affairs	<ul style="list-style-type: none">• Provides regulatory input based on relevant regulatory guidelines• Approves design control documents, activities or efforts

Commented [LS2]: The roles need discussion. We need to be able to assign clear responsibility so that we can determine who should train on this SOP.

Commented [JAH3R2]: Given current division of responsibilities and the way this is managed at other companies, I would recommend Quality Assurance be the overall owner of the RM process at Altimmune. Agree that this should be made clear within this section.

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4.0 References

Commented [JAH11]: See updates above

Document Number	Document Title
[1] ISO 13485:2016	Combination products – Quality management systems – Requirements for regulatory purposes
[2] EN ISO 14971:2019/A11:2021	Combination products – Application of risk management to combination products
[3] PD-001	Design Control Procedure
[4] PD-002-T01	Risk Management Plan Template
[5] PD-002-T02	Risk Management Report Template
[6] QA-008	Supplier Qualification and Management
[7] QA-018	Controlled Document Management System
[8] QA-019	Training Program
[9] QA-021	Record Retention and Archiving
[10] QA-024	Writing, Review, Approval, and Issuance of Controlled Documents
[11] QA-026	Management Responsibility
[12] WI-PD-006	Design Review Work Instruction
[13] WI-PD-003	Design Verification Work Instruction
[14] WI-PD-004	Design Validation Work Instruction

5.0 Definitions

Term	Definition
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.
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.
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

Commented [LS12]: Or combination product?

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Term	Definition
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.
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.
Harm	Injury or damage to the health of people, or damage to property or the environment [2]
Hazard	Potential source of harm [2]
Hazardous Situation	Circumstance in which people, property, or the environment is/are exposed to one or more hazards [2]
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/manufacture [2]
Lifecycle	Series of all phases in the life of a combination product, from the initial conception to final decommissioning and disposal [2]

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Term	Definition
<u>Medical Device</u>	An instrument, apparatus, implement, machine, contrivance, implant, reagent for in vitro use, software, material, or other similar or related article, intended by the Applicant/manufacture to be used, alone or in combination, for human beings for one or more of the specific medical purpose(s) of [1] [2]: <ul style="list-style-type: none">• diagnosis, prevention, monitoring, treatment or alleviation of disease,• diagnosis, monitoring, treatment, alleviation of or compensation for an injury,• investigation, replacement, modification, or support of the anatomy or of a physiological process,• supporting or sustaining life,• control of conception,• disinfection of combination products,• providing information for medical purposes by means of in vitro examination of specimens derived from the human body,• 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.
Objective Evidence	Data supporting the existence or verity of something, which can be obtained through observation, measurement, test or by other means [2]
Post-production	Part of the lifecycle of the combination product after the design has been completed and the combination product has been manufactured [2]
Process	Set of interrelated of interacting activities that use inputs to deliver an intended result.
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.
Residual Risk	Risk remaining after risk control measures have been implemented [2]

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Term	Definition
Risk	Combination of the probability of occurrence of harm and the severity of that harm [2]
Risk Analysis	Systematic use of available information to identify hazards and to estimate the risk [2]
Risk Assessment	Overall process comprising a risk analysis and a risk evaluation [2]
Risk Control	Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels [2]
Risk Estimation	Process used to assign values to the probability of occurrence of harm and the severity of that harm [2]
Risk Evaluation	Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk [2]
Risk Management	Systemic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk [2]
Risk Management File	Set of records and other documents that are produced by risk management [2]
Safety	Freedom from unacceptable risk [2]
Severity	Measure of the possible consequences of a hazard [2]
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.
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.
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. [2]
Verification	Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled. [2]
Validation	Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled.

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6.0 Safety Precautions

N/A

7.0 Materials, Supplies and Equipment

N/A

8.0 Procedure

8.1 Background

8.1.1 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.

8.1.2 Risk management is integrated within the Design Control Procedure [3] 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.

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

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

- Identifying hazards and hazardous situations associated with the combination product
- Estimating and evaluating the associated risks
- Controlling risk and monitoring the effectiveness of the risk control measures
- Monitoring the effectiveness of the risk control measures
- Risk reviews driven by new information
- Periodic review of identified risks

8.1.5 [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.

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- 8.1.6 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 QA-026, *Management Responsibility*. [11]
- 8.1.7 Documented records, including evidence of decisions and actions taken, shall be maintained to ensure and demonstrate the effective planning, operation and control of this process.
- 8.1.8 Persons performing risk management tasks shall 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 QA-019, Training Program [8].
- 8.1.9 Risk management tasks may be performed by representatives of several functions, each contributing their specialist knowledge.
- 8.1.10 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.
- 8.1.11 Major risks shall be communicated to Senior Product Development and Quality Assurance Management.
- 8.1.12 A risk profile for the combination product shall be established and reviewed periodically.

Commented [LS13]: This language sounds more like a guidance document. If this SOP is defining how we do this, is this language necessary here?

Commented [JAH14R13]: Agreed, this is the procedure of concern - see redlines to address.

Commented [LS15]: This language sounds more like a guidance document. If we want to include a responsibility for management to ensure people have the appropriate qualifications and training, that would be fine. The last sentence is part of our Training SOP QA-019 and should be there instead of in this SOP.

Commented [JAH16R15]: Overall, I believe this is a valid requirement and is reflective of the relevant standard (14971). I agree that the competence/training should point to the relevant Altimmune SOP and should be revised to incorporate.

Commented [LS17]: Are critical or major risks defined somewhere?

Commented [SR18R17]: Mapped to the rating scale used. Only Major risks need to be communicated to Senior Management.

Commented [LS19]: Are the details of the establishment of the risk profile and review of it documented somewhere else in this SOP?

Commented [SR20R19]: The steps in this SOP describe how the risk profile is established. This is typically how it is done.

Plan
Hazards Analysis
FMEA
Initial risk established
Mitigations for risks produced through design, testing or inspection
Update HA and FMEAs to reduce risk
Evaluate residual risk
Determine Benefit Risk
Report

Commented [SR21R19]: There is a lot of detail in the SOP about what the HA and FMEAs need to evaluate.

Commented [JAH22R19]: Generally this should be accomplished via the RM Report and periodic updates to the RMF which is covered in Section 9.

I would not propose any modification to this requirement.

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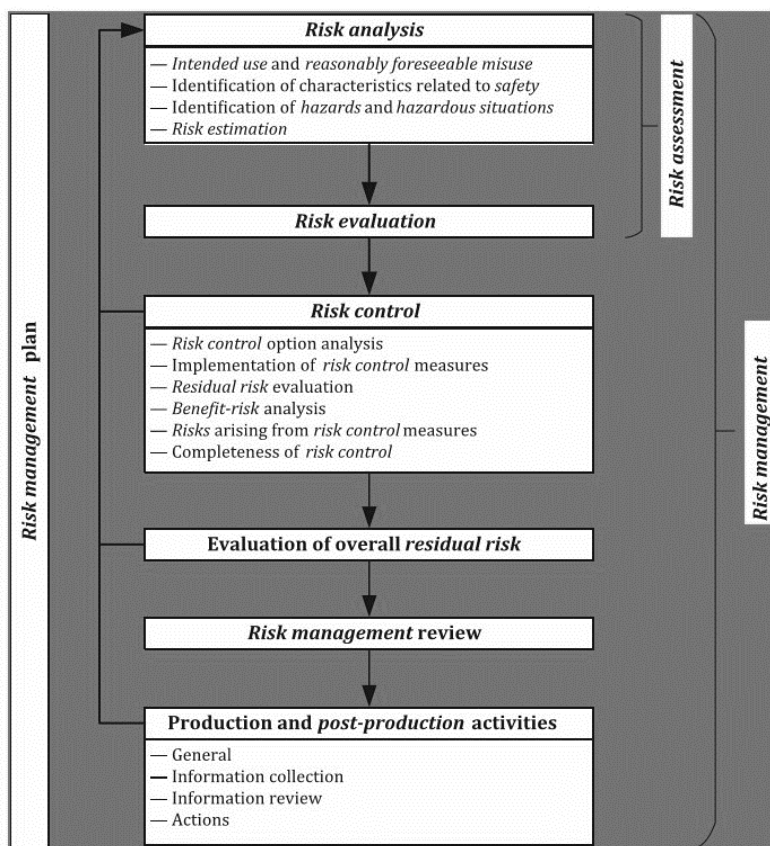


Figure 1 – Schematic Representation of the Risk Management Process

8.2 Risk Management Plan

- 8.2.1 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.

Commented [BL23]: The first column at the left, ie "RM Plan" can be removed as Fig. 1 illustrates the entire RM process

Commented [JAH24R23]: Note that this figure is taken directly from the standard and the RM Plan along the left denotes that the RMP covers the entirety of the RM process. I'm not opposed to modifying if this is a point of confusion.

Commented [BL25R23]: OK. Added a sentence to 8.1.5 to reflect this



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8.2.2 Risk management activities shall be planned.

8.2.3 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:

8.2.3.1 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

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

- Identification by function or area of expertise the necessary reviewers, contributors, and personnel responsible for risk management execution throughout the product lifecycle
- Top management of Product Development, Clinical Development, Regulatory Affairs and Quality Assurance establish acceptable thresholds for residual risk acceptance within this procedure.
- When a product exceeds thresholds, but still has clinical benefit as designed, a benefit risk analysis is required to justify acceptance of risk.
- 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).

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

8.2.4.1 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 WI-PD-006, Design Review Work Instruction [12] and PD-001, Design Control Procedure [3].

8.2.5 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 is based on the following

Commented [DP26]: Should the following (applicable) sections be indented or bulleted?

Commented [LS27]: Need to indicate how this is documented. Is there a template to be used? If it's the Risk Management Plan Template, we'll just want to put a reference here.

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decisions:

- The risk presented by the current standard of care
- The potential health benefits of using the combination product
- The generally acknowledged state of the art defined in recognized consensus standards

8.2.6 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.

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

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

8.2.7.2 Other potential sources of verification/validation information include, but are not limited to:

- Scientifically valid characterization studies

8.2.8 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 regards to post-market surveillance activities appropriate for the product.

8.2.8.1 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:

- Commercial & Clinical complaints (if applicable)
- Manufacturing and process performance data

8.2.9 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.

8.2.10 The risk management plan may be developed for a specific product or for a family of

Commented [LS28]: Is this intended to be another bullet for information that is included in the Risk Management Plan? If not, the wording needs attention as it doesn't start with a complete sentence.

Commented [LS29]: Where is this documented?

Commented [LS30]: This is not a complete sentence. If it's part of a list, it's not clear what it goes with.

Commented [LS31]: This is not a complete sentence. If it's part of a list, it's not clear what it goes with.

Commented [LS32]: We do not currently have a defined complaint handling process.

Commented [JAH33R32]: See modification, I would leave this in for when this will (eventually) come into play

Commented [BL34]: I can understand the need of inclusion of this element (documentation of decisions) in the RM plan. But at the planning phase, the specifics are not yet available

Commented [SR35R34]: The Risk Management Plan evolves as product development happens.

It starts out high level.

Some organizations leave it that way and include the detail in the report.

The process is designed to be iterative.

Commented [JAH36R34]: Agree that this should be considered a living document and can be modified as the project progresses. For our immediate purposes (clinical PFS) this would likely be N/A and would be defined in a different process for a commercial product.

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similar products, as appropriate.

8.2.11 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.

8.2.12 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.

Commented [LS37]: Is this process detailed somewhere else in this SOP?

8.2.13 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.

8.2.14 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.

8.3 Risk Management File

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

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

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

- Risk analysis
- Risk evaluation
- Implementation and verification of the risk control measures
- Results of the evaluation of residual risks

8.3.4 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:

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- Hazards Analysis
- Master Harms and Severity List
- Risk Management Plan
- Risk Analyses (internal and external)
- Benefit Risk Analysis (when applicable)
- Risk Management Report(s)
- Post-production Risk Management Report(s) (when appropriate)
- Any supporting or referenced documents or records of activities required by the risk management plan

8.3.5 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 QA-018[7], QA-021[9] and QA-024[10]. |

Commented [LS38]: Need to link QA-018, QA-021, and/or QA-024 here based on what is applicable.

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

Commented [JAH39R38]: Agreed

8.4 Master Harms and Severity List

8.4.1 This document provides the severity assignments for identified harms based on the potential health and environmental consequences. The risk management plan may identify or plan for the development of a Master Harms and Severity List that maps specific harms 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 Master Harms and Severity List, it shall specify the approval requirements for the list. Clinical Development shall be involved in the development, review and approval of the list.

8.5 Criteria for Verification of Risk Controls

8.5.1 Verification that a risk control has been implemented into the design is conducted in accordance with the Design Verification procedure. Refer to PD-001, *Design Control Procedure* [7] and WI-PD-003, *Design Verification Work Instruction* [13] for more information.

8.5.2 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

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probability content) and statistical confidence.

8.5.3 Verification that the risk control is effective is conducted in accordance with PD-001, *Design Control Procedure* [8], WI-PD-003, *Design Verification Work Instruction* [13] and WI-PD-004, *Design Validation Work Instruction* [14].

8.5.4 Verification that the risk control remains effective is conducted per Section 9.0, Periodic Reviews of this procedure.

8.6 Risk Analysis

8.6.1 Risk Analysis Process

- The purpose of the risk analysis is as follows.
 - 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)
 - Estimate the probability of the occurrence and severity of the harms in order to estimate risk
 - Identify the risk controls necessary to mitigate and control risk
 - Estimate the reduction or elimination of the probability of occurrence due to the implementation of the risk controls.
- The risk analysis shall take into consideration the intended use, the user(s) and the use environment for the combination product.
- 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.
- At a minimum, a usability risk analysis and a system risk analysis are required. The risk management plan may specify additional risk analysis (i.e., process) as appropriate.
 - The usability risk analysis is used to analyze the risk of the use of the combination product.
 - The system risk analysis is used to analyze the risk of the design

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

- The usability and system risk analyses utilize the same basic structure and methods of risk estimation.
- The documentation describing the execution and results of the risk analysis shall include the following, at a minimum.
 - Identification and description of the combination product that was analyzed
 - Identification of the person(s) and organization(s) who carried out the risk analysis
 - Scope and date of the risk analysis
- 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.
- 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.

Commented [LS40]: Where is this documented?

8.6.2 Intended Use, Reasonably Foreseeable Misuse, and Identification of Characteristics Related to the Safety of the Combination product

- 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 FMEAs.
- 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 characteristic shall be defined. These characteristics are documented in the Hazards Analysis and FMEAs.
- Annex A of ISO 24971:2020 contains identification of hazards and

Commented [LS41]: Where is this documented?

Commented [LS42]: Where is this documented?

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characteristic 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 are modified, removing items that are not relevant to our devices.

- Documentation collected during this phase of the risk management project shall be maintained in the risk management file.

8.6.3 Identification of Hazards

- 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.
- Hazards resulting from interfaces with external (to the combination product) systems and processes shall be considered.
- For each identified hazard, the reasonably foreseeable sequences or combinations of events that can result in a hazardous situation 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:
 - 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).)
 - Usability flow chart identifying the steps that shall be performed by the user and the combination product to meet intended use
 - Known interfaces with external (to the combination product) systems and processes (may be documented in the risk management plan).

8.6.4 Identification of Hazardous Situations

- 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.

Commented [BL43]: This should be expanded to include a summary of the approach or a diagram

Commented [JAH44R43]: Relevant portions (applicable to the types of products being designed/manufactured by Altimmune) could be summarized or included as an appendix to this document, which I have seen done in the past.

Commented [SR45R43]: Need guidance on direction we wish to take with this comment.

Commented [SR46R43]: Add bolded list from standard.

Commented [LS47]: Where is this documented?

Commented [JAH48R47]: This would typically be captured in the Hazard Analysis document or other related docs (e.g. FMEAs). This could be clarified if needed, but I think this requirement is reasonable as is

Commented [LS49]: What document does this go in?

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

8.6.5 Identification of Harms

- 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).
- The harm identification documentation shall be maintained in the risk management file. Harm identification methods may include the following.
 - 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).)
 - Review of identified hazards and hazardous situations
 - Expert medical opinion (as applicable)

8.6.6 Reasonably Foreseeable Sequence of Events or Cause(s)

- 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.
- Reasonably Foreseeable sequence of event or cause(s) may include the following:
 - Faults during use (documented in the Usability Risk Analysis), use faults related to misuse, and intentional misuse shall be considered.
 - Faults in design (or manufacturing as applicable) or interactions with external systems and processes (documented in the System Risk Analysis)
 - Hazardous situations may result from no-fault conditions (documented in the System Risk Analysis)

Commented [LS50]: Where is this documented?

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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)

8.7 Risk Estimation

8.7.1 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.

8.7.2 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.

Commented [LS51]: Is there a particular document that this resides in?

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

- Published standards
- Scientific or technical investigations
- Field data from similar combination products already in use, including publicly available reports of incidents
- Usability tests employing typical users
- Clinical evidence
- Results of relevant investigations or simulations
- Expert opinion
- External quality assessment schemes

8.7.4 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.

- Occurrence is estimated by first estimating two (2) probabilities referred to as P1 and P2.
 - P1 is the probability that the hazardous situation will occur.
 - P2 is the probability that the hazardous situation will result in harm.

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- The overall occurrence is $P = P1 \times P2$.
- Methods for estimating occurrence may include the following.
 - 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).)
 - Use of fault tree analysis (FTA) to decompose the probability estimation
 - Use of bench data (laboratory) or simulations
 - Use of data from clinical trials
 - Use of expert judgement
- 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.
 - If it is not possible to estimate P1, assume that the P1 probability is equal to 1. If it is not possible to estimate P2, assume that the P2 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.
- An example of overall occurrence is presented in **Table 1**. The probability limits listed in this table are the products of P1 and P2.

Table 1 – Overall Occurrence $P = (P1 \times P2)$

Occurrence Rating	Likelihood Term	Probability Low Limit	Probability High Limit	Description
5	Frequent	$>10^{-2}$	1	Harm is almost inevitable
4	Likely	$> 10^{-3}$	$\leq 10^{-2}$	Harm is likely and will occur in most circumstances and has been repeatedly observed
3	Occasional	$> 10^{-4}$	$\leq 10^{-3}$	Harm is probable at some time and has been observed
2	Unlikely	$> 10^{-5}$	$\leq 10^{-4}$	Harm could occur at some time and isolated incidents have been observed

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Occurrence Rating	Likelihood Term	Probability Low Limit	Probability High Limit	Description
1	Remote	0	$\leq 10^{-5}$	Harm is extremely unlikely and has not been observed

- Severity is a measure of the consequence(s) of the harm
 - In general, severity should be assigned based on expert medical judgement or literature review.

Table 2 – Assignment of Severity Level

Harm Rating	Harm Term	Description
5	Severe	Catastrophic - Results in patient death or life-threatening injury
4	Major	Critical - Results in permanent impairment or irreversible injury
3	Moderate	Serious - Results in injury or impairment requiring professional medical intervention
2	Minor	Minor - Results in temporary impairment nor requiring professional intervention
1	Insignificant	Negligible - Results in an inconvenience, annoyance, or temporary discomfort

Commented [JAH52]: Updating per our discussion on Sep 23

- The Risk Index is assigned based on the estimated occurrence and severity. **Table 3** below defines how the Risk Index is determined.

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Table 3 – Example Risk Index Determination

		Occurrence				
		1	2	3	4	5
Harm Rating	5	Moderate	Moderate	Major	Major	Major
	4	Minor	Moderate	Moderate	Major	Major
	3	Minor	Minor	Moderate	Moderate	Major
	2	Minor	Minor	Minor	Moderate	Moderate
	1	Minor	Minor	Minor	Minor	Moderate

8.7.5 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.

8.8 Risk Evaluation

8.8.1 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 8.9.6 and the estimated risk shall be treated as residual risk.

8.9 Risk Control

8.9.1 Risk Reduction

- When risk reduction is required, risk control activities, as described in Sections 8.9.2 to 8.9.7 shall be performed.
- Risk reduction shall be achieved by any combination of designing for inherent safety and/or implementation of protective measures.
- Information for safety, intended for residual risk disclosure, provided to users and patients is not considered a mechanism for reducing risk.
- All foreseeable and/or known risk controls shall be identified and included in the applicable risk analysis.
- 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.
- Risks shall be reviewed after risk reduction actions are implemented, or

Commented [BL53]: Should also give numerical limits:

Major: > 15
Moderate: 8 - 15
Minor: < 8

Commented [JAH54R53]: Can revise to include these if desired

Commented [SR55R53]: Table on the left (we can delete) shows an inconsistency in the Risk Index Table.

Harm 5, Occ 1 and Occ 5, Harm 1 should both be minor according to their values.

Commented [JAH56]: Recommend reverting back:

Regarding the Risk Acceptability Matrix and updates/changes you provided - I'll defer to David Plescia regarding those details. I prefer the top chart (where the 5 severity/1 occurrence & 1 severity/5 occurrence are both moderate vs. minor) as it doesn't conceptually make sense as to why those would be minor. Note that per Annex C of ISO/TR 24971:2020 this is only a semi-quantitative exercise and direct application of numerical approach is not necessarily required (this was commonly done in prior risk approaches where an RPN was calculated, though that method is generally considered to be deprecated). So, my recommendation would be to not use a purely quantitative/numerical approach and stick with the initial (top) matrix as a semi-quantitative approach only.

Commented [BL57]: Is this the action or plan?

Commented [JAH58R57]: I would propose modifying as indicated for clarity.

Commented [LS59]: Is this part of Section 9.0, Periodic Review?

Commented [SR60R59]: See modified comment.

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following sufficient monitoring time to accumulate required data, to confirm that the desired risk reduction was achieved.

- 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.

8.9.2 Risk Control Option Analysis

- The Applicant shall identify risk control measure(s) that are appropriate for reducing the risk(s) to an acceptable level.
- The Applicant shall use one or more of the following risk control options in the priority listed.
 - a) Inherent safety by design
 - b) Protective measures in the combination product itself or in the manufacturing process
 - c) Information for safety
- If implementing option b) or c) above, reasonably practicable control measures to reduce risk should be evaluated to determine if the reduced risk is acceptable.
- 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.
- The risk control measure(s) selected shall be recorded in the Hazards Analysis and/or the FMEAs.

Commented [LS61]: Is there a particular document that this goes in?

Commented [JAH62R61]: See above, likely FMEAs

8.9.3 Implementation of Risk Control Measures

- The Applicant shall ensure implementation of the risk control measures selected from the risk control option analysis.
- 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.

Commented [LS63]: Is there a particular document that this goes in?

Commented [JAH64R63]: See above, this is also usually contained in the FMEAs.

8.9.4 Residual Risk Evaluation

- After the risk control measures are implemented, the applicant shall evaluate the residual risk using the criteria for risk acceptability defined in

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the risk management plan. The results of this evaluation shall be recorded in the Hazards Analysis and/or the FMEAs.

- If a residual risk is deemed unacceptable using these criteria, further risk control measures shall be applied in accordance with Section 8.9.2.
- The actions required, based on the residual risk evaluation, are defined in [Table 4](#) below. The specific action(s) taken will depend on the nature of the risk analysis and the acknowledged industry state of the art technological limitations.

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Table 4 – Required Action Based on Residual Risk Evaluation

Risk Index	Required Actions
Critical	<ul style="list-style-type: none">• Benefit-risk analysis specifically addressing the risk• Technical analysis detailing the barriers to additional risk reduction• Residual risk disclosure within product labeling
Major	<ul style="list-style-type: none">• Benefit-risk analysis specifically addressing the risk• Residual risk disclosure within product labeling
Moderate	<ul style="list-style-type: none">• Benefit-risk analysis specifically addressing the risk
Minor	<ul style="list-style-type: none">• Overall benefit-risk analysis within the Risk Management Report

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

8.9.5 Benefit-Risk Analysis

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

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benefits of the intended use outweigh this residual risk.

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

8.9.6 Risks Arising from Risk Control Measure(s)

- The effects of risk control measures shall be reviewed with regard to the following.
 - a) If new hazards or hazardous situations are introduced
 - b) If the estimated risks for previously identified hazardous situations are affected by the introduction of risk control measures.
- Any new or increased risks shall be managed in accordance with this procedure.
- The results of this review shall be recorded in the risk management file.

8.9.7 Completeness of Risk Control

- 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 8.6.1, 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.
- The results of this activity shall be recorded in the Risk Management Report.

8.10 Evaluation of Residual Risk

- 8.10.1 After all risk control measures have been implemented and verified, the Applicant shall evaluate if 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.

Commented [LS65]: Is there a trigger in the Design Change Form to consider new or changed risks?

Commented [JAH66R65]: Not explicitly, only implied as a part of the DHF (here's the link to the form for David & Sandra: <https://suttonscreekinc.box.com/s/cbbt2tdhj99xiz3cn018bhl65g8wmjw>)

David & Sandra: we should consider adding an explicit question concerning impact on the risk management file

Commented [SR67R65]: It was there but it was the last question in that section - 2M. Re-ordered so it is now question 2B.

Commented [LS68]: Is there a particular document in which this is recorded?

Commented [JAH69R68]: Individual FMEAs, see above

Commented [LS70]: Is there a particular document in which this is recorded?

Commented [JAH71R70]: RM Report, see above

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8.10.2 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.

8.10.3 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.

8.10.4 The results of the overall residual risk evaluation shall be recorded in the Risk Management Report.

8.11 Risk Management Report

8.11.1 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.

- The risk management plan has been appropriately implemented
- The risk management process has been appropriately implemented in accordance with this procedure
- The overall residual risk acceptability and overall benefit risk analysis have been determined
- Appropriate methods to collect and review the information in the production and post-production phases have been determined and are in place
- Requirements for disclosure of overall and individual residual risks through product labeling and other forms of user communication have been determined
- Top management of Product Development, Clinical Development, Regulatory Affairs and Quality Assurance from must approve the Risk Management Report if the benefit risk assessment is needed to justify release of the product according to established risk thresholds.

8.11.2 The results of this review shall be documented and maintained in the risk management report and included in the risk management file.

8.12 Production and Post-Production Activities

8.12.1 Information relevant to the combination product shall be actively collected and

Commented [BL72]: Is this the only time point for the review? There should be multiple reviews, interim or stage gated reviews and reports

Commented [JAH73R72]: Also added clinical usage. Periodic reviews included in a separate section, later

Commented [SR74R72]: Note that this section is discussing the report. The report will not be available to review until all risk activities have been completed which is why it only addresses the two release scenarios.

Risk reviews will be specified in the Design and Development Plan along with other stage gate reviews. Risk Reviews can be done separately but are most commonly done at a time that syncs with the other milestones (Design Freeze, Design Verification and Validation, or Design Transfer).

In the case of a product that has already been designed, it may only be necessary to have one Risk Review prior to release.

Risk Reviews are also conducted when Adverse Events happen or a threshold is reached for complaints or if there is a question about product safety.

Commented [BL75]: How should the information collected be documented and stored. I assume it is not in the RM files.

Commented [JAH76R75]: Agree this is worded generically. David & Sandra: I'd recommend revising this section or removing.

Commented [SR77R75]: Referring to processes we do not yet have but they are necessary to implement this requirement.

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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.

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

- Information generated during production and monitoring of the production process
- Information generated by the user
- Information generated by those accountable for the installation, use and maintenance of the combination product (as applicable)
- Information generated by the supply chain
- Publicly available information
- Information related to the generally acknowledged state of the art.

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

- Previously unrecognized hazards or hazardous situations are present
- An estimated risk arising from a hazardous situation is present
- The overall residual risk is no longer acceptable in relation to the benefits of the intended use
- The generally acknowledged state of the art has changed

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

- The risk management file shall be reviewed to determine if reassessment of risks and/or assessment of new risks is necessary.
- If a residual risk is no longer acceptable, the impact on previous implemented risk control measures shall be evaluated and should be considered as an input for modification of the combination product
- Consider the need for actions regarding combination products on the market
- Evaluate the impact on previously implemented risk management activities

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- 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 9.4.

8.12.4 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.

9.0 Periodic Reviews

9.1 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).

Commented [LS78]: Can this clarify when the clock starts on the periodic reviews?

Commented [SR79R78]: Added.

9.2 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.

9.3 The risk management process shall be reviewed as part of the management review following requirements in QA-026, Management Responsibility [11]. At a minimum, the review shall include the following.

Commented [LS80]: Is this the Management Responsibility SOP?

Commented [JAH81R80]: Yes; see earlier comments

- Risk management process
- Summaries of responses for critical and high risks
- Risk profile(s)

10.0 Appendices, Forms and Templates

10.1 PD-002-T01 – Risk Management Plan Template

10.2 PD-002-T02 – Risk Management Report Template

10.3 Appendix A – Characteristics related to safety

10.4 Appendix B – Examples of Hazards

Commented [LS82]: All forms and templates need to be referenced somewhere in the body of this SOP.

Commented [JAH83R82]: Agreed, update with references from earlier

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11.0 Revision History

Version #	DCR #	Summary of Changes	Effective Date
1	YY-XXX	New Document	dd-MMM-yyyy

DRAFT

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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 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

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Appendix A – Characteristics Related to Safety

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

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 combination products, 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.

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Appendix A – Characteristics Related to Safety

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.

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, 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

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Appendix A – Characteristics Related to Safety

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.

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

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Appendix A – Characteristics Related to Safety

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.

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.

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Appendix A – Characteristics Related to Safety

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 60601-4-1 for 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.

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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

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