'Risk Management' Refer to / taken from Ensuring Compliance: Navigating the EU MDR for Drug-Device Combination Products

This item addresses Risk Management

A. QMS Requirements

1. EU Requirements

EU medicinal product Directive **2001/83/EC** has the requirements for Single Integral DDC to comply with **GSPR Annex I of MDR 2017/745** (Article 117). The requirements for risk management are in Section 3 of Annex I of the Regulation MDR.

2. US Requirements

- Specific to combination products, FDA is now referring to **AAMI TIR 105:2020** Combination Products Risk Management. This document mentions the integration of **ICH Q9, ISO 14971:2019, and references ISO 24971:2020**.
- In the QMSR, **per ISO 13485**, Risk Management is also mentioned under **§7.1** Planning of product realization, **§7.3.3** Design and Development (D&D inputs, **§7.3.9** Control of D&D changes and **§8.2.1** Feedback.
- In **21 CFR 820.10**, per ISO 13485, risk the **organization shall apply risk-based approach to the control of the appropriate processes** needed for the quality management system. Processes are, e.g., Outsourcing, Software (re)validation, Training, (Re)evaluation and selection of suppliers, Verification of purchased product, Process validation and Control of monitoring and measuring equipment. Per QMSR, corrective / preventive actions shall be proportionate to the effects of the of the nonconformities encountered / potential problems.

Similarities and Differences
Similarities:
EU MDR2017/745, ICHQ10 and 21 CFR 820 require ongoing risk management (based on ISO 14971 for Medical Device and ICHQ9 for Medicinal Products) that spans the product quality throughout lifecycle. To satisfy those requirements, risk management must be integrated into new product development, design change, manufacturing, CAPA, purchasing controls and post market surveillance.

Differences
EU MDR has specific requirements defined in Annex I as part of the regulation.

The preferred steps you can take to address these differences
Document in the risk management procedure that:

1) Devices must be designed and manufactured to ensure safety and performance under normal conditions of use. **Risks must be reduced as far as possible** without adversely affecting the benefit-risk ratio.
2) Establish, implement, document, and maintain a **risk management system**. This system should be a continuous iterative process throughout the entire lifecycle of the device.
3) A **risk management plan** must be established and documented for each device. This includes identifying and analyzing known and foreseeable hazards, estimating and evaluating associated risks, and implementing measures to control these risks.
4) Risk control measures must conform to safety principles and take into account **the generally acknowledged state of the art**
5) Risks related to **human factors** must be addressed, ensuring that the device remains safe and effective throughout its lifecycle
6) All foreseeable residual **risks must be outweighed by the benefits** of using the device.

Note: AAMI TIR105:2020 Risk management guidance for combination products, provides recommendations for identifying and proactively avoiding risks to patients and users throughout the life cycle of combination products, integrating ICH Q9 and ISO 14971 risk management requirements.

B. Background of Risk Management

Risk management is essential for protecting users, ensuring regulatory compliance, maintaining quality and building trust in the marketplace. It's a critical component of any effective quality management system.

(Text from Section 3 Quality Management Systems (QMS) from an MDR Perspective - Subsection 2 Risk Management)

- Risk Management: The QMS must include documented processes for risk management in product realization (see item Product Realization), consistent with the risk class of the device.
- Standards
  Risk management for medical devices is primarily guided by ISO 14971:2019. This standard provides a structured methodology for managing risk throughout the lifecycle of medical devices1. It is complemented by ISO/TR

24971:2020, which offers detailed guidance on the application of ISO 14971. Note: AAMI TIR105:2020 Risk management guidance for combination products, provides recommendations for identifying and proactively avoiding risks to patients and users throughout the life cycle of combination products, integrating ICH Q9 and ISO 14971 risk management requirements.

- Design risk management and usability testing

  Risk management and usability testing are paramount in the success of a drug-device combination product, beginning in the early stages of product planning and development and being completed during the validation of the device design (§7.3 of ISO 13485:2016) or even continued throughout product realization (§7.1 of ISO 13485:2016).

  A risk analysis is defined to include the identification of potential hazards, determination of the risks of those hazards, and reduction of the risks to an acceptable level without introducing new risk factors.

  An initial design risk assessment should take place in the planning phase of a new product or product subject to revision and evolve during the design process in order to minimize risk by inherently safe design principles. By employing risk analysis throughout design and development, the device manufacturer benefits from lower costs of development / production and reduced costs of a product recall. The end user will receive a safer product.

  Note: in the EU, risk should be reduced to as far as possible (AFAP). It is good practice that all risk reduction measures should be employed to reduce risks AFAP even if the risk has been reduced to an acceptable level.

  The risk analysis must besides potential hazards from device and drug-device interaction failures also include potential hazards resulting from use error or misuse. It is mandatory to apply the risk management process to all phases of the device's lifecycle including the entire device manufacturing process. See Phases during a device lifetime.

  Risk reducing actions of risk management are input for the design control process and the CAPA process. Accepted standards are ISO14971 for risk management and IEC 63266 (usability engineering) and ANSI/AAMI HE75 (human factors engineering).

  Usability and human factors engineering (UE and HFE) are also intrinsic to the success of any drug-device combination product design: ease of use and

ability to operate the device correctly and effectively are design input requitements from the user's point of view (EN ISO 13485 § 7.3.3). Usability testing is not only a device validation activity (EN ISO 13485 § 7.3.6) but plays also a role in design verification testing (EN ISO 13485 § 7.3.5).

In terms of risk management, the manufacturer should perform a risk management process for addressing use-related hazards and HFE/UE approaches should be applied for this process to work effectively.

- Phases During the Device's Lifetime

The risk management process is applied throughout the entire lifecycle of a medical device, from initial concept to final decommissioning. The key phases include:

1. Risk Management Planning: Establishing the risk management plan, defining roles and responsibilities, and setting objectives.
2. Risk Identification: Identifying potential hazards associated with the device, including those related to normal use and foreseeable misuse.
3. Risk Analysis: Analyzing the identified hazards to determine their potential risks.
4. Risk Evaluation: Comparing the estimated risks against predetermined risk criteria to determine their acceptability.
5. Risk Control: Implementing measures to control identified risks, ensuring they are reduced to an acceptable level.
6. Risk Monitoring and Review: Continuously monitoring the effectiveness of risk control measures and reviewing the risk management process throughout the device's lifecycle.
7. Post-Market Surveillance: Collecting and analyzing data on the device's performance once it is on the market to identify any new risks or changes in risk profile.

C. Background on Risk-based Approach

The per ISO 13485 required risk-based approach to QMS processes is essential for ensuring that products and processes meet regulatory requirements and are safe, effective, and of high quality. This approach is a fundamental part of a robust QMS.

(Text from Section 3 Quality Management Systems (QMS) from an MDR Perspective - Subsection 1 Documented Quality Management System)

1. **As manufacturer of a drug-device combination product, the QM shall, *e.g.*:**
   - **Identify the processes needed** for the QMS and their application throughout the organization, and define their sequence and interaction.
   - **Apply risk-based approach to the control of the appropriate needed processes** by:
     - Providing resources and information needed to support these processes and to meet the QMS requirements
     - Monitoring, measure and analyse these processes
     - Implementing the review and the actions necessary to achieve planned results
   - **Determine the responsibilities** (including those of the person responsible for regulatory compliance of the device part) and scope of these processes

2. **Processes that must be addressed with a risk-based approach include:**

Document Control (gradation in document training requirements; impact assessment), Project Management (projects versus tasks; risk management to manage project risks), Quality Objectives Management & Management Review (KPIs; different means to follow-up on MR-actions), Training (training verification depends on criticality of trained process), Software Verification and Validation (software risk assessment), Customer Order Handing (customer satisfactory level determines action), Design and Development Controls (output of risk management is design and development input), Device Risk Management (design, application and process risk management), Management of Suppliers (product-risk criteria), Purchasing (classification of spend; product-risk criteria), PQ (risk-based sample size determination), Handling and Storage (limited access; limited shelf life; special storage conditions; FEFO), Maintenance and calibration (scheduling), Statistical Techniques (risk-based sample size determination), PMS, PMCF & PSU (input for risk management), Internal Audits (risk-based audit program; gradation of findings), Nonconforming Product Procedure (input for risk management process; requirements for concession), Investigation of Returned Products (risk of contamination by returned product), Customer Complaint Handling Process (timelines; reporting criteria; input for risk management process), Regulatory Reporting (incident types / gradation in reporting timelines), Corrective and Preventive Action (risk categories with associated action timelines; extension of implementation / verification target dates).