'Product Realization, Design & Development and Installation' Refer to / taken from Ensuring Compliance: Navigating the EU MDR for Drug-Device Combination Products

This item addresses Product Realization: Design & Development (ISO 13485 §7.3), Product Realization (ISO 13485 §7.5.1) and Installation (ISO §7.5.4)

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)**. Art 117 applies post-authorization to all marketing authorizations, irrespective whether they are already compliant with Annex I to Directive 2001/83/EC, point 12 of section 3.2, as amended by Article 117 MDR at the time of the initial MAA, in case of changes that may affect the safety and performance of the device part or the intended use of the device.

- However, there is no requirement to comply with **EU MDR 2017/745** Article 10 General obligations of a manufacturer:

  9 (g) product realization, including planning, design, development, production and service provision.
- Nevertheless, complying with GSPR implicitly means that the requirements for design and development of the device component and its interaction with medicinal product, should be understood and incorporated into pharma company QMS.

- MDR Annex I, Chapter II, 10.3 states: if the devices are intended to administer medicinal products they shall be designed and manufactured in such a way as to be compatible with the medicinal products concerned in accordance with the provisions and restrictions governing those medicinal products and that the performance of both the medicinal products and of the devices is maintained in accordance with their respective indications and intended use.

- ICH Q10 section 3.1.1. directly refers to ICH Q8 "Pharmaceutical development" for the product development approaches and to ICHQ9 "Quality risk management" to ensure that the product and its manufacturing process will consistently deliver the intended performance and meet the needs of patients and healthcare professionals, and regulatory authorities and internal customers' requirements. The results of exploratory and clinical development studies, while outside the scope of ICHQ8, are inputs to pharmaceutical development.

2. US Requirements

- **Under US 21 CFR §4A regulation and guidelines,** if the combination product include both device constituent and drug constituent parts, and the current good manufacturing practice operating system has been shown to comply with the drug CGMPs, the following provisions of the QMS regulation must also be shown to have been satisfied: 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §7.3 Design and development and §7.5.3 Installation activities.

B. Design and Development

Similarities and Differences
Similarities:

- Using **ICH Q10 (Pharmaceutical quality system)** and **Q8 (Pharmaceutical Development)**, industry can demonstrate an effective pharmaceutical quality system to enhance the quality and availability of medicines for both EU and US in the interest of public health.
- Moreover, both EU & US are similar with regards to GSPR (Extended Producer Responsibility (EPR) in US; a policy approach that holds producers accountable for the entire lifecycle of their products) and clinical data evaluation, which need to be embarked in the design and development of the drug device combination product.

Differences :
As previously stated, EU MDR is very specific about expectations, e.g., under Annex 1. There is currently no guidance about the level of detailed information and data to submit to Notified Body in order to obtain a satisfactory Notified Body opinion (NBOp). A NBOp is required for any new MAA from 26 May 2021 onwards.
US FDA is more prescriptive for drug constituent parts and has yet to clarify essential performance requirement expectations for the device constituent part(s).

The preferred steps you can take to address these differences:

1. To demonstrate conformity with the **Annex I of EU MDR**, ensure comprehensive documentation, especially for labeling, instructions for use and safety measures. This includes detailed information on design, materials, and safety measures to meet requirements of Annex I of EU MDR.
2. Since there is no specific guidance on the level of detailed information required, it's crucial to provide thorough and clear documentation to obtain a satisfactory Notified Body Opinion.

3. Ensure compliance with **21 CFR Part 4**, which provides a regulatory framework for combination products. This includes cGMP requirements and postmarketing safety reporting.

With regards to QMS requirement for design development. **21 CFR 820.10** Requirements for a quality management system incorporated from the **ISO 13485:2016: §7.3** Design and development provide a comprehensive stepwise approach from design input up to design transfer, including Design and development files and management of changes.

EMA/CMDh "Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations (EU) 2017/745 and (EU) 2017/746), Rev.2", June 2021) requires that, if after the granting of the marketing authorization there is a change to the design or intended purpose of the device (part), or a new device is introduced, any required declaration of conformity / EU certificate / notified body opinion should be submitted as part of the appropriate regulatory procedure to EMA/NCA.

The preferred steps you can take to address these differences:

1. Set up a documented system to manage quality that follows **ICH Q10, ICH Q8, and ISO 13485:2016**. This includes planning, controlling, and documenting all stages of product development.
2. Plan and document the design process in steps.
3. Identify possible risks early on and find ways to prevent them. This helps ensure the product is safe and effective.

C. Product realization (Manufacturing)

Similarities and Differences
Similarities
Using ICH Q10, industry can demonstrate an effective pharmaceutical quality system to enhance the quality and availability of medicines for both EU and US in the interest of public health.

Differences
There are no differences

Background of Product Realization Requirements
Product realization requirements are crucial for meeting regulatory requirements for a QMS because they **ensure that every stage of a product's life cycle** is meticulously planned, executed, and documented. This includes design, development, manufacturing, packaging, shipping, installation and maintenance.

By adhering to these requirements, companies can set and maintain quality standards, apply necessary controls, and ensure that the final product meets customer needs and regulatory standards. This not only helps in achieving regulatory compliance but also enhances the overall quality and safety of the product.

(Text from Section 5: Product Realization - Ensuring Compliance at Every Stage)

Product Realization includes processes for design and development, production and service provision, ensuring that all stages meet regulatory requirements.

Product Realization encompasses the entire lifecycle of a medical device, from its initial concept through design and development, production and finally to service provision (including installation). Each stage must adhere to stringent regulatory requirements to ensure safety, efficacy, and compliance, for both the drug and the device parts of the combination product. This Section will focus on the ISO 13485 / QMSR requirements for the device.

1) Design & Development (ISO 13485 §7.3)

Design and Development (D&D) is crucial in meeting regulatory requirements for devices because it ensures that the device is safe, effective, and meets all necessary standards before it reaches the market.

D&D consists of

- Design Planning: Establish a plan that outlines the design and development stages, including timelines, responsibilities, and resources. Do this for new designs and design changes.
- Design Inputs: Define requirements based on regulatory standards, customer needs, and risk management. This includes, amongst many others, functional, performance, usability and safety criteria.
- Design Outputs: Develop detailed specifications, drawings, and production processes that meet the design inputs. These outputs must be verifiable against the initial requirements.
- Design Review: Conduct formal reviews at various stages to ensure the design meets all inputs and requirements. This involves cross-functional teams to provide comprehensive assessments.
- Design Verification and Validation: Verify that the design outputs meet the design inputs (verification) and validate that the final product meets user needs and intended use (validation). This often includes prototype testing and clinical evaluations.

- Design Transfer: Ensure that design information is accurately translated into production specifications, including all necessary manufacturing and inspection processes.
- Design Changes: Design and development changes must be controlled.

The required design and development documentation shall be maintained in a design and development file for each medical device type or medical device family (see Definitions in ISO 13485:2016).

2) Product Realization (ISO 13485 §7.5.1)

In ISO 13485, product realization refers to the sequence of processes and activities required to bring a medical device from its initial design and development stages through to its production and delivery to the end user. It encompasses a comprehensive set of requirements and procedures to ensure that the product meets regulatory standards and customer expectation.

- Process Validation: Establish and validate manufacturing processes to ensure consistent production quality. This includes process control, monitoring, and documentation.
- Production Planning: Develop production plans that align with demand forecasts and resource availability. This ensures timely and efficient manufacturing.
- Manufacturing Control: Implement controls to monitor and maintain product quality during production. This includes in-process inspections, quality checks, and equipment maintenance.
- Supplier Management: Ensure that all suppliers and subcontractors meet regulatory and quality requirements. This involves evaluating, selecting and monitoring suppliers. Depending on the criticality of the product or service provided by the supplier, this may include regularly auditing of the supplier.
- Identification and Traceability: Identify and maintain traceability of materials and components throughout the production process. Implement a tracking system to also monitor the movement of finished product from warehouse to the user. This may involve .suppliers of distribution services or distributors. Identification and traceability include recording dates, quantities, and locations to the to ensure accountability and compliance with regulatory requirements. Under the MDR, devices should bear a UDI that complies with the MDR's UDI System (referred to in Article 27 of the MDR and with the registration obligations referred to in Articles 29 and 31 of said Regulation).

3) Installation (ISO §7.5.4)

Installation refers to the process of setting up and putting into service a medical device at the user's site. This includes all activities necessary to ensure that the device is correctly installed, calibrated, and functioning as intended before it is used for its intended purpose.

- Installation and Commissioning: Provide clear instructions for the installation and commissioning of the device, ensuring it operates as intended in the user environment.
- Training and Support: Offer training programs for users and service personnel to ensure safe and effective use of the device. Provide ongoing technical support and resources.
- Maintenance and Servicing: Establish procedures for regular maintenance and servicing to ensure the device continues to meet safety and performance standards. This includes scheduling, documentation, and tracking of maintenance activities.
- Feedback and Improvement: Collect and analyze feedback from users to identify areas for improvement. Use this data to enhance product design, production processes, and service provision.
- By carefully overseeing each phase of product realization, organizations can ensure that their medical devices, as components of drug-device combination products, consistently comply with regulatory standards and provide safe, effective performance for users.