The following pages contain an amendment by Combination Products Device Specialists. This amendment focuses on Single Integral Drug-Device Combination (DDC) products and Single Entity Combination products (non-CE marked devices) as described in the EFPIA's document, "EU-US Quality Management System (QMS) Requirements Comparison for Drug-Device Combination Products and Medicinal Products Co-packaged with Medical Devices." Published on August 23, 2022, by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the document provides an industry perspective on the similarities and differences between EU and US Quality Management System requirements for Drug-Device Combination Products and Medicinal Products co-packaged with medical devices. This comparison is based on the respective regulatory pathways of the EU and the US., i.e.:

- For Europe (EU):
  - EU medicinal product Directive 2001/83/EC and the related Pharmaceuticals Quality System requirements, as set forth in Eudralex Vol. 4 Ch. I
  - European Medical Device Regulations MDR 2017/745
  - EMA Guideline on quality requirements for medicinal products used with medical devices (EMA/CHMP/QWP/BWP/259165/2019), EMA Questions & Answers (Rev 2 - June 2021) on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)).
- For US:
  - US 21 CFR PART 3.2 Product Jurisdiction - Definition,
  - 21 CFR PART 4 Regulation of Combinations product,
  - 21 CFR PART 862-892 Devices Regulations,
  - 21 CFR PART 820 Quality System Regulation.
- For both EU and US: ICH Guidelines Q8 – Pharmaceutical development, Q9 - Quality risk management and Q10 – Pharmaceutical quality system.

With the mandatory revision of 21 CFR 820 effective February 2, 2026 (transitioning QSR to QMSR based on ISO 13485:2016), we have amended the EFPIA document. This revised document compares the quality management system requirements for Drug-Device Combination (DDC) products. It serves as a tool for industry and regulators to identify and compare the applicable regulatory requirements.

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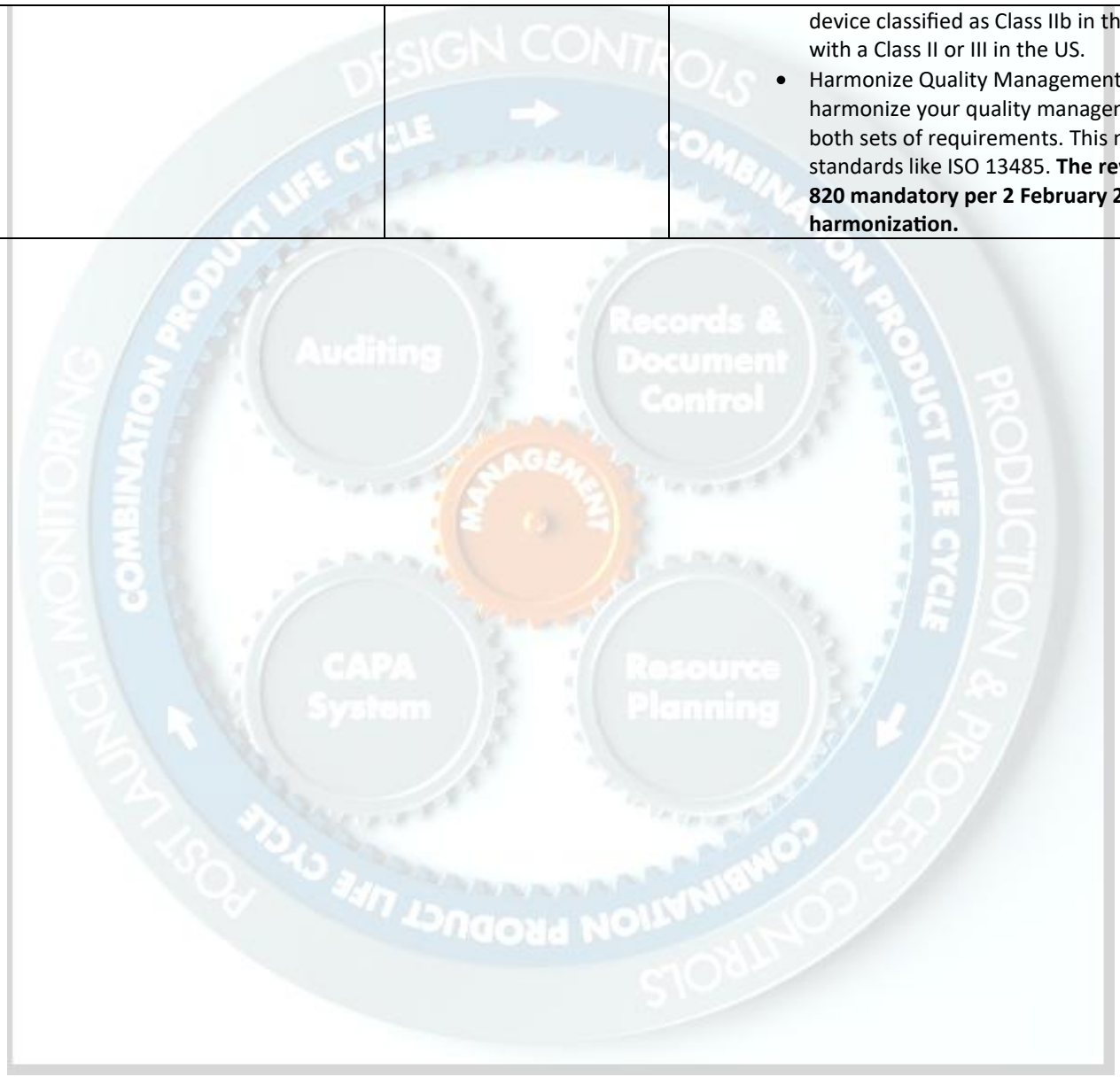
January, 2025

EU-US QMSR comparison – Single Integral Drug-Device / Single Entity Combination products (non-CE-marked device)				
QMS - Streamlined process for DDC		**EU Requirements**	**US Requirements mandatory Febr. 2, 2026**	**Similarities or Differences / The preferred step you can take to address these differences**
Key QMS Chapter	**QMS chapter features**			
General ISO 13485 §3 (Terms & Definitions) ISO 13485 §4 (Quality Management System) ISO 9000 §3 (Terms & Definitions)	DDC Product definition	***EU MDR 2017/745**, a medical device (part) that falls under the second subparagraph of Article 1 (8) and Article 1 (9)* ***EMA Guideline on Quality Requirements for Medicinal Products used with a Medical Device*** (EMA/CHMP/QWP/BWP/259165/2019, Section 1. Introduction, *under "**Integral**" configuration):* *"Single Integral: 2. Devices intended to administer a medicinal product, where the device and the medicinal product are placed on the market in such a way that they form a single integral product intended exclusively for use in the given combination and which is not reusable (second sub-paragraph of Article 1(9)).Typically, these devices have measuring or delivery functions."*	*US 21 CFR 3.2(e): -Single entity	**Similarities:** Definitions are similar, in the way that both refer to DDC that are produced to form a single integral product, placed as such on the market, and intended exclusively for use in the given combination. **Differences:** There are some regulatory differences: – European regulation (MDR 2017/745) states that DDC with medicinal product being the principal mode of action falls under medicinal product directives 2001/83/EC. The Annex I of this Directive has been revised to include the requirements of Article 117 (see note) of MDR 2017/745 about the requirement to comply with GSPR of MDR 2017/745 (Annex I) only. • European regulations do also make distinction between integral and single integral, the latest referring to single use. • For US, Single entity means *a product composed of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.* Note: Article 117 does not apply in the case of combined advanced therapy medicinal products as defined under Article 2(1)(d) of Regulation (EC) No 1394/2007. ➢ **The preferred step** you can take to address these differences: Develop a Compliance Plan: Create a detailed plan that outlines how you will meet the requirements of both regulatory frameworks. This may involve setting up separate quality management systems or, preferably, finding ways to harmonize them. **The mandatory 2 February 2026 revision of 21 CFR Part 820 facilitates QMS-harmonization.**

QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	**QMS chapter features**			
General ISO 13485 §3 (Terms & Definitions) ISO 13485 §4 (Quality Management System) ISO 9000 §3 (Terms & Definitions)	DDC classification (As per device regulation)	*__EMA Questions & Answers (June 2021) on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)__ – Question & Answer 2.3 "*How will the MDR and in particular Article 117 impact marketing authorization applications?*" *EU MDR 2017/745 – Article 51 & Annex VIII Classification rules	***Classification** via description and intended use and matching definition in **21 CFR 862-892**	Please note that in EU classifications of the device part applies indirectly: There are mentioned for Single Integral DDC products in EMA Q&A (Rev. June 2021). EMA Guideline on DDC refers to this Q&A document in its section 5.4 Module 3.2.R., Regional Information, Medical Device, specifying therefore that in accordance with Article 117 of the MDR, all applications for an integral medicinal product should include evidence of the conformity of the device (part) with the relevant GSPRs set out in Annex I of Regulation (EU) 2017/745. **Similarities:** Device classification in the European regulation (MDR 2017/745) is similar to that of the US Quality Management System Regulation (QMSR) as both processes are based on risk to user and patients **Differences:** The classifications are also different between EU and US: – EU MDR divided Device into four classes: I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks. There are also three sub-classes under class I: Class Is: It's a class I product that is delivered sterile Class Im: It's a product with a measuring function Class Ir: New sub-class for products that are reprocessed. – In the U.S., medical devices are in 3 classes either Class I, Class II, or Class III. The FDA CDRH classification is based primarily on risk the medical device poses. ➢ **The preferred steps** you can take to address these differences: • Map Out Classifications: Create a detailed mapping of your products under both EU MDR and US FDA classifications. This will help you understand how a

					device classified as Class IIb in the EU, for instance, aligns with a Class II or III in the US. • Harmonize Quality Management Systems: Aim to harmonize your quality management system to meet both sets of requirements. This might involve adopting standards like ISO 13485. **The revision of the 21 CFR Part 820 mandatory per 2 February 2026 facilitates QMS-harmonization.**



QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	**QMS chapter features**			
General ISO 13485 §3 (Terms & Definitions) ISO 13485 §4 (Quality Management System) ISO 9000 §3 (Terms & Definitions)	QMS framework	***EMA Guideline on Quality Requirements** EMA has stated clearly in its section 3 "Legal references, Application of Standards and Guidelines", that all other relevant directives and regulations forming part of the pharmaceutical *acquis*, the European Pharmacopeia and all relevant European Commission, ICH and CHMP guidelines, Q&A documents and other documents as linked to, or published on, the European Medicines Agency (EMA) website should be read in conjunction with Directives and Regulations already cited in this QMS comparison document. Therefore ICH Q10 " *Pharmaceutical Quality System*" should be considered for developing and marketing single integral DDC in Europe. How to adapt it to DDC is not described yet.	***21 CFR PART 4 Regulation of Combinations product part A** *** 21 CFR Part 210 and 211 (drug) and 21 CFR Part 820 (device) cGMPs** *** 21 CFR Part 600 cGMPS for Biologics**	**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. In EU, single integral DDC are regulated under the medicinal product Directive 2001/83/EC and its QMS framework set forth in the EU GMP Guide, which is aligned on ICH Q10 Guideline. In US, 21 CFR Part 4 clarifies the application of current good manufacturing practice regulations to combination products, and provides a regulatory framework for designing and implementing the current good manufacturing practice operating system at facilities that manufacture co-packaged or single-entity combination products. **Differences:** In EU, without clarifying how to adapt the Pharmaceutical Quality System (PQS), the Pharma Company should produce evidence to demonstrate compliance with General Safety & Performance Requirements Annex I EU MDR 2017/745 (GSPR). All these activities and data remain under the oversight of EMA or national authority competent for medicinal products, and therefore cGMP rules do apply. This is also true for other key QMS elements not included in MDR Annex I, such as clinical data and evaluation requirements, post-market surveillance requirements and assessment of device part change type. In US the drug combination product needs compliance to 21 CFR Part 210 and 211 (drug) and 21 CFR Part 820 (device) cGMPs. In addition, for a combination product that includes a biological product, the manufacturer must demonstrate compliance with the cGMP requirements specific to biological products in parts 600 through 680 (21 CFR parts 600 through 680). 21 CFR part 4 greatly clarified which elements of all applicable regulations must be included for drug-device single entity. Most of the Pharma companies chose the integrated approach, i.e., PQS plus additional chapters from 21CFR Part 820. ➢ **The preferred steps** you can take to address these differences:

					➢ Harmonize PQS: Align your PQS to address both EU and US requirements, ensuring a unified approach to quality management. ➢ Regular Audits: Conduct regular audits to ensure that both systems are compliant with the respective regulations. ➢ Maintain clear and comprehensive documentation to demonstrate compliance with both regulatory frameworks. This includes technical files, risk management reports, and clinical evaluations. ➢ Reporting: Develop standardized reporting procedures to streamline compliance efforts across both regions.

QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	**QMS chapter features**			
Management Responsibilities ISO 13485 §5 (Management responsibility)	***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). There is therefore no requirement to comply with **EU MDR 2017/745** Article 10 General obligations of a manufacturer (c) responsibility of the management. However, complying with ICH Q10, section 2 "*Management Responsibility*", ensures that the responsibilities of the (*Senior*) management should be understood and incorporated into pharma company QMS. There are specific requirements in medicinal product directives related to Qualified Person (SP) responsibilities (Article 51 of Directive 2011/83/EC), including Annex 16 of EU GMP Guide for batch certification		*** 21 CFR part 4** **Under 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §5 Management responsibility** ensures executive commitment to quality.	**Similarities:** The management responsibilities are quite similar in EU and US thanks to the alignment on ICH Q10 (Section 2 "*Management Responsibility*"). **Differences:** In the US, 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §5.5.2 Management representative provides more detail on specific requirements for Management Representative. Under 21 CFR Part 4, if compliance to cGMPs for drug has been demonstrated, then all the Quality Management System requirements for Management Responsibility must be shown to be also satisfied. In Europe, in addition to Management Responsibility, QP batch certification and QP responsibilities for medicinal product (Article 51 of Directive 2001/83 and EU Annex 16) should be followed. ➢ **Preferred steps:** US manufacturers of Single Integral DDC should document and implement the requirements that a Qualified Person (QP) by review and approval certifies the batch release of each batch of medicinal products for human or veterinary use before it can be released to the market or exported outside the EU. The QP takes the responsibility that the quality, safety, and efficacy of these products are ensured and that the products comply with the regulatory requirements which apply to them. This ensuring also encompasses that the products comply with the EU GMP guidelines, including meeting the standards for manufacturing, testing, and quality control.

QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	**QMS chapter features**			
Management commitment (ISO 13485 §5.1) Resource management ISO 13485 §6 (Resource management) Purchasing controls ISO 13485 §7.4 (Purchasing)	***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). There is therefore no requirement to comply with **EU MDR 2017/745** Article 10 General obligations of a manufacturer: (d) resource management, including selection and control of supplier and subcontractors. However, ICH Q10, section 2.7 "*Management of Outsourced Activities and Purchased Materials*" have requirements that apply to Single Integral DDC product.		*** 21 CFR Part 4** **21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §5 Management responsibilities** **21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §6.2 Human resources** describes the requirements for personnel **721 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §7.4 Purchasing** describes the purchasing controls	**Similarities** EU MDR2017/745, ICHQ10 and 21 CFR 820 have similar requirements for Resource management and Purchasing controls. **Differences** Under 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §6.2 Human resources, ensure that personnel are made aware of the relevance and importance of their activities and how they contribute to the achievement of the quality objectives. ➢ **The preferred step** to address this difference is to include training relevant to device defects.

QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	**QMS chapter features**			
Corrective and preventive action ISO 13485 §8.5.2,§8.5.3 (Corrective) and Preventive action ISO 13485 §7.3.6, §7.3.7, §7.5.6, §8.1, §8.4 (Application of statistical techniques	***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). There is therefore no requirement to comply with **EU MDR 2017/745** Article 10 General obligations of a manufacturer: (l) management of corrective and preventive actions and verification of their effectiveness. However, ICH Q10, section 3.2.2 "*Corrective and Preventive Action (CAPA) System*" have requirements that apply to Single Integral DDC product.		***Under US 21 CFR §4A regulation and guidelines**, if the combination product include a device constituent part and a drug constituent part, 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: §8.5.2 Corrective action and §8.5.3 Corrective action	**Similarities:** No significant difference when considering the 21 CFR 820.10 as to CAPA and ICH Q10. ICH Guideline and US requirements for QMS are similar in procedural requirements and records for Corrective and Preventive action. **Differences:** Small differences lie in the following points: – The use of statistical analysis: ○ 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §7.3.6 D&D verification, §7.3.7 D&D validation, §7.5.6 Validation of processes for production and service provision, §8 (Measurement, analysis and improvement) - §8.1 General and §8.4 Analysis of data, all underline the need to use statistical methodology. ○ ICHQ10 underlines the need to use statistical analysis to understand product or process variability only. ➢ **The preferred steps** you can take to address these differences: Integrate both approaches by using statistical methods to meet the broader requirements of 21 CFR 820.10 various paragraphs incorporated from Requirements for a quality management system from the ISO 13485:2016 (including design and development verification, validation, and process control) while also focusing on understanding variability as emphasized by ICH Q10. – The quality system: ○ US21 CFR 810.10 §8.5.2 Corrective action and §8.5.3 Preventive action underline the need to investigate root

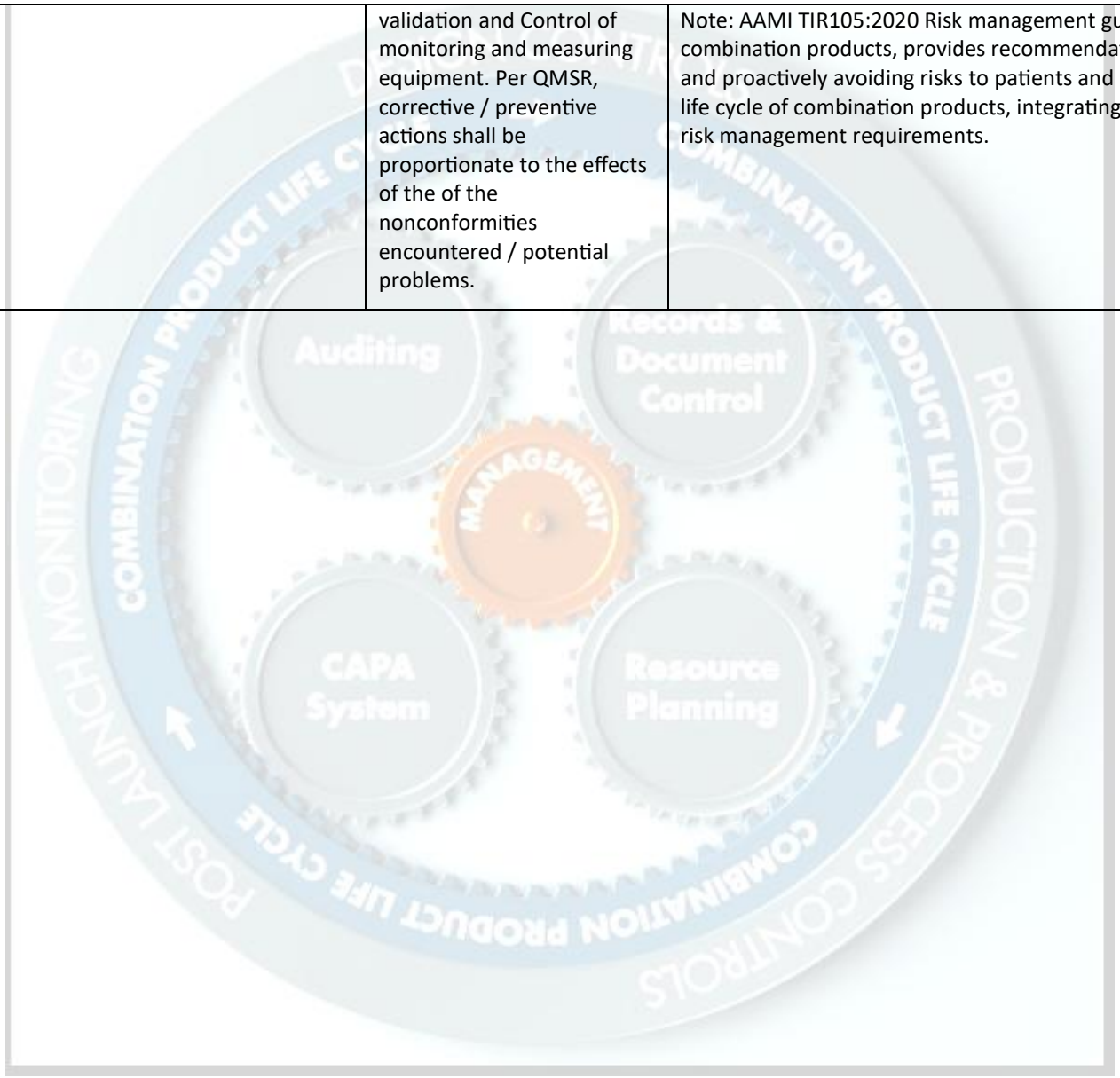
				cause that might affect product, manufacturing process but also the quality system applicable to medical devices. ○ ICH Q10 stays more general when requiring that a structured approach should be used to determine the root cause and refers explicitly to product and process impacts. ➢ **The preferred steps** you can take to address these differences: Implement a Structured Approach by (1) using root cause analysis (RCA) tools such as the 5 Whys, Fishbone Diagram, Pareto Chart, Fault Tree Analysis and Failure Mode and Effects Analysis (FMEA) and (2) ensuring that the RCA process is thorough and systematic, addressing all potential areas of impact. – 21 CFR Part 820.10 §8.5.2 Corrective action and §8.5.2 Corrective action imply that the CAPA information are disseminated to all those who are directly responsible for assuring the product quality. Furthermore, pertinent information related to CAPA is input for management review. – ICH Q10 specifies that the level of effort, formality and documentation of the investigation should be commensurate to the risk as per ICH Q9. ➢ **The preferred step** you can take to address these differences: Develop or update the SOPs to reflect the integration of both ISO 13485 CAPA processes and ICH Q10. Include specific sections that address the communication and documentation requirements of 21 CFR 820.10 and the risk-based approach of ICH Q10.

QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	**QMS chapter features**			
Product realization design and development Product realization ISO 13485 §7.1 (Product realization) ISO 13485 (§7.3 (Design and development) ISO 13485 (§7.5.3 (Installation)	**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		***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.	A) Design and Development **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

	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.		NBOp; 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. B) Product realization (Manufacturing) **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.

QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	**QMS chapter features**			
Risk management ISO 13485 §7.1 (Planning of product realization) ISO 13485 §7.3.3 (Design and development inputs) ISO 13485 §7.3.9 (Control of design and development changes) ISO 13485 § 8.2.1 (Feedback)		***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.	*****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 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	**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.

			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.	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.



QMS - Streamlined process for DDC		EU Requirements	US Requirements mandatory Febr. 2, 2026	Similarities or Differences / The preferred step you can take to address these differences
Key QMS Chapter	QMS chapter features			
Measurement improvement and analysis ISO 13485 §8 (Measurement, analysis and improvement) ISO 13485 §7.4.3 (Verification purchased product) ISO 13485 §7.3.6, §7.3.7, §7.5.6, §8.1, §8.4 (application of statistical techniques) ISO 13485 §8.2.2 (complaint records ISO 13485 §8.2.4 (Internal audits)	***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). There is therefore no requirement to comply with EU MDR 2017/745 Article 10 General obligations of a manufacturer: 9 (m) processes for monitoring and measurement of output, data analysis and product improvement.		***21 CFR Part 4A** ***Under 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016:** **§8.2.5 Monitoring and measurement of Processes;** **§7.4.3 Verification of purchased product;** **Application of statistical techniques for Design and development verification (§7.3.6) and validation (§7.3.7), Validation of processes for production and service provision (§7.5.6), demonstrate product conformity, ensure QMS conformity and maintain the effectiveness of the quality management system (§8.1) and analysis of data (§8.4);** **21 CFR 820.35 Control of records - (a) Records of complaints;** **§8.2.4 Internal audit.**	**Similarities:** EU MDR2017/745, ICHQ10 and 21 CFR have similar requirements for monitoring and measurement of process and product from both internal and external sources

Post market surveillance, Vigilance and handling communication with competent authorities ISO 13485 § 8.2.1 (Feedback) ISO 13485 §8.2.3 (Reporting to regulatory authorities)	* **The regulatory pathway determines the reporting procedure**. Since SI DDCs are registered as medicinal products, Pharma Company should report to EMA or Competent Authority (CA) only. There is therefore no requirement to comply with EU MDR 2017/745 Article 10 General obligations of a manufacturer, section 9: - (*i*) *setting-up, implementation and maintenance of a post-market surveillance system, in accordance with Article 83;* - *(j) handling communication with competent authorities, notified bodies, other economic operators, customers and/or other stakeholders;* - *(k) processes for reporting of serious incidents and field safety corrective actions in the context of vigilance;* - *(m) processes for monitoring and measurement of output, data analysis and product improvement.* A) Vigilance reporting EU MDR Articles 87 & 88 do not apply to Pharma Company manufacturing and marketing single integral DDCs. **Medicinal Products reporting rules in EU are as per following;** The reporting concerns either: • Adverse reactions/adverse events, where Pharmacovigilance rules apply. in line with Directive 2010/84/EU, Regulation (EU) No 1235/2010, Commission Implementing Regulation (EU) No 520/2012, Regulation (EU) No 1027/2012 and Directive 2012/26/EU. • Quality defect: EMA has a dedicated system for reporting quality defects (including suspected quality defect) for centrally approved products	***21 CFR 4 subpart B PMS reporting for Combination Products** ***Under 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §8.5.2 (corrective action and (Preventive action)** ***21 CFR Part 803** Under 21 CFR §4B regulation and guidelines, there is an intent to ensure comprehensive reporting consistent with the underlying requirements called out in the rule associated with each of the constituent parts. Reporting is driven by Combination Product Application Type (i.e., NDA/ANDA, BLA or Device application) and Applicant Type (Combination Product Applicant or individual constituent-part applicant). Combination products submitted under NDA/ANDA report through CDER. Combination products submitted under BLA report through CBER. Device Applications are reported through CDRH. (Field Alert	**Similarities:** Both EU & US requires an adequate pharmacovigilance system for the medicinal product to comply with obligations on the recording or reporting of suspected adverse reactions, and with post-marketing surveillance requirements regarding the medicinal product. **Differences:** A) Vigilance In the US post marketing safety reporting is driven by application type and applicant type. Application-based reporting is supplemented with specific reporting elements for each of the other constituent part(s) of the combination product. Same-similar reporting requirements also apply, whereby if a reportable event occurs on a same-or-similar constituent part of a combination product, there is an expectation that such event be reported in the US against the US-marketed product. In the EU, reporting to the competent authority for medicinal product is sufficient (CA / EMA only). There is however no clear recommendation of reporting of device complaints with potential impact of drug delivery between National Competent Authority where the NB is located and the Reference Authority of the medicinal product. ➢ **The preferred steps** you can take to address these differences: For the US, implement a documented procedure for medical device reporting per 21 CFR Part 803 and for submission of reports of corrections and removals per 21 CFR Part 806; For the EU, implement a documented procedure for a medical devices vigilance system and also to issue advisory notices. B) Post Market Surveillance

	https://www.ema.europa.eu/en/human-regulatory/post-authorisation/compliance/quality-defects-recalls/reporting-quality-defect-ema B) Post-marketing surveillance From a QMS perspective, **an annual market surveillance** for the device component, **as per MDR Annex II which refers to article 83-86, is not required.** Directives 2010/84/EU amending as regards with pharmacovigilance 2001/83/EC, should therefore be considered. The authors recommend industry to adapt its PQS system so that post production activities are monitored and feed-in the CAPA system for continuous improvement.	Reports (FARs) and Biologic Product Deviation Reports (BPDRs) do not follow this application-based approach.) Combination products submitted under NDAs/ANDAs are subject to the safety reporting requirements described in 21 CFR Part 314. Combination products submitted under BLAs are subject to the safety reporting requirements described in 21 CFR Parts 600 and 606. Device Applications are subject to the safety reporting requirements described in 21 CFR Parts 803 and 806. This foundational reporting is supplemented with specific reporting elements for each of the other constituent part(s) of the combination product Same-similar reporting requirements also apply (see 21 CFR 803.50).	In contrast to the US (21 CFR 4 subpart B), in the EU, there is no requirement to comply with the EU MDR 2017/745 Articles 83-86 requirements for post marketing surveillance of the device component of a Single Integral DDC product that is not CE marked.