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EU-US Quality Management System (QMS) Requirements Comparison for Drug-Device Combination Products and Medicinal Products Co-packaged with Medical Devices

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An Industry perspective on similarities and differences between EU and US Quality Management System requirements for Drug Device Combination Products and Medicinal Products Co-packaged with Medical Devices, resulting from their respective regulatory pathways, 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

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Executive Summary

This document reflects on similarities and differences between quality management system requirements for „Drug Device Combination (DDC) products," i.e. single-integral drug device combination product and medicinal product co-packaged with medical device, when the drug product has the primary mode of action, and therefore being registered as medicinal products under EU[1] and US regulations. This is intended to be a tool to help industry and regulators to identify and compare the applicable combination products regulatory requirements for EU versus US regulations. From a QMS perspective, this comparison is valid for Advanced Therapy Medicinal Products (ATMP) DDCs[2] as well.

We conclude that:

1) Quality System expectations for medicinal products used with a medical device are, for the most part, similar under EU and US regulations, and may be addressed through one Quality Management System in a company. Where key differences in the regulations exist, these need to be reconciled in the company QMS. For instance, the concepts of pharmaceutical development set forth in ICH Q8, adopted by EMA in 2006, and Design Controls, as required by US regulations, are close to each other. However the deliverables are different.

2) The Mutual Recognition Agreement (MRA) approved between EU and US applies to both single integral (Single Entity single use AND reusable) and co-packaged with a medical device, even if Medical Devices are not included in the scope of the MRA. In the US, 21 CFR part 4 greatly clarified which elements of all applicable regulations must be included for drug-device combination. Most of the Pharma companies chose the integrated approach, i.e., Pharmaceutical Quality System (PQS) plus additional chapters from 21CFR Part 820. To facilitate mutual recognition, CDER/CBER will look at some medical device QMS requirements to close the gaps relative to the device called-out provisions (See Tables I and II, and CFR Part 4). EFPIA advocates for recognized application of EU-US MRA, confirming therefore the oversight of EMA and National Competent Authorities in Europe on medicinal products when used with a medical device, from both inspection and regulatory activities perspective.

To support these conclusions, this document provides a comparison on quality system requirements from a Pharma Industry perspective, addressing both the requirements for the Device constituent part and the Device when combined with the Drug product, as described:

a) In pertinent sections of Regulation (EU) 2017/745 on Medical Devices (MDR), US-FDA 21 CFR part 4 & 21 CFR Part 820;

b) In the pharmaceutical quality system (PQS) requirements set forth in ICH Q8, 9 & 10, or pertinent quality requirements set forth by EMA in its Guideline on quality requirements for medicinal products when used with a medical device.

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[1] EU MDR 2017/745 – Articles 1(8) & (9), and , EMA Guideline on quality documentation for medicinal products when used with a medical device.

[2] Co-packaged ATMPs with medical devices, and devices used as container closure for ATMPS are in the scope of EMA Guideline on quality documentation for medicinal products when used with a medical device.

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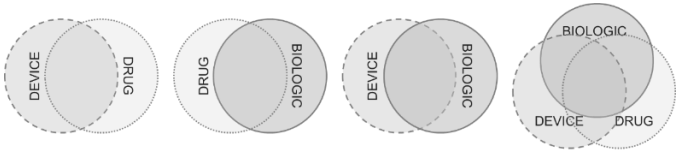
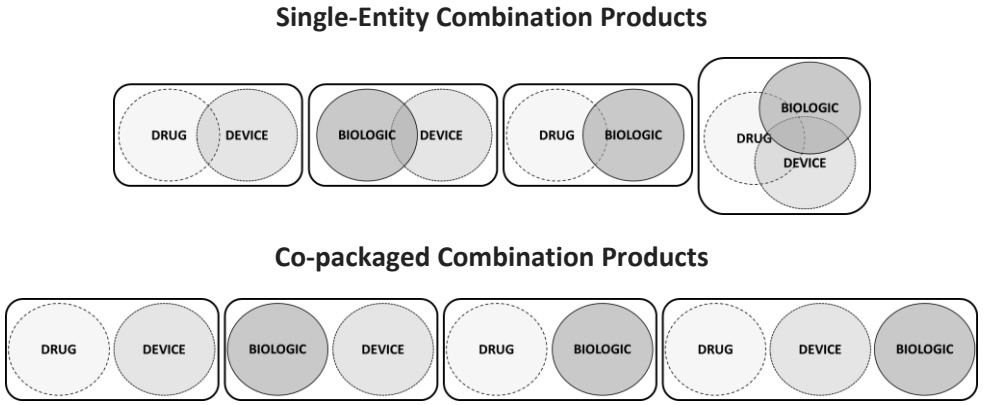
1. Introduction

The term „combination product" is used across multiple regions around the globe, however the interpretation of these words varies. In the United States, FDA formally defines a combination product under 21 CFR §3.2(e) as a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic. Combination products are then further categorized as either single entity, co-packaged or cross-labeled combination products (**Figure 1**, used with permission from Combination Products Consulting Services, LLC)

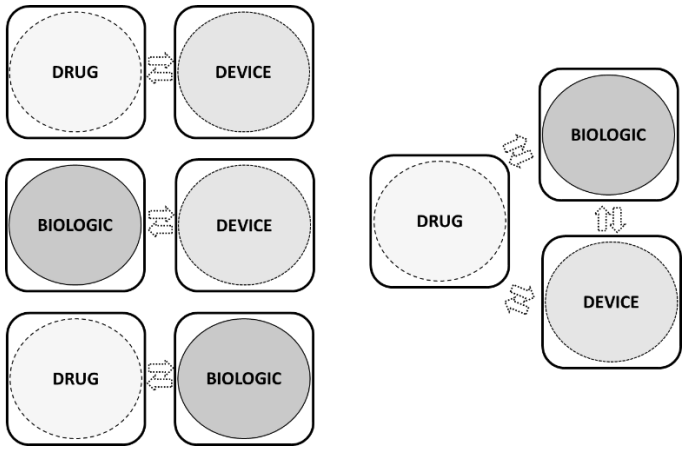
Figure 1: „Combination Products" under US FDA 21 CFR §3.2(e) (Figure used with permission. ©2021 Combination Products Consulting Services LLC. All Rights Reserved.)



Categories*:



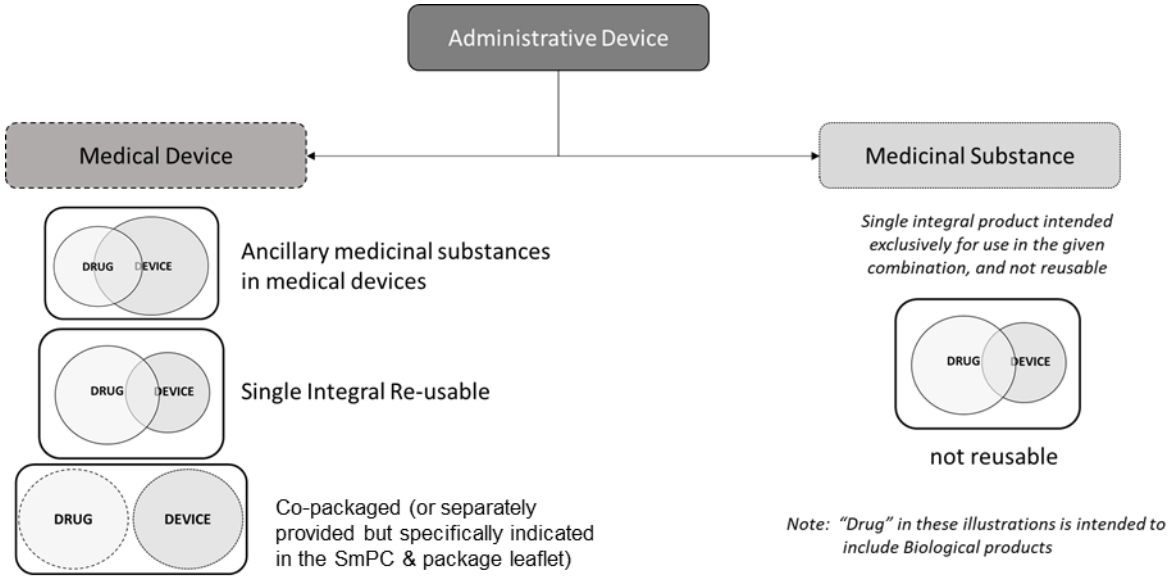
Cross-labeled Combination Products



Under EU MDR there is not a formal legal definition for the term „Combination product". The interpretation guidance *MDCG 2022-5 "Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices*" describes the regulatory pathways for different combination of medical devices and medicinal products without introducing the definition of "Combination product". EMA "*Guideline on quality requirements for medicinal products used with medical devices* (EMA/CHMP/QWP/BWP/259165/2019)", uses the terminology of medicinal product „Integral", "Co-packaged" or "Referenced" medical device: *A medicinal product(s) with device component necessary for administration, correct dosing or use of the drug product that is (are) either single integral and not re-usable, or non-integral (Co-packaged or separately provided but specifically indicated in the SmPC & package leaflet).*

In EU, while a medicinal product co-packaged or referenced with a CE marked medical device, is registered as a medicinal product, the device constituent should comply with the requirements as laid down by the applicable medical device legal framework described in EU MDR 2017/745, WITHOUT prejudice to the provisions of Directive 2001/83/EC and of Regulation (EC) No 726/2004 with regard to the medicinal product (Article 1 (9), first sub-paragraph, of EU MDR 2017/745).

Figure 2: „Combination Products" under EU MDR (2017/745) Article 117 (Figure used with permission. ©2021 Combination Products Consulting Services LLC. All Rights Reserved.)



The differences between US and EU combination product definition, classification and associated expectations have partially subtle and partially obvious impacts throughout the product lifecycle, from development, premarket pathways and market authorization application review, through manufacturing and post market expectations . Regardless, the intent of the regulations is to ensure that these medical products -both in combined use, and their drug, biologic, and medical device components and constituent parts by themselves - are safe, efficacious, and usable, while efficiently navigating the associated regulatory pathway and lifecycle management expectations. This turns the focus to what is (are) the intended use(s)/ therapeutic effect of each product, and to the associated quality management system expectations that support their safety, efficacy and usability.

This comparison is broken into two parts: (1) Quality Management System (QMS) expectations for single entity/ single integral drug device combination products; and (2) QMS expectations for medicinal products co-packaged with medical device (Combined use products). For section (1) it is assumed that the Medical Device part of the single integral drug device combination product does **not** bear a CE mark on it. In case of a

single integral drug device combination product with a CE mark please take section (2) into account. Each table introduces the QMS element, highlights the specific language from EU and US regulations, and provides a comparison of similarities and differences.

2. EU-US QMS comparisons

2.1 Single Integral DDC / Single Entity Combination products (non CE marked device)

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
General	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*	***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[3] 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.* [3] 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.

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		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."		
	DDC classifica-tion (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 authorisation 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 System Regulation (QSR) 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 4 classes: I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks. There are also 3 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

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
				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.
	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	***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 manufa cturing 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.

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		adapt it to DDC is not described yet.		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.
Management Responsibili-ties	***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 820.20, 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, 21CFR 820.20 provides more detail on specific requirements for Management Representative. Under 21 CFR Part 4, if compliance to cGMPs for drug has been demonstrated, then the all the Quality 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.

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
Resource management and Purchasing controls	***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 820:20 Management Responsibilities.** **21 CFR 820:25 Personnel** **21 CFR 820:50 Purchasing Controls**	**Similarities** EU MDR2017/745, ICHQ10 and 21 CFR 820 have similar requirements for Resource management and Purchasing controls. **Differences** Under 21 CFR 820.25, personnel training requirements does specifically include training relative to device defects.

Corrective and preventive action	***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 QS regulation must also be shown to have been satisfied: 21 CFR 820:100 Corrective and Preventive Action.	**Similarities:**
				No significant difference when considering the 21 CFR 820.100 and ICH Q10. ICH Guideline and US requirements for QS 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:
				  ○ US 21 CFR 820.100 underlines the need to use statistical methodology where necessary to detect recurring problem.
				  ○ ICHQ10 underlines the need to use statistical analysis to understand product or process variability only.
				- The quality system:
				  ○ US21 CFR 810.100 underlines the need to investigate root cause that might affect product , process but also the quality system

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
				○ 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. - 21 CFR Part 820.100 is very explicit about ensuring that the CAPA information are disseminated to all those who are directly responsible for assuring the product quality, and submitting pertinent information related to CAPA 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.

Product realization design and development	**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-authorisation to all marketing authorisations, 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	***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 QS regulation must also be shown to have been satisfied: 21 CFR 820:30 Design Controls and 820:170 Installation	A) <u>Design and Development</u> **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 (EPR in US) 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). With regards to QMS requirement for design development, 21 CFR part 820.30 Design Controls provide a comprehensive stepwise approach from design input up to design transfer, including history 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 authorisation 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.

	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.		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	Similarities or Differences
Key QMS Chapter	QMS chapter features			
Risk management	***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 US , Risk Management is also mentioned briefly under Design Controls 21 CFR 820.30(g), but also multiple times throughout the pre-amble. -21CFR820.30 Design controls, and Preamble 61 Fed. Reg. at 52620, Comment 83 (Design Controls) -21CFR820.50 Purchasing controls and Preamble 61 Fed. Reg. at 52626, Comment 115 (Purchasing Controls) -21CFR 820.100 CAPA and Preamble 61 Fed. Reg. at 52633-52634, Comment 159 (CAPA)	**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. 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	Similarities or Differences
Key QMS Chapter	QMS chapter features			
Measurement improvement and analysis	***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** **21CFR820.70 Production and process controls** **820.80 Receiving, in process, and finished device acceptance** **21CFR820.250 Statistical technique** **21CFR820.198 Complaint files** **21CFR820.22 Quality 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	* **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;*		***21 CFR 4 subpart B PMS reporting for Combination Products** ***21 CFR Part 820.100 CAPA** ***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).	**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

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
	- *(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 https://www.ema.europa.eu/en/human-regulatory/post-authorisation/compliance/quality-defects-recalls/reporting-quality-defect-ema B) Post-marketing surveillance		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 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	National Competent Authority where the NB is located and the Reference Authority of the medicinal product. B) Post Market Surveillance 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.

QMS - Streamlined process for DDC		EU Requirements	US Requirements	Similarities or Differences
Key QMS Chapter	QMS chapter features			
	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.		part(s) of the combination product Same-similar reporting requirements also apply (see 21 CFR 803.50).	

2.2 Medicinal Product Co-packaged with Medical Device / Co-packaged Combination products

As illustrated in Figure 2, co-packaged medical products, medical devices with ancillary medicinal substances or single integral re-usable combination products in the EU are not considered as “Drug Device Combinations.” Rather, from regulatory pathway and cGMP perspectives, each of the constituent parts of these products is treated separately: the device constituent parts are regulated as medical devices; the drug constituent part(s) are regulated as medicinal products. Under EU MDR, there is a coordination mechanism between Notified Bodies and the Competent Authority for overall combined use product approval.

Contrast this approach to that of the US FDA under 21 CFR §4A. As depicted in Figure 1, co-packaged medical devices, medical devices with ancillary medicinal substances, or single integral re-usable combination products all indeed meet the formal 21 CFR §3.2(e) definition of “Combination Product.” The US FDA gives manufacturers two options to demonstrate compliance for such products. A manufacturer can choose to demonstrate compliance with all the regulations applicable to each constituent part (akin to EU’s approach), or a manufacturer can choose to implement a “Streamlined or integrated Approach” that entails demonstration of compliance to a “base Quality Management System” aligned to one of the constituent parts of the combination product, coupled with called out provisions for the other constituent part(s) of the combination product. The EU and US approaches are illustrated in **Figure 3 (**used with permission from Combination Products Consulting Services, LLC).

Figure 3: Co-packaged Product cGMP approach in EU (per EU MDR (2017/745) versus US (21 CFR §4A) (Figure used with permission. ©2021 Combination Products Consulting Services LLC. All Rights Reserved.)

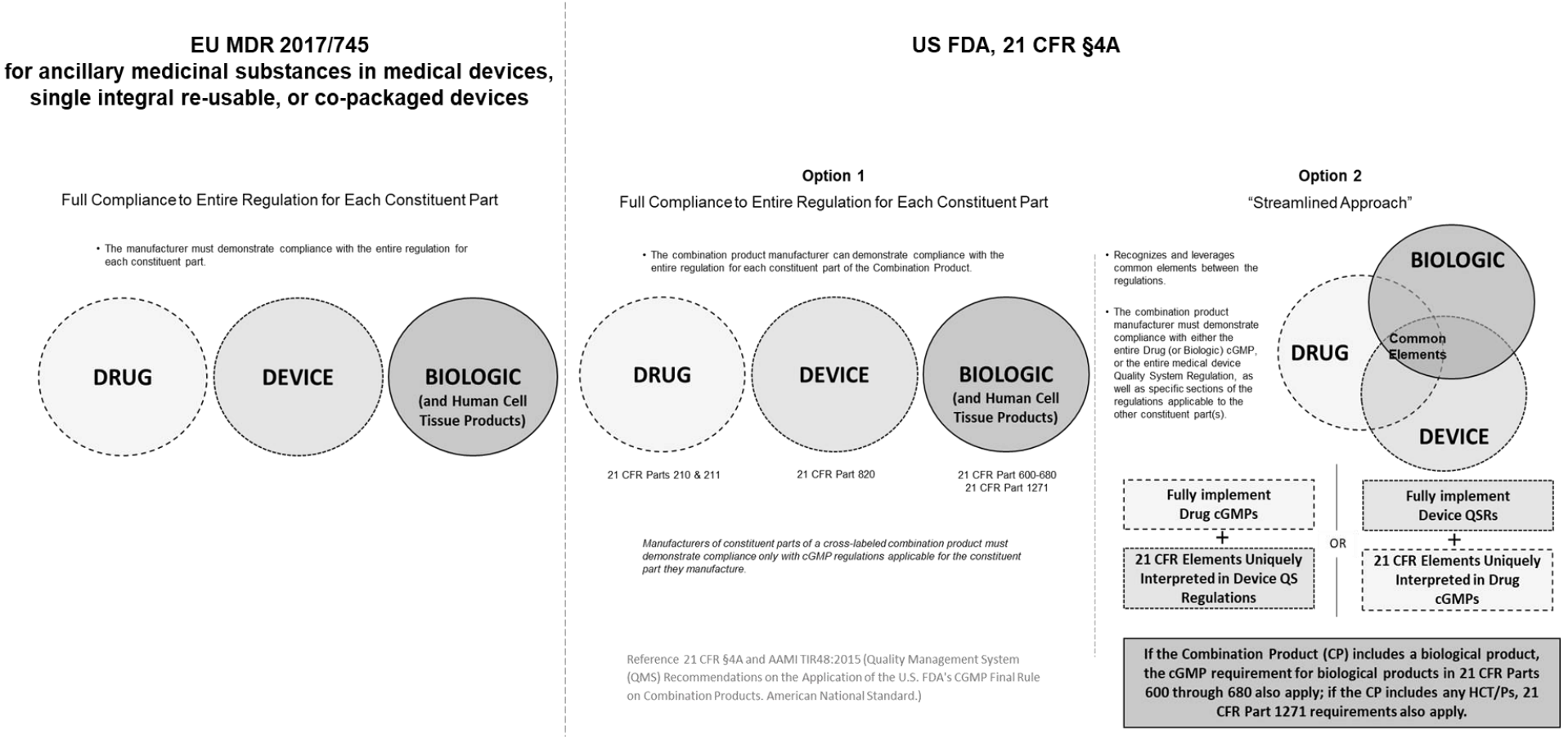
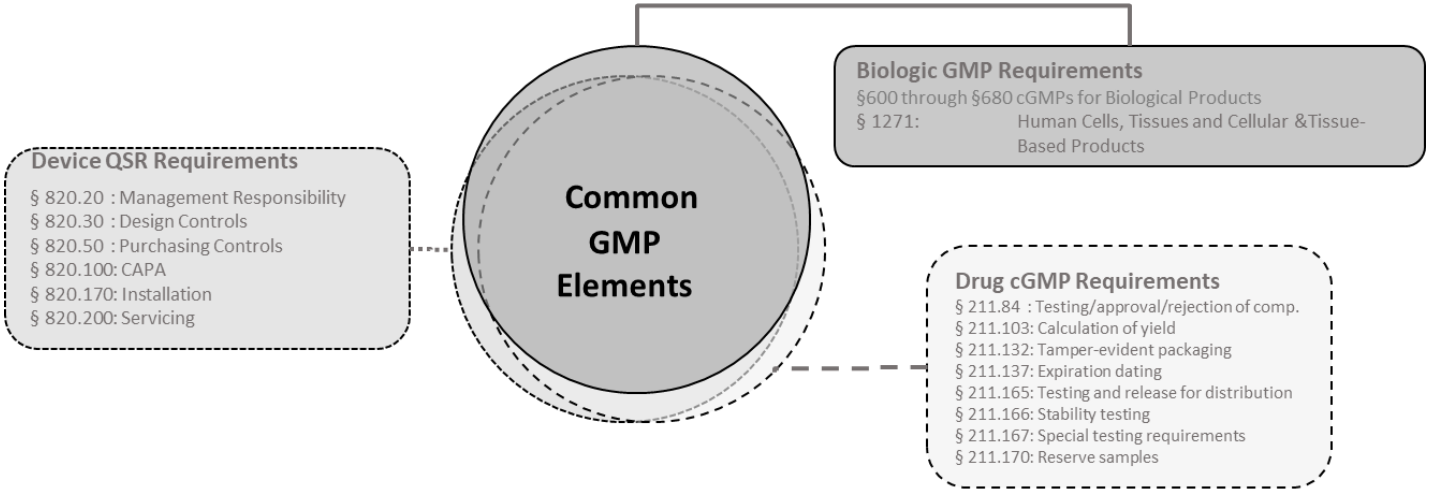


Figure 4: Called out provisions under "Streamlined Approach" for 21 CFR §4A (Figure used with permission. ©2021 Combination Products Consulting Services LLC. All Rights Reserved.)



21 CFR Part 4 (Subpart A, CGMP): **Regulation** https://goo.gl/qjZZfY; Preamble https://goo.gl/6GWHiB; ; Guidance https://goo.gl/GtGLsk

Table 2 summarizes a comparison between the EU and US "streamlined" cGMP approach to co-packaged drugs and devices. Per illustration in Figure 3, the traditional (non "streamlined" cGMP approach in US is similar to that in EU).

ISO 13485 Medical devices — Quality management systems —Requirements for regulatory Purposes

ISO13485 is the international consensus standard used by the medical device industry to define quality management systems for the design and development, production, storage and distribution, installation, servicing and final decommissioning and disposal of medical devices. **The table 2** references ISO 13485 elements in the EU, Similarities and Differences column as widely recognize framework that supports compliance.

It is recognized that adoption of ISO 13485:2016 facilitates compliance to the EU MDR and additional elements are required to meet the regulations. Adoption and certification of ISO 13485:2016 may be considered as an asset for a Pharmaceutical Company, but is not a regulatory requirement for EU MDR.

In US, FDA issued the recent Medical Devices Quality System Regulation Amendments Proposed Rule on February 23, 2022: „The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend the device current good manufacturing practice (CGMP) requirements of the Quality System (QS) Regulation to align more closely with the international consensus standard for devices by converging with the quality management system (QMS) requirements used by other regulatory authorities from other jurisdictions (i.e.,other countries). We propose to do so through incorporating by reference an international standard specific for device qualitymanagement systems set by the International Organization for Standardization (ISO), the 2016 edition of ISO 13485 (ISO 13485)."

Table 2: : EU-US QMS Requirements Comparison for Medicinal Products co-packaged with Medical Device

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
General	DDC product definition	EU MDR 2017/745 - Article 1 (9) **EMA Guidance on Quality Requirements for DDC** (EMA/CHMP/QWP/BWP/ 259165/2019, Section 1. Introduction): Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and device(s)) are not	***US 21 CFR 3.2(e) :** Co-packaged - Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;	**Differences:** Regulatory differences: EU emphasis on two individual regulated components. If separate Medical Device is co-packed, EU MDR 2017/745 applies. The drug constituent part is regulated under EU medicinal product Directive 2001/83/EC *In US, traditional approach allows for separate regulated components; streamlined approach allows for leveraging common elements of drug and device cGMPs, and addressing called-out provisions.*

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		physically integrated during manufacturing but where the medicinal product and the specific device(s) are combined for administration.		
	DDC classification	In EU, the device and drug co-packaged constituent parts are each regulated separately. The device constituent part is classified and regulated by a Notified Body according to EU MDR 2017/745 – Article 51 & Annex VIII Classification rules. The drug constituent part is separately regulated by the Competent Authority.	In US, a co-packaged drug-device is considered a combination product. The primary mode of action drives classification of the product as either device-led or drug-led (or biologic-led). The device constituent part is classified according to risk level, regardless of whether the combination product is drug- or device-led. Drug-led co-packaged products have lead center regulation by CDER or CBER. Device-led co-packaged products have CDRH as the lead center. Review and regulation of these products is done jointly between FDA	**Similarities:** . Device classification in the European regulation (MDR 2017/745) is similar to that of the US Quality System Regulation (QSR) as both processes are based on risk to user and patients. **Differences:** The classifications are different: -EU MDR divided Device into 4 classes: I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks. There are also 3 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 and level of complexity of the medical device. • The nuances of the device classification are different • In EU, the device is regulated separately from the drug. For co-packaged device-drugs, CE mark is required for the device constituent part; The CA reviews the drug and applicable device considerations prior to approving the drug-device co-pack. • In US, regulation under the streamlined approach is coordinated between FDA Centers, with a Lead Center based on PMOA of the combination product.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
			Centers, based on the constituent part types.	
	DDC product registration	EU MDR 2017/745 Article 29 Registration of devices Article 31 Registration of manufacturers, authorized representatives and importer ANNEX VI Information to be submitted upon registration of devices and economic operators in accordance with articles 29(4) & 31, core data elements to be provided to the UDI database together with the UDI-DI in accordance articles 28 & 29 and the UDI system.	*Note October 2019 guidance* Identification of Manufacturing Establishments in Applications to CBER and CDER Q&A Combination Product Manufacturer definition: An entity (facility) engaged in activities for a combination product that are considered within the scope of manufacturing for drugs, devices, biological products, and HCT/Ps. Such manufacturing **activities include, but are not limited to, designing, fabricating, assembling, filling, processing, sterilizing, testing, labeling,**	Differences EU MDR is only applicable to the device registration, and applies to the legal manufacturer, importer, and/or authorized representative. The drug constituent part is registered with the Competent Authority / EMA. In the US, the scope of the word "Manufacturer" registration is inclusive of both drug and device sites, and both are to be registered aligned to *Identification of Manufacturing Establishments in Applications to CBER and CDER Q&A*.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
			packaging, repackaging, holding, and storage, including a contract manufacturing facility (see 21 CFR §4.2)	
	QMS FRAMEWORK *Reference* ***Figure 3: Co-packaged Product cGMP approach in EU (per EU MDR (2017/745) versus US (21 CFR §4A)*** *(Figure used with permission. ©2021 Combination Products Consulting Services LLC. All Rights Reserved.)*	EU MDR 9a) a strategy for regulatory compliance, including compliance with conformity assessment procedures and procedures for management of modifications to the devices covered by the system: - For management of modifications to the devices covered by the system; - ISO 13485:2016 - 7.3.9 Control of design and development changes Drug constituent part changes are managed under the drug QMS.	For US Market, you must define your QMS approach aligned to Part 4A (either traditional approach or "streamlined approach". Procedures for management of modifications to the device constituent part are aligned to 21 CFR 820.30(i) Design Changes. Drug/biologic constituent part changes are managed under the drug/biologic QMS. Consideration of the product as a whole is required under 21 CFR Part 4A as part of change management.	**Similarities:** A QMS Framework expectations exist both for EU and US. Design change control is required for both. **Differences:** In US, under 21 CFR Part 4, there is an expectation to consider the combined use of the drug and device throughout the QMS. This includes change management. Under EU MDR, the constituent parts are managed separately, but in the US a lead FDA center is assigned who has primary jurisdiction and will coordinate review, as needed, of combination product changes with other FDA centers.
		b) identification of applicable general safety	US FDA indicates that Essential Performance	**Similarities:**

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		and performance requirements and exploration of options to address those requirements; these are reflected in EU MDR Annex 1.	Requirements (akin to Essential Conditions) are required; guidance is expected to clarify.	Both US and EU have expectations to ensure the safety, efficacy and usability of the medical product. **Differences:** EU MDR is very specific about expectations, e.g. under Annex 1. US FDA is more prescriptive for drug constituent parts, and has yet to clarify essential performance requirement expectations for the device constituent part(s).
	MANAGEMENT RESPONISIBITIES	EU MDR 2017/745 Article 10 General obligations of a manufacturer (c) responsibility of the management; ISO 13485 :2016 5 Management Responsibility	Irrespective of whether a product is drug- (or biologic-) led or device-led Primary mode of action (PMOA), in US, the manufacturer must meet 21 CFR 820:20 Management Responsibilities. Under 21 CFR 820.20, Management Responsibility ensures executive commitment to quality.	**Similarities** The management responsibilities are generally similar in EUMDR 2017/745 /ISO13485:2016 and in 21CFR820 **Differences** Where generally similar there are differences in the detail. The ISO13485:2016 has an additional requirement for promotion of awareness of regulatory and Quality Management System requirements throughout the organization and has also more details for Management review (inputs and outputs). 21CFR 820.20 provides more detail on: • requirements for quality policy; • the structure of the documentation for quality system procedures; • awareness of device defects • specific requirements for Management Representative.
	RESOURCE MANAGEMENT AND PURCHASING	d) resource management, including selection and control of suppliers and sub-contractors; ISO 13485 :2016 6 Resource management 7.4.1 Purchasing process	Irrespective of whether a product is drug- (or biologic-) led or device-led PMOA, in US, the manufacturer must meet 21 CFR 820.20 Management	**Similarities** Resource management and Purchasing controls are similar in EU MDR 2017/745/ISO13485:2016 and 21CFR820.20 **Differences** ISO 13485:2016 is more explicit expectations in purchasing controls

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
			Responsibilities (e.g., 21 CFR 820.20(b) organization) and 21 CFR 820.50 Purchasing Controls. 21 CFR 820.25 calls out more specific personnel requirements for device constituent part manufacturers, including specific training about device defects. The drug provisions are for resource management are otherwise similar to the device expectations.	Under 21 CFR 820.25, personnel training requirements must include training relative to device defects.(Note: This is not required if a GMP streamline approach is applied)
	RISK MANAGEMENT	EU MDR 2017/745 Article 10 General obligations of a manufacturer 9 (e) risk management as set out in in Section 3 of Annex I of EU MDR 2017/745; ISO 13485:2016 7 Product realization 7.1 Planning of product realization	In US , Risk Management is mentioned briefly under Design Controls 21 CFR 820.30(g), but also multiple times throughout the pre-amble. -21CFR820.30 Designs control, and Preamble 61 Fed. Reg. at 52620, Comment 83 (Design Controls)	**Similarities:** EU MDR2017/745, ISO13485:2016 and 21 CFR 820 require ongoing risk management (based on ISO 14971 as a recognized consensus standard in US, and harmonized standard in EU published in the Official Journal of the European Union) that spans the medical device lifecycle. To satisfy those requirements, risk management must be integrated into new product development, design change, manufacturing, CAPA, purchasing controls and post market surveillance systems. **Differences:** EU MDR has specific requirements defined in Annex I as part of the regulation. 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: integration of ICH Q9 and ISO 14971.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		ISO 14971:2019 Medical devices — Application of risk management to medical devices	-21CFR820.50 Purchasing controls and Preamble 61 Fed. Reg. at 52626, Comment 115 (Purchasing Controls) -21CFR 820.100 CAPA and Preamble 61 Fed. Reg. at 52633-52634, Comment 159 (CAPA) 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.	
	CLINICAL	EU MDR 2017/745 Article 10 General obligations of a manufacturer 9 (f) clinical evaluation in accordance with Article 61 and Annex XIV, including PMCF	Under 21 CFR 820.30(g) Design validation. *Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on*	**Similarities** Both in EU and US, clinical data is required, and the extent of that clinical evaluation is commensurate with the risk of the device (mode and duration of contact). **Differences** In the EU, a discrete clinical evaluation plan and report are required, on equal footing with the technical requirements documentation.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		• Chapter VI Clinical Evaluation and Clinical Investigations • Annex XV Clinical Investigations • Paragraph 5 Article 61: A manufacturer of a device demonstrated to be equivalent to an already marketed predicate device, may justify not performing a clinical investigation provided that: - The two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the tech documentation on an ongoing basis, and - The original clinical evaluation has been performed in compliance with the requirements of this regulation, and the manufacturer of the second device	*initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. … The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.* 21 CFR Part 814 - The PMA process includes the submission of clinical data to support claims made for the device. 21 CFR part 812 Investigational Device Exemptions allows this data to be collected as well as to support 510K	There is increased control on references to predicate devices based on expectations of contractual agreement between the product under investigation and the predicate manufacturer.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		provides clear evidence thereof to the NB. • There is a grandfather clause for devices put on the market under MDD 90/385/EEC or MDD 93/42/EEC for which the clinical evaluation is sufficient.		

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
	DESIGN CONTROLS & PRODUCTION AND SERVICE PROVISION (PRODUCT REALISATION)	EU MDR 2017/745 Article 10 General obligations of a manufacturer 9 (g) product realization, including planning, design, development, production and service provision; EU MDR 2017/745 Annex I Chapter II Requirements regarding Design and Manufacture ISO 13485 :2016 7 Product realization 7.3 Design and Development 7.4 Purchasing 7.5 Production and Service Provision	Irrespective of whether a product is drug- (or biologic-) led or device-led PMOA, in US, the manufacturer must meet 21 CFR part 4 called out provisions (e.g. For the drug constituent part not just the device constituent part) in addition to the base quality management system.	**Similarities:** Both EU MDR/ 2017/745/ISO 13485 clause 7.3 Design and Development and 21CFR 820.30 describe similar design controls process: Input, Output, Review, Verification, Validation, Transfer, Changes & Documentation. Both EU & US are similar with regards to GSPR (EPR in US) and clinical data evaluation, which need to be embarked in design control process. EU MDR 2017/745 / ISO13485:2016 and QSR have similar requirements for production and service provision. **Differences:** As previously stated, EU MDR is very specific about expectations, e.g., under Annex 1 and in EMA Guidance on Quality Requirements for DDC (EMA/CHMP/QWP/BWP/259165/201. US FDA is more prescriptive for drug constituent parts, and has yet to clarify essential performance requirement expectations for the device constituent part(s). ISO 13485 clause 7 Product Realization, is more explicit about: - The importance of a customer related process to identify & review the user requirements prior to initiate the design control process. - ISO 13485 7.3 Design and development has the requirement to perform Clinical valuation or performance evaluations in line with applicable regulations. Clinical Evaluation is the assessment and analysis of clinical data pertaining to a medical device safety and performance of the device, similarly to EU MDR 2017/745 Article 61 (Although not explicit in Annex I of EU MDR), it is required by EU medicinal product Directive. - EMA Guidance on Quality Requirements for DDC (EMA/CHMP/QWP/BWP/259165/2019 requires to provide bridging clinical study results when the device was not used in pivotal clinical trials. Embarking Clinical Evaluation in Design Controls is therefore key. In the US during Design Review an independent reviewer need to be involved. This is not the case for Europe and ISO13485.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
	IDENTITY AND TRACEABILITY (UDI)	EU MDR 2017/745 Article 10 General obligations of a manufacturer h) verification of the UDI assignments made in accordance with Article 27(3) to all relevant devices and ensuring consistency and validity of information provided in accordance with Article 29; ISO 13485 :2016 7.5.8 Identification	For a co-packed Drug / Device constituents which are not single integral the Device needs to follow US UDI requirements stated in 21 CFR 820.120 Device labeling	**Similarities:** No significant difference in system and technical requirements for UDI for US and EU **Differences:** The data elements required for EU (EUDAMED) and US (GUDID) differ. - In US, if medicinal product led product (Approved with NDC code), UDI does not apply. - In the EU, there is still a need to registered in EUDAMED with UDI for Device, and a UDI code should appear on the device for traceability reason. The device requires a basic UDI-DI as a primary identifier of device model. For EU Devices that are reusable shall bear a UDI carrier on the device itself.
	POST MARKET SURVEILLANCE & VIGILANCE	EU MDR 2017/745 Article 10 General obligations of a manufacturer i) setting-up, implementation and maintenance of a post-market surveillance system, in accordance with Article 83; • Chapter VII Post-Market Surveillance, Vigilance and Market Surveillance ISO 13485:2016	Irrespective of whether a product is drug- (or biologic-) led or device-led PMOA, in US, the manufacturer must meet 21 CFR 820:100 Corrective and Preventive Action. Under US 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	**Similarities:** Both regulations have requirements to collect data that relates to quality, performance and safety of a medical device throughout its entire lifecycle, and to report certain events that meet specific criteria and commensurate to product risk. **Differences:** The Regulations, coding requirements, reporting times, and specific reporting expectations differ between the EU and US. See high level overview in the respective EU and US columns.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		8.2 Monitoring and measurement 8.2.1 Feedback 8.5 Improvement 8.5.1 General **AND** EU MDR 2017/745 Article 10 General obligations of a manufacturer 9 k) processes for reporting of serious incidents and field safety corrective actions in the context of vigilance; • Chapter VII Post-Market Surveillance, Vigilance and Market Surveillance • Annex III Technical Documentation on Post-Market Surveillance	the constituent parts. Reporting is driven based on the Primary Mode of Action designated for the combination product. Drug-led combination products submitted under NDAs/ANDAs are subject to the safety reporting requirements described in 21 CFR Part 314. Biologic-led 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.	

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
	POST MARKET SURVEILLANCE & VIGILANCE	EU MDR 2017/745 Article 10 General obligations of a manufacturer 9 j) handling communication with competent authorities, notified bodies, other economic operators, customers and/or other stakeholders; ISO 13485 :2016 7.2.3 Communication 8.2.3 Reporting to regulatory authorities	FDA (2020) U.S. Department of HHS, FDA, OCP, CBER, CDER, CDRH. Requesting FDA Feedback on Combination Products – Guidance for Industry and FDA Staff In the US the Office of Combination Products acts as a coordinating body with FDA centers (CDER/CDRH/CBER). On a day to day basis the lead center assigned based on Primary Mode of Action (PMOA) of a product is primary point of contact. In the event of confusion OCP can facilitate conversation. .	**Similarities:** Communication is driven by PMOA (Primary Mode Of Action. **Differences** Communications for Co-packaged combination products in the US is streamlined to the lead center based on PMOA. Additional communication may take place with other centers as needed, but the lead center based on PMOA is the driver. The reporting requirements are dictated based on application type, applicant type, and constituent parts. In the EU, different constituents of a co-package combination product drug / medical device are treated independently with regards to communication with Notified and EU Competent Authority.
	CAPA	EU MDR 2017/745 Article 10 General obligations of a manufacturer 9 (l) management of corrective and preventive actions and verification of their effectiveness; ISO 13485 :2016	Under US 21 CFR §4B regulation and guidelines, whether a product is drug- (or biologic-) led or device-led PMOA, in US, the manufacturer must meet 21 CFR 820:100 Corrective and Preventive Action.	**Similarities:** No significant difference in analysis of data or record expectations when considering the QSR and preamble comment 161 and EU MDR 2017/745/ISO 13485. **Differences** There are differences of interpretation on validation and verification relevant to actions taken and effect on finished device. Details of implementation are different.

QMS - Streamlined process for DDC		EU Requirements	US Requirements (FDA "Streamlined Approach")	Similarities or Differences
Key QMS Chapter	QMS chapter features			
		8.5.1 General 8.5.2 Corrective Action 8.5.3 Preventive Action	The expectation is that the device-type CAPA aligned to 21 CFR 820.100 will be applied for co-packaged products that include a device constituent part.	When considering a co-packaged combination product in the US, CAPA applies to each individual constituent parts and the product as a whole. Whereas in the EU, device CAPA is applied to device constituent part and Drug CAPA to drug constituent part. Also CAPA system for Device expects preventive action based on the trending and management review, and systematically requires effectiveness check.
	MEASUREMENT IMPROVEMENT AND ANALYSIS	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 ISO 13485 :2016 8.2.5 Monitoring and measurement of processes	Under US 21 CFR §4B regulation, depending on whether a product is drug- (or biologic-) led or device-led PMOA, in US, the manufacturer streamline approach would meet 21 CFR 820.70 (a) Production and process controls and/or 21 CFR part 210. Under the streamline approach either 820.70 or 21 CFR 210 are recognized as long as the additional call out provisions under part 4 are addressed.	**Similarities:** EU MDR 2017/745 / ISO13485:2016 and QSR have similar requirements for monitoring and measurement of process and product. **Differences:** The US QS Regulation is more specific about complaint.

3. Authors, Contributors and Limitations

Authors

This Document was developed by the EFPIA-MQEG/GMP Working Group on Drug-Device Combinations (DDC) and published under the authority of the EFPIA on 23 August 2022. It represents an industry association perspective and does not confer any legal aspect, nor any immunity to its user (Person or Legal Entity). The perspective is built on the study of the regulation, industry discussion and consensus, and is not set in stone or agreed by the Regulators (EU or US) at this time.

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About EFPIA

The Manufacturing & Quality Expert Group (MQEG) is a specialized group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), which is recognized as the leading (bio)pharmaceutical association in Europe. Within MQEG, a Good Manufacturing Practices (GMP) Working Group (WG) addresses quality and compliance aspects related to Drug-Device Combination (DDC) products.

The EFPIA initiative for GMP aspects of DDCs was driven by a group composed mainly with Quality Experts in Development and Quality of DDCs, and supported by 3 Regulatory Experts, representing the majority of EFPIA company members; The composition of the WG is provided on next page.

"Pharma Industry" or "Pharma Company" mentioned in the title and throughout this paper refers to EFPIA member companies.

EFPIA Initiative for GMP Aspects of DDCs – Composition of the Working Group

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Limitations

This is a living document which will evolve with the issuance of interpretative guidance documents by the Regulators and experience and feedback from EFPIA Pharma Industry members. Any question, suggestion or feedback will be welcomed by the Authors. Last but not least, the comparisons provided in Tables 1 & 2 represent the consensus within the Working Group. However, these comparisons are not exhaustive for comparing and interpreting QMS requirements for Drug

Device Combination Product and Medicinal Product Co-packaged with Medical Device. It is up to each Pharma Company to design an adequate PQS that meets regulatory requirements.
