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An Industry Perspective About Quality Management System (QMS) for Drug-Device Combination Products

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A Pharma Industry perspective on the relationship between European Medical Device Regulations MDR 2017/745 and the Pharmaceuticals Quality System, as set forth in Eudralex Volume 4 Chapter I and in other Pharmaceutical Quality System documents such as ICH Q10 and 21 CFR (US-FDA), aimed at facilitating the implementation of MDR 2017/745 for Pharma Industry manufacturing and/or marketing Drug Device Combination Products in Europe.

Foreword

This Document was developed by the EFPIA-MQEG/GMP Working Group on Drug-Device Combinations (DDC).

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About EFPIA

The Manufacturing & Quality Expert Group (MQEG) is a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), which is recognised 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.

This document was published under the authority of the EFPIA-MQEG Committee on 31 October 2019. 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 (EMA, CAMD) at this time.

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

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Mike Wallenstein	Novartis	Executive Director QA, Senior Compliance Officer
Michael Karl Ledinegg	Sandoz	Senior Manager Global Development QA External Collaboration
Claude-Alain Piguet	Merck Serono	Head of Device Quality Management
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Executive Summary

The present industry perspective represents the current level of understanding of QMS requirements for MDR 2017/745 which would be pertinent to Pharma Industry designing, developing, manufacturing and marketing Drug-Device Combination (DDC) products, taking into account the clarifications brought by EMA in its draft Guidance on Quality Requirements for DDC Products (dGQR-DDC), EMA/CHMP/QWP/BWP/259165/2019 dated May 29, 2019.

This document aims to clarify and facilitate the implementation of MDR requirements for QMS by Pharma Industry being considered the legal manufacturer of the DDC, and not being considered as the legal manufacturer of the Device [1]. Drug Device Combination products (DDCs) *intended to administer a medicinal product* are in the scope of this document. The DDCs, for which the Device has the primary mode of action, is out of scope of this document.

To achieve this objective, the document provides a Pharma Industry perspective on one holistic Quality System approach addressing the requirements provided in the pertinent quality system in Regulation (EU) 2017/745 on Medical Devices (MDR) and the pharmaceutical quality system (PQS) requirements set forth in Eudralex Volume 4, Chapter I, Pharmaceutical Quality System (PQS), and in other relevant quality system requirements such as ICH Q10, US-FDA 21 CFR part 4, 21 CFR Part 820 and ISO 13485 [1]. We conclude that the intention of all these expectations on Quality Systems have similar intentions in the specific scope they are written for and can be combined in one QMS in a company addressing all expectations for DDCs.

The Working Group members performed a mapping of MDR 2017/745 towards a better understanding of the quality system requirements for Pharma Industry manufacturing and/or marketing DDCs. The outcome of this mapping was further discussed and consolidated in workshops held in October 2018 and February 2019. Where appropriate, clarification and alignment obtained on specific MDR Article with other Industry Associations are mentioned in this document. Indeed, in February 2019, EFPIA initiated a collaboration on a set of 16 questions with MedTech Pharma Platform (MPP) and Medicines for Europe (MFE). Feedbacks from both MPP & MFE were obtained and resulted in alignment and clarification obtained for 8 questions, need for clarification from Stakeholders (Regulators) for 7 questions, and 6 points for further advocacy, at least for EFPIA.

The target audience of this document are the EFPIA members. There are essentially two reasons for that:

1) At this stage the regulatory pathway and how to submit CMC data, for DDC intended to administer a medicinal product, are not fully clear; This document identifies 15 so-called ‘Requests for clarification from Stakeholders’, and 10 ‘EFPIA points for advocacy’, as described in Section 5 (Appendix 1) and 6. These are or will be conveyed to Stakeholders using different media as underlined in Section 6. Therefore, clarification of GMP and more specifically QMS requirements remain open to several options depending on the responses to EFPIA requests.

2) The EFPIA Quality Expert Working Group for GMP Aspects of DDCs (EFPIA WG) makes recommendations for QMS. However, these do not represent the only possible approach, and the EFPIA WG would not like to interfere in the current EMA consultation process on its dGQR-DDC. Therefore, the recommendations should remain internal to Industry.

This reflection paper is structured with 6 Sections:

- Section 1 describes the scope of the document,
- Section 2 provides a description of the challenges and considerations for the Quality Management System (QMS) when implementing the MDR 2017/745 for Drug-Device Combinations (DDC),

- Section 3 explains the precautions recommended by the EFPIA WG,
- Section 4 indicates regulatory document references for terminology and definition,
- Section 5 introduces the way Appendix 1 was built, which provides the applicability and relevance of MDR requirements as a function of the type of combination product, the link between MDR 2017/745 and PQS (Eudralex Vol 4) and the key messages to interpret MDR 2017/745 within the context of DDCs,
- Section 6 provides an exhaustive list of the 'Request for clarification from Stakeholders (Regulators)' and the 'EFPIA points for advocacy'. These questions and points for advocacy are collected by EFPIA-EBE and will be provided to EMA either through the EMA consultation process on its draft Guidance on Quality Requirements for DDC, or through EFPIA-EBE reflection papers.

Actually, it is expected that a Pharma Company manufacturing and distributing DDCs (but that is not the legal manufacturer of the Device) would not be audited by a Notified Body (NB), but instead inspected by the relevant Supervisory Authority) for medicinal products. Therefore, a PQS would be sufficient. However, there are certain quality requirements in MDR to consider:

1. Despite the fact that DDCs are registered as medicinal products, there are Articles and Annexes in MDR 2017/745 to comply with when commercialising DDCs, especially Annex I (GSPR),

2. There is a need to confirm the applicability / non-applicability of MDR 2017/745 beyond CE marking for Non-Integral DDCs mainly,

3. There is a need for the Pharma Company to check for appropriate understanding and interfacing between PQS and Medical Device QMS aspects,

4. Understanding key MDR requirements for QMS will facilitate the Pharma Company to design, develop, manufacture and distribute DDCs,

5. Understanding MDR requirements makes it easier for the Pharma Company to ensure appropriate quality oversight on Device legal Manufacturers or their Authorized Representatives if located outside of EU, and to establish quality assurance agreement (QAA) that fits for purpose.

(1) For legal manufacturer of Medical Devices, the Authors refer the readers to the excellent document establishing the relationship between MDR 2017/745 and ISO 13485:2016 as described in CEN/TR 17223:2018: **Guidance on the relationship between EN ISO 13485: 2016 (Medical devices – Quality management systems – Requirements for regulatory purposes) and European Medical Devices Regulation and In Vitro Diagnostic Medical Devices Regulation.**

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1. Scope

This reflection paper provides a Pharma Industry perspective on the relationship between the pertinent quality system requirements in Regulation (EU) 2017/745 on Medical Devices (MDR) and the pharmaceutical quality system requirements set forth in Eudralex Volume 4, Chapter I, Pharmaceutical Quality System (PQS), and in other relevant quality system documents such as ICH Q10 and US-FDA 21 CFR part 4.

It aims to clarify and facilitate the implementation of MDR requirements for QMS by Pharma Industry and raises a series of points for clarification and advocacy to promote harmonisation of QMS requirements for designing, developing, manufacturing and marketing Drug-Device Combination (DDC) products in Europe. DDCs *intended to administer a medicinal product* are in the scope of this document. Combination products, for which the Device has the primary mode of action, are not within scope for this document.

This industry perspective represents our current understanding of which QMS requirements in MDR 2017/745 that are pertinent to Pharma Industry for DDC products. Account has been taken of the clarifications made by the EMA in its draft Guidance on Quality Requirements for DDC Products (dGQR-DDC), EMA/CHMP/QWP/BWP/259165/2019 dated May 29, 2019.

Our perspective on the relationship between quality system requirements of both domains (Medical Devices and Medicinal Products) is provided in Appendix 1 in six (6) different sections, as suggested by the MDR Flowchart developed by MedTech Europe(2):

- MDR Process Part I - Obligations of the manufacturer and Annex I for General Safety and Performance requirements	Appendix 1 – Pages 32 to 66
- MDR Process Part II - Clinical Evaluation	Appendix 1 – Pages 67 to 73
- MDR Process Part III – Device Classification and Conformity Assessment	Appendix 1 – Pages 74 to 85
- MDR Process Part IV - Registration Process	Appendix 1 – Pages 86 to 89
- MDR Process part V - Post-Marketing Surveillance	Appendix 1 – Pages 90 to 92
- MDR Process Part VI - Obligations of the Other Economic Actors	Appendix 1 – Pages 93 to 97

(2) MedTech Europe - Overview of requirements under the Medical Devices Regulation 2017/745/EU on Medical Devices – Flowchart – December 2017
(3) It is recognized that the meeting between EFPIA/EBE and TEAM-NB WG on July 5th 2019 also provides some insight with regards to NB expectations for SI DDC products and clinical data expectations as part of the NB assessment to meet Article 117.

2. Challenges and considerations for Quality Management System (QMS) when implementing the MDR 2017/745 for Drug-Device Combinations (DDC)

2.1 Definition of Drug-Device Combination Product (DDC)

Neither the MDR 2017/745 nor the Medicinal Product Directive 2001/83/EC on medicinal products for human use define explicitly a Drug Delivery Device Combination (DDC) to the extent that the reader would know clearly which requirement of the MDR would or would not apply to the Device when combined with a Medicinal Product. There is a need for clarification in order to assess the impact on the QMS.

The recent EMA draft Guidance on Quality Requirements for Drug-Device Combination (EMA dGQR-DDC) provides more clarity. However,

- There are remaining questions and potential issues to address for both (Single-) Integral and Non-Integral DDCs, which could have an impact on the Pharma Industry QMS
- EMA dGQR-DDC document primary focus are is for DDCs falling within the definition of Article 1(9) of the MDR (Line 99 of EMA dGQR-DDC), which leaves CE Marked Devices for Non-Integral DDC with questions related to the applicability of MDR beyond CE marking,
- The draft clarifications provided in dGQR-DDC require confirmation through finalisation of the EMA guidance document.

a) Definition of Single-Integral and Non-Integral DDC

MDR 2017/745 states that products combining a medical device and a medicinal product follow specific rules (Article 1 (8) and Article 1(9)).
These specific rules provide subject matter and scope of the Regulation for Devices when used in combination with a Drug and introduce the concept of Integral and Single Integral Drug-Device Combination Products.

Although the concept of 'Single Integral' is well defined in Article 1 (9), the terminology 'Integral' described in Article 1 (8) is not defined in the regulations and leaves the 'Non-Integral' Drug-Device Combination Product undefined as well.

The following aspects related to ***DDC definition*** need clarification or confirmation:

- ***What does 'Integral' mean and when does a DDC product become Integral? When placed on the market, or at the point of use?*** Article 1 (8) seems to leave the possibility that the concept of integral product could be considered at the point of use, i.e., 'when put into service'. However, it seems that this is only applicable to combination products for which the Device has the principal mode of action. The second part of Article 1 (8) states

that, if the Drug has the principal mode of action, then the combination product is considered as a medicinal product under Directive 2001/83/EC or Regulation (EC) No 726/2004. And in that case, it seems necessary to refer to Article 1 (9), second sub-part, that defines and limits the concept of **single-Integral at the point when the product is placed on the market.** The EMA guidance document (Lines 67-69 EMA dGQR-DDC) appears to confirm this interpretation.

- ***What is a Non-Integral DDC?*** The concept of Non-Integral combination product is not defined in MDR 2017/745. However, EMA dGQR-DDC provides a clear definition of Non-Integral DDC in the Introduction (Lines 81-83) by stating that *Devices not falling within the scope of Article 1(8) and 1(9) of the MDR should be CE marked* (Lines 86-87). As per MDR 2017/745, Article 1 (9) first subpart, *Any device which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC shall be governed by this Regulation,* ***without prejudice to the provisions of that Directive and of Regulation (EC) No 726/2004 with regard to the medicinal product.*** The last sentence requires clarification in order to identify which Articles of MDR 2017/745 would or would not apply to Pharma Industry manufacturing (combining) Non-Integral DDC beyond CE marking. This question is pertinent mainly for the MDR Articles defining requirements for Labelling, Distribution, UDI for Traceability and Post-marketing surveillance.

b) QMS impact arising from the potential applicability of MDR 2017/745 to the Device when combined with the Drug

Subsequent to the issues with the definition of DDC (With Drug having the principal mode of action), the ***applicability of MDR to the Device WHEN COMBINED with the drug*** was questioned.

The EMA dGQR-DDC brings clarification in order to avoid a potential conflict of requirements between MDR 2017/745 and Directive 2001/83/EC or Regulation (EC) No 726/2004. Indeed, *The* ***core precept*** *of the EMA guideline is that the Competent Authority for the regulation of medicines (CA) will evaluate the device-specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal product, and that, as applicable, the NB will assess the relevant General Safety and Performance Requirements (GSPRs) (Lines 155-157):*

- ***For (Single) Integral*** *(4)* ***Product****, if the Device is not CE marked and if it would require the involvement of an NB, then a Notified Body opinion (NBOp) on the conformity of the device with the relevant GSPRs should be issued by an appropriately-designated NB (Lines 151-153);*

- ***For Non-Integral DDCs:*** *The Device must be CE marked in accordance with the MDR. Where a CE marked device for the administration of the medicinal product is co-packaged or is referred to in the SmPC of a marketing authorisation, additional information may need to be provided by the applicant* (To CA) *with regards to the device if the device may have an impact on the quality, safety and/or efficacy of the medicinal product (Lines 157-160).*

The issuance of EMA dGQR-DDC brings much clarification, but also raises new questions, mainly related to "How to provide the information to CA" and to the respective roles of NBs vs CAs. These questions are raised in Section 2.2 below **"QMS for Drug Delivery Devices combined with Medicinal Product"**, here-below, and in the core part of the document, i.e., Section 5 **"A Pharma Industry perspective on the relationship between European Medical Device Regulations MDR 2017/745 and the Pharmaceutical Quality System".**

(4) Note: EMA uses two terminologies Integral, which includes Single-Integral, and Non-Integral (Lines 61-69). The scope of this document includes Single-Integral DDC and Non-Integral Co-packaged DDC

For ease of review, Section 6 provides an exhaustive list of the 'Request for clarification from Stakeholders (Regulators)' and the 'EFPIA points for advocacy'.

2.2 QMS for Drug-Device Combination Product (Device used as a drug delivery system)

In Europe, the publishing of MDR 2017/745 implies new QMS considerations for Pharma Industry designing, manufacturing and/or marketing DDC.

a) Application of Standards & ISO 13485:2016 for QMS

While it is clear that Notified Bodies (NBs) will assess the conformity of the Device alone against requirements set forth in MDR 2017/745, the question was raised whether Pharma Industry would require EN ISO 13485:2016 (5) certification for the manufacture of DDCs. It is also expected that CA GMP inspectors, not Notified Bodies (NBs) will inspect the development and manufacture of Single-Integral DDCs and the co-packaging of drugs with CE marked devices as per cGMP requirements.

Adoption and certification of ISO 13485:2016 may be considered as an asset for the Pharma Company, but is not an absolute regulatory requirement, at least not in EU.

Moreover, EMA has stated clearly in its dGQR-DDC under section 4.1 „Application of standards (Lines 169-171), that *Compliance of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards.*

If a Pharma Company has a CE marked Device that is part of a DDC and if this Pharma Company is the legal manufacturer of the Device, then there are additional benefits of having ISO 13485 to comply with the MDR QMS requirements; The relationship between EN ISO 13485:2016 (5) and MDR 2017/745 and IVDR 2017/746 is provided in a Guidance document issued under the authority of Technical Committee CEN/TR 17223:2018 entrusted to quality management and corresponding general aspects for medical devices.

(5) EN ISO 13485:2016, Medical devices - Quality management systems - Requirements for regulatory purposes.

b) MDR challenges for Pharma Industry QMS (PQS)

The new challenges brought by MDR 2017/745 depend on the type of DDC product and experience of the Pharma Company with Medical Devices. The following challenges could impact Pharma Industry QMS and/or quality/technical workload:

a. For both Single-Integral and Non-Integral DDCs:

i. **A reduced number of Notified Bodies (NBs)**, since MDR 2017/745 brings more stringent requirements on their designation.
QMS impact for Pharma Company: Securing new a NB requires extensive vendor management activity.
   1. For Non-Integral DDC, each Pharma Company should check with the legal manufacturer of the Device whether NBs, ensuring the CE certification of Device under MDD, re-apply for their role of NB under MDR 2017/745 requirements or not, and for which Device designation. The need for NB is key to ensure that the Device is followed for Post-Market Surveillance (PMS) and for Post-Market Clinical aspects (PMCF). The need for re-certification of Device by May26, 2020 is only required for new Device or for Device with modified intended purpose, major design or production changes classification, and after May 26, 2020 as a function of CE certificate expiration date. Vendor management activity for new Third Party (NB) requires substantial technical and quality works.
   2. For Single-Integral DDC, Pharma Company should also contract a NB for any new DDC for which a NBOp would be required to support file submission after May 26, 2020. This would also be the case for changes to existing devices on the market that have a change and would require a variation to the file after 26 May 2020. See also Paragraph b.i. here-below.

ii. The MDR **reclassifies certain devices and has a wider scope** (MDR Annex VIII).
QMS impact for Pharma Company: Change of Device classification imply technical and quality works associated with re-certification activities.
   1. For Non-Integral DDC, each Pharma Company should check whether the CE marked Device class is modified. If the Device risk classification is modified, then the Pharma Company should liaise with the Device manufacturer to determine any potential impact pertinent (PMS-PMCF) to the revision of the Quality Agreement approved with the Device manufacturer.
   2. EMA has also mentioned the use of MDR 2017/745 classification rules for Single-Integral DDC in its Q & A document EMA/37991/2019 issued on February 28, 2019, and in its dGQR-DDC (Lines 411-412). However, the practical aspects associated with device classification for NBOp is unclear at this stage.

iii. The MDR introduces **a clinical evaluation consultation procedure for Class IIb active devices, intended to administer and/or remove a medicinal product**, as referred to in Section 6.4 of Annex VIII (Rule 12), by an independent expert panel (Article 54).
QMS impact for Pharma Company: Not known at this stage, since clarification about the applicability of this requirement is requested from EMA

1. For both Single-Integral and Non-Integral DDC, each Pharma Company should for new CE marked Devices (used as parts of DDCs) check if they may fall in Class IIb as per MDR rule 12 and *in cases of doubt as to the proposed classification of the device according to the MDR, it is recommended that an opinion be sought from a medical device CA* (Lines 162-163 of EMA dGQR-DDC).
2. The use of classification rules for a device, mentioned by EMA, does not mean that a DDC classified IIb would need to be reviewed by the Expert Panel (clinical evaluation consultation) since DDCs are registered as medicinal products.

b. **For Single-Integral DDCs:**

i. If the device part would not be CE marked, and would require the involvement of an NB, then the MDR 2017/745 introduces **a Notified Body Opinion (NBOp)** made obligatory for the conformity of the device part of DDC product with the relevant general safety and performance requirements (GSPR) set out in MDR 2017/745 Annex I issued by a NB designated in accordance with that Regulation for the type of device in question (MDR 2017/745 Article 117).
QMS impact for Pharma Company: Need to comply with the relevant GSPR of MDR Annex I.

c. **For Non-Integral DDCs:**

i. The MDR will also provide increased transparency, with **information on devices and studies being made public**.
QMS impact for Pharma Company: Not known at this stage. Clarification about the applicability of requirements of MDR 2017/745 beyond CE marking is requested from stakeholders (EMA, DG HEALTH, DG GROW).
The new European Database for Medical Devices – EUDAMED – will play a central role in making data available and increasing both the quantity and quality of data (Article 33): This Article is pertinent for legal Manufacturers of CE marked Devices; The Authors of this document consider that Pharma Industry manufacturing Non-Integral DDC would not be impacted by these requirements. However,
- This would require confirmation by both EMA & the competent authority for Medical Device, i.e., at EC DG GROW level.
- Accessing EUDAMED is free for public information. Would Pharma Company need access to additional information to assess the use of a Device? In such a case, how would Pharma Company require a Registration Number (SRN) to be registered as an economic actor under MDR?

ii. A new **Unique Device Identification (UDI) system** (Article 27) will significantly enhance the traceability and the effectiveness of post-market safety-related activities, and **Information** to supply with the device (Article 23).
QMS impact for Pharma Company: Not completely understood at this stage. Clarification about the applicability of requirements of MDR 2017/745 beyond CE marking is requested from stakeholders (EMA, EC Health, EC Growth).
This requirement is not pertinent to Single-Integral DDC and the extent of its applicability to Non-Integral DDC is not clear yet. This would require clarification from both EMA & the National Competent Authority for medical devices, i.e., at EC DG GROW level.

iii. MDR introduces specific requirements for **Importers of Medical Devices** (Article 13, 16, 30 & 31): This is applicable to Pharma Industry directly responsible for the importation of Devices into EU. EFPIA, MPP & MFE are aligned on the applicability of this MDR requirement.
QMS impact: Need to comply with registration of economic operators (Articles 30 & 31) and with requirements for Importers (Article13). Obligations of manufacturers of Medical Device should not apply to importers if some specific conditions are met (See Article 16, below).
For importation of Non-Integral DDC into EU, the applicability of MDR beyond CE marking remains a request for clarification from stakeholders, similar to points under c.i. & c.ii.

iv. MDR introduces specific requirements for **Distributors of Medical Devices** (Article 14);
QMS impact: The requirements for Distributor would mean, among other requirements, that Pharma Company marketing DDC, wholesaler, hospital & pharmacy would need to check for UDI and other aspects as per Article 14 (2). The potential issue is developed further here-below.

Potential issue with Article 14:
a) *Regulatory-wise*: As soon as a device is put into the folding box together with the drug, the distributor role according to the MDR should not apply anymore. In that moment the individual medical devices with CE mark received becomes part of the "Drug" from a physical and market authorization perspective.

b) *Quality-wise*:

- First of all it needs to be said that the distributor in the MDR is understood to be a legal-entity based view, not something which applies to a group of companies as a whole. That said there are typically multiple legal entities within a pharmaceutical company which constitute a separate distributor and would have to fulfill the requirements of Article 14. In addition there are 3rd party companies which are mandated to further distribute medical devices on behalf of the pharmaceutical company.

- When it comes to medical devices co-packaged with the drug (e.g. needles, transfer devices, alcohol swabs, dry powder inhaler etc.), it is neither appropriate nor possible that every legal entity in the distribution chain fully performs all obligations of Article 14, e.g. to check/confirm the compliance is not possible anymore. This would require to open individual drug packages, which in many cases have to be sealed with a tamper evident seal in Europe.

- Instead EFPIA would consider the medical devices not falling under the distributor obligations of MDR Art 14 anymore, as soon as the folding box with the device and the drug has been manufactured. Pharma company would follow cGMP & cGDP regulatory requirements.

- That means that the pharmaceutical manufacturing site (1st distributor) which receives the device from the manufacturer would perform all the necessary checks and would maintain files for documentation. Furthermore compliance to medicinal product directives for Good Distribution Practices (2013/C 343/ 01) and to Regulation 2016/161 for serialization and safety measures by each distribution actor would ensure patient safety and protection along the supply chain. Affiliate(s), wholesaler, hospital and pharmacy would not repeat those checks, however they would of course forward complaints to the legal manufacturer of the device (via the MAH and the 1st distributor).

- One argument why this process could be sufficient is that the relevant distributors in that chain are either affiliates of the pharmaceutical company which fall under the global quality management system or they are contractors which are covered by supplier qualification process.

Result of the survey performed with other industry associations:
EFPIA contacted other Industry Associations (MedTech Pharma Platform & Medicines for Europe). There is no clear alignment among the Industry Associations. EFPIA requires clarification from the Stakeholders since Non-Integral DDC is registered as a medicinal product. See Section 6 for "Clarification request" and "EFPIA point for advocacy". EFPIA advocates for non-applicability of this Article to Pharma Industry distributing DDCs, since it would duplicate the requirements set forth in Directive for Good Distribution Practices (2013/C 343/ 01) and the COMMISSION DELEGATED REGULATION (EU) 2016/161 for traceability (Serialisation code) and safety measures for medicinal products. This would require clarification from both EMA & the competent authority for Medical Device, i.e., at EC DG Growth level.

v. MDR introduces potential requirements for **Distributors and Importers to comply with manufacturer obligations** (Article 16);
As described in the rationale (37) of the MDR, the Article 16 has been introduced to define conditions which allow relabelling and repackaging as required to support parallel trading.
QMS impact: Applicability of manufacturer obligations to the Pharma Company would represent a huge impact, since the whole MDR would then apply. There are two different scenarios, developed here-below, in order to prevent applicability of manufacturer obligations to the Pharma Company manufacturing Co-packaged DDC.

Scenario 1: The Pharmaceutical Company receives devices in bulk packaging from the manufacturer. In this case the further distribution of the device(s) in that packaging is not intended, but the bulk packaged devices are intended to be separated by the Pharmaceutical Company. Bulk packaging also means that the boxes are typically unlabeled, or labelled with the minimum requirements as per MDR 2017/745.This should be carried out in such conditions that the original condition of the device cannot be affected by this operation (Article 16(2)). Complying with the other paragraphs of MDR Article 16 (1) would prevent the Pharma Company from Medical Device manufacturer obligations. **QMS impact** would therefore be limited to appropriate Quality Agreement to delineate responsibilities between manufacturer and pharma company.

Scenario 2: The pharmaceutical company receives devices in a large sales unit (e.g. cannulas, or single-use syringes) which is already on the market. This folding box of the sales unit has separate labelling (incl. information not covered by the individual unit labelling) and includes one single IFU. Now, the Pharmaceutical Company separates this sales unit by co-packaging only one device out of this sales unit.

- This "changes of pack size" would mean that the Pharmaceutical Company as distributor would become the legal manufacturer of the Device. The only reason for this separation of sales unit is that the marketing authorization for the drug requires a "change of pack size", for the intended procedure with the drug, and not to allow for marketing of the device itself in certain countries.

- The exemption clauses of Art. 16(2) might not apply and would lead the Pharma Company to endorse the manufacturer obligations.

- In order to prevent to fall into the requirements of Article 16, the Pharma Company should perform the separation under (Purchasing) agreement with the legal manufacturer.

- **QMS impact** could be minimized if the legal manufacturer provides the medical device in a pack size which does not require separation, with either an IFU included in the pack or an IFU master in the required languages which can be included in the PIL without any modification.

Considering the various MDR challenges, the Authors recommend Pharma Companies, who currently work according to the existing Medical Device Directive (MDD) or are using their Pharmaceutical Quality Systems (PQSs) with no specific Medical Device QMS, to check for adequate coverage of pertinent MDR requirements by its current PQS/QMS. There is no one QMS solution fit for all. It is up to each Pharma Company to adapt its QMS in order to meet the pertinent MDR requirements for both Single-Integral and Non-Integral DDCs.

The following endpoints should be kept in mind when revising the Pharma Company PQS:

- For Single-Integral DDC, the QMS helps to comply with General Safety and Performance Requirements (GSPRs) set forth in MDR Annex I,
- For Non-Integral DDC, the intended use set forth in the Conformity Assessment for the CE marked Device is maintained, and if not, a new conformity assessment is performed as per MDR towards NB certification.
- The overall combination of Device and Medicinal Product is taken into consideration, at the point to place the DDC on the market and at the point of use.

The Authors consider that the following Device specific QMS areas should receive particular attention from the Pharma Company when revising its PQS:

- Product realisation (Design Controls): This process, as described in ISO 13485:2016, or in MDR Annex IX, should be used right at the beginning of the development of a new Single Integral Product and/or Non-Integral DDC, and should include Usability Engineering to address the design requirements at point of use of DDC.
- Purchasing Controls,
- Management Responsibilities (especially Management Representative),
- Effective and pro-active CAPA system,
- Product-specific risk management, ISO14971 and/or ICH Q9. The role of the risk management and especially benefit-risk analysis becomes more and more important, with input from the post-market surveillance system.

This document explores the options in sufficient detail and provides insight how to assess the potential impact of MDR on QMS. The decision to select QMS options is always a choice not a regulatory requirement.

This document provides an industry perspective about:

1. The applicability and relevance of MDR requirements as a function of the type of drug-device combination product (Single Integral or Non-Integral DDC)
2. The possibility to use the Pharmaceutical Quality System. It outlines its potential limitations and suggests opportunities to adapt it at company level in order to adequately address the requirements set forth in MDR 2017/745.

3. Limitations

Not all Articles of MDR 2017/745 or it's annexes were reviewed and analysed by the Authors. The selection of Articles and Annexes was based on the best technical and quality judgment of the Authors after mapping of MDR 2017/745 towards a better understanding of the quality system requirements for Pharma Industry manufacturing and/or marketing DDCs.

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 recommendations provided in Table 1 represent the consensus within the Working Group after mapping of the MDR text and discussion. However, these recommendations are not the sole possible approach for interpreting the MDR requirements or for designing a QMS for DDCs. It is up to each Pharma Company to design an adequate PQS that meets regulatory requirements.

4. Terms and Definitions

For the purposes of this document, the terms and definitions used in Eudralex Volume 4, in MDR 2017/745 and in EMA draft Guidance on Quality Requirements for DDC apply.

5. A Pharma Industry perspective on the relationship between European Medical Device Regulations MDR 2017/745 and the Pharmaceutical Quality System (Introduction to Appendix 1)

Appendix 1 provides the Pharma Industry perspective on key requirements of the European Regulations on Medical Devices (MDR EU 2017/745), together with commentary on the extent to:

- Which PQS could be used in alignment with Eudralex Volume 4, or with ICH Guidelines
- How to interpret MDR clause (Key message)
- Which clarification is needed from the Regulators (Request for clarification from Stakeholders)
- Advocate for a position on the applicability of a requirement (Point of advocacy)
- Recommend to Pharma Industry-specific MDR interpretation for DDCs
- When pertinent, how the requirement is interpreted in US-FDA 21CFR part 4, mainly because:
    - It would underline similarities or divergences in requirements,
    - 21 CFR Part 4 suggests for a streamlined QMS approach, combining PQS and Medical Device QMS, when considering DDC products.

The perspective on the relationship between quality system requirements of both domains (Medical Devices and Medicinal Products) is provided in six (6) different sections, as suggested by the MDR Flowchart developed by MedTech Europe[(6)]:

- MDR Process Part I - Obligations of the manufacturer and Annex I for General Safety and Performance requirements — Appendix 1 – Pages 32 to 66
- MDR Process Part II - Clinical Evaluation — Appendix 1 – Pages 67 to 73
- MDR Process Part III – Device Classification and Conformity Assessment — Appendix 1 – Pages 74 to 85
- MDR Process Part IV - Registration Process — Appendix 1 – Pages 86 to 89
- MDR Process part V - Post-Marketing Surveillance — Appendix 1 – Pages 90 to 92
- MDR Process Part VI - Obligations of the Other Economic Actors — Appendix 1 – Pages 93 to 97

(6) MedTech Europe - Overview of requirements under the Medical Devices Regulation 2017/745/EU on Medical Devices – Flowchart – December 2017

6. Summary of the Requests for Clarifications from Stakeholders (Regulators) and EFPIA Points for Advocacy

6.1. Requests for Clarifications from Stakeholders (Regulators)

Legend: SI = Single-Integral / NI = Non-Integral

MDR Process Part I - Obligations of the manufacturer and Annex I for General Safety and Performance requirements	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)	Decision about process to convey the requests to Stakeholders
	Article 1 (9)	NI	The part of the first sentence of Article 1 Section 9 ("…, without prejudice to the provisions of that Directive (2001/83/EC) and of Regulation (EC) n° 726/2004 with regard to the medicinal product.") lacks clarification about which Articles of the MDR 2017/745 would not apply to the Medical Device when co-packaged with the medicinal product.	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs
	Article 8	SI & NI	Article 8 might presume that conformity with harmonized standards related to system or process is a must. EFPIA will work with Stakeholders to ensure a correct interpretation of this article, which should be: Device products and / or systems being in conformity with relevant harmonized standards as published in the Official Journal of the European Union would facilitate conformity assessment, but Ph.Eur. requirements and European and ICH guidance-take precedence over ISO and other international standards.	Consultation process on EMA dGQR-DDC – Comment to lines 170-171 (Chapter 4. General considerations for integral DDC)
	Article 10 (3)	NI	It is not clear whether the Pharma company would need to contribute to Post Market Clinical Follow-up (PMCF) as per Annex XIV. Complying to MDR 2017/745 beyond CE marking should be clarified by EMA for Co-packaged DDC.	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs

MDR Process Part I - Obligations of the manufacturer and Annex I for General Safety and Performance requirements	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)	Decision about process to convey the requests to Stakeholders
	Article 10 (8)	SI & NI	MDR specifies archiving timeframes of 10 years (15 years for implantable) after the last device put on the market. This would be a confirmed requirement for the device legal manufacturer only. For Pharma company manufacturing a DDC , this would be defined by the registration type, i.e., by medicinal product directives if registered as a medicinal product. EFPIA will work to clarify MDR 2017/745 requirements beyond CE marking.	New set of questions for EMA Q&A format document
	Annex I Chapter II Section 10.4.3.	SI & NI	Will Stakeholders look for harmonization with international standards ICH or with EMA existing guidelines on Phtalates (EMA guideline EMA/CHMP/SWP/362974/2012)	Consultation process on EMA dGQR-DDC – Comment to lines 170-171 (Chapter 4. General considerations for integral DDC) – See Article 8 here-above
	Annex I Chapter III (Sections 23.1. , 23.2, 23.3 and 23.4)	SI	EFPIA will work with EMA to define the labelling requirements specific to the device part, especially for Single-Integral DDC.	EFPIA-EREG Reflection paper for labelling of SI DDC

MDR Process Part II - Clinical Evaluation[7]	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)	Decision about process to convey the requests to Stakeholders
	Article 61 (1)	SI	- Annex I does not mention Clinical Evaluation nor Article 61. Clarification is required as Clinical Evaluation does not necessarily mean clinical data, and DDC clinical data do not necessarily include the use of the single integral device. - What level of evidence would be required by NB, as a function of the device component risk class and on the available clinical evaluation ?	Consultation process on EMA dGQR-DDC – Comment to lines 249-253 and 254-259 (Chapter 5.2.Module3.2.P. Drug Product) + Meeting between EFPIA/EBE and TEAM-NB WG on July 5th 2019
	Article 61 (1)	NI	Beyond CE marking, clarification is required with regards to requirement for Clinical Evaluation, and MDR 2017/745 Article 61 especially, as DDC clinical data do not necessarily include the use of the same CE marked device.	Consultation process on EMA dGQR-DDC – Comment to lines 611 (Chapter 7 – Bridging to devices used in

				clinical development)

(7) It is recognized that the meeting between EFPIA/EBE and TEAM-NB WG on July 5th 2019 also provides some insight with regards to NB expectations for SI DDC products and clinical data expectations as part of the NB assessment to meet Article 117.

MDR Process Part III – Device Classification and Conformity Assessment	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)	Decision about process to convey the requests to Stakeholders
	Article 86 (3)	NI	However, it is not clear yet to what extent Pharma Company would need to provide data Periodic Safety Update Reports (PSUR) to legal manufacturer for the Devices used in Non-Integral DDCs	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs
	Annex IX Chapter I,Section 4.10	SI & NI	Change of an approved device: EFPIA would like clarifications with regards to the translation of DDC change types in EMA variation procedures (Type IA, IB and II).	Consultation process on EMA dGQR-DDC – Comment to lines 615-640 (Chapter 8 Lifecycle management) + EFPIA Reflection Paper on substantial changes (Initiated)
	Article 117	SI	For the submission of a new Single Integral DDC product after 26 May 2020, would a relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device under the MDD be acceptable regulatory-wise providing that the certificate is still valid ?	EMA dGQR-DDC – Comment to lines 145-147 (Chapter 4. General

MDR Process Part III – Device Classification and Conformity Assessment	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)	Decision about process to convey the requests to Stakeholders
				considerations for integral DDC)

MDR Process Part IV – Registration Process	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)
	NA	NA	NA

MDR Process Part V – Post-Market Surveillance (PMS)	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)	Decision about process to convey the requests to Stakeholders
	Article 83	SI & NI	While the reporting pathway would be clear for DDCs registered as medicinal products, a Post-Market Surveillance System is required as part of Annex I (GENERAL SAFETY AND PERFORMANCE REQUIREMENTS), Chapter I General Requirements, Section 3.e. Risk-Management system. This could be interpreted as indirect need to establish a PMS system according Article 83 also for DDC products as described in MDR 2017/745 article I(9) and article 117. EFPIA will work with the Stakeholder to obtain guidelines with regards to applicability of MDR Article 83 to SI & NI DDCs.	Consultation process on EMA dGQR-DDC – Comment to lines 641-642 (Chapter 8 Lifecycle management) + For NI DDC: EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs

MDR Process Part VI – Obligations of the Other Economic Actors (Distributors and Importers)	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	Requests for Clarifications from Stakeholders (Regulators)	Decision about process to convey the requests to Stakeholders
	Article 14	NI	Applicability of MDR 2017/745 Articles, such as Article 14, beyond CE marking would require clarification from Regulators. It is EFPIA opinion that there is no need for Pharma Company distributing Non-Integral Co-Packaged DDC to be considered as Distributor of Device under MDR Article 14, since the CE marked Device is co-packaged with the medicinal product and must be distributed as per GDPs, including as per Regulation 2016/161 for Safety Features. Therefore Complying with requirements set forth in Article 14 is ensured by default. This is valid for all Sections of Article 14 (1, 3, 4, 5 & 6), with a specific point for advocacy related to UDI check (See Article 14 Section 2 in Section 6.2. EFPIA Points for Advocacy).	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs
	Article 13	NI	EFPIA will work with EMA and Medical Device Regulators to clarify the applicability of MDR 2017/745 Article 13 for Pharma Company importing Non-Integral, co-packaged, DDC.	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs
	Article 16	NI	EFPIA will work with EMA and Medical Device Regulators to clarify the applicability of MDR 2017/745 Article 16 for Pharma Company importing Non-Integral, co-packaged, DDC.	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs

6.2. EFPIA Points for Advocacy

MDR Process Part I - Obligations of the manufacturer and Annex I for General Safety and Performance requirements	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	EFPIA Points for Advocacy	Decision about process to convey the requests to Stakeholders
	Article 10 (3)	SI	MDR 2017/745 Annex I (GSPR) does not refer to Article 61 (Clinical Evaluation). Therefore Single Integral DDC are excluded from this MDR requirement	The meeting between EFPIA/EBE and TEAM-NB WG on July 5th 2019 also provides some insight with regards to NB expectations for SI DDC products and clinical data expectations as part of the NB assessment to meet Article 117.
	Article 10 (9)	SI & NI	The description of the QMS requirements does not include expectations with regards to device change management. Pharma Industry would advocate for major change to the device being covered in the QMS using recognized guidance document, which would be aligned with conditions described in paragraph 4.9 of Annex VII of the MDR, i;e., changes to the approved type of Device, to its design, to its intended purpose or claim made for it, or to any substance incorporated in or used for the manufacture of the Device	- For SI DDC: Question 15 of EFPIA-EBE set of questions communicated to EMA on June 12, 2019

MDR Process Part I - Obligations of the manufacturer and Annex I for General Safety and Performance requirements	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	EFPIA Points for Advocacy	Decision about process to convey the requests to Stakeholders
				+ Consultation process on EMA dGQR-DDC – Comment to lines 615-640 (Chapter 8 Lifecycle management)
	Article 10 (9)	SI	Article 83 is not included in Annex I, and is therefore not applicable to Single Integral DDC. The post-market surveillance system should comply with medicinal product directives	EFPIA-EBE Reflection Paper for Substantial Changes of SI DDC + Consultation process on EMA dGQR-DDC – Comment to lines 641-642 (Chapter 8 Lifecycle management)
	Article 10 (9)	NI	Article 83 is applicable to the Device legal manufacturer. Pharma Company shall report adverse event and complaint caused by the device component to the National Competent Authority of the medicinal product, and would need to communicate this type of information to the Device manufacturer	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs

MDR Process Part II - Clinical Evaluation[7]	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	EFPIA Points for Advocacy	Decision about process to convey the requests to Stakeholders
	Article 61 (1)	SI & NI	It is EFPIA advocacy point that there is no need to apply MDR 2017/745 Article 61 requirement for DDC product that are supported by drug clinical data delivered with the device of the DDC product.	- For SI DDC: See MDR Process part I - For SI & NI DDC: Consultation process on EMA dGQR-DDC – Comment to lines 611 (Chapter 7 – Bridging to devices used in clinical development)

(7) It is recognized that the meeting between EFPIA/EBE and TEAM-NB WG on July 5th 2019 also provides some insight with regards to NB expectations for SI DDC products and clinical data expectations as part of the NB assessment to meet Article 117.

MDR Process Part III – Device Classification and Conformity Assessment	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	EFPIA Points for Advocacy	Decision about process to convey the requests to Stakeholders
	Article 56 (1 & 2)	SI & NI	EFPIA advocate for a simplified procedure, when considering no or few changes, also on a guidance or rule, using a risk-based approach for NB to decide on the minimum validity of a certificate. This would promote harmonization as much as possible.	EFPIA Reflection Paper on substantial changes (Initiated)
	Article 117	SI & NI	EFPIA would like clear process about how fees and timelines are made public, how fees are derived, and how Device legal Manufacturer and Pharma Industry can use these information in the NB engagement process (Cfr Art. 53, engagement of 1 NB at a time)	To be defined at EFPIA-MQEG level - Meeting with NB and/or MDCG (? TBC)

MDR Process Part IV – Registration Process	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	EFPIA Points for Advocacy	Decision about process to convey the requests to Stakeholders
	Article 29 (1)	NI	The PQS ensures that the device information is traceable; EFPIA advocates for UDI being affixed on the device itself or its primary packaging, not on the secondary packaging of the DDC, similar to US-FDA 21 CFR Part820. The UDI will be checked and documented in DDC batch records and SmPC. Non-Integral DDCs registered as medicinal product must indeed comply with serialisation for safety measure and traceability along the distribution chain.	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs
	Article 30 (2)	NI	On top of EFPIA request for streamline approach of GDP for Non-Integral DDC, i.e., with limited application of Article 29, EFPIA advocates for non- applicability of Articles 14 & 30 to Pharma Company distributing Non-Integral DDCs.	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs

MDR Process Part V – Post-Market Surveillance (PMS)	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	EFPIA Points for Advocacy
	NA	NA	NA

MDR Process	MDR Article or Annex	Type of DDC (SI or NI or SI & NI)	EFPIA Points for Advocacy	Decision about process to convey the requests to Stakeholders
Part VI – Obligations of the Other Economic Actors (Distributors and Importers)	Article 14	NI	Requirements set forth under (a), (b), (c) & (d) are normal requirements for a Pharma Company operating under the PQS: Purchasing a CE marked Device, combining it with a medicinal product and placing it on the market require controls at reception of the Device, during manufacturing of the Non-Integral DDC and before QP batch certification. Therefore EFPIA would recommend an interpretative guidance, which would allow for DDC product, registered as medicinal product, to be exempt of the requirements set forth in Article 14. If Pharma Company would be considered as Distributor under MDR Article 14, then EFPIA would advocate for UDI check performed at the DDC assembly site only, and not along the supply chain (Wholesalers, hospital, …), since it would not be feasible (UDI on primary packaging), or would require UDI on each packaging (First, second, third,…).	EFPIA-MPP-MFE Reflection Paper for Non-Integral DDCs

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APPENDIX

A Pharma Industry perspective on the relationship between European Medical Device Regulations MDR 2017/745 and the Pharmaceutical Quality System

Table 1 provides the Pharma Industry perspective on key requirements of the European Regulations on Medical Devices (MDR EU 2017/745), together with commentary on the extent to:

- Which PQS could be used in alignment with Eudralex Volume 4, or with ICH Guidelines
- How to interpret MDR clause (Key message)
- Which clarification is needed from the Regulators (Request for clarification from Stakeholders)
- Advocate for a position on the applicability of a requirement (Point of advocacy)
- Recommend to Pharma Industry specific MDR interpretation for DDCs
- When pertinent, how the requirement is interpreted in US-FDA 21CFR part 4, mainly because:
    - It would underline similarities or divergences in requirements,
    - 21 CFR Part 4 suggests for a streamlined QMS approach, combining PQS and Medical Device QMS, when considering DDC products.

The perspective on the relationship between quality system requirements of both domains (Medical Devices and Medicinal Products) is provided in six (6) different sections, as suggested by the MDR Flowchart developed by MedTech Europe[(1)]:

(1) MedTech Europe - Overview of requirements under the Medical Devices Regulation 2017/745/EU on Medical Devices – Flowchart – December 2017

MDR Article reference	MDR text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
Article 1 Section 9 **Subject matter and scope**	Any device which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC shall be governed by this Regulation, without prejudice to the provisions of that Directive and of Regulation (EC) No 726/2004 with regard to the medicinal product. However, if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part of the single integral product are concerned.	Annex I General Safety & Performance Requirements (GSPR)	EU Directive 2001/83/EC 21 CFR 3.2(e), defines combination product. 21 CFR 4 refers to 21 CFR 3.2(e)	**Links with PQS** 1) **EU MDR** defines 2 categories of drug-device combination products for which the medicinal product has the primary mode of actions: - Single Integral drug delivery devices, for which only compliance with Annex I of MDR is required , - and other drug delivery devices, for which MDR applies and must be CE marked. For the latest, EMA dGQR-DDC introduces the terminology “Non Integral”, which includes Co-packaged DDC and so called ‘Cross labelled DDC”, although this terminology used in the US is not used by EMA (EMA dGQR-DDC Line 85, 86: „or where the Product Information (SmPC and Package Leaflet) refers to a specific device to be used with the medicinal product but the device is obtained separately” 2) **Directive 2001/83/EC** defines Medicinal product: 2. Medicinal product:… (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis. The term “Administration” is often used as “administration to patients, route of administration prior to administration, proper administration, method of administration”. Requests for clarification from Stakeholders: The part of the first sentence of Article 1 Section 9 (“…, without prejudice to the provisions of that Directive (2001/83/EC) and of Regulation (EC) n° 726/2004 with regard to the medicinal product.”) lacks of clarification about which Articles	

MDR Article reference	MDR text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
				of the Medical Device Regulation (MDR) would not apply to the Medical Device when co-packaged with the medicinal product.	
				US FDA defines 3 types of DDC: Single entity, Co-packaged, Cross-labelled. **US FDA 21CFR4**: There is no differentiation of combination products regarding the applicability of the regulation/guidance. 21CFR4 is a mix of 21CFR210/211 and 21CFR820 in its essential points.	
Article 2 Section 30 **Definition of Manufacturer**	'Manufacturer' means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark	NA	COMMISSION DIRECTIVE 2003/94/EC of 8 October 2003 Article 2 Definitions 3. US FDA : 21CFR820 o)	**Links with PQS** **EU GMP**: 'Manufacturer' means any person engaged in activities for which the authorization referred to in Article 40(1) and (3) of Directive 2001/83/EC or the authorization referred to in Article 13(1) of Directive 2001/20/EC is required; Article 40 1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required. **Key messages**: 1) The manufacturer of the drug delivery device part of a Single Integral DDC might not fall into the definition of MDR, nor of EU Directive 2003/94/EC. The manufacturer of the device component might comply with ISO 15378 "Primary packaging	**Links with PQS** The manufacturer of the CE marked device component of co-packaged DDC (= "Non-integral" DDC) falls under the definition of **MDR EU745/2017.** The manufacturer of the co-packaged DDC falls under the definition of **EU Directive 2003/94/EC**, unless the Pharma company performs activities that fall under the scope of **MDR Article 16 (1a), (2b), (3) & (4).** See development of MDR Article 16. As per **MDR Article 14**, the Pharma company manufacturing and marketing a co-packaged DDC would fall under the requirements of Distributor (See development of MDR Article 14). **Key messages**: Two causalities come together to define a manufacturer as per MDR:

MDR Article reference	MDR text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
				materials for medicinal products — Particular requirements for the application of ISO 9001, with reference to good manufacturing practice (GMP)". 2) The manufacturer of the DDC falls under the definition of EU Directive 2003/94/EC.	The manufacturer always markets the device under its name or tradename: However if the legal entity only markets the device without having any design, manufacturing or refurbishment steps the legal entity is not defined as manufacturer but potentially as distributor (Article 14). **Point of advocacy** EFPIA would recommend an interpretative guidance, which would allow for DDC product, registered as medicinal product, to be exempt of the requirements set forth in Article 14, or limited the requirements to added value aspect, like the check of UDI at the manufacturing site only. See MDR Process part VI- Obligations of the Other Economic Actors

MDR Article reference	MDR text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
				US FDA 21cfr820.1 o): Manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions. According to FDA: manufacturer does not market the Medical Device under its name or trademark.	

MDR Article reference	MDR Text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
Article 5, sections 2 & 3 **Placing on the market and putting into service**	A device shall meet the general safety and performance requirements set out in Annex I which apply to it, taking into account its intended purpose. Demonstration of conformity with the general safety and performance requirements shall include a clinical evaluation in accordance with Article 61.	Annex I General Safety and Performance Requirements (GSPR)	EU Directive 2001/83/EC	**Key message:** Single-Integral DDC is registered as medicinal product which must comply with MDR Annex I (GSPR). The latest does not refer to Article 61.	**Key messages**: The device part of the Co-packaged DDC must be used within the intended purpose. If the Pharma company used the device for a purpose which was not intended by the device manufacturer, then the Pharma company becomes manufacturer as per **MDR definition** and needs to comply with manufacturer obligations as per MDR Article 16. See development of **MDR Article 16** (MDR PROCESS PART VI – OBLIGATIONS OF THE OTHER ECONOMIC ACTORS)
Article 8 **Use of harmonized standards & the monographs of the European Pharmacopoeia**	Devices that are in conformity with the relevant harmonized standards, or the relevant parts of those standards, the references of which have been published in the Official Journal of the European Union, shall be presumed to be in conformity with the requirements of this Regulation covered by those standards or parts thereof.	NA	Eudralex Vol 4	**Request for clarification from Stakeholders** Article 8 might presume that conformity with harmonized standards related to system or process is a must. EFPIA will work with Stakeholders to ensure a correct interpretation of this article, which should be: Device products and / or systems being in conformity with relevant harmonized standards as published in the Official Journal of the European Union would facilitate conformity assessment, but Ph.Eur. requirements and European and ICH guidance-take precedence over ISO and other international standards.	

MDR Article reference	MDR Text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
	The first subparagraph shall also apply to system or process requirements to be fulfilled in accordance with this Regulation by economic operators or sponsors, including those relating to quality management systems, risk management, post-market surveillance systems, clinical investigations, clinical evaluation or post-market clinical follow-up ('PMCF'). References in this Regulation to harmonized standards shall be understood as meaning harmonized standards the references of which have been published in the Official Journal of the European Union.			2. **Article 8, section 2**, considers the monographs of the relevant European Pharmacopoeia as harmonized standards, especially those related to interaction between medicinal products and materials used in devices containing such medicinal products. Recommendations to Pharma Industry a) As outlined in the introduction, Pharma company manufacturing and/or marketing DDC products could rely on the Pharma Quality System (PQS) and complement the QMS with key specific requirements of device quality system. Certification to **ISO 13485** is not deemed a requirement. Applying principles of ISO 13485 does facilitate the compliance with some of the **MDR** requirements. b) Note: Some Rest of the World (ROW) countries, , like Canada, Taiwan,require an ISO 13485 certification. FDA announced also on December 5th, 2018 a transition from the 21 CFR part 820 to ISO13485:2016. ISO 13485:2016 has gained significant recognition globally in the world.	
Article 10 Section 2 **General Obligation of the Manufacturer** Risk Management System	Manufacturers shall establish, document, implement and maintain a system for risk management as described in Section 3 of Annex I.	Annex I General Safety and Performance Requirements (GSPR)	Eudralex 4 – Chapter 1 PQS – QRM 1.12 & 1.13 ICH Q9 ISO EN 13458 ISO 14971 EMA dGQR-DDC	**Link with PQS** **EU GMP** provides the expectations with regards to review of risk to the quality of product and link with the protection of patient, and refer to **ICH Q9** for the framework (How to do). See Review for Annex I Section 3 Risk Management System. As per EMA dGQR-DDC lines 241, 242 RM is expected for single integral DDC, while the EMA document mentions risk in non-integral DDC section (Lines 506-507) to indicate that the amount of product development information in Module 3.2.P. should	

MDR Article reference	MDR Text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
				reflect the risk of the device to impact the safety, efficacy & quality of the medicinal product. **Recommendation to Pharma Industry** The development of the DDC needs to be embarked in risk management process, which should comply with ISO 14971 and/or ICH Q9. Risk management is part of the overall review of the product with the device. See also notes about ISO 14971 and ISO EN 62366 here-below. **ISO 14971**, Medical Devices – Application of risk management to medical devices. If the results of risk analysis indicate that use errors could cause serious harm to the patient or the device user, then the manufacturer should apply appropriate human factors or usability engineering processes. ISO EN 62366 “Human factors”: Should be a consideration , in relation with ISO 14971. **US FDA** 21 CFR 820.30: As part of their Design Controls, manufacturers conduct a risk analysis that includes the risks associated with device use and the measures implemented to reduce those risks.	

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Article 10 Section 3 **General Obligation of the Manufacturer** Clinical evaluation including Post Marketing Clinical Follow-up (CE & PMCF)	Manufacturers shall conduct a clinical evaluation in accordance with the requirements set out in Article 61 and Annex XIV, including a PMCF.	Annex XIV Clinical Evaluation and Post-Marketing Follow-up (CE & PMCF)	EU Directive 2001/83/EC USFDA 21CFR820.30 Design controls	**Point of advocacy** MDR Annex I (GSPR) does not refer to Article 61. Therefore Single Integral DDC are excluded from this MDR requirement. **Recommendation to Pharma Industry** a) Pharma company need to take into consideration Annex I, Chapter II (10.3). 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. b) Clinical aspects of the device component are to be embarked in Design control for DDC product, as outlined in the Introduction. c) It is assumed that drug clinical data cover the device constituent for safety and performance, and therefore Art 61 would not apply. Let us pay attention that the Regulator must confirm that	**Key messages**: No additional requirements if Pharma company use the CE marked device within its intended use. **Request for clarification from Stakeholder** It is not clear whether the Pharma company would need to contribute to PMCF as per Annex XIV. Complying to MDR beyond CE marking should be clarified by EMA for Co-packaged DDC. **Recommendation to Pharma Industry** Clinical aspects of the device component are to be embarked in Design control for DDC product, as outlined in the Introduction. **US FDA** 21 CFR 820.30: As part of their Design Controls, manufacturers conduct a

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				no other requirements than Annex I would be necessary for Single Integral products, as Risk management for Benefit/Risk ratio is required. d) For well-established device, Clinical Evaluation Report (CER) should contain Drug Clinical Data and Scientific Data & Literature on the device in order to support clinical claims. e) For novel device, clinical investigation and data would be required. **US FDA** 21 CFR 820.30: As part of their Design Controls, manufacturers conduct a risk analysis that includes the risks associated with device use and the measures implemented to reduce those risks. Clinical evaluation aspects should be embarked in Design Control of the DDC product.	risk analysis that includes the risks associated with device use and the measures implemented to reduce those risks. Clinical evaluation aspects should be embarked in Design Control of the DDC product.

Article 10 Section 8 **General Obligation of the Manufacturer** Technical documentation	Manufacturers shall keep the technical documentation, the EU declaration of conformity and, if applicable, a copy of any relevant certificate, including any amendments and supplements, issued in accordance with Article 56, available for the competent authorities for a period of at least 10 years after the last device covered by the EU declaration of conformity has been placed on the market. In the case of implantable devices, the period shall be at least 15 years after the last device has been placed on the market. Upon request by a competent authority, the manufacturer shall, as indicated therein, provide that technical documentation in its entirety or a summary thereof. A manufacturer with a registered place of business outside the Union shall, in order to allow its authorised representative to fulfil the tasks mentioned in Article 11(3), ensure that the authorised representative has the necessary documentation permanently available.	NA	Eudralex Vol 4 Chapter 4 documentation 4.11 Batch documentation 4.12 Other type of documentation ICH M4 : The Common Technical Document	**Link with PQS** In contrast to the registration procedures for Medicinal products with ICH CTD format, the registration procedure of MDs product completely differs and is not comparable. Pharma company should comply with **Eudralex Vol 4 and ICH M4 requirements**, as MDR is not applicable to manufacturer of Single Integral DDC beyond Annex I GSPR, nor to Co-packaged DDC assuming that Pharma would not be the device manufacturer, nor would fall under Article 16 requirements (Cases when general obligations of the manufacturer apply to other economical actors). **a) Eudralex Vol 4:Chapter 4 documentation** 4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Qualified Person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. 4.12 For other types of documentation, the retention period will depend on the business activity which the documentation supports. **b) ICH M4 : The Common Technical Document:** The CTD is organised into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. In July 2003, the CTD became the mandatory format for new drug applications in the EU and Japan, and the strongly recommended format of choice for NDAs submitted to the FDA, US. **Request for clarification from Stakeholders** MDR specifies archiving timeframes of 10 years (15 years for implantable) after the last device put on the market. This would be a confirmed requirement for the device legal manufacturer only. For Pharma company manufacturing a DDC product , this would be defined by the registration type, i.e., by medicinal product directives if registered as a medicinal product. EFPIA will work to clarify MDR requirements beyond CE marking.

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Article 10 Section 9 **General Obligation of the Manufacturer** Quality Management System	Manufacturers shall ensure that procedures are in place to keep series production in conformity with the requirements of this regulation. Changes in device design or characteristics and changes in the harmonised standards or CS by reference to which the conformity of a device is declared shall be adequately taken into account in a timely manner. Manufacturers of devices, other than investigational devices, shall establish, document, implement, maintain, keep up to date and continually improve a quality management system that shall ensure compliance with this Regulation in the most effective manner and in a manner that is proportionate to the risk class and the type of device. The quality management system shall cover all parts and elements of a manufacturer's organisation dealing with the quality of processes, procedures and devices. It shall govern the structure, responsibilities, procedures, processes and management resources required to implement the principles and actions necessary to achieve	Annex I General Safety and Performance Requirements (GSPR) Annex XIV Clinical Evaluation and Post-Marketing Follow-up (CE & PMCF)	Eudralex Vol 4 Chapter I, Pharmaceutical Quality System (PQS) ICH Q10 Pharmaceutical Quality System implementation US FDA: 21CFR211 for GMP Medicinal products 21CFR820 for QMS for Medical Devices.	**<u>Link with PQS</u>** For Pharma company designing, manufacturing and/or marketing DDC, a holistic approach for its QMS is necessary. All depend on the conformity assessment requirements to comply with MDR. A review of the possible requirements is provided here below for Single Integral and Co-packaged DDC. The Publication of titles and references of harmonised standards under European Union harmonisation legislation contains ISO/EN Standards for specific Medical Devices technical requirements. This includes EN ISO 13485:2016 Medical devices — Quality management systems — Requirements for regulatory purposes. This is a commonly acknowledged standard for Manufacturers designing and manufacturing medical devices. **Eudralex Vol 4, Chapter I, PQS**, opens the door to a holistic approach, taking into consideration several aspects: - Section 1.3 The size and complexity of the company's activities should be taken into consideration… compare to "in a manner that is proportionate to the risk class" - Section 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required; - Art 6 of Directives 2003/94/EC and 91/412/EEC require manufacturers to establish and implement an effective pharmaceutical quality assurance system. The term Pharmaceutical Quality System is used in this chapter in the interests of consistency with ICH Q10 terminology	

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	compliance with the provisions of this Regulation. The quality management system shall address at least the following aspects:			**ICH Q10 – Pharmaceuticals Quality System** 1.5.1 Achieve Product Realisation to establish, implement and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers. 1.5.2 Establish and Maintain a State of Control To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. Quality risk management can be useful in identifying the monitoring and control systems. **Points of advocacy** The description of the QMS requirements does not include expectations with regards to device change management. Pharma Industry would advocate for major change to the device being covered in the QMS using recognized guidance document, which would be aligned with high level conditions described in paragraph 4.9 of Annex VII of the MDR, i.e., changes to the approved type of Device, to its design, to its intended purpose or claim made for it, or to any substance incorporated in or used for the manufacture of the Device. **Recommendation to Pharma Industry** 1. For Pharma company designing, manufacturing and/or marketing DDC, a holistic approach for its QMS is necessary. All depend on the conformity assessment requirements to comply with MDR. A review of the possible requirements is provided here below for Single Integral and Co-packaged DDC. EFPIA recommends Pharma company to check its PQS and complement it with specific aspects from MDR QMS as described in Annexes IX, X and XI, or	

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				from ISO 13485:2016, such as Design Control (See below for QMS expectations with regards to GSPR). **US FDA** 21 CFR Part 4 suggests for an integrated QMS when considering DDC products. Eudralex Vol 4 and ICH Q10 incorporate flexible QMS references which require adaptation of the quality system to the complexity of activities, the risk to patient and needs for compliance: For pharmaceutical manufacturers complying with 21CFR210/211 US 21CFR4 allows to implement an integrated QMS with the implementation of distinct aspects of 21CFR 820.	
	The quality management system shall address at least the following aspects: (a) a strategy for regulatory compliance, including compliance with conformity assessment procedures and procedures for management of modifications to the devices covered by the system;	NA	ICH Q10 Sections 1.5.1. & 1.5.2. US FDA 21CFR820.20	**Link with PQS**: A strategy for regulatory compliance should be established. Similar requirements in **PQS** address these expectations: **ICH Q10:** 1.5.1 Achieve Product Realisation To establish, implement and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers. 1.5.2 Establish and Maintain a State of Control To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. Quality risk management can be useful in identifying the monitoring and control systems.	

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				With regards to modifications to the devices, MDR Annex VII, Para 4.9 provides some conditions to assess changes to a Device. The Authors have also noted the following source document for Medical Devices: NBOG_BPG_2014_3 (Substantial Change Guidance). However, nor MDR, nor EMAdGQR-DDC provide clear criteria for classifying changes to Device and/or to DDCs. **Request for clarification from Stakeholders** EFPIA would like clarifications with regards to the translation of DDC change types in EMA variation procedures (Type IA, IB and II), and their expectations on content and format of data. **Recommendations to Pharma Industry** 1. The Legal Manufacturer should maintain a procedure for change assessment aligned with conditions described in paragraph 4.9 Annex VII of the MDR. 2. Review of the change assessment procedure should be part of the application process for engaging a Notified Body for purposes of undertaking Notified Body Opinions. 3. A change assessment should be made for every proposed change to device part of a DDC product and not include PQS QMS changes which do not fall under NB scope of responsibility **US-FDA 21CFR820.20 Management responsibility** Management responsibility requires an effective QMS while regulatory compliance is considered intrinsic to the medical device operations in order to obtain the marketing authorizations.	

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	The quality management system shall address at least the following aspects: (b) identification of applicable general safety and performance requirements and exploration of options to address those requirements;	This refers to GSPR without explicit reference to Annex I	US FDA 21CFR820.30 ISO 13485	**Recommendation to Pharma Industry** The Authors recommend that applicable requirements of Annex I be identified through implementation of Design Control in QMS , as described in ISO 13485:2016 and 21CFR820.30	
	The quality management system shall address at least the following aspects: (c) responsibility of the management;	NA	Eudralex Vol. 4 Section 1.4 (v) Managerial responsibilities 21CFR820 ISO 13485	**Link with PQS** Management responsibility is part of every QMS. Eudralex Vol 4 addresses this requirement, as described here below. **EudraLex Vol 4 - Chapter I Pharmaceutical Quality System:** 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: 1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System. **Chapter 2 Personnel:** 2.4 Senior management has the ultimate responsibility to ensure an effective quality management system is in place to achieve the	

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				quality objectives, and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality and should ensure continuing suitability and effectiveness of the quality management system and GMP compliance through participation in management review.	
	The quality management system shall address at least the following aspects: (d) resource management, including selection and control of suppliers and sub-contractors;	NA	EudraLex Vol 4 Chapter I Pharmaceutical Quality System Chapter V Production Chapter VII Outsourced activities ICH Q10 Section 2 Management responsibilities 21CFR820.20 Management responsibilities (2) Resources	**Link with PQS** a) Eudralex Vol 4 addresses this requirement, as described here below. **EudraLex Vol 4 - Chapter I Pharmaceutical Quality System** 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (vi) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain; (vii) Processes are in place to assure the management of outsourced activities. **Chapter 4 documentation** Technical Agreement are agreed between contract givers and acceptors for outsourced activities. **Chapter 5 production** Suppliers 5.27 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical	

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				quality system… The supporting evidence for each supplier / material approval should be maintained. **Chapter 7 outsourced activities** b) **ICH Q10 Section 2 Management responsibilities** **2.7 Management of Outsourced Activities and Purchased Materials** These requirements are similar to Eudralex Vol 4. **Recommendation to Pharma Industry** The Authors recommend that applicable requirements of Article 10 (9) (d) be managed as per ISO 13485:2016 and 21CFR820.50 for Purchasing Controls. **US FDA 21CFR820.20 Management responsibility** (2) Resources. Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities, including internal quality audits, to meet the requirements of this part. **21CFR820. Subpart E—Purchasing Controls** Evaluate, select, maintain records clearly includes consultants	
	The quality management system shall address at least the following aspects:	Annex I	ICH Q9	See Article 10 Section 2	

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	(e) risk management as set out in Section 3 of Annex I;	General Safety and Performance Requirements (GSPR)			
	The quality management system shall address at least the following aspects: (f) clinical evaluation in accordance with Article 61 and Annex XIV, including PMCF;	Annex XIV Clinical Evaluation and Post-Marketing Follow-up (CE & PMCF)	EU Directive 2001/83/EC	See Article 10 Section 3	
	The quality management system shall address at least the following aspects: (g) product realisation, including planning, design, development, production and service provision;	NA	EudraLex Vol 4 Chapter I Pharmaceutical Quality System ICH Q10 Section 3.1 Lifecycle stage goals 3.1.1 Pharmaceutical Development US FDA 21CFR820: Subpart C—Design Controls	**Link with PQS** a) **Eudralex Vol 4 Chapter I PQS** 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: :i Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes; b) **ICH Q10 Section 3.1 Lifecycle stage goals** **3.1.1 Pharmaceutical Development** **US-FDA 21CFR820.70: Subpart G—Production and Process Controls**	
	The quality management system shall address at least the following aspects: (h) verification of the UDI assignments made in accordance with Article 27(3) to all relevant devices and ensuring consistency	NA	NA	NA	**Key messages**: Potentially applicable to Co-packaged DDC. See EFPIA point for advocacy in MDR Process

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	and validity of information provided in accordance with Article 29;				Part IV – REGISTRATION PROCESS.
	The quality management system shall address at least the following aspects: (i) setting-up, implementation and maintenance of a post-market surveillance system, in accordance with Article 83;	NA	ICH Q10 3.2 PQS 3.2.1 Process Performance and Product Quality Monitoring System	**Point of advocacy** Article 83 is not included in Annex I, and is therefore not applicable to Single Integral DDC. The post-market surveillance system should comply with medicinal product directives.	**Point of advocacy** Article 83 is applicable to the Device legal manufacturer. Pharma Company shall report adverse event and complaint caused by the device component to the National Competent Authority of the medicinal product, and would need to communicate this type of information to the Device manufacturer.
	The quality management system shall address at least the following aspects: (j) handling communication with competent authorities, notified bodies, other economic operators, customers and/or other stakeholders;	NA	ICH Q10 3.2 PQS 3.2.1 Process Performance and Product Quality Monitoring System	**Key messages**: No modification of existing PQS	**Key messages**: Pharma company shall report adverse event and complaint caused by the device component to both the Device Manufacturer and the National Competent Authority of the medicinal product. Every communication to authorities for market action, registration etc. is

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					unique and need to be setup country by country.
	The quality management system shall address at least the following aspects: (k) processes for reporting of serious incidents and field safety corrective actions in the context of vigilance;	NA	NA	**Key message:** No modification of existing PQS	**Key messages**: Pharma company shall report adverse event and complaint caused by the device component to both the Device Manufacturer and the National Competent Authority of the medicinal product. General reporting strategies are already in place at every Pharma company. **Recommendation to Pharma Industry** Depending on the question who is the manufacturer additional reporting lines and timelines need to be established.
	The quality management system shall address at least the following aspects:	NA	ICH Q10 3.2 PQS	**Link with PQS**	

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	(l) management of corrective and preventive actions and verification of their effectiveness;		3.2.2 Corrective Action and Preventive Action (CAPA) System 21CFR820 Subpart J - § 820.100 Corrective and preventive action.	Based on ICH Q10 every pharmaceutical manufacturer shall have a CAPA System in place. **Recommendation to Pharma Industry** EFPIA recommends to verify that the CAPA system already includes proactive improvement CAPA, where pertinent decisions from quality management reviews, and CAPA effectiveness check. The idea is to reinforced the preventive action concept (cf ISO13485:2016)	
	The quality management system shall address at least the following aspects: (m) processes for monitoring and measurement of output, data analysis and product improvement.	NA	Eudralex Vol. 4 Section 1.4 US FDA 21CFR820.70 Production and process controls.	**Link with PQS** QMS for medicinal products is similar to MDR requirements. Eudralex Vol 4 addresses this requirement, as described here-below a) **Eudralex Vol. 4 Section 1.4** (i) Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes; (ii) Product and process knowledge is managed throughout all lifecycle stages; **US-FDA § 820.70 Production and process controls.** (a) General. Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications.	

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				(b) (2) Monitoring and control of process parameters and component and device characteristics during production;	
Article 10 Section 10 **General Obligation of the Manufacturer** Post Market Surveillance	Manufacturers of devices shall implement and keep up to date the post-market surveillance system in accordance with Article 83.	NA	EU Directives 2001/83/EC US-FDA 21 CFR822	**Key messages**: For Single Integral DDC, reporting to the competent authority would mean reporting to NCA / EMA only. There is no provision for double reporting as it is the case in Japan and US. If Articles 83_88 would not apply directly to Single Integral DDC products, the indirect relevance of these requirements remains, especially for high-risk class/type of device. MDR stipulates that the PMS system shall be proportionate to the risk class/type of the devices. A similar expectation is set forth by FDA. See recommendations here-below. See also MDR Process Part V – POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET. **Recommendation to Pharma Industry:** PMS, as per MDR Articles 83-86, should be performed and keep	**Key messages**: MDR requirements apply to the Device Manufacturer only. Assuming that Pharma would not fall under the applicability of Article 16, this requirement does not apply directly to Pharma manufacturing a Co-packaged DDC. However, the indirect relevance of these requirements remains, especially for high-risk class/type of device. MDR stipulates that the PMS system shall be proportionate to the risk class/type of the devices. A similar expectation is set forth by FDA. See recommendations here-below. Adverse event (AE) caused by a Co-packaged

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				internally if not required by NB or by CAMD. Same recommendation for article 93 (PSUR data). EFPIA underlines that this requirement might depend on the device risk profile, as requires in the US by 21CFR822. See also note here-below pertinent to both Single Integral and Co-packaged DDC products.	DDC would be reported to the respective competent authority through 2 channels: The device part would be reported to CA for medicinal product by the MAH and to CAMD by the legal Device manufacturer of the device. These requirements should be described in the quality agreement approved between Pharma and medical device manufacturer. It would mean that Pharma need to report complaints to legal manufacturer of the device. See also MDR Process Part V – POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE.

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				Recommendation to Pharma Industry: Pharma should continuously evaluated all device-related complaints for understanding of the safety, quality and performance impact of the device. As per Medical Device QMS requirements, this evaluation closes the loop with design control and/or manufacturing robustness. Especially, ISO 14971 requires: The manufacturer shall establish, document and maintain a system to collect and review information about the medical device or similar devices in the production and the post-production phase. E.g. To review risk/benefit and ensure the risk management file is a reflection of marketed device. **US-FDA 21 CFR822** Post Market Surveillance according to 21CFR822 requires manufacturers to perform studies of high-risk medical devices that have been granted 510(k) clearance or PMA approval.	
Article 10 Section 12 **General Obligation of the Manufacturer** Ensure implementation of corrective actions	Manufacturers who consider or have reason to believe that a device which they have placed on the market or put into service is not in conformity with this Regulation shall immediately take the necessary corrective action to bring that device into conformity, to withdraw it or to recall it, as appropriate. They shall inform the distributors of the device in question and, where applicable, the authorised representative and importers accordingly. Where the device presents a serious risk, manufacturers shall	NA	Eudralex Vol. 4 Part 1 Chapter 8: Complaints, Quality Defects and Product Recalls US FDA 21 CFR Part 806: Corrections and Removals (Recalls)	**Link with PQS** See Article 10 Section 10 here-above.	

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	immediately inform the competent authorities of the Member States in which they made the device available and, where applicable, the notified body that issued a certificate for the device in accordance with Article 56, in particular, of the non-compliance and of any corrective action taken.				
Article 10 Section 13 **General Obligation of the Manufacturer** Reporting incident and field safety corrective actions	Manufacturers shall have a system for recording and reporting of incidents and field safety corrective actions as described in Articles 87 and 88.	NA	Eudralex Vol. 4 Part 1 Chapter 8: Complaints, Quality Defects and Product Recalls US FDA 21 CFR Part 4 – Subpart B: Post-Marketing Safety Reporting for Combination Products	**Link with PQS** See Article 10 Section 10 here-above.	
Article 15 Section 1 **Person Responsible for Regulatory Compliance** Requirements	Manufacturers shall have available within their organisation at least one person responsible for regulatory compliance who possesses the requisite expertise in the field of medical devices. The requisite expertise shall be demonstrated by either of the following qualifications: (a) a diploma, certificate or other	NA	EU Directive 2001/83/EC – Article 49 US FDA 21CFR820	Not directly applicable to Single Integral DDC manufacturer, since MDR Annex I is pertinent only. **Link with PQS** In Article 49 of Directive 2001/83 , the qualification level as well as the necessary experience of a QP is defined:	Not applicable for Pharma manufacturing a Co-Packaged DDC assuming that requirements of Article 16 would not apply.

MDR Article reference	MDR Text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
	evidence of formal qualification, awarded on completion of a university degree or of a course of study recognised as equivalent by the Member State concerned, in law, medicine, pharmacy, engineering or another relevant scientific discipline, and at least one year of professional experience in regulatory affairs or in quality management systems relating to medical devices; (b) four years of professional experience in regulatory affairs or in quality management systems relating to medical devices. Without prejudice to national provisions regarding professional qualifications, manufacturers of custom-made devices may demonstrate the requisite expertise referred to in the first subparagraph by having at least two years of professional experience within a relevant field of manufacturing.			(2) "A qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology (…). The course shall include theoretical and practical study bearing upon at least the following basic subjects: … (See Art 49) Note: Qualifications of PRRC and QP are comparable, but experience type and duration in medical devices should be demonstrated. **Recommendation to Pharma industry:** Although Article 15 would not apply directly to Pharma , PRRC duties, as set forth in Article 15 Section 3 (See here-below), are pertinent to both type of DDC products. Therefore, EFPIA recommends to have systems and Quality & Regulatory specialists to address the specific requirements set forth in MDR, pertinent to drug administration devices and companion device applications, in order to make the appropriate link with other quality and regulatory Pharma quality systems, including Pharmacovigilance. This recommendation is also justified for Pharma marketing DDC Products in US and Japan markets, which have clear requirements for DDC products.	

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MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
				US FDA 21CFR820 Management representative	
Article 22 **System and procedure packs** **Sections 1, 2 & 3** Basic requirements	1. Natural or legal persons shall draw up a statement if they combine devices bearing a CE marking with the following other devices or products, in a manner that is compatible with the intended purpose of the devices or other products and within the limits of use specified by their manufacturers, in order to place them on the market as a system or procedure pack: (a) other devices bearing the CE marking; (b) in vitro diagnostic medical devices bearing the CE marking in conformity with Regulation (EU) 2017/746; (c) other products which are in conformity with legislation that applies to those products only where they are used within a medical procedure or their presence in the system or procedure pack is otherwise justified.	NA	NA	**Industry association position** (With the courtesy of MedTech Pharma Platform and Medicines for Europe (MFE), opinions received and supported by EFPIA (Responses to EFPIA Survey – February 2019): Article 22 is not applicable to DDCs (Drug Delivery Device Combination products). Indeed, the entire DDC presentation is governed by the medicinal product directive because the medicinal product is the primary mode of action so provisions for procedure packs (Primary mode of action is that of the devices) would be irrelevant to the whole presentation. Let us make sure the intended use is covering this, i.e., not “Combination product”, “System” or “Procedure pack” but, delivery/dosing of drugs or liquids. If not, i.e., **in case of where the intended use does not include use in a combination product**, then the system or procedure pack shall be treated as a device in its own right and shall be subject to the relevant conformity assessment	

MDR Article reference	MDR Text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR Part 3 or 4 reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
Annex I – General Safety and Performance Requirements					
Chapter I **General requirements** **Section 3** Risk management system	Manufacturers shall establish, implement, document and maintain a risk management system. Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall: (a) establish and document a risk management plan for each device; (b) identify and analyse the known and foreseeable hazards associated with each device; (c) estimate and evaluate the risks associated with, and occurring during, the intended use and	NA (Annex I)	EU Eudralex Vol 4 Chapter I – PQS EU Medicinal Directive 2001/83/EC – Risk Management for Pharmacovigilance ICH Q9 & Q10 US-FDA	**<u>Link with PQS:</u>** For Medicinal product Risk Management is divided in GMP/CMC Risk Management (ICHQ9) and Pharmacovigilance Risk Management (DIRECTIVE 2001/83/EC): a) The general principles set forth is ICH Q10 & ICH Q9 for GMP Risk Management are the same as for Medical Devices: identify, analyse, evaluate, report and mitigate. b) The principles for Risk Management Pharmacovigilance (DIRECTIVE 2001/83/EC) are similar to ICH Q9, but with a focus on safety & efficacy: Risk Management System is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions. Companies are required to submit a risk management plan (RMP) to the European Medicines Agency (EMA) when applying for a marketing authorisation. To help applicants, EMA developed guidance on how to submit RMPs. It should include information on: - A medicine's safety profile; - How its risks will be prevented or minimised in patients;	

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MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
	during reasonably foreseeable misuse; (d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4; (e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and (f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.			- Plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; - Measuring the effectiveness of risk-minimisation measures. If agreed with the competent authority and where needed for risk management planning purposes, the safety specification may include additional elements if they are resulting in important identified risk, important potential risk or missing information such as: - The disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches); - Innovative pharmaceutical forms (e.g. to contain a higher percentage of active substance which reduces the dose burden for patient and related side effects; long-term delivery gastricresident dosage forms for ultra-long-acting drug delivery may improve patients adherence to treatment and to reduce the gastro-intestinal side effect); - **Use of a medical device and risks associated with the medical device;** - Quality aspects relevant in relation to the safety of the product and not adequately addressed **Key messages**: The Risk Management for Medical Devices comprises GMP and Post-Market Surveillance (Vigilance). MDR directly refers to Plan and report structure. Topics to be in the Risk Management Plan and report are described. Risk Management is linked to the Post Market Surveillance System and is mentioned in EN ISO 14971.	

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MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements					
				EN ISO 14971 "Medical devices — Application of risk management to medical devices (ISO 14971:2007, Corrected version 2007-10-01) is mentioned in The Publication of titles and references of harmonised standards under Union harmonisation legislation **US-FDA** ISO 14971 is also a recognized consensus standard for the FDA 21CfR 820 does not directly mention Risk Management but does point out Management responsibility to check the adequacy of the Quality Management System. Risk Analysis is mentioned in Design validation.	
Annex I – General Safety and Performance Requirements – Chapter I					
Chapter I **General requirements** **Section 5** Risks related to use error	In eliminating or reducing risks related to use error, the manufacturer shall: (a) reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety). (b) give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).	NA (Annex I)	EU : EMA/606103/2014 US-FDA :21CFR820-30 Design Control	**Link with PQS:** EMA has issued a guideline document on risk minimization and prevention of medication errors: EMA/606103/2014 "Pharmacovigilance key principles of risk management planning in relation to medication errors arising from the medicinal product and its delivery system". This good practice guide outlines the key principles of risk management planning in relation to medication errors arising from the medicinal product and its delivery system. Please note that medication errors covers more than use error. **US-FDA** :21CFR820 30 Design Control	

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<tr><td colspan="6">MDR PROCESS PART I – Obligations of the Manufacturer and General Safety and Performance Requirements</td></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td colspan="2">The need for human factors is implied:
c) Design input – includes “needs of the user and patient”
f) Design verification – performance criteria met
g) Design validation – “… devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis….”

FDA Draft Guidance (2016): Human factors studies and related clinical study considerations in combination product design and development. Draft Guidance for Industry and FDA Staff.</td></tr>
<tr><td><u>Key messages:</u>
Question for Single Integral device component is how these checks are documented and what is the basis for the notified bodies to get their opinion on the Drug-Device Combination.</td><td><u>Key messages</u>: No comment</td></tr>
</table>

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MDR PROCESS PART I – Obligations of the manufacturer and general safety and performance requirements					
Annex I – General Safety and Performance Requirements – Chapter III					
Requirements Regarding The Information Supplied with the Device (Sections 23.1. , 23.2, 23.3 and 23.4)	Each device shall be accompanied by the information needed to identify the device and its manufacturer, and by any safety and performance information relevant to the user, or any other person, as appropriate. Such information may appear on the device itself, on the packaging or in the instructions for use, and shall, if the manufacturer has a website, be made available and kept up to date on the website, taking into account the following: (a) The medium, format, content, legibility, and location of the label and instructions for use shall be appropriate to the particular device, its intended purpose and the technical knowledge, experience, education or training of the intended user(s). In particular, instructions for use shall be written in terms readily	NA (Annex I)	EU Directive 2001/83/EC	**Key message:** Chapter 3 provides the rRequirements regarding the information supplied with the device • Instruction of use and warning/precaution of use • Instruction of safe disposable • Instructions for software and hardware IT network and security plan (Optional, it depends on the type of device) • Website of the manufacturer (Not relevant for SI DDC, as SMPC) **Request for clarification from Stakeholders:** EFPIA will work with EMA to define the labelling requirements specific to the device part, especially for Single-Integral DDC.	

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MDR PROCESS PART I – Obligations of the manufacturer and general safety and performance requirements					
Annex I – General Safety and Performance Requirements – Chapter III					
	understood by the intended user and, where appropriate, supplemented with drawings and diagrams. (b) The information required on the label shall be provided on the device itself. If this is not practicable or appropriate, some or all of the information may appear on the packaging for each unit, and/or on the packaging of multiple devices. (c) Labels shall be provided in a human-readable format and may be supplemented by machine-readable information, such as radio-frequency identification ('RFID') or bar codes. (d) Instructions for use shall be provided together with devices. By way of exception, instructions for use shall not be required for class I and class IIa devices if such devices can be used safely without any such instructions and unless otherwise provided for elsewhere in this Section.				

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MDR PROCESS PART I – Obligations of the manufacturer and general safety and performance requirements					
Annex I – General Safety and Performance Requirements – Chapter III					
	(e) Where multiple devices are supplied to a single user and/or location, a single copy of the instructions for use may be provided if so agreed by the purchaser who in any case may request further copies to be provided free of charge. (f) Instructions for use may be provided to the user in non-paper format (e.g. electronic) to the extent, and only under the conditions, set out in Regulation (EU) No 207/2012 or in any subsequent implementing rules adopted pursuant to this Regulation (g) Residual risks which are required to be communicated to the user and/or other person shall be included as limitations, contra-indications, precautions or warnings in the information supplied by the manufacturer (h) Where appropriate, the information supplied by the manufacturer shall take the form of internationally recognised				

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MDR PROCESS PART I – Obligations of the manufacturer and general safety and performance requirements					
Annex I – General Safety and Performance Requirements – Chapter III					
	symbols. Any symbol or identification colour used shall conform to the harmonised standards or CS. In areas for which no harmonised standards or CS exist, the symbols and colours shall be described in the documentation supplied with the device.				

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MDR Process Part II - Clinical Evaluation					
Article 2 **Definition** (44) Clinical Evaluation	'clinical evaluation' means a systematic and planned process to **continuously** generate, collect, analyse and assess the **clinical data** pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer;	NA	ICH E Guidelines Regulation (EU) No 536/2014	**<u>Link with PQS:</u>** Although the term Clinical Evaluation is also used in ICH E guidelines, it is used as a general term designating the assessment of clinical trials performed to evaluate the safety of Medicinal Products. The term Clinical Evaluation is not used in Regulation EU 536/2014. Only Clinical Study and Clinical Trials are used. The use of the term Clinical Evaluation under MDR 2017/745 is clearly defined and covers specific meanings like relevant scientific literature, which is not considered per se in ICH E guidelines or EU 536/2014. **<u>Key message:</u>** Clinical Evaluation does not necessarily mean Clinical Investigation (Study). MDR makes clear distinction between both terms. A critical evaluation of all available clinical investigation data and demonstration to GSPR (Annex I) might form the basis of an appropriate clinical evaluation. It is recognized that the meeting between EFPIA/EBE and TEAM-NB WG on July 5th 2019 also provides some insight with regards to NB expectations for SI DDC products and clinical data expectations as part of the NB assessment to meet Article 117. **See also Article 61 Section 3**	

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MDR Process Part II - Clinical Evaluation					
Article 2 **Definition** (48) Clinical data	'clinical data' means information concerning safety or performance that is generated from the use of a device and is sourced from the following: — clinical investigation(s) of the device concerned, — clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated, — reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated, — clinically relevant information coming from post-market	NA	ICH E Guidelines Regulation (EU) No 536/2014	**Link with PQS:** The term Clinical Data under MDR 207/745 covers more meanings than the same term under EU 536/2014. For medicinal products, clinical data derived from clinical trial only.	

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MDR Process Part II - Clinical Evaluation					
Article 2 **Definition** (51) Clinical evidence	Clinical evidence: means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer	NA	Not mentioned in EU 536/2014, nor in US-FDA 21 CFR Part 4 or 820	**<u>Key message:</u>** This definition uses the term Clinical Benefit which is also defined in MDR . See definition (53) here-below.	
Article 2 **Definition** (53) Clinical benefit	Clinical benefit: means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health	NA	ISO 14971	**<u>Key message:</u>** This term is mentioned in risk management for Medical Device EN ISO 14971.	
Article 61 Section 1 **Clinical Evaluation**	Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the	Annexe I (GSPR) Annexe III (CONFORMITY TO THE TECHNICAL DOCUMENTATION REQUIREMENTS ON POST-MARKET SURVEILLANCE	NA	**<u>Key message:</u>** This section points out the requirements to provide the clinical evidence of fulfilling Annex 1 with a clinical evaluation with reference to Annex III and Annex XIV (Part A). It is important to consider Annex I, Chapter II (10.3): *„**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*	

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MDR Process Part II - Clinical Evaluation					
	acceptability of the benefit-risk-ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III. The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose. To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.	OF THE MEDICAL DEVICES REGULATION 2017/745) Annexe XIV (EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP) Part A (CLINICAL EVALUATION)		*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.* This overall requirement implies to evaluate the clinical aspects but not necessarily to generate clinical investigation data (Clinical studies). See also: - **Article 5, sections 2 & 3 - Placing on the market and putting into service.** **- Article 61 Section 3 and EFPIA recommendation to Pharma Industry.** **Point of advocacy** It is EFPIA advocacy point that there is no need to apply MDR Article 61 requirement for DDC product that are supported by drug clinical data delivered with the device of the DDC product.	
				Request for clarifications from Stakeholders: - Annex I does not mention Clinical Evaluation nor Article 61. Clarification is required as DDC clinical data do not necessarily include the use of the single integral device. - What level of evidence would be required by NB, as a function of the device component risk class and on the available clinical evaluation ?	**Key messages**: The device part of the Co-packaged DDC must be used within the intended purpose. If the Pharma company used the device for a purpose which was not intended by the device manufacturer, then the Pharma company becomes manufacturer as per **MDR definition** and needs to comply with manufacturer obligations as per MDR Article 16. See development of **MDR Article 16**.

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MDR Process Part II - Clinical Evaluation					
					Request for clarifications from Stakeholders: Beyond CE marking, clarification is required as DDC clinical data do not necessarily include the use of the same CE marked device.
Article 61 Section 3 **Clinical Evaluation**	A clinical evaluation shall follow a defined and methodologically sound procedure based on the following: (a) a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where the following conditions are satisfied: — it is demonstrated that the device subject to clinical evaluation for the intended purpose is equivalent to the device to which the data relate, in accordance with Section 3 of Annex XIV, and — the data adequately demonstrate compliance with the	Annex XIV (EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP) Annex XV (CLINICAL INVESTIGATIONS)	EU Eudralex Volume 1 US-FDA: NA	**Link with PQS:** EudraLex Vol. 1 only mentions clinical trials for medicinal products and not for medical devices. However, it is mentioned in ISO 13485: 2016 – Design and development validation. **Key messages:** Clinical Evaluation does not necessarily mean Clinical Investigation (Study). **A critical evaluation of all available clinical investigation data and demonstration to GSPR (Annex I) might form the basis of an appropriate clinical evaluation.** For Non Integral device, it is key to demonstrate that the intended purpose declared in the Conformity Assessment is respected. **Request for clarification from Stakeholders** EFPIA would like clarity about differences between well-established and novel devices. For novel device, the Clinical Evaluation Report should contain Drug Clinical Data, Scientific Data & Literature on the device in order to support clinical claims. Post-workshop note: EMA dGQR-DDC provides basic guidance about emerging technologies (Chapter 9 – Emerging Technologies). **Recommendation to Pharma Industry:**	

MDR Article Reference	MDR Text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR Process Part II - Clinical Evaluation					
	relevant general safety and performance requirements; (b) a critical evaluation of the results of all available clinical investigations, taking duly into consideration whether the investigations were performed under Articles 62 to 80, any acts adopted pursuant to Article 81, and Annex XV; and (c) a consideration of currently available alternative treatment options for that purpose, if any.			Clinical aspects should be be embarked in Design control for DDC product (Cfr ISO 13485:2016) **US-FDA:** Clinical Evaluation is not mentioned in 21 CFR Part 4 or 820.	
Article 61 **Section 11** **Clinical evaluation** Update	The clinical evaluation and its documentation shall be updated throughout the life cycle of the device concerned with clinical data obtained from the implementation of the manufacturer's PMCF plan in accordance with Part B of Annex XIV and the post-market surveillance plan referred to in Article 84. For class III devices and implantable devices, the PMCF evaluation report and, if indicated, the summary of safety and	Annex XIV – Part B (EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP)	NA	**Point of advocacy:** It is assumed that drug clinical data cover the device constituent for safety and performance, and therefore Art 61 would not apply.	**Request for clarification from Stakeholders:** Non Integral DDC product would be regulated under medicinal product Directive 2001/83/EC and would therefore be exempt from post-market surveillance plan as referred under MDR in Article 83 & 84. See MDR Process Part V – POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE

MDR Article Reference	MDR Text	MDR Annex reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device constituent)
MDR Process Part II - Clinical Evaluation					
	clinical performance referred to in Article 32 shall be updated at least annually with such data.				
ANNEX XV CLINICAL INVESTIGATIONS					
Annex XV Chapter II section 1.7 page 168	if the application is submitted in parallel with an application for a clinical trial in accordance with Regulation (EU) No 536/2014, reference to the official registration number of the clinical trial;	NA (Annex XV)	Regulation (EU) No 536/2014	**Link with PQS:** This paragraph of Annexe XV, Chapter II, indicates that conformity assessment for device used in combination with drug could be based on clinical data generated under medicinal product regulation for clinical trial.	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
CLASSIFICATION OF DEVICES					
Article 51 **Section 1** **Classification of devices** General rule	Devices shall be divided into classes I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks. Classification shall be carried out in accordance with Annex VIII.	**Annex VIII** (Classification rules)	NA	**Link with PQS:** There is no device classification system described in medicinal product directives. **Key messages**: - Application of the MDR classification rules shall be governed by the intended purpose of the CE marked devices; - Single-Integral DDCs are not Medical Devices and can therefore not be classified as per MDR Annex VIII Classification Rules. However, EMA has mentioned the applicability of the classification rules to the device component of a Single Integral DDC (See EMA document published on 27 February 2019, page 5, question 1.3 - Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)); Therefore, when applying these rules to the Device part of a Single-Integral DDC, Pharma Industry should consider the device component as it would be used alone. The use of MDR to classify Single-Integral DDC would need confirmation with the issuance of upcoming guidance documents by EMA and/or NBs. **Recomendation to Pharma Industry:** EFPIA recommends Pharma Industry to follow all definitions, implementing and classification rules defined in Annex VIII for CE marked device classification. For ease of review by Pharma Industry, the Authors provide a series of classification example for device parts of frequently marketed DDC products.	

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<tr><td colspan="6">MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td></td><td></td><td><u>Examples for Single-Integral Device component:</u>

1° Pre-filled syringe – Class IIa (Rule 6) (**) if the administration of the medicinal product is done in a manner that is not potentially hazardous; Otherwise Class IIb.

2° Patch – Class I (Rule 2) (*)</td><td><u>Examples for CE marked Device:</u>

1° Vial adaptor – Class IIa (Rule 2) (*)

2° Reconstitution syringe – Class IIa (Rule 2) (*)

3° Stand-alone syringes with needles - Class IIa (Rule 6) (**)

4° Electronic injector – Class IIa (Rule 12) (***)

5° Nazal or buccal syringe for oral administration – Class IIa (Rule 20) (****)</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2"><u>(*) Rule 2</u> : All non-invasive devices intended for channelling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are classified as class IIa:
— if they may be connected to a class IIa, class IIb or class III active device; or
— if they are intended for use for channeling or storing blood or other body liquids or for storing organs, parts of organs or body cells and tissues, except for blood bags; blood bags are classified as class IIb. In all other cases, such devices are classified as class I.

<u>(**) Rule 6</u> : All surgically invasive devices intended for transient use are classified as class IIa unless they are intended to administer medicinal products by means of a delivery system, if such administration of a medicinal product is done in a manner that</td></tr>
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MDR Article Reference	MDR Text	MDR Annex Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device
MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
				is potentially hazardous taking account of the mode of application, in which case they are classified as class IIb. **(***) Rule 12 : All active devices intended to administer and/or remove medicinal products, body liquids or other substances to or from the body are classified as class IIa**, unless this is done in a manner that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode of application in which case they are classified as class IIb. **(****) Rule 20: Invasive device for administration of medicinal product by inhalation - All invasive devices with respect to body orifices, other than surgically invasive devices, which are intended to administer medicinal products by inhalation are classified as class IIa,** unless their mode of action has an essential impact on the efficacy and safety of the administered medicinal product or they are intended to treat life- threatening conditions, in which case they are classified as class IIb.	
CONFORMITY ASSESSMENT					
Article 52 **Sections 1 & 2** **Conformity assessment procedures**	Prior to placing a device **on the market**, manufacturers shall undertake an assessment of the conformity of that device, in accordance with the applicable conformity assessment procedures set out in Annexes IX to XI. Prior to putting **into service** a device that is not placed on the	**Annex II** (Technical Documentation) **Annex III** (Technical Documentation post-market surveillance) **Annex IX** (Conformity Assessment Based on QMS and Assessment of	NA	**Key messages :** 1) There is no need for Pharma Industry manufacturing DDCs to comply with conformity assessment procedures, since both Single-Integral and Co-Packaged DDCs are governed by medicinal product directives, and CE marked devices for Co-Packaged DDCs are supplied by Device Manufacturers. However, there is a need for Pharma Industry to understand Medical Device QMS aspects as outlined in Section 2.2 of this document, in order to: - Use a streamline approach when developing DDC products, similar to US-FDA 21 CFR Part 4 , - Be able to define mutual expectations and responsibilities in quality agreement and contract between Pharma Company	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	market, manufacturers shall undertake an assessment of the conformity of that device, in accordance with the applicable conformity assessment procedures set out in Annexes IX to XI.	Technical Documentation) **Annex X** (Examination of assessment) **Annex XI** (QMS for Product Conformity Verification)		and Third Party (Device Manufacturer, or Device Component Manufacturer). The Authors underline that the QMS requirements under MDR Article 52 are developed as a function of the Device class. The interesting information for Pharma Industry is the reference to Annex IX and XI which describe in more details QMS requirements for Device Manufacturers and surveillance by NBs (Audits) as a function of Device classification. 2) Pharma Industry would need to report PMS & vigilance to Device Manufacturers. Respective responsibilities and process for this reporting should be described in Quality Agreement. There is a need for a clear agreement for Safety Data exchange between Pharma & Device Manufacturer. See also MDR Process Part for PMS.	
Article 55 **Clinical evaluation consultation procedure for certain class III and class IIb devices**	In addition to the procedures applicable pursuant to Article 52, a notified body shall also follow the procedure regarding clinical evaluation consultation as specified in Section 5.1 of Annex IX or as referred to in Section 6 of	**Annex VIII** (Classification rules) **Annex IX** (Conformity Assessment Based on QMS and Assessment of	NA	**<u>Key messages</u> :** 1) Article 55 applies to Class III implants and Class IIb active, drug-delivery devices. Note: Class III would not be relevant to DDC for which the drug has the primary mode of action. 2) MDR regulates expert panels and the conflict of interests in Art. 106 and 107.	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
Section 1	Annex X, as applicable, when performing a conformity assessment of the following devices: (a) class III implantable devices, and (b) class IIb active devices intended to administer and/or remove a medicinal product, as referred to in Section 6.4 of Annex VIII (Rule 12).	Technical Documentation) **Annex X** (Examination of assessment)		**Key message :** The use of classification rules for device, mentioned by EMA in its Q & A document (28 Feb 2019) does not mean that Single-Integral DDC, falling into class IIB for its device component, would be reviewed by the Expert Panel regarding clinical evaluation consultation. Indeed, EMA states that specific impact of the device on the medicinal product is under the authority of CA/EMA.	**Key message :** Class IIb device used in Non integral DDC might impose the consultation of the Expert Panel by NB. **Recommendation to Pharma Industry:** It is recommended to identify and engage in discussions with a NB and to engage with medicines CAs in a timely manner, in order to confirm the device classification and the procedure for clinical evaluation.
Article 56 **Declaration of Conformity** **Sections 1 & 2**	The certificates issued by the notified bodies in accordance with Annexes IX, X and XI shall be in an official Union language determined by the Member State in which the notified body is established or otherwise in an official Union language acceptable to the notified body. The minimum content of the certificates shall be as set out in Annex XII.	**Annex IX** (Conformity Assessment Based on QMS and Assessment of Technical Documentation) **Annex X** (Examination of assessment) **Annex XI** (QMS for Product Conformity Verification)	NA	**Key message :** The period of validity of the certificate is the decision of the Notifed Body. The NB defines in his Terms and Conditions how long his certificates will be valid. There is no consistency ensured among NB. NB will give max 3 years for QMS and max 5 years for CE marking. **Point of advocacy:** EFPIA advocate for a simplified procedure, when considering no or few changes, and also on a guidance or rule, using a risk-based approach for NB to decide on the minimum validity of a certificate. This would promote harmonization as much as possible.	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	The certificates shall be valid for the period they indicate, which shall not exceed five years. On application by the manufacturer, the validity of the certificate may be extended for further periods, each not exceeding five years, based on a re-assessment in accordance with the applicable conformity assessment procedures.	**Annex XII** (Certificates issued by a Notified Body)			
Article 86 **Periodic safety update report (3)**	For devices other than those referred to in paragraph 2 (i.e. Class III devices), manufacturers shall make PSURs available to the notified body involved in the conformity assessment and, upon request, to competent authorities.	**NA**	Medicinal Product Directive 2001/83/EC	**Link with PQS:** Article 86 is not applicable to DDCs registered as medicinal products. **Request for clarification** However, it is not clear yet to what extent Pharma Company would need to provide data PSUR to Device Manufacturer for the Devices used in Non Integral DDCs. EFPIA requires clarification from Stakeholders.	
Article 117 **Amendment to Directive 2001/83/EC '(12)**	In Annex I to Directive 2001/83/EC, point 12 of Section 3.2. is replaced by the following: '(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (*), a product is governed by this Directive, the marketing authorisation dossier shall include,	**Annex I (GSPR)**	Medicinal Product Directive 2001/83/EC	**Link with PQS:** MDR Article 117 includes Integral or Single-Integral drug device combination products in its scope. Non Integral DDCs are not included in Article 117, as per MDR scope and matter for DDC products described in Article 1 Sections 8 & 9. For Single-Integral DDCs, the content and format of the NBOp is partially addressed by EMA in its dGQR-DDC: See Section 5 – Integral DDCs.	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device. If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.			However, NBs work also with EC and EMA to develop guidelines pertinent to the content, the format and the process by which NB will establish its NBOp for Single-Integral DDC. At this stage, the assumptions are that: - NBs should focus on content of NBOp, not on QMS; - Timing for establishing NBOp would be NB dependent; It is not yet 100% clear how NB and CA/EMA respective GSPR data review roles will be; The same set of data might be necessary for NB & CA/EMA, but with complementary assessment objectives. **Request for clarification from Stakeholders about a specific case:** For the submission of a new Single Integral DDC product after 26 May 2020, would a relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device under the MDD be acceptable regulatory-wise providing that the certificate is still valid ? **Point of advocacy:** EFPIA would like clear process about how fees and timelines are made public, how fees are derived, and how Device Manufacturer and Pharma Industry can use these information in the NB engagement process (Cfr Art. 53, engagement of 1 NB at a time) **Recommendation to Pharma Industry:** It is recommended to carefully review and define timelines in the applicant-NB contract when engaging a NB.	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	(*) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1).				
ANNEX IX CONFORMITY ASSESSMENT BASED ON QMS AND ASSESSMENT OF TECHNICAL DOCUMENTATION					
Chapter I **Section 2.2 (c)** Design of the device	(c) the procedures and techniques for monitoring, verifying, validating and controlling the design of the devices and the corresponding documentation as well as the data and records arising from those procedures and techniques. Those procedures and techniques shall specifically cover: — the strategy for regulatory compliance, including processes for identification of relevant legal requirements, qualification, classification, handling of equivalence, choice of and compliance with conformity assessment procedures,	NA	NA	**<u>Key messages:</u>** 1) For both Single-Integral and Non integral DDCs, EMA states in its draft Guidance on Quality Requirements for DDCs, under section 4.1 „Application of standards (Lines 169-171), that *Compliance of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards.* 2) MDR 2017/745 places **Design of the device** at the core of QMS for Medical Device. Of particular interest are: a) The need to define the regulatory strategy b) The need to identify the applicable GSPR and solutions to fulfill these requirements (Applicable CS, harmonized standards or other adequate solutions) ➢ For instance, ISO10993 for biocompatibility	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	— identification of applicable general safety and performance requirements and solutions to fulfil those requirements, taking applicable CS and, where opted for, harmonised standards or other adequate solutions into account, — risk management as referred to in Section 3 of Annex I, — the clinical evaluation, pursuant to Article 61 and Annex XIV, including post-market clinical follow-up, — solutions for fulfilling the applicable specific requirements regarding design and construction, including appropriate pre-clinical evaluation, in particular the requirements of Chapter II of Annex I, — solutions for fulfilling the applicable specific requirements regarding the information to be supplied with the device, in particular the requirements of Chapter III of Annex I, — the device identification procedures drawn up and kept up to date from drawings,			c) The focus on risk management throughout the entire life of the product: ➢ Compliance with ISO14791 or ICH Q9 ➢ Design risk analysis ➢ Risk analysis of medication errors (e.g. due to some similarity of devices) ➢ Risk of patient not administrating the correct dose ➢ Manufacturing risk analysis ➢ Risk from potential contamination arising from the device design, manufacturing, packaging storage and shipment to the patient d) The clinical evaluation, pursuant to Article 61 and Annex XIV, including post-market clinical follow-up e) The need for pre-clinical evaluation as per Chapter II of Annex I (GSPR) **Recommendation to Pharma Industry:** Using Design Control as per ISO 13485:2016, or as per 21 CFR Part 820, or as per MDR Annex IX, right from the beginning of the development of a new Single Integral Product or Non-Integral DDC, including Usability Engineering, provides a structured development path, to facilitate compliance with regulatory requirements as expected by EMA in its draft Guidance on Quality Requirements for DDCs. This is not in conflict with the key message sated here-above.	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	specifications or other relevant documents at every stage of manufacture, and — management of design or quality management system changes;				
Chapter I **Section 4.10** Change of an approved device	Changes to the approved device shall require approval from the notified body which issued the EU technical documentation assessment certificate where such changes could affect the safety and performance of the device or the conditions prescribed for use of the device. Where the manufacturer plans to introduce any of the above-mentioned changes it shall inform the notified body which issued the EU technical documentation assessment certificate thereof. The notified body shall assess the planned changes and decide whether the planned changes require a new conformity assessment in accordance with Article 52 or whether they could be addressed by means of a supplement to the EU technical documentation assessment certificate. In the latter case, the	NA	EUDRALEX Vol 4 EU 2001/83/EC Medicinal Product Directives EMA draft Guidance on Quality Requirements for DDC (EMAdGQR-DDC)	**<u>Link with PQS:</u>** EMA dGQR-DDC describes the expectations in Section 8 – Lifecycle Management : *A change listed in the variation guideline will require a variation of the appropriate category to be submitted to the medicines CA(s). All changes to medical devices and/or device components within DDCs should be presented in accordance with the relevant EU Variations Regulation and associated variation guidelines in place and should be submitted under the appropriate category.* *Depending on the nature of the change, the MAH should consider whether updates to relevant documentation (e.g. NBOp, Declaration of Conformity, CE mark etc.) associated with the device in question are required to support the change. The category of variation should take into consideration the impact of the change, e.g. a change to a device that impacts any DDC CQAs and/or any element(s) of the overall DDC control strategy may be considered a higher category of variation. In cases where the need for a variation is unclear and/or the category of the change is unclear, it is recommended that the medicines CA that issued the MA is consulted to agree the category prior to submission of the variation application.*	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	notified body shall assess the changes, notify the manufacturer of its decision and, where the changes are approved, provide it with a supplement to the EU technical documentation assessment certificate.			**Key message :** The medicines CA are the main contacts for Pharma Industry, for both Single-Integral and Non Integral DDCs. **Request for clarifications from Regulators:** EFPIA would like clarifications with regards to the translation of DDC change types in EMA variation procedures (Type IA, IB and II).	
ANNEX XIV CLINICAL EVALUATION AND POST-MARKET FOLLOW-UP					
PART B **POST-MARKET CLINICAL FOLLOW-UP (5)**	PMCF shall be understood to be a continuous process that updates the clinical evaluation referred to in Article 61 and Part A of this Annex and shall be addressed in the manufacturer's post-market surveillance plan. When conducting PMCF, the manufacturer shall proactively collect and evaluate clinical data from the use in or on humans of a device which bears the CE marking and is placed on the market or put into service within its intended purpose as referred to in the	NA	EUDRALEX VOL 4	**Link with PQS:** The Device Manufacturer of a Non integral DDC would be considered as a supplier of the Pharma Company. Although it is not clear yet to what extent Pharma Industry will need to feed in the PMCF plan of the Device Manufacturer, the quality agreement (QAA) shall describe the mutual responsibilities of Pharma Company and Device Manufacturer with regards to pertinent data for updates of clinical evaluations. The exchange of data should be defined for both directions.	

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MDR PROCESS PART III – CLASSIFICATION AND CONFORMITY ASSESSMENT					
	relevant conformity assessment procedure, with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks on the basis of factual evidence.				

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<tr><th>MDR Article Reference</th><th>MDR Text</th><th>MDR Annex and Reference</th><th>Eudralex Vol 4 or ICH or 21 CFR reference</th><th>Comments for Single Integral DDC (With device being not CE marked)</th><th>Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device</th></tr>
<tr><td colspan="6">MDR PROCESS PART IV – REGISTRATION PROCESS</td></tr>
<tr><td colspan="6">The Guideline EMA/CHMP/QWP/BWP/259165/2019 provides guidance on the documentation expected for Drug-Device Combinations (DDCs) in the quality part of the dossier for a marketing authorisation application or a variation application.</td></tr>
<tr><td rowspan="2">Article 29

Section 1

Registration of devices</td><td rowspan="2">Before placing a device, other than a custom-made device, on the market, the manufacturer shall, in accordance with the rules of the issuing entity referred to in Article 27(2), assign a Basic UDI-DI as defined in Part C of Annex VI to the device and shall provide it to the UDI database together with the other core data elements referred to in Part B of Annex VI related to that device.</td><td rowspan="2">Annex VI (European UDI system)

Part B

(CORE DATA ELEMENTS TO BE PROVIDED TO THE UDI DATABASE TOGETHER WITH THE UDI-DI IN ACCORDANCE WITH ARTICLES 28 AND 29)

Part C

(THE UDI SYSTEM)</td><td rowspan="2">EU Directive 2001/83/EC: NA

US-FDA 21 CFR Part 820.120</td><td colspan="2"><u>Key message:</u>

DDC registered as medicinal product does not require UDI; DDC labeling needs to follow medicinal product regulations and traceability requirements. However, CE marked devices have UDI affixed (See below).</td></tr>
<tr><td><u>Key message:</u>

Single-Integral DDCs are not subjected to MDR requirements for UDI. This was confirmed by MDCG (Guidance 2019-2, published in February 2019).</td><td><u>Key message:</u>

CE marked devices, used in Non Integral DDCs, have UDI affixed, as per MDR Article 29.

<u>Point for advocacy</u>
The PQS ensures that the device information is traceable; EFPIA advocates for UDI being affixed on the device itself or its primary packaging, not on the secondary packaging of the DDC, similar to US-FDA 21 CFR Part820 (See below).
The UDI will be checked and documented in DDC batch records and SmPC. Non Integral DDCs registered as medicinal porduct must indeed comply</td></tr>
</table>

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MDR PROCESS PART IV – REGISTRATION PROCESS					
					with serialisation for safety measure and traceability along the distribution chain. **US-FDA** **21cfr820.120** requires an UDI for medical Devices: However there is an exemption (b) National Drug Code (NDC) Numbers. If a combination product properly bears an NDC number on its label-- (1) The combination product is not subject to the requirements of 801.20. (2) A device constituent of such a combination product whose components are physically, chemically, or otherwise combined or mixed and produced as a single entity as described by 3.2(e)(1) of this chapter is not subject to the requirements of 801.20. (3) Each device constituent of such a combination product, other than one described by 3.2(e) (1) of this chapter, must bear a UDI on its label unless paragraph (a) (11) of this section applies.

MDR Article Reference	MDR Text	MDR Annex and Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device
MDR PROCESS PART IV – REGISTRATION PROCESS					
Article 30 **Section 2**	Member States may maintain or introduce national provisions on registration of distributors of devices which have been made available on their territory.	NA	NA	**Key message:** This requirement is not applicable to Pharma Industry marketing and distributing Single-Integral DDC.	**Point for advocacy** On top of EFPIA request for streamline approach of GDP for Non Integral DDC, i.e., with limited application of Article 29, EFPIA advocates for non-applicability of Articles 14 & 30 to Pharma Company distributing Non Integral DDCs.
Article 31 **Sections 1 & 2** **Registration of manufacturers, authorised representatives and importers**	Before placing a device, other than a custom-made device, on the market, manufacturers, authorised representatives and importers shall, in order to register, submit to the electronic system referred to in Article 30 the information referred to in Section 1 of Part A of Annex VI, provided that they have not already registered in accordance with this Article. In cases where the conformity assessment procedure requires the involvement of a notified body pursuant to Article 52, the information referred to in Section 1 of Part A of Annex VI shall be provided to that electronic system before applying to the notified body.	**Annex VI (European UDI system)** **Part A** INFORMATION TO BE SUBMITTED UPON THE REGISTRATION OF DEVICES AND ECONOMIC OPERATORS IN ACCORDANCE WITH ARTICLES 29(4) AND 31	NA	**Key message:** These requirements are only pertinent to Pharma Company that would import CE marked devices into EU.	

MDR Article Reference	MDR Text	MDR Annex and Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device
MDR PROCESS PART IV – REGISTRATION PROCESS					
	After having verified the data entered pursuant to paragraph 1, the competent authority shall obtain a single registration number ('SRN') from the electronic system referred to in Article 30 and issue it to the manufacturer, the authorised representative or the importer.				

MDR Article Reference	MDR Text	MDR Annex and Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device)
MDR PROCESS PART V – POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE					
Article 83 **Section 1** **Post-market surveillance system of the Manufacturer**	For each device, manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device. That system shall be an integral part of the manufacturer's quality management system referred to in Article 10(9) (= General Obligation of the Manufacturer – QMS)	NA	Medicinal product directive 2001/83/EC	**Link with PQS:** The reporting pathway determines the reporting procedure. Since DDCs are registered as medicinal products, Pharma Company should report to EMA or Competent Authority (CA) only. Therefore MDR Articles 83, 84, 85, 86, 87, 88, 89 & 95 would not apply to Pharma Company manufacturing and marketing DDCs. PQS requires to report complaints to the supplier of the device, and to the competent authority for medicinal product. The Device manufacturer will do the post- market surveillance. This role and responsibilities should be in the quality agreement. The QAA should include reporting responsibilities and timing as specified in MDR. PQS has also similar requirements for Distributor of medicinal product than the requirements set forth in MDR Article 14 Section 5 (General obligations of Distributors for market complaints). See also Point for Advocacy under section specific to Non Integral DDC. **Request for clarification from Stakeholders:** While the reporting pathway would be clear for DDCs registered as medicinal products, a Post-Market Surveillance System is required as part of Annex I (GENERAL SAFETY AND PERFORMANCE REQUIREMENTS), Chapter I General Requirements, Section 3.e. Risk-Management system. This could be interpreted as indirect need to establish a PMS system according Article 83 also for DDC products as described in MDR 2017/745 article I(9) and article 117.	

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<tr><td colspan="6">MDR PROCESS PART V – POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE</td></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td colspan="2">EFPIA will work with the Stakeholder to obtain guidelines with regards to applicability of MDR Article 83 to SI & NI DDCs.

<u>Recommendations to Pharma Industry:</u>
- Pharma should have the technical knowledge and processes in house to handle device complaints appropriately. Market complaints can arise from User not using the device as appropriate, from a device defect (Manufacturing cause) or from the design of the device. It is important to define the market complaint investigation expectations clearly with the legal manufacturer of the device in the Third party QAA.

- Pharma should continuously evaluated all device related complaints for understanding of the safety, quality and performance impact of the device (In order to close the loop with design control and/or manufacturing robustness).</td></tr>
<tr><td><u>Key message</u> (Input from EFPIA-MPP-MFE survey):

- For SI DDC, reporting to the competent authority would mean reporting to CAMS / EMA only. There is no provision for double reporting as it is the case in Japan and US where device directly related post-market surveillance is required.

<u>Recommendations to Pharma Industry, specific to SI DDC:</u></td><td><u>Key message</u> (Input from EFPIA-MPP-MFE survey):

Adverse event (AE) caused by a Co-packaged DDC would be reported to the respective competent authority: The device part would be reported to both EMA/CA and CAMD, by the MAH to EMA/CA and by the legal manufacturer of the device to CAMD.
This requirement implies to define the data flow and confidentiality requirements in quality agreement (QAA)</td></tr>
</table>

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MDR PROCESS PART V – POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE					
				(As an input from EFPIA-MPP survey) Should the Pharma company perform an **annual market surveillance** for the device component **as per Annex II which refers to article 83-86** ? The response was no, since SI DDC must comply with MDR Annex I only. However, recommendation is to do it and keep it internally if not required by NB. Requirement might depend on the device risk profile.	approved between the Pharma Company and the legal manufacturer of the device. - It is also assumed that Pharma Company would not be considered as Distributor under MDR Article 14. See point for advocacy here-below. **Point for advocacy (EFPIA & MFE):** It is EFPIA and MFE point for advocacy that MDR Article 14 Section 5 should not apply to Pharma Company marketing and distributing Device that is Co-Packed with a medicinal drug, since the DDC is governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable. See also MDR Process Part VI – OBLIGATIONS OF THE OTHER ECONOCMIC ACTORS

MDR Article Reference	MDR Text	MDR Annex and Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device)
MDR PROCESS PART VI – OBLIGATIONS OF THE OTHER ECONOMIC ACTORS (Distributors and Importers)					
Article 13 **General obligations of Importers** **Sections 1 to 10**	Importers shall place on the Union market only devices that are in conformity with this Regulation.	NA	Directive 2001/83/EC, Regulation (EC) No 726/2004	**Link with PQS:** Pharma Company importing Single-Integral DDC must comply with EC Directives and Regulations pertinent to medicinal products, and with Article 1 Section 9, Article 117 and Annex I (GSPR). Therefore Article 13 does not apply to SI DDC.	**Key message:** Pharma Company importing CE marked Device into EU must comply with MDR Article 13, Article 25 (Identification within the supply chain), Article 27 (Storage of UDI data), Article 30 Para 3 (Verify registration of Manufacturer, Authorised Representative; Add in Eudamed own details), Article 31 (Registration of Importer SRN). All these requirements are not mapped against medicinal product directives since CE marked Device must comply with new MDR 2017/745 requirements. It is therefore Pharma Company considered as an Importer to ensure compliance with MDR requirements. Pharma Company, considered as an Importer under MDR, would then need to nominate or establish contract agreement with an Authorized Representative. The latest represents the Device legal manufacturer located outside of EU and must comply with

MDR Article Reference	MDR Text	MDR Annex and Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device)
MDR PROCESS PART VI – OBLIGATIONS OF THE OTHER ECONOMIC ACTORS (Distributors and Importers)					
					several MDR articles, especially Article 11 which defines the minimum requirements for Authorised Representative. **Request for clarification from Stakeholders:** EFPIA will work with EMA and Medical Device Regulators to clarify the applicability of MDR for Pharma Company importing Non Integral, co-packaged, DDC.
Article 14 **General obligations of Distributors** **Section 1** **(Comments also valid for Article 14 Sections 3,, 4, 5 & 6)**	In the context of their activities, when making a device available on the market, distributors shall act with due care in relation to the requirements applicable.	NA	Directive 2001/83/EC, Regulation (EC) No 726/2004, Commission Delegated Regulation 2016/161 For Safety Features	**Link with PQS:** Pharma Company distributing Single-Integral DDC must comply with EC Directives and Regulations pertinent to medicinal products. Therefore Article 14 does not apply to SI DDC.	**Request for clarifications from Regulators:** Applicability of MDR Articles, such as Article 14, beyond CE marking would require clarification from Regulators. It is EFPIA opinion that there is no need for Pharma Company distributing Non Integral Co-Packaged DDC to be considered as Distributor under MDR Article 14, since the CE marked Device is co-packaged with the medicinal product and must be distributed as per GDPs, including as per Regulation 2016/161 for Safety Features. Therefore Complying with requirements set forth in Article 14 is ensured by default.

MDR Article Reference	MDR Text	MDR Annex and Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device)
MDR PROCESS PART VI – OBLIGATIONS OF THE OTHER ECONOMIC ACTORS (Distributors and Importers)					
					This is valid for all Sections of Article 14 (1, 3, 4, 5 & 6), with a specific point for advocacy related to UDI check (See Article 14 Section 2 here-below).
Article 14 **General obligations of Distributors** **Section 2**	Before making a device available on the market, distributors shall verify that all of the following requirements are met: (a) the device has been CE marked and that the EU declaration of conformity of the device has been drawn up; (b) the device is accompanied by the information to be supplied by the manufacturer in accordance with Article 10(11); (c) for imported devices, the importer has complied with the requirements set out in Article 13(3); (d) that, where applicable, a UDI has been assigned by the manufacturer. In order to meet the requirements referred to in points (a), (b) and (d) of the first subparagraph the distributor may apply a sampling method that is representative of	NA	Directive 2001/83/EC, Regulation (EC) No 726/2004, Commission Delegated Regulation 2016/161 For Safety Features	NA	**Points for Advocacy:** Requirements set forth under (a), (b), (c) & (d) are normal requirements for a Pharma Company operating under the PQS: Purchasing a CE marked Device, combining it with a medicinal product and placing it on the market require controls at reception of the Device, during manufacturing of the Non Integral DDC and before QP batch certification. Therefore EFPIA would recommend an interpretative guidance, which would allow for DDC product, registered as medicinal product, to be exempt of the requirements set forth in Article 14. If Pharma Company would be considered as Distributor under MDR Article 14, then EFPIA would advocate for UDI check

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MDR PROCESS PART VI – OBLIGATIONS OF THE OTHER ECONOMIC ACTORS (Distributors and Importers)					
	the devices supplied by that distributor. Where a distributor considers or has reason to believe that a device is not in conformity with the requirements of this Regulation, it shall not make the device available on the market until it has been brought into conformity, and shall inform the manufacturer and, where applicable, the manufacturer's authorised representative, and the importer. Where the distributor considers or has reason to believe that the device presents a serious risk or is a falsified device, it shall also inform the competent authority of the Member State in which it is established.				performed at the DDC assembly site only, and not along the supply chain (Wholesalers, hospital, …), since it would not be feasible (UDI on primary packaging), or would require UDI on each packaging (First, second, third,…).
Article 16 **Section 1** **Cases in which obligations of manufacturers apply to importers, distributors or other persons**	A distributor, importer or other natural or legal person shall assume the obligations incumbent on manufacturers if it does any of the following: (a) makes available on the market a device under its name, registered trade name or registered trade mark, except in	NA	NA	**Key message:** This MDR Article is not pertinent to Single-Integral DDC.	**Key message:** Article 1 16 (2b), 16 (3) and 16 (4) should be applied as long as an individual sales unit is separated into individual units (typically this is seen with single-use syringes).

MDR Article Reference	MDR Text	MDR Annex and Reference	Eudralex Vol 4 or ICH or 21 CFR reference	Comments for Single Integral DDC (With device being not CE marked)	Comments for Non-Integral DDC (Where Pharma company is not considered as legal manufacturer of device)
MDR PROCESS PART VI – OBLIGATIONS OF THE OTHER ECONOMIC ACTORS (Distributors and Importers)					
	cases where a distributor or importer enters into an agreement with a manufacturer whereby the manufacturer is identified as such on the label and is responsible for meeting the requirements placed on manufacturers in this Regulation; (b) changes the intended purpose of a device already placed on the market or put into service; (c) modifies a device already placed on the market or put into service in such a way that compliance with the applicable requirements may be affected. The first subparagraph shall not apply to any person who, while not considered a manufacturer as defined in point (30) of Article 2, assembles or adapts for an individual patient a device already on the market without changing its intended purpose.				As per alignment obtained between 3 Industry Associations (EFPIA-MPP-MFE) in March 2019, it is our understanding that a Pharma company does not become a manufacturer as per MDR Article 16 while co-packaging of DDC requires to re-pack the CE marked device, as long as the following criteria are met: - There is no change of device intended use, - An agreement with the device manufacturer would prevent the application of article 16 as the supplier would meet Pharma needs.