Reflection paper on regulatory uncertainties for co-packaged and cross-labelled drug-device combinations under the new Medical Devices Regulation

Authors: Jeary Theresa[1], Bacou Elisabeth[1], Schulze Karin[1], Foster Ruth[1], Gollob Barbara[1], Wallenstein Mike[1], Godeau Guy[2], Ericson Mats[2], Hunter Bjorg[2], Matthews Amanda[2], Neadle Susan[2], Varenne Hervé[2], Almeida Susana[3], Javor Judit[3], Scannell Paul[3]

Affiliations: [1]Medtech & Pharma Platform (MPP), [2]European Federation of Pharmaceutical Industries and Associations (EFPIA), [3]Medicines for Europe

Corresponding author: Medtech & Pharma Platform (MPP)

Published: December 2019

Objectives

The objectives of this paper are as follows:

- To inform key decision makers and raise the pharmaceutical industry's concerns regarding the regulatory challenges on the impact of the Medical Device Regulation (MDR) on non-integral drug-device combination (DDCs) (co-packaged and cross-labelled) with senior experts at EU decision making bodies.

- To obtain clarification and a common understanding on the roles and responsibilities of Competent Authorities (CAs) / Notified Bodies (NBs) for non-integral DDCs across all manufacturing and commercial phases.

Table of Contents

Introduction

The Medical Device Regulation (EU) 2017/745 (MDR), which enters into force from May 26th 2020, has been the most significant change in the legislation of medical devices since the publication and introduction of the Medical Devices Directive (MDD) 93/42/EEC in 1993. The new MDR seeks to maintain the principles of the 1990s 'new approach directives', while also encouraging innovation, encompass new technological advancements, address legislative gaps, and provide a regulation that can be applied to future developments and associated regulatory challenges.

In the past five years, the area of drug-device combination products in the medtech sector has undergone significant development and advancements, and while the MDR does address the requirements for integral drug-device products through Article 117, and explicitly includes expectations for the assessment of the device aspects and provision of a Notified Body opinion, there are some aspects of the new Regulation that still require additional guidance and clarification.

The following document presents a pharmaceutical industry perspective on the perceived gaps in the legislation and challenges in the implementation of the new MDR, specifically for co-packaged or cross-labelled devices.

Background/context

The MDR states that products combining a medical device and a medicinal product follow specific rules (Article 1(8) and Article 1(9)).
Although the concept of 'Single Integral' is well defined in Article 1(9) of the MDR, the terminology 'Integral' described in Article 1(8) is not defined in the regulations and leaves the 'Non-Integral' drug-device Combinations undefined in EU law.

The recent EMA draft Guideline on quality requirements for drug-device combinations (EMA dGQR-DDC) provides a clear definition of non-integral DDC in the document introduction:

"Non-Integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and device(s)) are not physically integrated during manufacturing but where the medicinal product and the specific device(s) are combined for administration.

Devices in non-integral DDCs are those that are co-packaged and supplied along with the medicinal product, or where the Product Information ((Summary of Product Characteristics, SmPC, and Patient Information Leaflet)) refers to a specific device to be used with the medicinal product but the device is obtained separately. In either case, Medical Devices not falling within the scope of Article 1(8) and 1(9) of the MDR should be CE marked".

Each component of a Non-integral DDCs (co-packaged/cross-labelled) should comply with their respective regulations.

The EMA dGQR-DDC leaves CE marked devices for non-integral DDC with questions related to the applicability of the following MDR articles and with other questions for pharmaceutical companies who co-package their medicinal product with a CE marked medical device;

- Art. 16: Cases in which obligations of manufacturers apply to importers, distributors or other persons"
- Art. 22: "Systems and procedure packs"
- Art. 27: "Unique Device Identification system"
- Art. 31: "Registration of manufacturers, authorised representatives and importers" (application of SRN)
- Art. 85 and 86: "Post-market surveillance report" and "Periodic safety update report"
- NB roles in conformity assessment, registration process by the CA
- NB roles in pharmaceutical inspection vs CA
- Batch release of co-packaged DDC product (registered as a medicinal product) by QP of a pharmaceutical company and required documents for device part
- Impact of EU mutual recognition agreement (MRA) with the US FDA

I. MDR Art. 16 Cases in which obligations of (medical device) manufacturers apply to importers, distributors or other persons

(1) 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 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.

(extract from Article 16)

Uncertainty/Issue statement

Pharmaceutical companies frequently co-package CE marked medical devices with their medicinal products for patient convenience, e.g.: placement of a drug administration device (measuring cup, spoon, plastic syringe) with an oral solution, or inclusion of a sterile syringe in the same carton as a vial solution for injection.

In these situations, the medical device is made available on the market in an outer carton together with the medicinal product (i.e. under the tradename of the medicinal product and under the name of the pharmaceutical company).

Various economic operator roles and related obligations for the pharmaceutical industry governing the manufacturing and/or marketing of a co-packaged DDC under the MDR require clarification.

While it is clear that each component is regulated under their relevant regulations (i.e. that the medical device component must meet the MDR requirements and the medicinal product meets the Medicinal Product Directive 2001/83/EC (MPD)), it is our opinion that the MPD take precedence over the requirements of the MDR, when considering the package as a whole, since the co-packaged DDC is registered by the medicinal product CAs as a medicinal product.

However, when taking into consideration the MDR requirements, it could be argued that the pharmaceutical company could be considered as having an economic operator role of distributor and potentially importer. In particular, Articles 16 (3) and 16 (4) of the MDR raise some uncertainties and may apply to the pharmaceutical companies performing the operations described in Article 16 (2b), such as the separation of bulk product units into individual sales units (as an example, this is typically conducted for single-use syringes, or sterile needles, purchased in bulk and then packaged into individual sales packs).

It is the opinion of the pharmaceutical industry participants of this position paper, that in the example provided, that multiple single sales units of syringes, provided in bulk to the pharmaceutical company, does not constitute a re-packaging activity. This does depend on the definition of a sales unit as defined by the legal manufacturer. It is our opinion that a change of the sales unit is re-packaging, however a separation of shipping units should not be defined as repackaging.

Therefore, it is our opinion that, to permit exemption from assuming the manufacturer's obligations as per Article 16 (1) of the MDR, the conditions to be met by the pharmaceutical company should be as follows:

- The pharmaceutical company should enter into agreement with the device manufacturer whereby:
    - The medical device manufacturer and Unique Device Identification (UDI) are identified as such on the label (i.e. as per MDR definition[1], either on the device itself, on its primary packaging if any, or on the outer packaging – see examples below).

On the device itself	On the packaging	
		
Plastic syringe co-packaged with a syrup	Sterile needle co-packaged with a pre-filled syringe	Dosing cup co-packaged with an oral solution

    - The device manufacturer remains responsible for meeting MDR requirements as the legal manufacturer.
    - The intended use of the medical device remains unchanged.
    - The pharmaceutical company does not modify the device in a way that could affect its compliance with the applicable requirements, as per MDR Article 16 (2)

It is understood that, in cases where the above conditions are not met, the pharmaceutical company would endorse the general manufacturer's obligations as described in Article 10 of the MDR.

The question that then remains is, when the above conditions are met, what obligations, if any, are applicable for pharmaceutical companies under Article 16 (3) and 16 (4) of the MDR?

Example

A pharmaceutical company co-packages a CE marked medical device with its medicinal product and the conditions as listed above, to be exempted from manufacturer's' obligations as per Article 16 (1a) MDR, are met. Nevertheless, the pharmaceutical company performs the following operations:

- Inclusion of the medical device Instructions for Use (IFU) provided by the supplier into the medicinal product labelling (Patient Information Leaflet)
- Introduction in the medicinal product box of the individual medical device units (received in bulk from the supplier).

Key Messages

In the above described situation, it is assumed that:

- The medical device manufacturer responsible for the CE marking has to fulfil its obligations according to the MDR, independently of the MPD.

[1] MDR Definition: 'label' means the written, printed or graphic information appearing either on the device itself, or on the packaging of each unit or on the packaging of multiple devices

- As per Article 16 (1a) of the MDR, the pharmaceutical company shall be exempt from assuming the general obligations of the medical device manufacturer (Article 10 of the MDR), since it complies with Articles 16 (1b & 1c) and 16 (2).
- However, as a distributor, and, potentially, importer of the medical device, does the pharmaceutical company still need to meet the MDR requirements for distributors (Article 14), and potentially, Importers (Article 13, 30 and 31)?
- Moreover, because the pharmaceutical company caries out activities described in points (a) and (b) of Article 16 (2). Article 16 (3) and (4), MDR obligations, as summarized below, could also be considered as applicable:
    - QMS in place covering the packaging activities and procedures ensuring information of any corrective action taken by the manufacturer
    - Retention (and submission to CA) of a certificate issued by a NB designated for the type of device
    - Information to manufacturer and CAs of the placing on the market at least 28 days in advance

Assuming that, since the co-packaged DDC is registered as a medicinal product, the MPD takes precedence over MDR requirements and pharmaceutical companies should be exempted from Article 16 (3) and (4) MDR obligations, which are already covered by the MPD.

Supporting discussion points

- With respect to the QMS and the certificate issued by a NB - pharmaceutical companies operate under the Pharmaceutical Quality System (PQS), and hold Good Manufacturing Practice (GMP) certificates issued by the medicinal product CA. While the Quality Management Systems (QMS) for medical devices and medicinal products are not strictly identical, they include a number of similarities. Assuming that the expectations underlying the requirements for a medical device QMS and NB certificate would actually be addressed by the PQS, and the GMP certification, it is our quality and regulatory judgement that the MPD requirements are sufficient to ensure that MDR requirements in the second subparagraph of Article 16 (3) are met (Original conditions of the device preserved, and Quality Agreement approved between the device manufacturer and the pharmaceutical company to respond to safety issues or to bring it into conformity with this MDR Regulation).
- Concerning the information of the manufacturer and CAs of the placing on the market at least 28 days in advance. From one perspective, the placement on the market of the co-packaged product will be notified to the medicinal product CA, according to the medicinal product legislation, however, the MDR does not provide any detail on the notification process to the medical device CAs about the placing on the market of a medical device by distributors (taking into account that a pharmaceutical company may place a co-packaged product on the market of several Member States, at different dates).
- On review, the greatest concern to the Pharmaceutical Industry, relates to Economic Operators under the MDR is Article 14, General obligations of distributors. From our interpretation, the requirements for Distributor would mean, among other requirements, that the Pharmaceutical Company marketing the DDCs or the wholesaler, would need to check for a UDI and other aspects as per Article 14 (2).
    - a) *Regulatory-wise*: As soon as a device is put into the folding box together with the drug, it was the consensus of opinion that the distributor role according to the MDR no longer applies to the individual medical CE marked devices contained in the carton, as the pack as a whole is registered as a medicinal product. However, the legal basis for this conclusion is not clear.

    - b) *Quality-wise*: 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 fulfil the requirements of Article 14. In addition, there are third-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 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.
- That means that the pharmaceutical manufacturing site (first distributor), which receives the device from the manufacturer would perform all the necessary checks and would maintain files for documentation. Furthermore, compliance to the MPD for Good Distribution Practices (2013/C 343/ 01) (GDP) and to Commission Delegated Regulation (EU) 2016/161 for serialization and safety measures by each distribution actor would ensure patient safety and protection along the supply chain. Affiliate(s), wholesalers, hospitals and pharmacies would not repeat these checks; however, they would forward complaints to the legal manufacturer of the device (via the MAH and the first 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 a supplier qualification process.

Need for additional action and clarification

Overall, the applicability of Article 16 to pharmaceutical companies, that co-package medical devices with medicinal products needs clarification and in particular:

- The pertinence of MDR economic operator roles for the pharmaceutical industry,
- The conditions under which Article 16 does / does not apply to co-packaged DDCs.

The exact expectations behind the QMS and NB certificate requirements for the activities detailed in Article 16 of the MDR also requires clarification, in order to confirm that they are appropriately addressed by the PQS and GMP certification of the pharmaceutical company, involved in co-packaging of DDCs. The exemption of pharmaceutical companies from the requirements of Article 16, could be formalized through a clarification document.

We advocate the non-applicability of this article to the pharmaceutical industry who distribute co-packaged non-integral DDCs, since it duplicates the requirements set forth in the GDP directive and the Commission Delegated Regulation (EU) 2016/161 for traceability (Serialisation code) and safety measures for medicinal products. This position requires consideration and clarification from both EMA and at the EC DG Growth level for the device aspects.

If applicable, practical guidance concerning the process to inform the manufacturer and the CAs about the placing on the market of a medical device co-packaged with a medicinal product, is in our view, also required.

II. MDR Art. 22 Systems and procedure packs

Article 2 of the MDR defines Procedure packs and systems as:

(10) 'procedure pack' means a combination of products packaged together and placed on the market with the purpose of being used for a specific medical purpose;

(11) 'system' means a combination of products, either packaged together or not, which are intended to be interconnected or combined to achieve a specific medical purpose;

Whereas "specific medical purposes" are defined by Art. 2(1) MDR as:

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*

providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means

Uncertainty/Issue statement

The MDR details the requirements for procedure packs and systems in terms of expectations on labelling and mutual compatibility declarations.

- As per Article 22 (1)c the concept of "products" has not been explicitly defined in the MDR, interpretation is needed on whether or not medicinal products fall under the concept of "products". Many medicinal products are co-packaged with a medical device for delivery of the medicinal product, is this configuration considered as a procedure pack or system, with Article 22 of the MDR therefore applicable?
- In the definition of a system within the MDR, it could also be interpreted that a medicinal product that defines and is cross-labelled for use with a specific device, meets the definition of a system and Article 22 of the MDR could therefore be interpreted as applicable to this scenario.

Examples

- A company co-packages a CE marked medical device (e.g. a dosing syringe) with their medicine; the medical device is CE marked by another legal entity (manufacturer) and the name/address of this legal entity (manufacturer) remains on the medical device.
- A drug provided in a pre-filled syringe co-packaged with CE marked administration needles
- A pre-filled syringe with diluent separately supplied with a vial containing a lyophilized drug and a vial adapter and CE marked administration needles in a convenience kit. (Under MDD, it is clear that combination product systems and kits are not included in scope, but under MDR, the intent of the scope is no longer clear.)

Key messages

Our interpretation is that Article 22 (1)c of the MDR ("other products") does not apply to combination of a drug and a CE marked administration device in a co-packaged configuration, on the basis that the

principal mode of action at the point of use shall be that of the drug, that this market presentation is for user convenience and safety, and that this configuration is never intended to be defined as a procedure pack, as per the concept used for medical devices and in the context of a medical procedure.

Supporting discussion points

The main purpose of the MDR procedure pack definition (Article 22) is to ensure that the compatibility of the different products is verified and that the person responsible for the assembly of such packs is identified. The recent EMA dGQR-DDC confirms that in the case of a non-integral DDC, this must be provided in the medicinal product Marketing Authorisation Application (MAA). In this sense it is fully covered by the medicine's legislation and MDR Article 22 is not-applicable for co-packaged, non-integral DDCs.

Need for action/potential resolution actions

Confirmation that MDR Article 22 is not applicable for co-packaged, non-integral DDCs would be welcomed by industry.

III. MDR Art. 27 Unique Device Identification system

1.The Unique Device Identification system ('UDI system') described in Part C of Annex VI shall allow the identification and facilitate the traceability of devices, other than custom-made and investigational devices,

Uncertainty/Issue statements

According MDR Article 27, *"before placing a device, other than a custom-made device, on the market, the manufacturer shall assign to the device and, if applicable, to all higher levels of packaging a UDI created in compliance with the rules of the issuing entity designated by the Commission in accordance with paragraph 2".*

It is our opinion that a co-packaged DDC is registered as a medicinal product and must comply with serialization for safety measures and traceability along the distribution chain.

However, it is not clear if the pharmaceutical company shall need to add an UDI on the packaging for the non-integral medical device.

Example

- A pharmaceutical company co-packages a CE marked medical device with their medicinal product. The device has already its own UDI assigned by the device manufacturer and the pack of the non-integral DDC has the serial number printed by the pharmaceutical company.

Key message

The UDI on the device and the serial number on the pack of non-integral DDC allow the identification and facilitate the traceability of the device and the co-packed sales unit

Supporting discussion points

The sales pack of the non-integral DDC is serialized under the Falsified Medicines Regulation (Commission Delegated Regulation EU 2016/161). The addition of a UDI on the outer pack (2d and 3r pack) does not provide benefit for the identification and traceability of the non-integral DDC.

Indeed, the PQS ensures that the device information is traceable; EFPIA / MPP / MFE advocate for UDI being affixed on the device itself or its primary packaging, not on the secondary nor the third packaging of the DDC, similar to US-FDA 21 CFR Part820.

The UDI will be checked by the Pharma company manufacturing the Co-packaged DDC, 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 (EU 2016/161)

Need for action and clarification

- Industry require confirmation that only the device of the co-packaged DDC shall have an UDI
- Confirmation is also required that it is not intended or necessary to document the UDI Number of the device per individual box of the serialized drug product

IV. MDR Art. 31 Registration of manufacturers, authorised representatives and importers (application of the Single Registration Number)

1.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.

2.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.

Uncertainty/ issue statement

The SRN relates to role of the economic operators linked to the co-packaged DDC. Generally, the SRN does not apply to the distributor unless Article 16 (1) of the MDR is determined to be applicable.
Should this be the case, then the distributor shall assume the obligations of the manufacturer
There are several Articles of the MDR to consider here, connected to economic operators, obligations and co-packaged DDCs:

- Article 31 Registration of manufacturers, authorised representatives (AR) and importers (application of Single Registration Number (SRN))
- Article 14 General obligations of distributors
- Article 16 Cases in which obligations of manufacturers apply to importers, distributors or other persons

Examples

- A pharmaceutical manufacturer is based in the EU. They import CE marked needles from a non-EU manufacturer, co-package them with their drug, and distribute them on the EU market. The needle manufacturer has an AR in EU. The needle manufacturer and their AR are required to each have an SRN. Does the pharmaceutical manufacturer require an SRN as an importer of the needle?
- A pharmaceutical manufacturer is based in the EU. They distribute devices co-packaged with their drug. The devices come from an EU based manufacturer. The EU based manufacturer is obliged to have an SRN. The pharmaceutical company does not need an SRN, provided Article 16 (1) of the MDR does not apply, as their role is distribution only.
- A pharmaceutical manufacturer markets prefilled syringes. Does the pharmaceutical company need to consider every step in the manufacturing process such as and including the fill of the barrel, insertion of the plunger and stopper, packaging or co-packing with needles and labelling? In such circumstances where multiple sites are involved, does each step in the manufacturing chain require an SRN?

Key messages

- The need for a single registration number depends on status of the economic operator dealing with co-packaged DDC (Article 31 MDR)
- It is our opinion that in the case where a Pharmaceutical Company is the authorisation holder and markets Co-packaged DDCs, they do not need to comply with MDR Article 14 since medicinal product directives, and in particular those pertinent to Good Distribution Practice (GDP), shall take precedence over the MDR for product distribution.
- Clarification and identification of Local Users who will interface with EUDAMED. Apply for SRNs as soon as possible

Supporting discussion points: Consideration to Annex VI; Part A; point 1 where distributors are NOT mentioned

- 1. Information relating to the economic operator
- 1.1. type of economic operator (manufacturer, authorised representative, or importer),
- 1.2. name, address and contact details of the economic operator,
- 1.3. where submission of information is carried out by another person on behalf of any of the economic operators mentioned under Section 1.1, the name, address and contact details of that person,
- 1.4. name address and contact details of the person or persons responsible for regulatory compliance referred to in Article 15.

Need for action:

Clarification on the application of SRN to companies who co-package non-integral DDCs

V. MDR Article 85 and 86 Medical device post-market surveillance, vigilance and market surveillance vs. pharmacovigilance

MDR Article 85 states that;

Manufacturers of class I devices shall prepare a post-market surveillance report summarising the results and conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan referred to in Article 84 together with a rationale and description of any preventive and corrective actions taken. The report shall be updated when necessary and made available to the competent authority upon request.

MDR Article 86 details the requirements for periodic safety update reports and states:

1.Manufacturers of class IIa, class IIb and class III devices shall prepare a periodic safety update report ('PSUR') for each device and where relevant for each category or group of devices summarising the results and conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan referred to in Article 84 together with a rationale and description of any preventive and corrective actions taken, ….

Uncertainty/Issue statement

Pharmacovigilance (PhV) vs device' post-market surveillance (PMS), vigilance and market surveillance: responsibility and liability of pharmaceutical and device company for a co-packaged DDC product, should be clarified.

Example

- A pharmaceutical company is the MAH of the co-packaged non-integral DDC.
  In accordance with the requirements of the Pharmacovigilance Directive 2010/84/EU, it is a legal obligation of a MAH to have a PhV and Risk Management System (RMS) in place and meet the obligations of Marketing Authorisation Holders (MAH) as per this Directive. Therefore, we acknowledge that the pharmaceutical company should have established procedures (standard operating procedures (SOPs), Working Instructions) for all related activities including reporting obligations (including PSUR, adverse drug reaction).
  However, according to the MDR, PMS and vigilance requirements have been revised and device manufacturers are required to amend current PMS and vigilance procedures and implement a PMS plan (including trend reporting of incidents) which shall also be part of the Technical Documentation. The MDR also introduces the concept of a new reporting obligation, the Periodic Safety Update Report (PSUR), with the PSUR part of the technical documentation and available for the NB involved in the conformity assessment, and, upon request, to CAs.
  The MDR also requires reporting of serious incidents (SI) and field safety corrective actions (FSCA), with timeframes for the reporting of these cases in the EU electronic system detailed in the MDR Chapter VII 'Post-market surveillance, vigilance and market surveillance'.

Key messages

In the above described situation, we interpret that:

- The medical devices contained within the co-packaged sales configuration are regulated as a medical device in accordance with the MDR, and the manufacturer of the device shall be obligated to satisfy the post-market surveillance, vigilance and market surveillance requirements, with reporting of any incidents to EUDAMED, which is the dedicated system for this activity and medical devices.
- The medicinal product contained within the co-packaged carton, are regulated in accordance with MPD and the MAH shall comply with the applicable EU regulations, directives, guidelines for the management of PhV, reporting of adverse reactions, issuance of PSURs and follow-ups of medicinal products. EUDRAVIGILANCE is the dedicated system for the reporting of incidents for medicinal products.
- As there is no interface between the EUDAMED and EUDRAVIGILANCE systems, it is expected that the reporting pathway determines the reporting procedure. The question arises that since co-packaged non-integral DDCs are registered as medicinal products, the pharmaceutical company should report to EMA or CA only, with MDR Articles 83, 84, 85, 86, 87, 88, 89 & 95 not applicable for the pharmaceutical company that manufactures and markets co-packaged non-integral DDCs. The PQS and contractual agreements with the device manufacturer shall ensure reporting of complaints to the supplier of the device, and to the CA for the medicinal product. The device manufacturer is expected to fulfil their PMS obligations as per the MDR requirements. We suggest that the role and responsibilities should be addressed in the quality technical agreement (QTA) between the pharmaceutical company and medical device manufacturer, which should also include and address reporting responsibilities and timing, to ensure legal responsibilities are explicitly stated and the requirements of both the MPD and MDR are met. The device manufacturer must comply with MDR requirements.

- We have also concluded that a PQS also has similar requirements for “Distributor of medicinal product” to the requirements detailed in MDR Article 14 (5) (General obligations of Distributors for market complaints) and therefore it is not the intent nor is it a requirement that the pharmaceutical company comply with these MDR requirements.

Supporting discussion points

The proposed approach is aligned with the MDR Article 1 (9) which states that “*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 Authors base their assumptions on the precedence of MPD over the MDR requirements, with additional assurances that a robust QTA would define the legal obligations and responsibilities between the pharmaceutical company and device manufacturer to ensure the appropriate legal obligations of each party are met

Need for action/potential resolution actions

- The pertinence of economical operator roles to pharmaceutical industry, as set forth in the MDR
- Harmonisation of terminology and “classification” of seriousness would be an asset since it has consequence on the reporting timelines.
- Confirmation on responsibility of pharmaceutical and device manufacturer related to the different reporting activities as suggested here above, or need for clarification from the regulators (who should report serious incidents attributed to the medical device of the co-packaged DDC and PSUR for medical device).
- Confirmation that the pharmaceutical company has to forward device complaints immediately to the device manufacturer
- Guidance on the expected responsibility for the reporting of events that cannot be clearly associated to either the medicinal product or medical device?
- Appropriateness and management of potential duplicate reporting if the same reported event is related to the medicinal product and the device, given that there are two different databases (Eudravigilance and EUDAMED)

VI. Batch release of co-packaged drug-device combination product by the pharmaceutical Qualified Person and required documents for device part

Uncertainty/Issue statement

The responsibility and liability of a Qualified Person (QP) of a pharmaceutical company in the batch release of co-packaged DDC product should be clarified.

Example

- A pharmaceutical company co-packages a CE marked device with a medicinal product.
  In our opinion the QP of the pharmaceutical company is responsible for the release of the final co-packaged DDC product. The basis of the release of a medicinal product is the Manufacturing Batch Record (MBR), which takes into consideration the registration status/documentation (approved or on-going variations) of the medicinal product. The medical device component in the co-packaged DDC product, shall in most cases be supplied by a third party (i.e. a different legal entity to that of the MAH of the medicinal product). It is our expectation that the device manufacturer will provide a CE declaration of conformity as well the Certificate of Analysis/Certificate of Compliance (CoA/CoC) for the device which should be recognized/accepted by the QP to allow the release of the co-packaged DDC product.
  In accordance with GMP, the device supplier shall be qualified and audited regularly by the pharmaceutical company and a QTA will be in place between the pharmaceutical company and device manufacturer.

Key messages

- The device manufacturer issues a CE Declaration of Conformity along with a CoA/CoC for device used in the non-integral DDC.
- The QP of the pharmaceutical company shall recognize and accept a CE Declaration of Conformity to permit release of the co-packaged DDC product.
- A QTA between the pharmaceutical company and device manufacturer shall be in place, however there are differences in the concept of GMP vs. the QMS for medical devices as detailed in the harmonized standard, ISO 13485 and the pharmaceutical QP has limited knowledge on ISO 13485.

Supporting discussion points

- The MDR has introduced some new requirements and documentation expectations for medical device manufacturers We believe that there is a risk that these new requirements shall have an impact on the QA/QMS of pharmaceutical company and its relationship with device manufacturer.
- The EMA dGQR-DDC is in consultation (final version has not been published yet), however there is a clear expectation that Module 3 should contain more data on the device component which shall have impact on the release of the co-packaged DDC product.

Need for action/potential resolution actions

- Clarification on the scope of responsibility of the pharmaceutical QP and the sharing of liability between the pharmaceutical and device manufacturer. We would appreciate clarification on the legal basis and liability responsibilities for the co-packaged DDC product and confirmation that agreements and a QTA between parties shall be sufficient as a mechanism for control.
- Guidance on the gaps between medicinal product and device concepts (such as and including GMP vs ISO 13485, Risk Management ICH vs ISO 14971, Laboratory Test Ph.Eur. vs Standards, Change Control and Life-Cycle management) is seen by industry as essential and the development of such a document is considered a high priority
- On review of the MPD there is no definition of a co-packaged DDC, therefore the legal basis for the release by the MAH QP of the non-integral co-packaged sales pack is not clear

VII. Non-integral drug-device combinations obtained separately / cross-labelled products

Uncertainty/Issue statement

Non-integral DDCs obtained separately are neither physically combined nor packaged together, but combined only through their labelling where each product label individually specifies the use of the other product. This is an increasingly common occurrence, however, the MDR has not defined nor taken into consideration such DDCs.

The concerns are that there is no clear legal basis for such a practice or specific regulatory body who supervise such claims. Non-integral DDCS obtained separately and which are cross-labelled can also include products that are not intended to be physically combined products (e.g. Digital health applications).

The recent EMA dGQR-DDC provides a clear definition of non-integral DDCs in the document introduction and refers to non-integral DDCs which are placed on the market separately.

Example

- Cartridge from company A is sold separately and it should be used with a pen from company B. Label from product A refers to label from product B. Who will ensure that the label from product B will also refer to product A?
- Digital tool to ensure patient adherence refers to its use with product A and B. The label in product A and B does not mention the use of a digital tool.

Key message

In non-integral DDCs obtained separately, typically two separate submissions (one for the medicinal product and one for the medical device), are connected by labelling, and the oversight and controls to verify such claims has not been defined. There is a concern that cross-labelling claims may be made for medicinal products or medical devices without the knowledge of the MAH / device manufacturer and in order to ensure a safe and consistent approach clear guidance is necessary.

It is our opinion that clear roles and responsibilities for each stakeholder in the provision of cross-labelled products and the expectations and guidance on any additional requirements, needs to be established to ensure the safe use of both products (medicinal product and medical device).

Areas of particular interest includes;

- the notification procedure to EudraVigilance / EUDAMED and communication between stakeholders of any emerging issues with either component.
- the expectations for clinical investigations; we believe that the clinical data obtained for the medicinal product should provide sufficient clinical evidence to support claims made for the use of the device.

Supporting discussion points

At present there exist different labelling approaches for medicinal products and devices. In the example of a medicinal product that references the use of a particular device, a two-way labelling approach where both components label claims, needs to be ensured by the appropriate regulatory authorities / stakeholders.

Need for action

The Instructions for Use (IFU) of the cross-labelled product must be provided in appropriate languages for the market(s) in which it will be sold (importers and distributors), and the obligations to report all complaints or reports to the manufacturer and their Authorised Representative (importer and distributors) must be fulfilled by the device manufacturer. It is our opinion that written agreements between the device and the medicinal product manufacturer should be in place prior to MAA.

Industry would welcome clear guidance on the appropriate regulatory controls for non-integral, cross-labelled DDCs, to ensure both the safety of patients and that all concerned parties fulfil and meet their legal obligations.

VIII. Notified Bodies roles in conformity assessment, registration and variation processes

Uncertainty/Issue statement

The expectations on requirements and the process for a Marketing Authorisation (MA) update, when a new or renewed CE certificate is needed for the medical device in a non-integral co-packaged DDC, are not clear.

Example

A pharmaceutical company co-packages a purchased, off-the-shelf CE marked medical device with a medicinal product and this co-packaged configuration is then registered as a drug-device combination under a medicinal product MAA. The medical device itself is covered by an EU NB Certificate of Conformity and Declaration of Conformity which is the evidence that the medical device has undergone a conformity procedure and conforms with the relevant general performance and safety requirements. However, there shall be circumstances whereby the CE Certificate of Conformity may not have a full five-year validity when provided to the pharmaceutical company, depending on when it was issued relative to the MAA date itself, and there is no clear guideline on expectations for submission of a variation or the management of such a situation.

Key messages

In our opinion the inclusion of the current Declaration of Conformity / CE certificate to the MA should be considered sufficient, with no further information relating to quality or safety of the medical device necessary, following CE Certificate renewal. We consider that the most critical requirement of the Applicant / MAH is to demonstrate compatibility of the medical device with the medicinal product and that it is appropriate for its intended use. Additionally, under the MDR, a co-packaged presentation of a medicinal product and a device, follows the appropriate regulatory controls for each component and non-integral co-packaged DDCs do not require any additional / separate assessment by a NB for the intended combination

Supporting discussion points

The renewal of the CE Certificate is within the control of the medical device manufacturer. However, the pharmaceutical company is obliged to ensure the information within the MAA remains current. Therefore, upon receipt of a renewed CE Certificate by the device manufacturer, the QTA should ensure that this is provided to the MAA holder, who will be required to ensure the revised information is filed within the common technical document (CTD). If the medical device itself remains unchanged, it is our opinion that this update to the MAA should be considered an administrative change, however, currently there is no suitable variation procedure type to cover this situation. The category B.IV.1, *addition or replacement of a device which is not an integral part of the primary packaging, but is CE marked*, is a IA_{IN} procedure, and therefore by analogy, it is within reason that management of CE certificate renewals could be a comparable category.

Need for action/potential resolution actions

Confirmation of acceptance of the approach suggested above and additional guidance on this subject area would be welcomed.

IX. Auditing activities by Notified Bodies and Competent Authorities

Uncertainty/Issue statement

The question “Could the NB audit a pharmaceutical company who co-packages a medicinal product with a purchased CE marked device? “has been raised by industry.

Example

A pharmaceutical company co-packages two separates items its own medicinal product and a purchased CE marked device. Examples include a reusable pen for insulin cartridges or a tablet delivery system with controller for pain management.

Key messages

It is our interpretation, that it is the responsibility of the pharmaceutical company to satisfy themselves that the device manufacturer conforms to the requirements of the MDR, through their supplier audit program and quality agreement. The pharmaceutical company is responsible for ensuring that the compatibility between the medicinal product and the device is evidenced, and that the IFU provides sufficient instructions on the use of the medicinal product and the device in a compatible manner. We also believe that there is no requirement or intent to have NBs conduct on-site audits of sites that co-package non-integral DDCs and that CAs are the appropriate body for conducting inspections of all matters registered in the MAA according to the cGMP and MPD.

Should the pharmaceutical company become an importer or a distributor of an CE marked device purchased externally to the EU, the cGMP and GDP of the pharmaceutical company should take precedence, with no requirement for NB inspection. It is also our opinion that MDR Article 93 would not be applicable.

Supporting discussion points

- The co-packaged drug-device product is registered in accordance with the MPD.
- The medical device is CE marked under the MDR

Need for action/potential resolution actions

- Clarification is required that a NB inspection of the site where co-packaging of the DDC is not a requirement and that Article 93 of the MDR is not applicable.
- Confirmation that the CA inspection of the pharmaceutical company, according to GMP of the MPD, is appropriate and there is no intention for assessment of such activities against MDR requirements.

X. Impact of the mutual recognition agreement of inspections between the EU and the US Food and Drug Agency

Background

On 11 July 2019, the EU-US Mutual Recognition Agreement (MRA) for inspections of manufacturing sites for human medicines was fully implemented following the recognition of the last outstanding EU Member State by the FDA. This means that both jurisdictions can rely on the other's GMP inspection results to replace their own inspection (with certain scope limitations for Slovakia and Malta). The batch testing waiver will also apply. This means that the qualified persons in the European or US pharmaceutical company will be relieved of their task for carrying out the quality controls when carried out already in the country party to the MRA.

Key messages

Most medicinal products are in the scope of the current MRA, if classified as such. Human vaccines and plasma-derived products are not immediately included within the operational scope of the agreement, but their inclusion will be considered by no later than 15 July 2022. Human blood, plasma, tissues and organs, as well as veterinary immunologicals are excluded from the scope.

Consequently, it is our understanding that products regulated as 'medicinal products' in the EU, with a device part falling under the EU MDR 2017/745, and as 'drug products' with Center for Drug Evaluation and Research (CDER) or Biologics License Applications Process (CBER), following the US requirements for 'combination products' (21 CFR part 4) are also in the scope the current MRA between the European Union and the United States. However, DDCs are not explicitly listed in the MRA (Appendix 3).

Supporting discussion points

The applicable product scope is defined by the provisions of Article 4 and Appendix 3 of the Sectoral Annex to the Commission Decision on determining the Union position for a Decision of the Joint Committee set up under Article 14 of the Agreement on Mutual Recognition between the European Community and the United States of America, in order to amend the Sectoral Annex on Pharmaceutical GMPs.

Need for action/potential resolution actions

Clarification as to how DDCs are covered by the MRA should be provided, i.e. DDCs should be listed in the MRA's sectoral annex.

Appendix I. Industry Group Descriptions

Medtech & Pharma Platform – www.medtech-pharma.com

The Medtech & Pharma Platform (MPP) is a cross-sectoral not-for-profit industry association focusing on combined products. MPP is made up of Medtech, Pharma and Software companies dedicated to enhancing synergies between the sectors and to provide a cross-sectoral forum to exchange knowledge, collaborate in technology and regulatory areas as well as to promote product development and innovation. The association aims to further strengthen advocacy work for companies to reduce time to market for drugs, devices and combinations thereof, improve access to innovative products and better match patients' needs.

European Federation of Pharmaceutical Industries and Associates (EFPIA) – www.efpia.eu

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 40 leading pharmaceutical companies, EFPIA is the voice of 1,900 companies in the EU committed to researching, developing and bringing to patients, new medicines that will improve health and the quality of life around the world.

Medicines for Europe – www.medicinesforeurope.com

Medicines for Europe began over 20 years ago as the European Generics Medicines Association (EGA) with the goal of representing the emerging generic industry, and later growing to include biosimilar medicines to its portfolio. As the pharmaceutical industry and the healthcare environment within which it operates have evolved, so too has the Association. Our members provide essential medicines that European patients, healthcare professionals and healthcare systems rely on to treat the most acute and chronic diseases ailments covering a wide range of diseases from cardiovascular, to diabetes and cancer. Better access to the most effective therapies means millions more patients are getting better and living longer, while healthcare inequalities are being reduced.