MEDTECH & PHARMA
PLATFORM

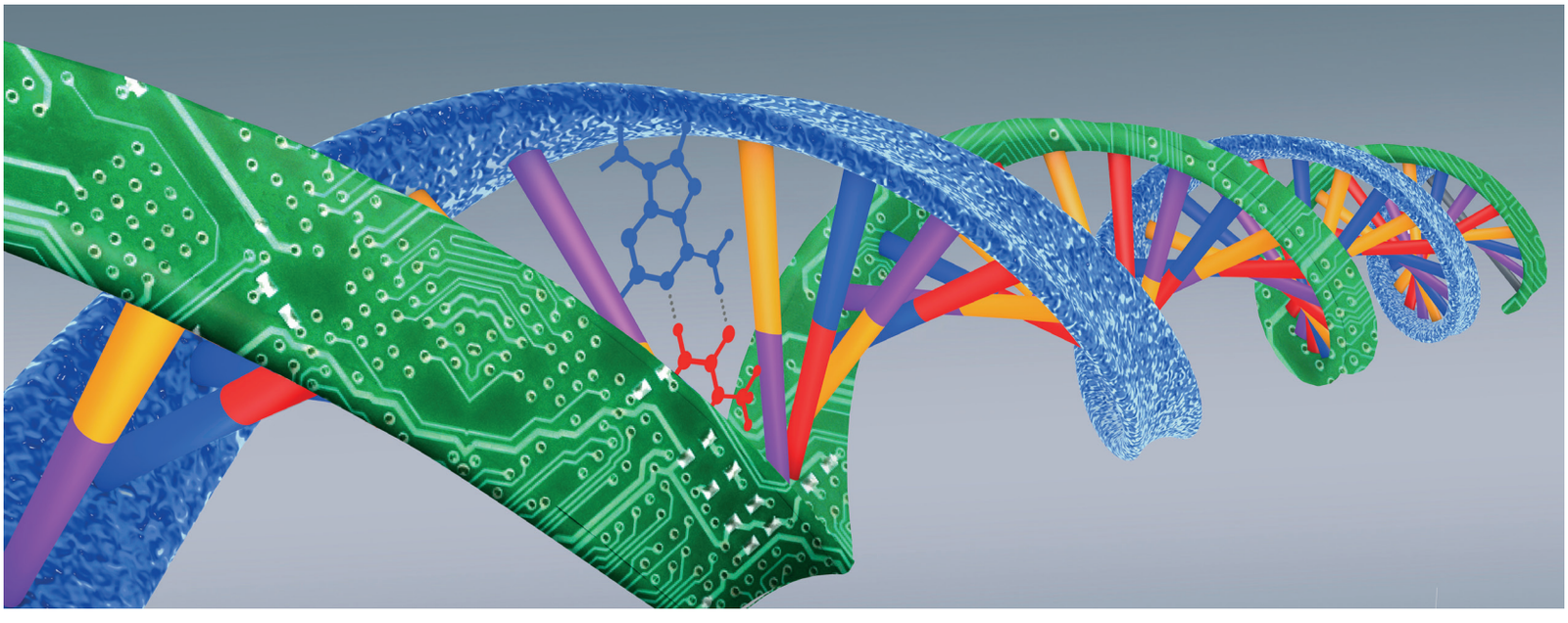
White Paper

on EU regulatory and policy framework

for combined products

October 2018

Innovative approaches for patients' health through joint pharma and medtech solutions



Foreword

As President of the Medtech & Pharma Platform (MPP) association, I am very pleased to introduce this MPP white paper. It addresses current regulatory challenges pharma and medtech companies face, in continuing to develop and market combined products under the new EU Regulations.

While this paper provides detailed insight into applicable regulatory and policy aspects, it is more than just a compilation of facts. It represents the core area of MPP's work as an industry association entering the political dialogue with European stakeholders in the pharmaceutical and medtech sector. The cross-industry approach of the MPP, which started as an international annual conference in 2014 to bring together pharmaceutical and medtech companies, clearly met a need of both industries to exchange knowledge and to collaborate in technology and regulatory areas.

Subsequently, following the request of many interested parties to generate a targeted political voice for combined healthcare products from pharma and medtech companies, the MPP industry association was founded in 2017. Today, the MPP presents itself with a Board of Directors coming from leading pharmaceutical and medtech companies, as well as a highly experienced secretariat composed of a former head of a notified body and experts with longstanding careers in European public affairs.

Together, we work on solutions for existing and upcoming regulatory uncertainties, which are almost inevitable at the highly dynamic intersection of pharmaceutical and medtech regulations.

With this white paper at hand, the MPP seeks to start a dialogue with relevant stakeholders to create an appropriate framework for combined products that fosters innovation, reduces time to market and addresses patients' needs.

Shayesteh Fürst-Ladani

President of the Medtech & Pharma Platform Association

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1. Executive summary

Combined pharma and medtech products are at the forefront of medical innovation, and their role in healthcare will become even more prominent over the next years due to science and technologies progress.

As pharma and medtech products are regulated by different legislations, roles and responsibilities at the edges of these two regulatory regimes have the potential to intersect, challenged by the dynamic evolution in this highly innovative sector.

Chapter 3 of this MPP white paper describes the most relevant examples of combined products, their characteristics and their respective regulatory pathways in the European Union. A comparison to the respective US legislation is given as well.

Chapter 4 summarizes the current key challenges for combined products in the EU and the fields of initial MPP's activities. Starting from go-to-market issues (in particular related to Article 117 of the Medical Devices Regulation), to questions relating to digital transformation, post market safety, and lifecycle management, the MPP reveals a multitude of open questions for which the association offers expertise and clarification.

The MPP working group (WG) is composed of members from leading pharmaceutical and medtech companies, which provides broad expertise in medicinal products, medical devices and combined products.

Based on this MPP white paper, the WG seeks a constructive dialogue with relevant stakeholders to jointly develop solutions for existing and upcoming challenges for combined products.

2. Scope of combined products

At EU level there is no official definition of combined products. Within the scope of this white paper, combined products refer to any combined use of a medicinal product, including biologics and advanced therapy medicinal products (ATMPs), with a device or diagnostic for medical purposes, without forming necessarily an integrated unit.

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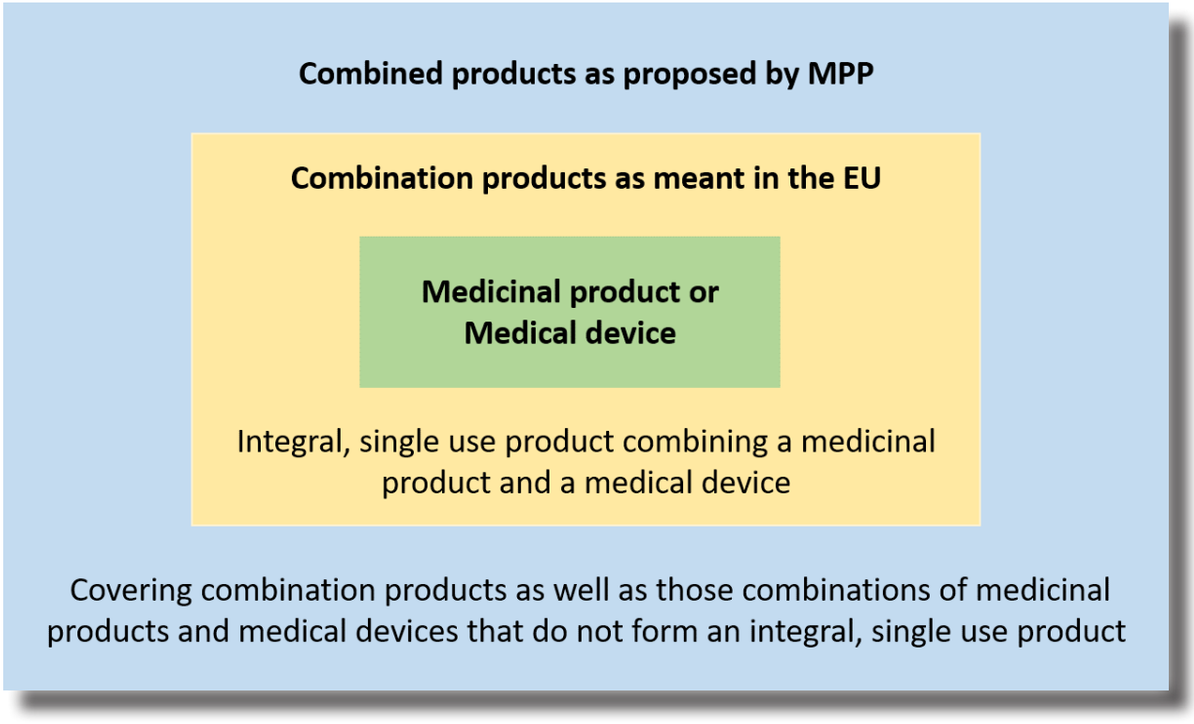
This covers also the use of e-/m-health products. The range of medical products covered by the definition of combined products is therefore very diverse and open to further expansion due to technological advancements.

The scope of combined products includes also combination products. In the EU, a combination product is meant as a medicinal product that has as an integral part a medical device, or a medical device that has a medicinal product as an integral part. Combination products are therefore a subgroup of combined products, as illustrated in the below table.



Combination products, which combine a medicinal product and a medical device as an integral part, are regulated either by the Medical Devices Directive (MDD 93/43) and as of 2020 by Medical Devices Regulation (MDR 2017/745), or the Directive 2001/83/EC on medicinal products. Notably, the following definitions apply:

§ MDD, Art. 1 (3, 4, 4a)[1]

"3. Where a device is intended to administer a medicinal product within the meaning of Article 1 of Directive 2001/83/EC (1), that device shall be governed by this Directive, without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product. If, however, such a device is placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC. The relevant essential requirements of Annex I to this Directive shall apply as far as safety and performance-related device features are concerned.

4. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device shall be assessed and authorized in accordance with this Directive.

4 a. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the human body with action ancillary to that of the device, hereinafter referred to as a 'human blood derivative', that device shall be assessed and authorised in accordance with this Directive."

§ MDR, Recital 10[2]

"Products which combine a medicinal product or substance and a medical device are regulated either under this Regulation or under this Regulation or under Directive 2001/83/EC of the European Parliament and of the Council. (...) For medicinal products that integrate a medical device part, compliance with the general safety and performance requirements laid down in this Regulation for the device part should be adequately assessed in the context of the marketing authorisation for such medicinal products."

[1]Medical Devices Directive 93/42/EEC, Art. 1.
Available at: : https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF.
[2]Medical Devices Regulation 2017/745, Recital 10.
Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN.

§ MDR, Art. 1 (8,9)[3]

"(8) Any device which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the device, shall be assessed and authorized in accordance with this Regulation.cHowever, if the action of that substance is principal and not ancillary to that of the device, the integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004 of the European Parliament and of the Council, 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 are concerned.

(9) 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."

[3]Medical Devices Regulation 2017/745, Art. 1, section 8 and 9.

2.1 Combined products: their characteristics, examples and regulatory pathways

Combined products include, but are not limited to, the following examples as set out in the below table:

Product categories	Characteristics	Examples	Regulatory pathway
Medicinal product and medical device combination product classified as **drug**	• Single integral product • **Intended exclusively for use in the given combination** • **The action of the medicinal substance is principal and not ancillary** • Non-reusable	Single use injection pen 	According to Art. 117 of the MDR, which amends the applicable Directive 2001/83/EC regulating medicinal products: • information on the device is submitted with a Marketing Authorization Application (MAA) dossier; • CE marking and conformity assessment by a notified body; or • non-CE marked device: applicant provides opinion on the conformity of the device part issued by a notified body.
Medicinal product and medical device combination product classified as **device**	• Integral product • The medical device incorporates **a medicinal substance or a human blood-derived substance** • **The medicinal product's action is ancillary** • Non-reusable	Drug-coated stent or a hemostatic matrix 	According to Rule 8 of the MDR: • classified as a class III high risk medical device; • conformity assessment by the notified body, with EMA or national competent authority consultation; • consultation evaluates drug component and the added value through incorporation.
Advanced Therapy Medicinal Product and medical device combination product classified as **ATMP**	• Integral product • The **ATMP's action is principal** • Non-reusable	Viable cells embedded in a biodegradable matrix or scaffold Examples of ATMPs: • Tissue engineered product • Gene therapy medicinal product • Somatic cell therapy medicinal product	Under Regulation 1394/2007 on advanced therapy medicinal products due to ATMP component: • scientific evaluation of MAAs carried out by the EMA's Committee for Advanced Therapies (CAT); • Committee for Medicinal Products for Human Use (CHMP) endorses CAT opinion to the European Commission; • the Commission adopts a decision binding in all Member States. *Exceptions: Products manufactured utilizing derivatives of tissues or cells of human origin that are non-viable or are rendered non-viable. Assessed according to Art. 117 of the MDR if they comply with the definition of medical device. (see Recital 11 of the MDR)*

Product categories	Characteristics	Examples	Regulatory pathway
Combined use of companion diagnostics (CDx) with a medicinal product	• **Non-integral product, most often in vitro diagnostic** medical device • Provides essential information for the use of a corresponding medicinal product on targeted patients • Determines suitability for tailored forms of therapy	Companion diagnostics 	CDx are regulated by the In Vitro Diagnostics Regulation (IVDR 2017/746). Under the IVDR, CDx will either fall into class C or in class D (second highest or highest risk class, respectively): • EU certificate issued by notified body after consulting EMA or the national medicinal product-competent authority; • EMA always consulted for CDx evaluation when centralized procedure used; • consultation procedure assesses the CDx in relation to the respective medicinal product. Notes: CDx are a very good examples of a combined, and not a combination product in the EU, as both the CDx and the medicinal product have each to comply with their respective regulatory requirements and be either CE marked or authorized independently.
Combined use of e-/m-health devices with medicinal products	• **e-/m-health apps** with a medical purpose that are software • Classified as active medical devices • The **information is used for treatment decision using medicinal products**	Glucose measurement app connected with an insulin pump 	According to Art. 117 of the MDR in case software is an integral part of the drug delivery device, OR according to the IVDR 2017/746: • products follow either the MDR or the IVDR conformity assessment procedures. Additionally: General Data Protection Regulation (GDPR 2016/679) and its requirements should also be considered as these apps collect patient data
Co-packaged combined product	• **Administration device** provided together with the Medicinal Product • **Not forming a single integral entity**	Drug with measuring spoon 	Administration devices not forming a single entity with the medicinal product are regulated under the MDR and must be CE marked. Additionally: MDR Article 16 would apply to the drug product manufacturer, as distributor of the medical device

Key messages

- Close collaboration and information exchange between pharma/medtech companies, competent authorities and notified bodies is required
- Responsibilities of competent authorities and notified bodies need to be further clarified
- Guidance needs to be given with the definitions of intended use and ancillary mode of action
- A clear definition of combined products needs to be reached at EU level

2.2 Comparison with other international regulations

Combination products are mentioned in the MDR and the medicinal products Directive 2001/83/EC will be amended to recognize medicinal product/medical device combination products. However, there is no official definition for either combination nor combined products at the EU level. This is in contrast to the US where combination products are explicitly defined by the Food and Drug Administration (FDA)'s Code of Federal Regulations, Title 21, part 3.2[4] . The definition of combination products includes:

- A product comprising two or more regulated components as a single entity: this applies to, for example, drug/device, biologic/device, drug/biologic, or drug/device/biologic combinations;
- Two or more separate products packaged together in a single package or as a unit;
- A drug, device or biologic that is packaged separately but intended to be used only with an approved individually specified drug, device or biologic, in order to achieve the intended use;
- An investigational drug, device or biologic that is packaged separately but, according to its proposed labelling, is intended to be used only with an individually specified investigational drug, device or biologic, in order to achieve the intended use.

Combination products in the US are classified according to the primary mode of action (FDA CFR 21, part 3.2), defined as the "the single mode of action of a combination product that provides the most important therapeutic action of the combination product". Therefore, the agency responsible for the aspect of the product with the greatest therapeutic effect will have jurisdiction over the product.

The US definition is broader than the legal text provided in the MDR, which mentions only integral single use medicinal products/medical device combination products, and is more similar to the MPP's suggested definition of combined products.

[4]FDA CFR 21, part 3.2.
Available at: https://www.ecfr.gov/cgi-bin/text-idx?SID=a721fa6588196c69a1781cocc667c546&mc=true&node=se21.1.3_12&rgn=div8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3. Challenges for combined products in the EU and MPP's areas of activities

Untapping the full potential of combined products requires an appropriate regulatory framework that guarantees the quality and safety of these products, while promoting innovative treatment options

The status of combined products at the intersection of the MDR and the Medicinal Product Directive 2001/83/EC, together with the lack of an official definition at the EU level, creates uncertainties for pharmaceutical and medical device companies. Furthermore, the majority of the MDR's implementing acts have not yet been published by the European Commission, even though it is more than a year since the Regulation entered into force.

Untapping the full potential of combined products requires an appropriate regulatory framework that guarantees the quality and safety of these products, while promoting innovative treatment options. Because of the complexity of these products, collaboration across the two industries and involvement of relevant stakeholders in the healthcare system (manufacturers, medicines and medical devices authorities, notified bodies) is required.

The MPP has established a working group consisting of members from the pharmaceutical and medtech sectors to collaborate on these challenges and to start a dialogue with relevant stakeholders.

MPP's focus is regulatory areas relating to combined products, starting from registration and go-to-market, lifecycle management, quality and safety, up to managing the digital transformation.

3.1 Go-to-market at the intersection of medicinal products and medical devices: Article 117 of Regulation (EU) 2017/745 amending Directive 2001/83/EC

Article 117 of the MDR represents a direct amendment to Directive 2001/83/EC on medicinal products with regard to combined products where the intended action of the medicinal product is ancillary. Notably, it states the following:

§ MDR, Art. 117[5]

"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, 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 sub-paragraph 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."

[5]Medical Devices Regulation 2017/745, Art. 117.

This amendment requires the applicant to include, in its MAA for a single integral medicinal (combination) product, the results of the conformity assessment of the device component (if CE marked), or the notified body's opinion on the conformity of a non-CE marked device with Annex I of the MDR.

This creates several uncertainties with the potential to considerably impact business in the pharma and medtech industry. The most significant aspects refer to content and procedures of the notified body writing the requested opinion, change control procedures for combined products including notification/approval by the respective stakeholders and the use of CE marked devices in combined products, which are discussed in further detail in the following sections.

- **Notified body opinion**

Article 117 of the MDR applicable as of May 26, 2020 foresees that medicinal product/medical device combination products classified as medicinal products will require a notified body opinion for a non-CE marked device components. Many aspects of this opinion are yet to be clarified.

The regulatory procedure for the assessment by the notified body has to address outstanding questions including: which documents are required to be provided, if and where audits will be performed and how and when a review of the quality management system needs to take place. Consequently, the content of the notified body opinion remains undefined.

In regard to timelines, it is important to note that not all the notified bodies that are currently active according to the MDD have applied for designation under the MDR. This situation is even more critical for notified bodies assessing in vitro diagnostics (IVDs). The number of notified bodies currently assessing IVDs is already limited, and the number of IVDs covered by the IVDR will drastically increase. If, in addition, the number of notified bodies assessing IVDs under the IVDR would decrease, a likely resulting scenario would be a bottleneck in the certification of IVDs, with such a delay having a major impact on the industry. In addition, it is not clear which scopes a notified body must have to provide an opinion about a combination product. Depending on the required scopes this may result in an additional reduction of available notified bodies for combination products.

Furthermore, a lack of detailed guidance on roles and responsibilities of the involved parties may lead to different opinions by the notified body and the competent authority and cause significant delays in the assessment of the MAA and patients' access to innovative therapies. Therefore, it is vital importance that a detailed guidance is issued before the application of the MDR in 2020 and IVDR in 2022.

Open questions the MPP will address

- Which documents have to be provided for the notified body opinion?
- What will be addressed in the content of the notified body's opinion?
- What measures are in place to ensure that the opinion of the notified body meets the expectations of the medicines competent authority?

- **Change Control**

Once a product is on the market, it is still subject to potential changes aiming to improve safety and efficacy of the marketed product. Under the MDR, it is unclear what happens when these changes occur to the device part of a combined product. A change can in fact impact the product substantially (e.g. design change, manufacturing process, intended use). Changes can differ greatly, and which changes will need to be reviewed and approved prior to implementation remains vague. Consequently, the possibility or need for the involvement of a notified body for an updated opinion also remains ambiguous.

Another important point concerns the recognition of combined products that will already be on the market when the MDR is fully applicable in 2020. Clarification is needed as to whether these products would fall under Article 117 of the MDR and if new conformity assessments will be needed for the device part.

Open questions the MPP will address

- What changes to the device part will need to be reviewed and certified/approved by the notified body and/or competent authority?
- When will an updated notified body opinion be needed?
- Will line extensions for new indications or other variations require a notified body review?
- Will grandfathering be possible for combined products already marketed when the MDR is fully implemented?

- **CE marked devices used in combined products**

Another point in relation to Article 117 MDR that the MPP will look closely at, is the use of CE marked devices whose intended purpose does not include the use in a combined product. If such devices are used in a combined product, would an updated conformity assessment be needed by the notified body? If so, notified bodies need to have procedures in place for such a use to be added.

Open questions the MPP will address

- For CE marked devices where the intended use does not include use in combined products, would an updated notified body conformity assessment be needed?
- How will it be ensured that notified bodies have appropriate procedures in place for such evaluations?

- **Clinical Evaluation Report requirements for the device portion of a combination product**

What is not clear from Article 117 requirements is the expectation in relation to the clinical evaluation of the device component, i.e. the product is regulated as a medicinal product and clinical trials of the medicinal product shall be presented, however what is not clear at this stage is the level of detail required regarding clinical evaluation for the device aspect and of course the product as a whole single entity should be considered within any evaluation conducted.

On review of Annex I of the MDR and the general safety and performance requirements, while it is not explicitly stated that a clinical evaluation is a general safety and performance requirement, the requirements detailed in section 1 and 8 of Annex I are linked to data obtained from such an evaluation.

In addition, Article 61 states:

§ MDR, Art. 61[6]
"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 acceptability of the benefit-risk- ratio shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data."

Article 61 requires that 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.

What is required is clarification and guidance on the expectations for a sufficient level of Clinical data for the device component, considering various potential scenarios.

Open questions the MPP will address

- For a combination product regulated as a medicinal product what is the expected level of detail relating to the clinical evidence for the device aspects? Is there a difference between when the device constituent is CE marked or when the device constituent is not CE marked?
- Are Clinical Investigations for the device aspects in isolation necessary?
- How will it be ensured that notified bodies have a consistent approach and appropriate procedures in place for the consideration of device safety and performance?

3.2 Digital transformation of health and care

Many medical devices nowadays are able to connect and exchange information with other products and databases. This network of connected devices allows manufacturers to better monitor the performance and safety of their products, and for patients to easily track their health. However, regulatory questions also become apparent in these aspects of digital health and data management.

In line with its focus area, the MPP association will especially examine the use of software in combined products. According to the MDR, software for medical purpose qualifies as a medical device and falls under rule 11 of the MDR, which classifies them according to their intended use. Classification varies from the lowest (class I) to the highest risk class (class III), and due to the implementation of stricter criteria, most software could subsequently be assigned to a higher risk class. As a result the conformity assessment procedure of the notified body might change. for further guidance and acts concerning software classification and its use in combined products. The additional documents will also seek to more clearly define the interaction between the MDR and the General Data Protection Regulation (GDPR) in terms of data management for software, as well as how to manage potential cybersecurity issues.

[6]Medical Devices Regulation 2017/745, Art. 61

Another important topic that the MPP will focus on is the use of digital data for treatment decisions with medicinal products. In this regard, it is unclear how the information flow will be managed between the software and the medicinal product manufacturers, as well as what will be required of them by in interactions with relevant authorities.

Open questions the MPP will address

- As software can be classified from the lowest to the highest risk class, will further guidance be provided on its classification?
- What level of interaction will there be between the MDR and the GDPR in terms of data management?
- How will cybersecurity issues be addressed?
- When digital data will be used for treatment decisions with medicinal products, how will proper interaction be ensured between the software and the medicinal product manufacturers, as well as between the manufacturers and the relevant authorities?

3.3 Requirements for products used in hospital settings

The IVDR foresees different requirements for IVDs that are manufactured and used in hospitals – the in-house tests – and for commercialized IVDs. Article 5 of the IVDR[7] states that in-house tests do not need to be CE marked, but must only show compliance with general safety and performance requirements that are applicable for all IVDs and fulfil the conditions described in Article 5 of IVDR. In order to ensure patients get the effective treatment and that all IVDs are adequately validated, the application of the in-house exemption needs to be carefully monitored.

A specific aspect to be considered is the fulfilment of different national requirements for devices used in hospitals. It remains unclear what the level of interaction will be among countries, and how this will ensure that these devices are all equally safe and have undergone appropriate and robust validation.
Guidelines need to be developed in order to create harmonization, and the MPP will specifically advocate and contribute to guidance for human factor studies.

Finally, another open question concerns the requirements for non-CE marked IVDs – other than companion diagnostics – used in and developed specifically for clinical trials. The potential involvement of different authorities for the review of such IVDs during clinical trials application evaluation needs to be clarified.

Open questions the MPP will address

- Will the implementation of the IVDR guarantee that all IVDs be sufficiently validated – regardless of whether commercialized or manufactured in-house?
- How will harmonization between the different national requirements be monitored and applied for in-house tests?
- Will a guidance for human factor studies for IVDs be developed?
- What will be the requirements for non-CE marked IVDs that are used in clinical trials for medicinal products?

[7] IVDR 2017/746, Art. 5, section 4 and 5.
Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746&from=EN

3.4 Responsibilities in post market safety and vigilance reporting

The post-market phase also presents some regulatory uncertainties for combined products. The primary concerns relate to the lack of clarity as to who should be the recipients of the post market surveillance reports and how these should be handled. Similarly, vigilance reporting presents the related issue: should the reporting involve notification of the medicines competent authority, the medical devices competent authority, or both? Especially when it comes to non-CE marked devices used in a combination product, vigilance reporting needs to be clarified.

For combined products, another open question concerns the reporting of vigilance cases specifically on the device component to the device manufacturer. Would these vigilance cases impact the risk class of the device? All the above points require clarification before the MDR is fully implemented.

Open questions the MPP will address

- Which authority(-ies) should be notified of vigilance and post market surveillance reports?
- Will there be special rules for non-CE marked devices used in combined products?
- Should vigilance cases concerning the device component of a combined product be reported to the device manufacturer?
- Will these vigilance cases affect the risk class of a device?

3.5 Lifecycle management: EUDAMED notifications, labelling issues, registration numbers

The European Databank on Medical Devices (EUDAMED) is an information system whose purpose is to increase market surveillance, traceability and transparency of medical devices in the EU. While EUDAMED already exists, significant changes are envisaged by the MDR in order to allow competent authorities to exchange more data, provide for different levels of access to data and facilitate the traceability of devices, by utilizing the unique identification number (UDI).

In relation to combined products, the notification procedure to EUDAMED a number of gaps in the current process need to be addressed. As combined products incorporate different components, it is unclear if there will be a specific UDI code and/or designation for combined products, as well as whose responsibility it will be to place the UDI on the labelling (e.g. device or drug manufacturer).

Further, the possibility of a single registration number (SRN) for manufacturer of combined products needs to be discussed. Upon registration in the electronic system, the manufacturer is in fact assigned an SRN, which is used during the application to the assessment procedure as well as to enter the UDI database. In the case of a combined product, it is unclear which manufacturer will need to apply for the SRN: the device or the medicinal product manufacturer.

Open questions the MPP will address

- Will further guidance be provided on the notification procedure for combined products in EUDAMED?
- Is a specific UDI code needed for combined products?
- Whose responsibility is it to place the UDI code on the labelling?
- Who will need to apply for the single registration number, the device or the medicinal product manufacturer?

3.6 Challenges for combined products in R&D and clinical trials

The development and design phase of a combined product will also be affected by the MDR. It is clear that the requirements of the MDR and the standard ISO 13485 "Medical devices - Quality management systems - Requirements for regulatory purposes" must be fulfilled by the manufacturer.

Requirements in the MDR are specified in Annex I (General Safety and Performance Requirements), which includes several additions compared to the MDD, especially for the design of products that incorporate a medicinal product or materials of biological origin, software, and active implantable devices. For combined products developers, this means that the device part will be affected and potentially changed.

Additionally, the design process of the quality management system will need to be updated to demonstrate the compliance of the design of a device with the new requirements. Consequently, the technical files of the existing devices needs to be updated and probably restructured, and the notified body will reassess the files. This relates to the regulatory uncertainties explained earlier in chapter 4.1.

Once these combined products are required to undergo clinical investigations additional questions become apparent. Clinical data will be required for the device part, but these data might not be sufficiently obtained through the clinical trial of the medicinal product. Consequently, the question is whether in such situation an additional investigation will be needed to specifically address the device part. If so, the potential of lacking clinical data for the device part being obtained in the initial clinical investigations represent an issue for manufacturers.

With regard to the clinical evaluation of software, a guidance document by the International Medical Device Regulators Forum (IMDRF)[8] is already available, but it is unclear if this will remain unchanged under the MDR.

Open questions the MPP will address

- For combined products' clinical investigations, will an additional investigation be required for the device part?
- How will the availability of sufficient clinical data for the device part be ensured?
- For the clinical evaluation of software, will the IMDRF guidance remain valid under the MDR?

[8] „Software as a Medical Device (SaMD): Clinical Evaluation", published in 2017 by the IMDRF. Available at: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170921-samd-n41-clinical-evaluation_1.pdf.


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4. About the Medtech & Pharma Platform

The Medtech & Pharma Platform (MPP) is an international non-profit industry association enhancing the synergies between pharmaceutical and medtech companies. By providing a forum for both industries, MPP fosters collaboration in order to develop healthcare solutions that combine pharma- and medtech components.

Objectives

- Make use of synergies between pharma and medtech industries
- Establish new collaboration models to ensure and accelerate market access for safe and innovative treatment options
- Work jointly on a balanced and proportionate regulatory and political framework for combined products

Members

- Novartis
- Merck Sharp & Dohme (MSD)
- Ypsomed
- Sanofi
- SFL Regulatory Affairs & Scientific Communication (SFL)
- Swiss Medtech

Governance

- The MPP Association is governed by its General Assembly, the Board of Directors and the Office.
- MPP is a not-for-profit association in accordance with Articles 60 et seq. of the Swiss Civil Code.
- MPP is registered in the EU Transparency register, ID 234427831877-10.
- MPP is registered as an EMA interested party

Activities

- **Advocacy work for pharma and medtech companies**
  The MPP Association seeks to address existing and forthcoming regulatory challenges for combined products with the aim to create a reasonable and proportionate regulatory framework.

- **MPP expert trainings and scientific knowledge base**
  MPP offers specialized, accredited training courses providing comprehensive and up-to-date insights on latest developments of relevant legislation for combined products.

- **MPP annual conference**
  The MPP annual conference is the leading conference in the sector of products and solutions that combine pharma and medtech components. The event is dedicated to enhancing partnership between actors in the pharma and medtech fields.

MEDTECH & PHARMA
PLATFORM

Medtech & Pharma Platform

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