MEDTECH & PHARMA
PLATFORM

Regulatory pathways for connected combined products

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1. Introduction

Connected drug delivery devices are increasingly being developed to complement drug treatments thanks to their potential to facilitate disease management in the home setting. Features may include dosing reminders, adherence trackers, tools for patient education, patient diaries, and monitoring tools. Comparative studies indicate initial evidence for a higher adherence to treatment and better outcomes among patients who use electronic tools[1].

A previous publication by the MedTech & Pharma Platform Association (MPP) issued in 2022[2] defined a *connected combined product* (CCP) as a medicinal product used with two or more of the following products with wireless connectivity: a drug delivery device or an *in vitro* diagnostic device (IVD), a standalone software on a mobile platform, and/or a cloud application, with the aim to deliver a medicinal product to patients and to monitor certain data and parameters, such as medical adherence.

The 2022 MPP publication highlighted the challenges in developing and releasing such products. Four areas were investigated: 1) clinical and regulatory frameworks; 2) usability and human factors engineering; 3) development process and lifecycle management; and 4) cybersecurity.

In regard to the regulatory framework applicable to CCPs, the 2022 MPP publication acknowledges that regulatory frameworks exist for the individual components of a CCP, however regulatory guidance is needed when combining products with different risk and safety profiles. Specifically, the gaps and challenges that the previous publication brought up are the following: 1) neither the Medical Devices Regulation (MDR) nor the *In-Vitro* Diagnostic Medical Devices Regulation (IVDR) address the regulatory framework of product connectivity including safety and the roles and responsibilities of different stakeholders when it comes to the individually registered components of the CCP, or non-regulated products used in a combined way for a medical purpose; 2) the CCP manufacturer must demonstrate safety and efficacy working with products that do not have a medical purpose, and hence have not been developed to comply with the Medical Devices Regulation. The paper called for joint discussions among the various stakeholders and regulatory authorities with the aim of devising pragmatic solutions and regulations.

Challenges concerning regulatory pathways for *digital health technologies*[3] used with medicinal products were also brought up by the European Federation of Pharmaceutical Industries and

[1] Bittner et al., Connected drug delivery devices to complement drug treatment: potential to facilitate disease management in home setting. Medical Devices: Evidence and Research 2019 (12), pp. 101-127. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419593/, last accessed on 18 September 2023.
[2] Kühler et al., Development and Regulation of Connected Combined Products – Reflections from the MedTech & Pharma Platform Association. Clinical Therapeutics. 2022 44(5), pp. 768-782. https://www.sciencedirect.com/science/article/pii/S0149291822001126, last accessed on 18 September 2023.
[3] A *Digital Health Technology* is defined by EFPIA as an electronic method, system, product, or process that generates, stores, displays, processes and/or uses data within a healthcare setting.

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Associations (EFPIA)[4]. As a result, EFPIA listed following revendications: 1) an integrated consultation platform to permit iterative dialogue between sponsors, European Medicines Agency (EMA), competent authorities for devices and medicines and notified bodies to allow timely advice; 2) harmonized review pathways (i.e., harmonized review) covering the entire lifecycle; 3) harmonization of EU guidance across all relevant regulators /notified bodies; 4) opportunities during the revision of the European Union (EU) pharmaceuticals legislation, in particular the European Commission's initiative aiming to streamline approval procedures, and the development of legal proposals that address the regulatory challenges at the interface between medicinal products and devices.

The present paper aims to examine the challenges associated with regulatory pathways in the EU for a subset of CCPs: those consisting of a medicinal product used with a delivery device with wireless connectivity to a standalone software; the software may be located on a mobile platform or be cloud-based. Furthermore, this paper will mainly focus on the most frequently encountered *delivery devices with wireless connectivity:* non-digital integral drug-delivery devices fitted with a separate digital element acting as a *sensor*. The *sensor* typically collects delivery device usage information and transmits it (possibly after intermediate storage) to the accompanying standalone software. The scope of this paper is finally restricted to the initial commercial regulatory clearance of the CCP. Regulatory pathways to manage software changes during the CCP's lifecycle (for example upgrades, bug fixes, addition of features, new operating system releases) are beyond the scope of this paper.

In this paper, we first present a number of existing CCPs as examples, detailing what are the components making up these CCPs and describing the intended purpose of the digital solution[5] within these CCPs. The paper proceeds by examining the applicable *regulatory identity*[6] of the components, and discusses the qualification of a CCP as a *system*. Subsequently, the potential impact of a CCP on *drug labeling* is addressed; such topic being important to be understood in order to proceed into a discussion of applicable regulatory pathways for market clearance of the CCP components and of the CCP as a whole (i.e., use of the digital solution with the medicinal product). In this context, the topics of harmonized review process, benefit/risk assessment, and evidence supporting label claims are addressed. The paper closes with a conclusion that includes a call for action.

2. Components of CCP

The table below presents examples of delivery devices with wireless connectivity that form a CCP when combined with a medicinal product and a mobile application. In most examples listed, the *delivery device with wireless connectivity* results from the fitting of a connected add-on sensor to a non-connected delivery device integral to the medicinal product (such as a pen injector or an inhaler). In a few instances (Betaconnect, AutoTouch Connect, Omnipod Dash), the component containing the

[4] EFPIA, Reflection paper on the Need for Better Defined Regulatory Pathways in the EU for Digital Health Technologies used concomitantly with Medicinal Products or as drug development tools during Clinical Development, 2021. https://www.efpia.eu/media/636454/efpia-rp-digital-health-technologies_november-2021.pdf, last accessed on 18 September 2023.

[5] For the purpose of this paper, the *digital solution* of a CCP is defined as the combination of the article possessing digital connectivity (either the delivery device with integrated wireless connectivity, or the add-on sensor for the delivery device) and the standalone software on a mobile platform or on a cloud.

[6] *Regulatory identity* designates in this paper whether a product is regulated as a medicinal product, a medical device, or a general-purpose product (which in turn could be an accessory to a medical device).

sensor also contributes to the drug delivery functionality once assembled with the medicinal product contained in a syringe, a pre-filled cartridge, or a pod.

Table 1: Examples of CCPs

Example number	Delivery device with wireless connectivity[7]	Medicinal product(s)	Standalone software on mobile application	Intended purpose of the digital solution
1	Breezhaler inhaler with Propeller Health	Enerzair	Companion application (proprietary name not found). Presents personalized content based on the patient's recorded medication usage.	Provision to patient of inhalation confirmation, medication reminders and access to objective data to better support therapeutic decisions[8].
2	Inhaler device with SmartHaler Hailie	Symbicort MDI Vannair HFA/MDI	The Hailie® App is a companion application for use with one or more Hailie® sensors which attach onto an inhaler. Amongst other features, the App tracks adherence and medication use, and captures clinical data that is sent in real time via a secure cloud to a physician portal[9].	Tracking of inhaler usage, provision of reminders in case of missed dose, display of inhaler usage over time, possibility to share the information with physician to help them better manage the patient's respiratory condition.
3	Tempo pen with Tempo Smart Button	Humalog Basaglar	Various: software and/or medical devices offered by Dexcom, Glooko, myDiabby Healthcare and Roche (mySugr app)	The Smart Button is intended to store and transfer insulin dose-related data from a Tempo Pen. The Tempo Smart button will allow it to pair with software and/or medical devices to facilitate the integration of personalized data and actionable insights. Allows the user to improve decision-making with diabetes with access to

[7] The name of the component containing the sensor is underlined.
[8] Novartis website, Novartis presents new findings at ERS reinforcing the efficacy of Enerzair Breezahler, https://www.novartis.com/news/media-releases/novartis-presents-new-findings-ers-reinforcing-efficacy-enerzair-breezhaler-highlighting-its-digital-companion-well-showcasing-commitment-low-carbon-footprint-asthma-solutions, last accessed on 18 September 2023.
[9] Hailie website, Meet the Hailie App, https://www.hailie.com/pages/hailie-app, last accessed on 18 September 2023.

Example number	Delivery device with wireless connectivity[7]	Medicinal product(s)	Standalone software on mobile application	Intended purpose of the digital solution
				accurate, real-time data collection.
4	Flextouch Pen injector with Biocorp Mallya	Insulin	The app complements the use of the Mallya medical device. It allows to view insulin injection data: dose injected, date, time, insulin type. In addition to the injection log, the application offers the possibility to create a report that can be shared with a healthcare professional[10].	The intended use of Mallya is to be a data collection and wireless transfer device for insulin doses administered by compatible injection pens. Mallya can be used without the standalone software to signal the end of the injections. The coupling of Mallya with a compatible mobile application enables improved adherence to insulin treatment, the generation of a recapitulative report on injected doses over a certain time period, and storage and sharing of data with a healthcare professional[11].
5	Syringe[12] with Betaconnect autoinjector	Betaseron[13]	BetaTrack App	Tracking of injection site rotation, calendar view of past and future injections, setting of injection schedule, recording of well-being feeling.
6	Enbrel Mini single-dose prefilled cartridge with AutoTouch Connect autoinjector	Enbrel[14]	Embark App	Tracking of injections, medication reminders, *Enbrel Support.*

[10] Mallya website, What is the Mallya app?, https://my-mallya.com/en/faq/, last accessed 18 September 2023.
[11] Mallya website, Instructions for use in French: https://my-mallya.com/wp-content/uploads/2021/01/IFU_MAL_AD_FR_V9_210317.pdf, last accessed 18 September 2023.
[12] The empty syringe is provided to the user as part of the Betaseron drug-device co-pack.
[13] Provided in a vial whose content must first be transferred into the syringe.
[14] Provided as pre-filled cartridge with needle.

Example number	Delivery device with wireless connectivity[7]	Medicinal product(s)	Standalone software on mobile application	Intended purpose of the digital solution
7	Pod in OmniPod DASH	Insulin[15]	OmniPod DASH PDM	Programmed delivery of insulin.
8	Rebif pre-filled cartridge in RebiSmart electronic injection device	Rebif[16]	MS Dialog App	Tracking of injections, medication reminders.
9	NovoPen® 6	Insulin	Can connect with various software such as: Glooko®, FreeStyle LibreLink, mySugr®, G6®	Automatic recording of insulin dosing information and viewing side-by-side with glucose information, potentially enabling insight into how injection behavior affects glucose levels.

Note: The table was prepared using publicly available information.

3. Regulatory identity of CCP components

The components of a CCP are each assigned their own regulatory identity based on their intended purpose; Table 2 shows the general description of a few common CCP components. The regulatory identity and classification of a component will dictate the competent review entity and the applicable governing rule, Regulation or Directive, and therefore the applicable regulatory pathway to be followed to obtain market clearance or approval for each component (see Chapter 6).

Table 2: Components of a CCP with their regulatory identity and governing regulation or directive

Component	Identity and governing regulation
Medicinal product, without integral delivery device	Medicinal product – Medicinal Products Directive (2001/83/EC, MPD)
Delivery device, not integral to drug	Medical device – Medical Devices Regulation ((EU) 2017/745, MDR)
Medicinal product with integral delivery device	Integral drug-device combination - MPD, MDR Art 1(9), Art 117
Medicinal product with integral delivery device including sensor	Integral drug-device combination - MPD, MDR Art 1(9), Art 117
Sensor, not integrated to drug delivery device	General purpose product – Various non-MD specific requirements may apply[17]

[15] Not provided as integral drug-device combination product; the Pod needs to be filled with insulin prior to use with the Omnipod DASH delivery device.
[16] Provided as pre-filled cartridge.
[17] For example, but not limited to, the Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety, Directive 2014/53/EU of the European Parliament and of the Council of 16 April 2014 on the harmonisation of the laws of the Member States relating to the making

	OR Medical device or accessory to a medical device - MDR
Standalone software (mobile application or cloud-based)	General purpose product – Various non-MD specific requirements may apply OR Medical device or accessory to a medical device - MDR

As stated above and exemplified by Table 1, the most frequently encountered *delivery devices with wireless connectivity* result from the fitting of a connected add-on sensor to a non-connected delivery device integral to the medicinal product. For such a CCP, the following aspects must be considered:

- The **medicinal product with integral delivery** device is a single integral product per MDR Art. 1(9) second paragraph; such products are overall regulated by the MPD, while the "device part" must conform to the relevant general safety and performance requirements of MDR Annex I.
- The **sensor** may either be a medical device itself or an accessory to a medical device governed by MDR, or a general-purpose product (i.e. non-medical device); please refer to section 3.1 of this paper for a more detailed discussion.
- The **standalone software** (mobile application or cloud-based) may either be a medical device itself or an accessory to a medical device governed by the MDR or a general-purpose product (i.e., non-medical device); please refer to section 3.2 of this paper for a more detailed discussion.

3.1 Digital sensors regulatory qualification

Sensors and the information from such sensors may be used for a variety of purposes. Whether or not a sensor qualifies as a medical device, an accessory to a medical device or is considered a general-purpose electronic product, depends on the sensor's intended purpose. Table 3 below illustrates the various regulatory qualifications[18] of existing sensors (from CCPs listed in Table 1 above), including the medical device class when applicable.

Table 3: Examples of sensors with their regulatory qualification

Sensor relationship to delivery device	Qualification of sensor in EU	Examples
Separate from delivery device	Medical device Class I	• Tempo Smart Button • Propeller Health • SmartHaler Hailie
	Medical device Class IIb	• Biocorp Mallya

available on the market of radio equipment, Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data

[18] *Regulatory qualification* designates in this paper whether an item qualifies or not as a medical device.

Sensor relationship to delivery device	Qualification of sensor in EU	Examples
Integrated to one part of the delivery device	No information, sensor not marketed in the EU	• Betaconnect • OmniPod DASH • RebiSmart • AutoTouch Connect

Although no such examples were identified, it can be conceived that some digital sensors are treated as general purpose products, rather than medical devices. Intended purposes that are limited to detection, storage in and transmission of injection events to the accompanying app would not be considered to be medical purposes, as they do not directly treat the disease but rather provide general support to the patients in their management of the disease. In such cases, clearance can be achieved with a Declaration of Conformity to the Radio Equipment Directive (2014/53/EU)[19] and the Directive on the restriction of the use of certain hazardous substances in electrical and electronic equipment (2011/65/EU)[20].

In contrast, Biocorp Mallya provides audio and visual signals to guide patients during injection process, in addition to injection event tracking. Since Biocorp Mallya's intended use includes that patients will rely on its signals to perform their injection, Biocorp Mallya clearly serves a medial purpose. Biocorp Mallya was classified as a Class IIb medical device.

While the examples provided above are not exhaustive, the flowchart in Figure 1 provides an overview of the main scenarios that can be differentiated when assessing the regulatory identity of the sensor in the context of a CCP.

[19] Directive 2014/53/EU of the European Parliament and of the Council of 16 April 2014 on the harmonisation of the laws of the Member States relating to the making available on the market of radio equipment, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014L0053, last accessed 18 September 2023.
[20] Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02011L0065-20160715, last accessed 18 September 2023.

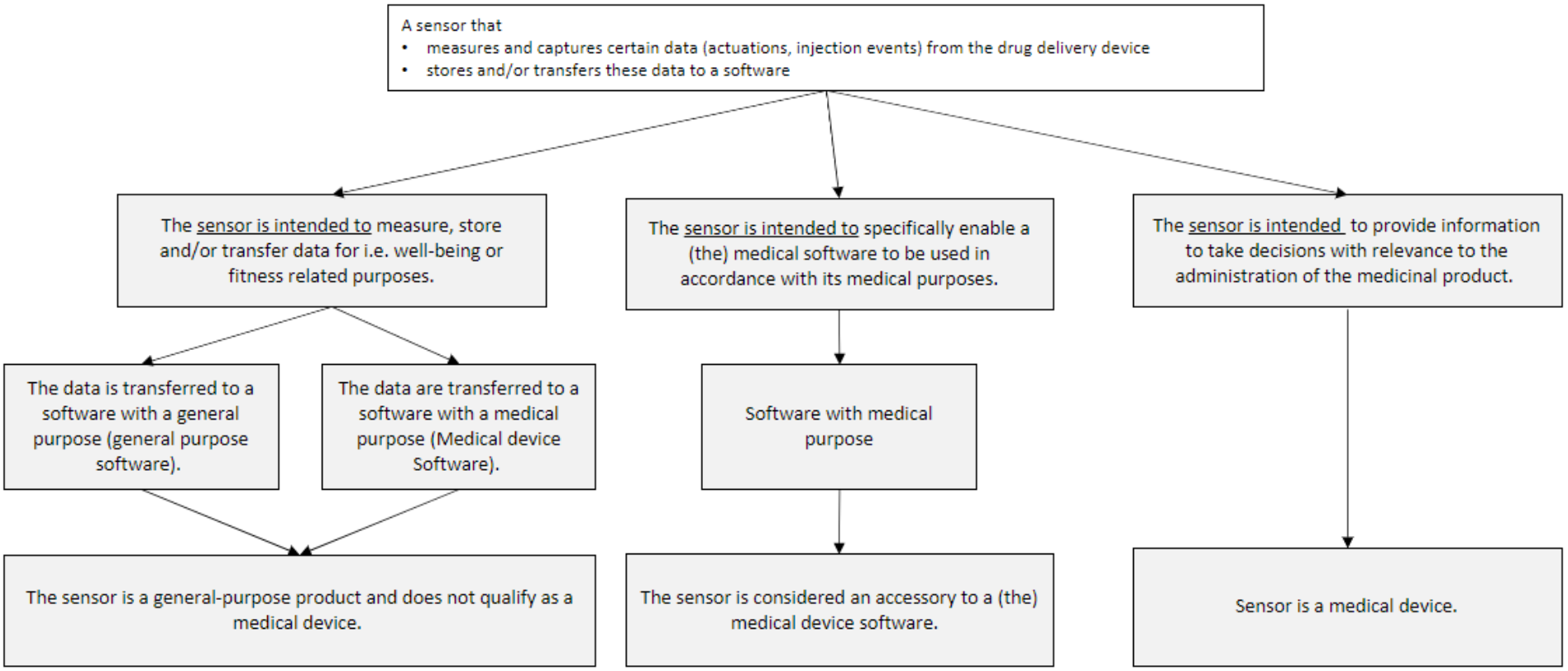

Figure 1: Flowchart for regulatory identity assignment of sensor[21]

[21] Note that the regulatory qualification of software applications is discussed separately in chapter 3.2 below; the software is included in this sensor decision flowchart to reflect the complete CCP context.

The flowchart in Figure 1 above takes into account that the qualification of a product – in this case the sensor – as a general-purpose product, medical device or accessory to a medical device is solely the intended purpose of the sensor. The connectivity of the sensor to a medical device, e.g., to a medical device software application, does not alone automatically qualify the sensor as a medical device. This also applies to the decision as to whether a sensor does or does not qualify as an accessory to e.g., a data receiving medical device software application. The decisive criterion to determine whether a product is an accessory to a medical device is whether or not the product, in this case the sensor, is intended to be specifically used together with a medical device; in other words, if the manufacturer of that sensor establishes an intended use in conjunction (specifically intended to be used together) with one or several medical devices. If a manufacturer was to claim that a sensor only fulfils fitness purposes without claiming any medical device (software) uses, the sensor would remain a general-purpose product

Please note that for better readability, Figure 1 does not explicitly display the event in which the sensor applies additional processing on the data it measures or captures, in which case the situation needs to be analyzed in more detail. If the sensor would, for example, convert measured raw data for a medical purpose, the sensor would qualify as a medical device or medical device accessory.

3.2 Standalone software regulatory qualification

In determining whether software qualifies as medical or non-medical device software, similar considerations and principles apply to those provided for sensors in section 3.1 above. The Regulations clarify that software *"should be qualified and classified depending on its intended purpose uniquely'* and *'regardless of its location"*[22]. The Medical Device Coordination Group (MDCG) guidance 2019-11 entitled "Guidance on Qualification and Classification of Software in Regulation" provides specific guidance pertaining to when software qualifies as medical device software (MDSW)[23].

Software needs to have a medical purpose to be qualified as a medical device software. In particular, software that is intended to process, analyze, interpret, create or modify medical information may be qualified as a medical device software if the creation or modification of that information is governed by a medical intended purpose. In the case of a CCP, the purpose of the software may be to process performed injection events to calculate the next date when an injection is due, using a dosing regimen-based algorithm. The software may also detect a missed dose based on a log of injection events, and as a follow-up to the detected missed dose, may indicate to the patient when and how to take the next dose to make up for the missed dose. In such cases, analysis of medical information (the injection log) occurs, and creation of new medical information triggering clinical action (e.g., the date of the next dose, the amount of medication to take at the next dose) takes place affecting medication treatment. Such purposes meet the definition of a medical device thus this software would be governed by the MDR. Similarly, when these operations occur at the level of the cloud and a software application, e.g. a mobile app, merely serves to capture, transfer or display data from a connected sensor or from the cloud application, the software running on the cloud would qualify as medical device software while

[22] Medical Device Coordination Group (MDCG), Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, 2019, https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2019_11_guidance_qualification_classification_software_en_0.pdf, last accessed 18 September 2023.
[23] Ibid.

the purposes of the mobile application (e.g. transfer or display) do not meet the medical device definition and hence are not governed by the MDR. Further, software that is intended to provide or create information for general purposes such as well-being or fitness purposes does not qualify as a medical device since such purposes to not meet the definition of a medical device (MDR Article 2(1)), even if the software receives input from a medical device sensor.

4. Qualification of CCP as a *system*

The concomitant use of each component of a CCP achieves a well-defined functionality and intended use. The functionality achieved by the digital solution of a CCP may be or not serving a specific medical purpose. Examples of medical purposes include the targeting of improved adherence to the prescription for the medicinal product and targeting improved dosing accuracy of the medicinal product.

In case a specific medical purpose is achieved by the CCP, it may fall under the definition of a *system* as defined by MDR Art. 2(11): a combination of products, either packaged together or not, which are intended to be inter-connected or combined to achieve a s*pecific medical purpose*.

For example, in the case of the digital solution consisting of SmartHaler Hailie and the Hailie App, reminders prompting the patient to take their medicine are issued in case of missed doses ; the *system* consisting of the medicinal product, the inhaler device, the SmartHaler Hailie and the Hailie App therefore fulfils a specific medical purpose . On the other hand, if the digital solution's purpose was limited to creating a list of dosing events without issuing any reminders or instructions concerning taking a dose, the digital solution would not have a specific medical purpose and would not fall under MDR's definition of a *system*.

5. Medicinal Product label impact

When a medicinal product *must* be used with a digital solution in order to achieve safety and efficacy, it is expected that the medicinal product's label mentions the digital solution. The digital solution therefore takes the status of *referenced device* according to the EMA guideline entitled "Quality documentation for medicinal products when used with a medical device".[24] The guideline states that "the product information should be sufficiently detailed to ensure correct use of the medicinal product with the referenced device". Reference is made to Section 6.1.1 of the guideline for the level of detail expected in the product information.

The case of a medicinal product that can *optionally* be used with a digital solution needs to be examined in more detail for drug label impact, as the guideline cited above does not offer an answer. In such as case, we wish to propose that it should be left at the discretion of the medicinal product Marketing Authorisation Holder (MAH) to either make a reference to the digital solution in the Product Information, or alternatively omit any reference to the digital solution in the Product Information and use other channels (for example training programs) to draw attention of patients and prescribers to the possibility of using the digital solution together with the medicinal product. In the case where Product Information does not contain a reference to the digital solution, it is clear that the Product Information can also not state any of the expected benefits achieved by the use of the digital solution.

[24] EMA, Guideline on quality documentation for medicinal products when used with a medical device, 2021, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-documentation-medicinal-products-when-used-medical-device-first-version_en.pdf, last accessed 18 September 2021.

Omission of referencing in the Product Information is also contingent on adequate instructions for use of the digital solution being provided together with the digital solution.

EMA's Questions and Answers document entitled "Qualification of digital technology-based methodologies to support approval of medicinal products" offers further insights into EMA's view regarding the Product Information. According to this document "*the principal mode of action* [of the connected combined product] *will determine the applicable regulatory framework and how (and if) the product will be reflected in the medicine's accompanying product information. For those technologies that are likely to have an impact on the safe and effective use of the product, and are to be reflected in the PI, it is important that the submitted Qualification briefing document clearly explains how they are going to be used, and the potential impact that they may have on the use of the medicinal product and the clinical outcomes"*.[25]

6. Regulatory pathways for CCP components

The regulatory identity assigned to each component of a CCP (see Table 2 above) forms the basis in assigning the appropriate regulatory pathway for initial clearance or approval of the component in the EU. The components of a CCP and the associated regulatory pathways are presented in table 4.

Table 4: Regulatory pathways to initial clearance/approval for each component of a CCP

Component	Regulatory pathway
Medicinal product, without integral device	Marketing Authorization Application (MAA), line extension, or variation to an existing MAA
Drug delivery device, not integral to drug	Conformity assessment per MDR Chapter V
Medicinal product with integral delivery device	MAA, line extension, or variation to an existing MAA; MDR Art. 117 (usually NBOp)
Sensor, not integrated to drug delivery device	• If non-medical device: Declaration of Conformity (to applicable Regulations, Directives and Standards) • If medical device: Conformity assessment procedure per classification • If accessory to medical devices conformity assessment procedure per classification
Standalone software (mobile application or cloud-based)	• If Software as a Medical Device (SaMD) or medical device accessory: Conformity assessment procedure per classification of the standalone software • If non-SaMD: No regulatory pathway applies, though specific requirements need be fulfilled (e.g., EU General Data Protection Regulation (GDPR), cybersecurity, etc., see also table 2)
CCP as system, if applicable (see section 4)	Statement per MDR Art. 22

[25] EMA, Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal product, 2020, https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf, last accessed 18 September 2023.

7. Regulatory pathways for a CCP

The following flowchart depicts the scenarios likely to be encountered by a pharmaceutical company aiming to launch a CCP. For the sake of simplicity, the scope of CCPs covered by this section is a non-digital integral drug-device combination product used together with a digital add-on sensor which is connected to an app.

The starting point may be a medicinal product that has already been approved in the EU, but without an accompanying digital solution (left side of the flowchart). In that case, applicable regulatory clearance for the sensor and software needs to be obtained, unless these clearances already exist in the intended use that the pharmaceutical company wishes to implement. The pharmaceutical company must file the use of the sensor and software with the medicinal product as a variation to the approved MAA, receive approval (if applicable) for that variation, and write an MDR Art. 22 Declaration for the system (if applicable). Once these steps are completed, the digital solution can be launched for use with the medicinal product, the latter with an updated label, if applicable.

In another scenario, the pharmaceutical company may wish to launch a connected combined product involving a medicinal product that has not yet received prior approval (right side of the flowchart). In such case, the initial MAA for the medicinal product will from the start encompass the use of the sensor and software. For the filing of such a MAA, a pre-requisite is that the sensor and software have already received applicable regulatory clearance. Upon receipt of MAA approval, the pharmaceutical company will write a MDR Art. 22 Declaration for the system (if applicable). Once these steps are completed, the connected combined product can be launched.

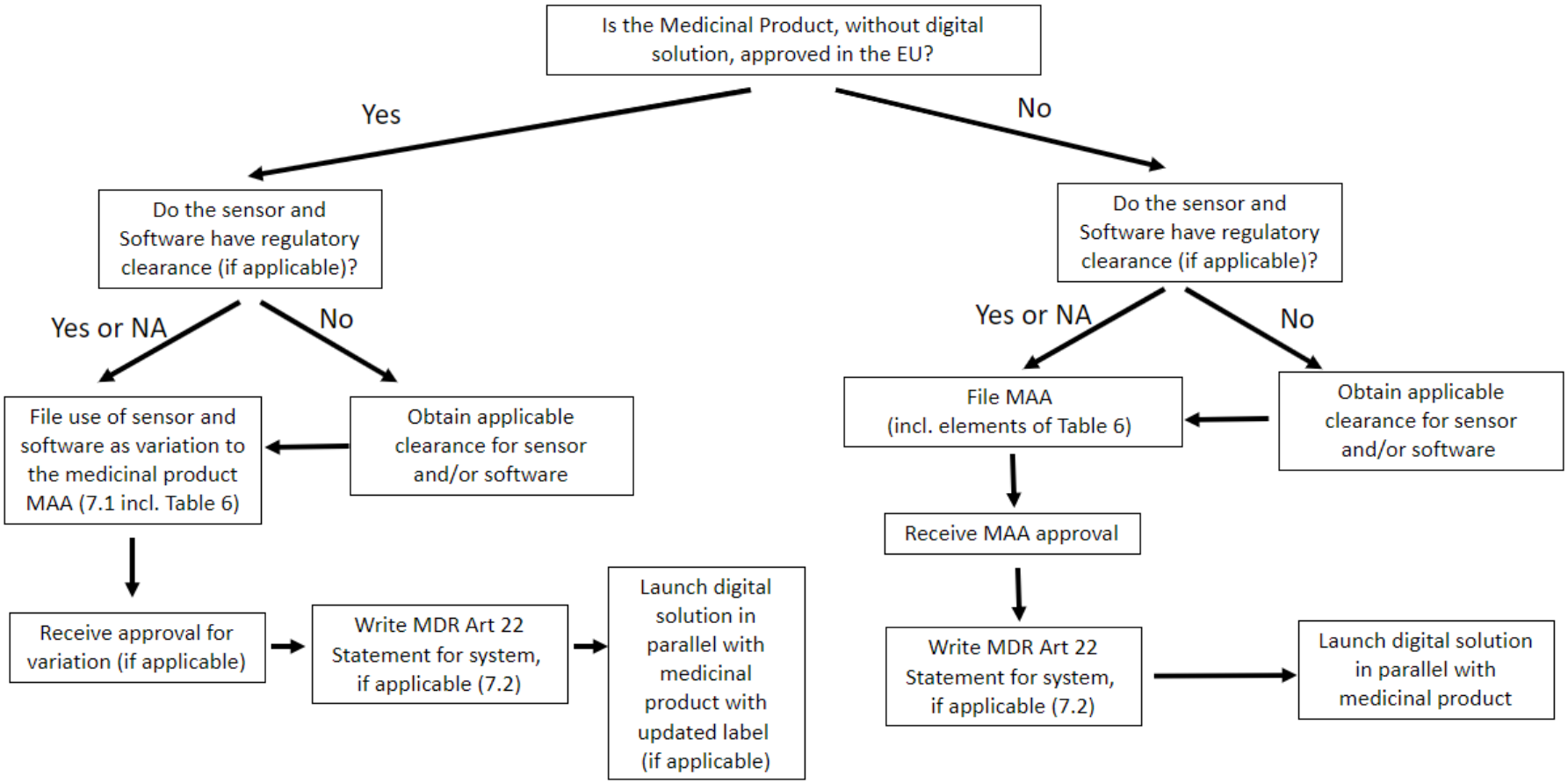

Figure 2: Flowchart of regulatory clearance pathways for a CCP

Subsection 7.1 describes in detail the regulatory pathway that involves filing a variation to the medicinal product's MAA to obtain clearance for the CCP below. The preparation of an MDR Art. 22 Statement if the CCP is classified as a *system* (see above section 4) is described in section 7.2. Finally, section 7.3 covers the concept and benefits of a harmonized review process, and subsection 7.4 addresses evidence requirements to support a new claim in the medicinal product label that may result from the implementation of the digital solution.

7.1 Variation to MAA

The European Commission's guideline entitled "guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008"[26] is the reference document that pharmaceutical companies consult to determine the appropriate filing route for post-approval changes to a medicinal product, and understand documentation requirements for the filing of the variation to the existing MAA. However, this document does not cover the case of the introduction of a digital solution for use with an approved medicinal product.

Keeping in mind that our objective is to identify a suitable filing route to allow the use of the digital solution together with the approved medicinal product, we identify section B.IV.1 *Change of a measuring or administration device*, *a) Addition or replacement of a device which is not an integrated part of the primary packaging*, *1. Device with CE marking* as the closest match for the change we seek to assess. The components of the digital solution will be CE marked for conformity with the MDR if they are medical devices, and a non-medical device digital sensor will be CE marked to reflect conformity with applicable directives. The digital solution (in this example) is not an integrated part of the medicinal product primary packaging, and while the digital solution would neither be a measuring nor an administration device, the concomitant use of the digital solution with the medicinal product suggests that the variation category identified above would be a pragmatic answer to the filing route identification problem statement.

The guideline entitled "guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008"[27] indicates that the variation in question would be a Type IA_{IN}, provided a number of conditions are fulfilled, as reproduced in the left column of Table 4 below. These conditions, strictly written for the introduction of a measuring or administration device, must be interpreted in terms applicable to a digital solution; the outcome of this exercise is reported in the right column of Table 4. When one condition or more is not fulfilled, the variation classification must be upgraded from a Type IA_{IN} to a Type IB. As discussed in section 5 above, it is possible that the digital solution impacts the medicinal product label. In such case, the appropriate post-approval filing route to obtain clearance for use of the digital solution with the medicinal product is proposed to be a Type IB variation.

[26] EMA, Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008, 2013, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations-human-medicines, last accessed 18 September 2023.
[27] Ibid.

Table 4: Conditions to meet for a Type IA_{IN} variation per B.IV.1a)1. – interpretation for introduction of a digital solution

Condition per Guideline, for variation in category B.IV.1 a) 1.	Interpretation of condition for introduction of a digital solution
Condition 1: The device must accurately deliver the dose as documented by studies.	The digital solution does not negatively impact the accurate delivery of the dose, as documented by studies or by a justification.
Condition 2: The device is compatible with the medicinal product.	The digital solution is compatible with the medicinal product (on aspects such as mechanical compatibility between the add-on sensor and the delivery device, non-obstruction of user interface elements, absence of impact of electromagnetic radiation on medicinal product quality attributes, etc.)
Condition 3: The change should not lead to substantial amendments of the product information.	The introduction of the digital solution does not lead to a substantial amendment of the product information.
Condition 6: The medical device is not used as a solvent for the medicinal product.	N/A - the digital solution cannot be used as solvent.
Condition 7: The CE marking should cover the measuring function (if any).	The digital solution's CE marking must cover its measuring function (if any).

Similarly, the guideline spells out the documentation requirements for a variation B.IV.1(a)1, as reproduced in the left column of Table 5 below. These documentation requirements, strictly written for the introduction of a measuring or administration device, must be interpreted in terms applicable to a digital solution; the outcome of this exercise is reported in the right column of Table 5.

Table 5: Documentation requirements for a Type IA_{IN} variation per B.IV.1a)1. – interpretation for introduction of a digital solution

Documentation requirement per Guideline, for variation in category B.IV.1 a) 1.	Interpretation of condition for introduction of a digital solution
Amendment of dossier section: description, detailed drawing, composition of device material and supplier	Amendment of section 3.2.R of the dossier to include description and suppliers of the digital solution's components and drawing for the sensor.
Proof of CE marking	EC certificate or Declaration of Conformity for the digital tools, as applicable.
Samples of the new device where applicable	TBD, see Note to Applicants

The guideline entitled "Guideline on Quality Documentation for Medicinal Products when used with a Medical Device"[28] offers under Section 6.2 further advice on medicinal product dossier content requirements for the case where the digital solution is referenced in the product information (refer to section 5 above). These information requirements are reproduced in the left column of Table 6 below; our interpretation of these requirements for coverage of a digital solution is presented in the right column of Table 6. Per Guidance, these requirements apply when a *medical device is referenced in the product information of the medicinal product and may have a potential impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product.*

Table 6: Quality requirements for referenced devices – interpretation for a digital solution

Quality Requirements per Guideline for referenced devices	Interpretation of condition for coverage of a digital solution
Consideration of impact of the referenced device on the medicinal product when used together should be considered using a risk-based approach, taking into account the need for a usability study.	If the connected combined product presents a usability profile different from the medicinal product used without the digital solution, the outcome of a usability evaluation or a usability study for the connected combined product needs to be presented.
Evidence of safety and/or bioequivalence/efficacy for the medicinal product used with the device should be provided as appropriate.	If the connected combined product presents a safety/efficacy profile different from the medicinal product used without the digital solution, an assessment of the impact of the digital solution on safety/efficacy of the medicinal product needs to be presented. Refer to Figure 3 for benefit/risk assessment.
In section 3.2.P.2, data on compatibility, dosing accuracy, functionality, handling, manipulation, etc., should be presented as appropriate.	Information on the digital solution's compatibility with the medicinal product (e.g., mechanical compatibility, non-obstruction of user interface elements, absence of interference to dose accuracy, injection speed, injection angle; impact of electromagnetic radiation on medicinal product quality attributes, etc.) should be presented.
In section 3.2.P.8, in-use stability data should be presented, if applicable.	N/A; the digital solution would normally not lead to a change in in-use conditions.
Information on usability studies should be presented, unless otherwise justified.	Usability study results for the CCP are expected, unless the use-related risk analysis allows to justify that such study is not needed.

[28] EMA, Guideline on quality documentation for medicinal products when used with a medical device, 2021, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-documentation-medicinal-products-when-used-medical-device-first-version_en.pdf, last accessed 18 September 2021.

7.2 CCP as system: compatibility statement per MDR Art. 22

As discussed above in section 4, a CCP may be classified as a system per MDR Art. 2(11). In such a case, the applicable requirements of MDR Art. 22 need to be followed.

MDR Art. 22 sets as prerequisite that the combination of articles to form a system must be done in a manner that is compatible with the intended purpose of each article, and within the limits of use specified by their manufacturers. In the case of a CCP, the *natural or legal person* referred to in MDR Art. 22 would be the pharmaceutical company promoting the use of the digital solution with the medicinal product for which it is MAH.

MDR Art. 22 implies that the pharmaceutical company shall draw up a statement declaring that it has verified the mutual compatibility of the articles.

7.3 Harmonized review process for a CCP

The sections above have highlighted that elements of a CCP will undergo separate regulatory review streams, as recapitulated below:

1. The initial filing of the integral medicinal product will be reviewed by the medicinal product reviewers (Rapporteur and Co-rapporteur, Committee for Medicinal Products for Human Use (CHMP). The review of the device part of the integral medicinal product must usually[29] have been completed by a notified body per MDR Article 117 prior to initial filing of the integral medicinal product (EC certificate or Notified Body Opinion available).
2. If the initial MAA already covers the digital solution, the medicinal product reviewers listed above will review MAA elements pertaining to the digital solution, as listed in Table 6, as well as any information pertaining to the digital solution that is placed in the medicinal product labeling. In case the digital solution needs to be implemented on an already approved medicinal product, the medicinal product reviewers will review similar information but as part of a variation to the MAA.
3. The elements of the digital solution must have been reviewed by a notified body in case they are medical devices in Class IIa, IIb or III, and resulting EC certificates must be available for MAA or variation filing. These elements do not undergo any regulatory review if they are general purpose products (non-medical-device) or medical devices in class I.

According to EMA's Questions and Answers document entitled "Qualification of digital technology-based methodologies to support approval of medicinal products" the document underlines that EMA's scope of assessment of a digital technology used together with a medicinal product is the impact or potential impact of the digital technology on the benefit/risks assessment of a MAA[30]. EMA will evaluate the digital technology as part of a MAA when there is impact or potential impact of the digital technology on the benefit/risks assessment of a MAA. In our opinion, only in seldom cases can a MAA

[29] Except when MDR Art. 117 allows otherwise.

[30] Quotation: *In summary, if a digital technology is used in the context of medicinal product development, evaluation or monitoring, and is expected to impact, even potentially, on the benefit/risk assessment of a Marketing Authorisation Application (MAA), then relevant aspects of the technology will be discussed at the time of MAA evaluation.* In: EMA, Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal product, 2020, https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf, last accessed 18 September 2023.

Applicant or a MAH justify exclusion of a potential impact of the digital technology on the benefit/risks assessment of a MAA of a medicinal product; therefore, assessment of the digital technology by the medicinal product reviewers will in most cases be taking place. Section 7.4 below further addresses the topic of benefit/risk assessment.

Overall, a complex, multi-stakeholder regulatory review may be needed to approve a CCP, possibly involving one notified body review for the integral device, another notified body‘s review for the sensor, a third notified body’s review for the software, and the EMA-remit-review (by Rapporteur and Co-rapporteur, CHMP) for the medicinal product with integral delivery device used together with the digital solution.

Figure 3 depicts these regulatory review streams and the health authorities with remit as the number of unique components in a product increases, culminating with the CCP that is the scope of this paper.

Complexity of regulatory review increases as number of components increases

Technology	Medicinal Product without integral delivery device	Medicinal product with non-digital integral delivery device	1) Non-digital delivery device not integral to medicinal product 2) Stand-alone sensor not integrated to drug delivery device 3) Stand-alone software on mobile or cloud application	**CCP**: Medicinal product with integral delivery device combined with digital feature (e.g., sensor with connection to software on mobile and/or cloud application, etc.)
Health authority with remit	EMA	EMA + Notified Body	Notified Body *or* no regulatory review	**EMA + Notified Body review of delivery device +/- Notified Body review of digital solution**

Figure 3: Regulatory review complexity increase with number of involved components

These separate regulatory review streams, their partial overlaps, and the fact that regulatory reviewers may be called to assess components outside of their normal area of expertise[31] highlight the opportunity for a more integrated evaluation mechanism for CCPs[32]. Also, with a multi-component system formed by a CCP, the risk exists that overall regulatory oversight is lost between the different parties involved in the review of the components. For example, a component of the digital solution (sensor or software) may be intended for non-medical purposes, but is then implemented in a CCP in a manner that it achieves a medical purpose; attention to such aspect should not escape overall regulatory review of the CCP.

In line with the EMA Regulatory Science Strategy to 2025[33], we support the establishment of a more streamlined benefit/risk assessment review process for CCPs. Within this process, all relevant stakeholders will be convened, ensuring the appropriate expertise is applied in future evaluations of CCPs through all product lifecycle stages (pre-authorisation, marketing authorisation, and lifecycle management).

The advantages of an integrated evaluation pathway for CCP innovators would include:

1. More **formalized approval pathway** for CCPs across the EU regulatory network.
2. **Streamlined regulatory review** for individual CCP components by appropriate members of the EU regulatory network.
3. **Reduced regulatory burden** for industry and regulatory stakeholders (i.e., less redundancy in assessments, potential time savings).
4. **Greater CCP innovation** through cross-regulatory network collaboration that more readily advances newer, more complex technologies (e.g., wearables and digital technologies like those described in the paper).

7.4 Benefit/risk assessment

As mentioned above, the EMA will evaluate the digital technology as part of a MAA when there is an impact or potential impact of the digital technology on the benefit/risk assessment of a MAA. In the most basic case, the digital solution does not bring any benefit to the patient; for example, the digital solution solely supports the collection of patient adherence data by the pharmaceutical company. In such a case, the tolerance for risk resulting from the addition of the digital solution will be very low as the risk must be non-existent of negligible. In cases where the digital solution brings a benefit to the patient (whether that benefit is claimed in the label or not), a risk resulting from the addition of the digital solution could be accepted if the benefits to the patient overweigh that risk. For example, the implementation of a digital solution may result in a risk of double dosing when both the sensor and the software issue a reminder to dose[34]. In such a case, the adverse effects resulting from a possible

[31] Kühler et al., Development and Regulation of Connected Combined Products – Reflections from the MedTech & Pharma Platform Association. Clinical Therapeutics. 2022 44(5), pp. 768-782. https://www.sciencedirect.com/science/article/pii/S0149291822001126, last accessed on 18 September 2023.
[32] EFPIA, Reflection paper on the Need for Better Defined Regulatory Pathways in the EU for Digital Health Technologies used concomitantly with Medicinal Products or as drug development tools during Clinical Development, 2021. https://www.efpia.eu/media/636454/efpia-rp-digital-health-technologies_november-2021.pdf, last accessed on 18 September 2023.
[33] EMA, Regulatory science strategy to 2025, https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy, last accessed 18 September 2023.
[34] For an example of such a situation, see Sections 6 and 7 of FDA's Approval report for of Betaconnect/myBeta App (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/103471Orig1s5189.pdf)

double dosing must be assessed against the benefit provided by the digital solution; for example, the digital solution may reduce the frequency of missed doses, providing a benefit that may overweigh the risk of double dosing. Risks shall be managed under the ISO 14971:2019[35] risk management process established by manufacturer. In case where digital solution introduces new hazards that cannot be eliminated, the benefit/risk analysis needs to conclude to an acceptable ratio prior to the filing.

Figure 4 below provides an overview of the benefit/risk scenarios that could be encountered with the addition of a digital solution to a medicinal product with delivery device, to form a CCP. Benefits claimed in the medicinal product label need to be supported by evidence, as further detailed in section 7.5.

[35] International Organization for Standardization ISO 14971:2019, Medical devices – Application of risk management to medical devices, https://www.iso.org/standard/72704.html, last accessed 18 September 2023.

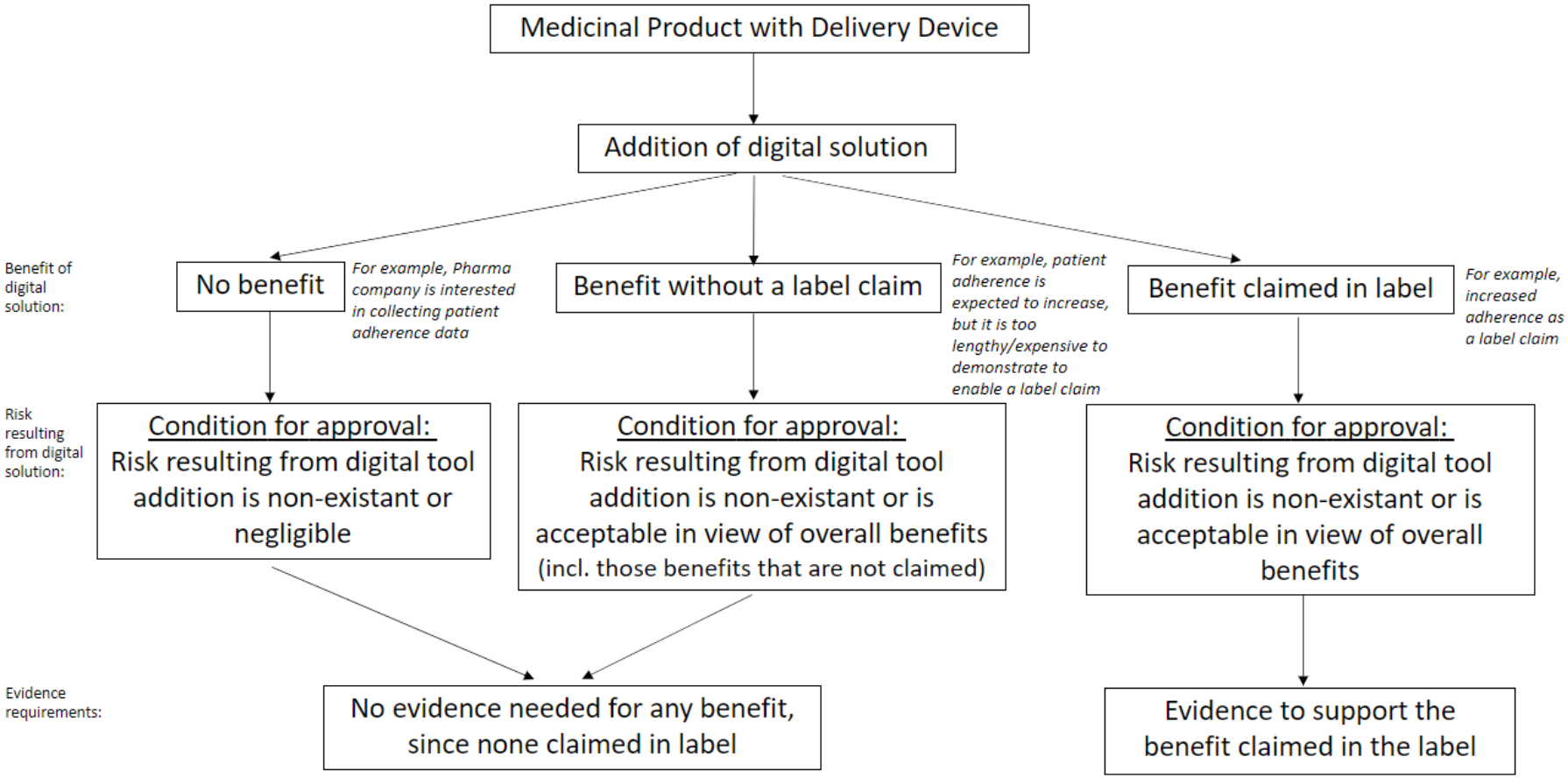

Figure 4: Flowchart for risk acceptance in relation to benefit of the digital solution

7.5 Evidence supporting label claims

A benefit of the digital solution that is claimed in the medicinal product label needs to be substantiated with evidence in the MAA or variation to a MAA introducing the digital solution. Figure 5 presents examples of benefits[36,37] that may be claimed for digital solution, and links these benefits to the evidence anticipated to be required in the medicinal product filing in order to support the claimed benefit.

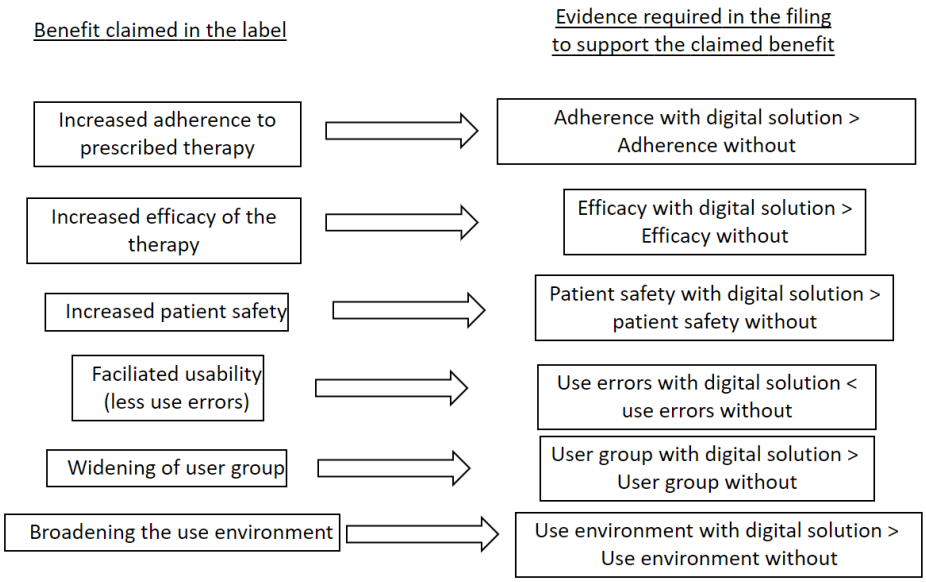

Figure 5: Required evidence to support claimed benefit examples

Clarity on the level and quality of evidence is needed. Table 7 lists areas where further integrated guidance/methodologies from drug and device regulators, particularly on standard evaluation techniques for digital technologies[38], could benefit the preparation of medicinal product MAA's.

Table 7: Aspects of evidence generation for digital health technologies requiring standard evaluation techniques

Digital technology's impact on...
Clinical outcome (including safety & efficacy of the medicine)
Adherence to the prescribed medicine
Patient care
Use contexts and subsequent usability assessments

[36] EMA, Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal product, 2020, https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf, last accessed 18 September 2023.
[37] Coravos et al., Modernizing and designing evaluation frameworks for connected sensor technologies in medicine. 2020 NPJ Digit Med. https://pubmed.ncbi.nlm.nih.gov/32195372/, last accessed 18 September 2023.
[38] See note 26.

In 2019, a review publication[39] pointed out the limited quantitative evidence on the impact of connected devices in relation to benefits. The publication reviewed five connected devices for clinical evidence supporting the benefits of electronic tools on treatment adherence and efficacy outcomes. Adherence and clinical outcome data were available for all selected connected devices; the review however points out that most clinical studies identified were uncontrolled trials. Standard evaluation techniques are desired to help Applicants design trials with the aim to optimally support label claims related to improved treatment adherence and improved health outcomes.

8. Conclusion

In response to increasing implementation of CCPs in healthcare, this paper has sought to provide an overview of regulatory pathways applicable to the obtention of initial authorization of such products in the EU. Particular consideration was given to CCPs consisting of a medicinal product used with a delivery device with wireless connectivity to a standalone software. Since a unique regulatory product category has not been created for CCPs in Europe, the regulatory framework that is proposed in this paper stands on the assignment of regulatory identities of the CCP's individual components to leverage and adapt closest-fitting component-level Regulations and Guidelines. Finally, it must be considered that the device/software component of a CCP may achieve a defined medical purpose and hence fall under the definition of a *system* per MDR Art. 2(11), with associated obligations described in MDR Art. 22.

We understand that the EMA's review remit for a CCP is the evaluation of the impact of the digital solution on the medicinal product's benefit/risk balance, including in the situation where the use of the digital solution is described to be *optional* by the MAH. The question remains whether a "demonstration of no impact to the benefit/risk balance" would be considered sufficient by the EMA to qualify a digital solution as being out of its review remit, and what such demonstration should contain. Furthermore, a closer understanding of the factors that make mentioning the digital solution *mandatory* in medicinal product labeling is desired, since existing guidance pertaining to *referenced devices* will be the trigger for whether and how the digital solution is to be covered within the medicinal product dossier.

Three key action areas have emerged, on which continued development may contribute to establishing a European regulatory framework for CCPs: MAA or MAA variation dossier content requirements, EMA remit in the review process for these MAAs and the need for a harmonized review. A future Guideline specific to CCPs and/or an update to the existing Guidelines that confirms, rectifies or expands on our interpretations will help to establish the MAA or MAA variation pathway and associated documentation requirements for CCP-related regulatory filings that are under EMA remit. Moreover, the MPP Association strongly supports the development of a harmonized review process for CCPs by all appropriate and qualified regulators and responsible stakeholders in the European network, as CCPs combine a medicinal product and a delivery device with connectivity to a standalone software.

[39] Bittner et al., Connected drug delivery devices to complement drug treatment: potential to facilitate disease management in home setting. Medical Devices: Evidence and Research 2019 (12), pp. 101-127. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419593/, last accessed on 18 September 2023.

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About the Medtech & Pharma Platform Association

The Medtech & Pharma Platform Association (MPP) brings together companies from the pharmaceutical, medtech, and tech sectors and provides opportunities to exchange knowledge and to collaborate in technology and regulatory areas related to combined products.

The MPP's objectives are:

- To enhance synergies between the pharma, medtech, and tech industries,
- To establish new collaboration models to ensure and accelerate market access for safe and innovative treatment options,
- To work toward the development of a balanced and proportionate regulatory and policy framework for combined products including connected combined products.