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**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**

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1. Glossary

Definitions related to digital technologies used in healthcare are still evolving; therefore, the terms presented in this glossary may change over time to reach harmonisation across stakeholders and Health Authorities. Most of the below glossary is aligned with the European Medicines Agency (EMA) Questions and Answers: Qualification of digital technology-based methodologies to support approval of medicinal products, the Medical Device Regulation (EU) 2017/745 or the International Medical Device Regulators Forum (IMDRF) definitions, as indicated. For the purpose of this paper, the definitions below are used; references and modifications thereof are indicated.

Digital Biomarker: A digital biomarker is a defined characteristic that is used as an indicator of biological, pathological process or response to an exposure or an intervention that is derived from a digital measure. The clinical relevance is established by a reliable relationship to an existing, validated endpoint.¹

Digital Endpoint: a precisely defined variable intended to reflect an outcome of interest that is statistically analysed to address a research question that is derived from, or includes, a digital measurement. Digital endpoints can be based on clinical outcome assessments or reliable relationship with existing clinical outcome can be established).¹

Digital Health Technology (DHT): is here defined as an electronic method, system, product, or process that generates, stores, displays, processes and/or uses data within a healthcare setting. Examples of digital technologies include hardware (e.g., wearable sensors used as biometric monitoring technologies, VR headsets, digitally enabled drug delivery devices), advanced analytics (e.g., algorithms, artificial intelligence, machine learning, sophisticated computation) and cloud services (e.g., storage, computing, and data processing), and software (e.g., mobile medical applications, software as a medical device).²

A DHT subset is used as diagnostics, therapeutics, or adjuncts to medical products (devices, drugs, and biologics). They may also be used to develop or study medical products and monitor disease.

Digital Measure: an objective, quantifiable measure of physiology and/or behaviour collected and measured through digital tools.¹

Electronic Clinical Outcome Assessment (eCOA): an eCOA is a quantifiable measure used as a measure of how patients feel, function, or survive that is derived from a digital measure (*digital measure*). The clinical meaning is established de novo. Clinical outcomes can be assessed through a report by a clinician, a patient, a non-clinician observer or through an active performance-based assessment or passive monitoring of patient behaviour or performance¹.

Intended Purpose/Intended Use: the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation³

In-Vitro Diagnostics Regulation (IVDR): Regulation (EU) 2017/746 of the European Parliament and of the Council

Medical Device: means any instrument, apparatus, appliance, software, implant, reagent, material, or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means, including organ, blood and tissue donations, [...] ³

Medical Device Regulation (MDR): Regulation (EU) 2017/745 of the European Parliament and of the Council

Medical Device Software (MDSW): Medical device software is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a “medical device” in the Medical Devices Regulation or In Vitro Diagnostic Medical Devices regulation.

[An alternative, partly overlapping, term in use is ‘**Software as a Medical Device (SaMD)**’ which is defined by the International Medical Device Regulators Forum (IMDRF) as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device. ⁴, which is also used in MEDDEV 2.1/6.] ⁵

¹ [EMA Q&A Qualification of digital technology-based methodologies to support approval of medicinal products](#),

² [Biopharmaceutical Digital Health Lexicon](#)

³ [Regulation \(EU\) 2017/745 of the European Parliament and of the Council of 5 April 2017](#)

⁴ [IMDRF Software as A Medical Device, Definition](#)

⁵ [Guidelines on the qualification and classification of standalone software used in healthcare within the regulatory framework of medical devices](#)

2. Executive summary

The evolution of Digital Health Technologies (referred to hereafter as DHTs) in the development of new medicines has the potential to advance research in healthcare, facilitate patient-centred drug development and increase the value proposition of medicinal products. Ultimately, the increased use of digital health technologies (DHTs) will help to improve patient care. The current complexity of the regulatory pathways for DHTs in the EU is leading to Europe being less attractive to develop these innovations, whether DHTs used as drug development tools in clinical studies or when used together with medicinal products or investigational medicinal products for a medical purpose.

The reflection paper covers DHTs used to support the development of a medicinal product as well as those to be placed on the market as a supplement to, or used concomitantly with, a medicinal product. In the different scenarios, and depending on the intended use, the digital technologies may fall under the definition of a medical device or not (i.e. a consumer grade DHT).

This reflection paper puts forward an EFPIA perspective on key uncertainties and hurdles faced by developers, regarding:

- use of Digital Health Technologies in drug development to advance early-stage research and support evidence generation for regulatory assessment
- Verification and validation requirements
- Preparation of clinical trial applications for protocols that include both an investigational medicinal product and an investigational DHT (or consumer grade DHT)
- Challenges in classification of medical device software under Rule 11 of MDR
- Navigation through the regulatory approval pathways for concomitant use of medicines and digital health tools in the European Union

In summary, EFPIA calls for:

A. An integrated consultation platform

A platform for continuous, iterative dialogue between the sponsors, EMA, competent authorities for devices and medicines and the notified bodies which would allow timely advice on:

- Use of Digital Health Technologies in drug development to advance early-stage research and support evidence generation regulatory assessment including development and validation of novel digital endpoints. The need for a continuous, iterative dialogue between the sponsors, EMA, competent authorities and the notified bodies during the development of novel digital endpoints is already recognised by EMA.
- Concomitant use of the medicinal product and a DHT in routine clinical practice, including

advice on required evidence to support claims in the product information.

B. Integrated review pathways covering the entire lifecycle

The concept of an integrated review process in the EMA 2025 Regulatory Science Strategy (EMA 2025 RSS) and the Joint EMA/HMA Network Strategy to 2025, is strongly supported by EFPIA.

Assessment pathways should clearly designate review tasks/remits for medicines- and device regulators and align on timelines for the following regulatory reviews:

- Pre-authorisation: A pathway should be designed to support the approval of clinical trials including an investigational medicinal product and an investigational DHT (investigational medical device, non-integral). Review tasks for the drug and the device regulators clearly designated, and with aligned review timelines. A risk-based approach (to be defined) depending on the impact the DHT may have on patient safety should be the way forward.
- At marketing authorisation: Concomitant use of the medicinal product and a DHT in routine clinical practice (when non-integral)
- Lifecycle-management: Integral pathway for timely reporting on lifecycle changes of digital health technologies using a technology agnostic approach, including software, used concomitantly with medicinal products.

C. EU guidance should be harmonised across all relevant regulators/notified bodies:

- Harmonised EU guidance on acceptance of the DHT classification when they are used in clinical trials for non-medical purposes and do not fall under the MDR.
- Lifecycle-management: Clear guidance on what is deemed to be a significant change . A process for reaching prior agreement on comparability protocols, describing nonsignificant and significant changes would be useful.

D. Opportunities during the Pharmaceutical Review

- EFPIA appreciates the flagship initiative on innovation of the European Commission's 'Pharmaceutical Strategy for Europe'. This initiative aims for simplification, streamlining of approval procedures and flexibility for the timely adaptation of technical requirements to scientific and technological developments.
- EFPIA supports the development of legal proposals that address the regulatory challenges at the interface between medicinal products and devices

1. Introduction

1.1. Potential of digital health technologies in drug development and for improving routine patient care

The evolution of digital health technologies in the development of new medicines has the potential to advance research in healthcare, increase the efficiency of drug development, improve patient outcomes and thus, the value proposition of medicinal products.

There is an increasing desire to use digital health technologies throughout the total product lifecycle of medicinal products to both improve the accuracy of clinical trial endpoint measurements as well as to make the drug development process, both pre- and post-market, faster more efficient (e.g. Remote Decentralised Clinical Trials).

Examples include remote continuous monitoring of clinically relevant parameters related to the medicinal product; support of patient enrolment in clinical studies; and tracking patient intake of a medicine to monitor treatment adherence.

Digital health technologies (DHTs) offer the potential of more granular, objective and clinically meaningful data on the effectiveness of a medicine, can solve unmet measurement needs in specific conditions and allow to monitor patient treatment adherence in real-time.

The reflection paper does not cover secondary use of electronic health data, e.g. electronic health records or qualification of digital measures or endpoints.

1.2. Different legal frameworks and regulatory pathways

Depending on the intended use and function of the DHTs used in healthcare, different legislative frameworks are applicable in the EU, with regulatory oversight provided by different bodies and competent authorities.

A recent US study found that the number of registered clinical trials featuring wearables, ingestibles, apps and other connected devices rose at a 34% compound annual growth rate between 2000 and 2017. While there were only eight trials registered in ClinTrials.gov in 2000, over 1,100 separate trials with a connected device could be identified in 2017 and 2018 (Marra et al).

For DHTs used as development tools, and according to the EMA Q&A Digital Technology (June 2020), EMA's remit is limited to the specific use of a methodology, considering the expected role of such technologies in the development, evaluation and ultimately use of medicines" (EMA, 2020). The overlaps between different frameworks (i.e. for medical devices and medicinal products) and stakeholders adds complexity for sponsors and manufacturers. They must find their way through different regulatory pathways with different authorities that are not well connected and may have different requirements.

The determination whether the DHT is a medical device (or not) must be made at the beginning of a development plan:

- Some DHTs based on their intended use may be classified as a medical device according to the EU Medical Device Regulation (MDR) (EU) 2017/745 as amended (see rule 11) or as In Vitro Diagnostics according to the EU In Vitro Diagnostic Regulation (IVDR) (EU) 2017/746 as amended (link to [EU infographic](#)).
- Others, such as integral, prefilled, single use drug delivery combinations incorporating a DHT may be classified as a medicinal product regulated under Directive 2001/83/EC, as amended (see Article 117, MDR 2017/745).

- DHTs purely used in drug development that do not have a medical purpose or benefit for individual patients in the clinical trial, do not qualify as medical devices according to the definition of Article 2(1) of the MDR (EU) 2017/745 as amended
- Consumer-grade DHTs, although not covered by the MDR, will have to comply with other applicable requirements (e.g., ICH E6 (GCP) requirements if used as a development tool).

1.3. Different scenarios for CE-marking of MDSW and purpose of use

DHTs may consist of stand-alone software or combine software with hardware (e.g. a wearable sensor). As per the above, a medical device determination will have to be made.

- **The DHT does NOT qualify as a medical device.**

In this situation, the DHT does not have a medical purpose.

For example, a software app used by patients in a clinical trial for remote patient monitoring and not intended for treatment, diagnosis, mitigation, or prevention of disease or a condition.

- **The DHT does qualify as medical device software under the MDR/IVDR.**

In this situation, additional considerations will determine the development pathway, like:

1. Does the DHT have a declaration of conformity/ CE mark per MDR and is the medical purpose in the clinical trial within the intended use of the MDSW?
2. Does DHT have a declaration of conformity / CE mark per MDR but the medical purpose in the clinical trial is outside of the intended use of the MDSW?
3. Does the MDSW not have a declaration of conformity/CE mark per MDR (i.e., investigational medical device)?

1.4. New EU risk classification rule for MDSW

The applicability of the overall regulatory framework for medical device software based on its intended medical purpose is provided in Article 2(1) of the MDR 2017/745 and article 2(2) of the IVDR 2017/746. Annex VIII of the MDR lists applicable implementing and classification rules.

The Medical Device Coordination Group (MDCG) Guidance 2019-11 (on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR) states that “Medical device software is software that is intended to be used, alone or used concomitantly, for a purpose as specified in the definition of a “medical device” in the MDR or IVDR, regardless of whether the software is independent or driving or influencing the use of a device.” Where a software does not fall under the definition of a medical device, or is excluded by the scope of the MDR, other European and/or national legislation may be applicable. Software that does not meet the definition of a medical device but is intended to be an accessory for a medical device, falls under the scope of the MDR.

The MDCG guidance details decision trees and interprets the applicability of classification rules (mainly MDR Annex VIII, Rule 11) for software. An overly strict interpretation of Rule 11 could become a significant barrier to innovation. There is a wide industry concern that Rule 11 could lead to a systematic upgrade from Risk Class I under the MDD to Class IIa under the MDR.

For example, a simple software application that is used to help patients with diabetes manage their disease by tracking and trending their food intake, exercise and lifestyle activities, and blood glucose value is a class I medical device under the MDD but becomes a class IIa medical device under the MDR. It therefore requires a conformity assessment by a Notified Body prior to placing on the market.

1.5. Combined scientific advice: Integrated technologies require an integrated and collaborative pathway

The present EFPIA reflection paper articulates the member companies' vision for a streamlined and well-defined pathway for DHTs to be used concomitantly with new medicinal products either as drug development tools or as medical device software, considering the rapidly evolving nature and scope of digital technologies.

The EMA 2025 RSS foresees the creation of an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics, and borderline products. Such integrated and collaborative evaluation and feedback pathway is welcomed as it would streamline approval processes in the light of rapid technological changes and address hurdles currently anticipated in the interplay of medicines and devices. However, it is unclear to what extent it can be achieved within the current legal framework.

In scope are digital health technologies that can be connected devices, digital applications and algorithms used concomitantly with a medicinal product which fall under the definition of a medical device or are used as drug development tools including consumer-grade tools. In some instances, several of these technologies might be used with the same medicinal product (e.g., connected device used concomitantly with an app to monitor adherence to a medicine). EFPIA intends to outline some of the key hurdles faced by developers and to propose a way forward.

2. The use of digital technologies during the clinical development

This section provides EFPIA reflections on different DHT clinical trial use cases. Sponsors may wish to include DHTs in clinical trial protocols for a range of different purposes. It might be as drug development tools (e.g., digital endpoints) or to be used concomitantly with the drug for a medical purpose (e.g., digital patient monitoring). Depending on the intended use of the software in the clinical trial and its status of registration, different regulatory pathways apply; different CTA submission requirements and different oversight by competent authorities are needed.

As described in the introduction, a key question that sponsors must consider is whether the digital health technology qualifies as a medical device under the MDR/IVDR or not. Other considerations are whether this technology already has a CE mark / Conformity assessment according to MDR/IVDR or whether the sponsor company has the intention to put the digital health technology on the market (see section 2.3). The recent MDCG 2021-6 Guidance Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation includes in annex I a decision tree that provides some helpful considerations.

DHT tools used to measure a treatment effect, or to facilitate patient management in a clinical trial, do not necessarily qualify as medical devices. The below table is intended to orient the reader to the appropriate subsections by pointing to relevant section numbering. Section 2.1 deals with pure drug development tools that do not qualify as medical devices. It is of importance to note that the principles to ensure data integrity laid out here for the DHT measuring endpoint as laid out in section 2.1.2 are also applicable in cases where the DHT does qualify as medical device under the MDR.

Table 1. To guide the structure of the reflection paper, DHTs have been classified according to their intended use in the clinical trial and their legal status of registration at the time they are used in the trial. These are mapped to the sections of the paper that provide EFPIA points of view for each of these.

Legal status of registration of Digital Health Technology (DHT)	The DHT does not qualify as a medical device	A declaration of conformity/CE mark per MDR is available and the medical purpose is within intended use of the MDSW	A declaration of conformity/CE mark per MDR is available and the medical purpose is outside of the intended use of the MDSW	The MDSW does not have a declaration of conformity/CE mark per MDR (i.e. investigational medical device).
Intended purpose				
DHT as a development tool	section 2.1			
Medical Device Software (MDSW)		section 2.2.1	Section 2.2.2	section 2.3
DHT + MDSW		section 2.2.1 +section 2.1 considerations*	Section 2.2.2 +section 2.1 considerations	section 2.3 +section 2.1. considerations

2.1. A digital development tool that is not a medical device ('consumer grade')

The intended purpose of the digital health technology is only to assist in the development of the drug or support the patient journey throughout the trial. It does not meet the criteria to qualify as a medical device as per the MDR.

2.1.1. No expected impact on the future Marketing Authorisation Application

DHTs that are only used within the development of the drug, that do not fulfil the medical device definition and that do not affect the benefit/risk evaluation of the medicinal product (i.e. are not part of the MAA dossier) are frequently deployed.

Some examples are:

- *Software that enables clinical communication and workflow including patient registration, scheduling visits, voice calling, and video calling (patient engagement tools or tools that facilitate remote data capture in Remote Decentralised Clinical Trials)*
- *Digital measures not used in benefit/risk evaluation, including to support patient screening or to provide data to involve early phase drug development.*
- *Software that monitors performance or proper functioning of a device for the purpose of servicing the device, (e.g., software that monitors x-ray tube performance to anticipate the need for replacement), or software that integrates and analyses laboratory quality control data to identify increased random errors or trends in calibration on IVDs.*
- *Software that provides parameters that become the input for MDSW is not a medical device if it does not have a medical purpose. For example, a database including search and query functions by itself or when used by MDSW.*

EFPIA point of view: When including these DHTs in clinical trials, the sponsor must respect standard requirements for data privacy, patient consent, and security for clinical trials. Furthermore, a safe use of the technology by the patient and other safety considerations must be considered. Safety of usage, cybersecurity aspects and data integrity considerations are usually covered by specific company measures, such as the implementation of EU GMP Annex 11 'Computerized systems' and Annex 15 'Qualification and Validation.' No specific regulatory pathway related to the specific use in clinical trials is otherwise needed.

2.1.2 An impact on the future Marketing Authorisation Application can be expected

As DHT development tools continue to evolve, ways of measuring endpoints will also evolve. The digital tools have the potential to offer measures that are more granular, and that can accurately and objectively reflect the patient experience over time. Furthermore, they can offer new ways of measuring health aspects that are more meaningful to patients. Finally, they allow for remote data collection, which is becoming ever more necessary. Therefore, it is important to consider how to

develop, validate, review, and align on data collection using a novel digital endpoint, while demonstrating clinical meaningfulness.

An example of digital endpoint is the Stride Velocity 95 Centile endpoint qualified in Duchenne’s Muscular Dystrophy derived from digital health technologies (e.g., ActiMyo wearable device), EMA/CHMP/SAWP/178058/201. Further examples are contained in the Digital Medicine Society Library on digital endpoints used in clinical trials.

In the recently published Questions and Answers: *Qualification of digital technology-based methodologies to support approval of medicinal products*, EMA notes that for (electronic) clinical outcome assessment (eCOA), content validity, construct validity, reliability, and sensitivity to change should be discussed prior to regulatory filing in a qualification procedure. Sponsors may want to discuss with the EMA whether and how these concepts apply to the use of a particular DHT development tool within a drug development program.

EFPIA point of view: It will be important to develop collaborative platforms with technology companies, regulators, notified bodies, sponsors, academic investigators, and patients as key stakeholders of the development and validation of novel digital endpoints. A continuous, iterative dialogue between the sponsors, competent authorities for devices and medicines will be needed during the development of novel digital endpoints. The legal framework should in the future allow notified bodies to take part in that dialogue.

The recommendations of ICH E6 Good Clinical Practices (GCP) on validation of “computerised systems” as well as the required standards of data privacy and cybersecurity, should be the basis to prove the acceptance for digital health technology tools used for regulatory decision making. In addition, the DHT should have evidence to ensure reliability and accuracy of the raw data collected. The sponsor also must consider patient safety and usability aspects as well the potential additional burden the use of the tool puts on patients. Once the DHT is validated and computer-system validation compliant, the standard endpoint validation criteria, as noted in the paragraph below, apply for the measure derived from the DHT.

Evaluation of technical aspects and analytical validation of the DHT itself may require development of further expertise at EMA or input from other relevant stakeholders, such as medical device authorities or notified bodies (either separately or in a parallel consultation with EMA) (see EMA Q&A), regardless of the regulatory status of the DHT in relation to MDR/IVDR. Early integrated/joint discussion regarding the data generation by digital health technology to gain alignment regarding the acceptability of the endpoint for MAA using the scientific advice and/or qualification advice, as appropriate, are considered key, provided the relevant technical experts are included in these conversations. The notified body to be involved in the discussion to provide reassurance on the functionality of the technology used to determine the endpoint as part of this discussion,

For Clinical Trial Applications (CTAs), there should be harmonisation (e.g., through guidance) across the EU regulatory network regarding the acceptance of the DHT classification and validation (when they are used in clinical trials for non-medical purposes and are not medical devices).

Finally, a more flexible, timely and iterative endpoint qualification procedure would be welcomed to accommodate the agile development of software and ensure the endpoint qualification can be

achieved before the pivotal trial is conducted, in cases where the sponsor intends to seek qualification and endpoint development and the medicinal product development are conducted in parallel.

2.2. The digital health technology tool is a medical device

This section covers the EFPIA point of view for DHTs that are used in drug clinical trials to impact the medical outcome (and therefore may pose more risk) and qualify as a medical device based on their intended use.

These DHT may be used simultaneously as development tools and MDSW (e.g. trial enrichment or diagnostic purpose that has an impact on patient inclusion, or MDSW that also collects digital endpoint data). In these cases, the considerations in section 2.1.2 regarding ICH E6 (GCP) compliance, verification and analytical validation need to be considered. Furthermore, content validity, construct validity, reliability, and sensitivity to change must be proven as part of the medical device development and CE marking.

Some examples are:

- *DHT that allows a smartphone to view images obtained from a magnetic resonance imaging (MRI) medical device for diagnostic purposes to Computer-Aided Detection (CAD) software that performs image post-processing to help detect breast cancer.*
- *DHT that is intended for diagnosis of a condition, such as using the tri-axial accelerometer that operates on the embedded processor on a consumer digital camera.*
- *DHT that is intended to be used as a predictive biomarker of a disease is used for drug clinical trial enrichment in phase III clinical trials.*

2.2.1. The medical purpose in the trial falls within the intended use of the medical device

In cases where the DHT is regulated as a medical device and already bears a CE mark as result of a completed conformity assessment, the study sponsor may obtain clinical trial authorisation to use the DHT (assuming in accordance with its intended use) in a clinical study of a medicine through the normal clinical trial authorisation process, involving a competent authority and an ethics committee.

Sponsors should be aware that the use in the clinical trial may bring different risks to the patients as compared to use in day-to-day clinical practice, a respective risk analysis should be conducted.

The EMA Q&A on digital technologies highlights the need to discuss the context of use upfront of a submission to a competent authority.

EFPIA point of view: When the use of a digital health technology is consistent with the existing declaration of conformity/CE mark covering the intended use and the user group within the clinical trial, no additional validation of the measurement tool supporting the drug clinical trial is to be

provided as evidence of safety and performance to the competent authority. The need for validation of the endpoint itself is to be considered by EMA. The use of DHT and the digital component in the trial should be described in the CTA. Hence, the competent authority as well as the ethics committee will be informed about the approach.

2.2.2. The medical purpose in the trial does falls outside the intended use of the medical device

There may be DHT uses strictly speaking beyond the declaration of conformity, yet consistent with how the digital device is intended to be used in broader terms.

An example might be a non-invasive wearable (e.g. measuring gait speed) that has a CE mark for a specific age range, but the use case may include people somewhat outside the age range.

The use of digital health technologies in research and development which is outside the scope of a current CE marking should follow a risk-based approach. For instance, a DHT is capturing data related to a validated primary endpoint and it would not be used by patients in the clinical setting/in real life. The sponsor should perform a risk assessment to evaluate the risk to the new user group (e.g. adult users only vs. adult and teenage populations) and present this analysis as part of the CTA package. The risk of use in this example might pose minimal risk to the user and the data as the DHT would be used in a manner consistent with the CE mark.

EFPIA point of view: no further investigations are warranted if the following conditions are met:

- minimal risk to the users and:
- assuming the data would be collected in a manner consistent with the intended use of the CE-Marking and:
- the justification of a risk-based CTA approach for the investigational medicinal product would align to the overall approach to QMS requirements/Good Clinical Practices (GCP) in clinical research and development.

The identified risk level would determine the need for further clinical investigations. EFPIA believes that this is in the spirit of Article 74 of the EU MDR on clinical investigations regarding devices bearing the CE marking.

2.3 The digital health technology qualifies as an investigational medical device

If the DHT meets the definition of a medical device but does not yet bear a CE mark, or in cases where the sponsor would like to use the device clearly outside of the intended use covered by the CE mark, the DHT has to be considered an investigational medical device. In such a case, the regulatory burden due to parallel protocols and submissions to CTIS (Clinical Trials Information System) and EUDAMED (EUropean DATabase on MEDical Devices) increases significantly and communication

between the different regulatory pathways/stakeholders are not currently covered in existing regulations or guidance.

The Clinical Trials Regulation (CTR) (EU) 536/2014 only requires notifying in the CTA cover letter any medical devices which are to be investigated in the clinical trial, but which are not part of the investigational medicinal product(s) (see Annex IB of CTR).

From what we understand, the CTIS will not provide an interface with EUDAMED. According to Article 33(2e) of the MDR, all clinical investigation applications must be submitted to the EUDAMED database; Article 73(2) of the MDR foresees interoperability between EUDAMED and CTIS. Article 78 (7) of the MDR provides for future implementing acts by the European Commission to cover concomitant clinical investigations of medical devices and medicinal products. According to MDR Annex XV, the medical device application form must reference to the official registration number of the drug clinical trial in case the device application is submitted in parallel with an application for a clinical trial in accordance with Regulation (EU) 536/2014. For medical device development, conformance with ISO and QMS design control principles is required.

EFPIA point of view: The use of non-CE marked DHTs that qualify as medical devices (e.g. used for a medical purpose in the trial) should be based on an individual risk assessment. It should consider the specific intended use within the clinical trial, the user group and the conformity of the device with the MDR General Safety and Performance Requirements should be proven and documented by the CTA applicant comparable to a design-control process for a medical device of a corresponding risk classification.

An example might be a new wearable sweat sensor for glucose monitoring to guide dosing of an investigative medicinal product

For the EU to remain a competitive place for innovation, regulatory burden and timelines for CTAs should be reduced. In the case of a concomitant use of an investigational medical device (e.g. MDSW) and investigational medicinal product, consideration should be given to a combined study protocol and a single CTA (meeting Regulations (EU) 536/2014 and (EU) 2017/745, as amended). Integrated consultation platforms should be available for early dialogue.

Explorative use of DHTs in early stage clinical trials should not qualify the DHTs as investigational medical devices, even though they may otherwise meet medical device criteria. The exploratory data generated will not be used for the clinical evaluation of the DHT. Moreover, the DHT is not being tested for a medical purpose within the trial and has no impact on the participants' medical treatment. However, the exploratory use should be described within the study protocol for the investigational medicinal product.

3. Development of a drug and a digital device for intended to be marketed together for concomitant use (e.g. connected products)

3.1 Evidence generation (development phase)

The intention of the sponsor may be to develop a medicinal product and a digital health technology (e.g. MDSW) for concomitant use. The concomitant use would be reflected in the product information. There is in this new scenario a strong need for regulatory guidelines from the EMA and the NCAs. Prior to designing clinical trial protocols (ultimately in support of a co-labelling claims) sponsors need to understand what the general expectations for the concomitant use of medicinal products are and MDSW. Currently, sponsors can only learn about these expectations through product-specific meeting requests.

An example is a software application that monitors respiratory symptoms or glucoses levels and notifies the patient to increase or decrease dosage of their medicine, where the labelling of that medicine specifically requires the patient use the software to adjust their dosage.

The concept of generating claims for the concomitant use of digital health technology and medicinal products is a new area of regulatory science. The methodologies best suited to substantiate such claims are yet to be defined. However, we do not believe the evidence burden should be fundamentally different from other labelling claims. Pertinent unknowns include the degree of DHT validation required and the design of clinical trials.

In the recently published Questions and Answers: '*Qualification of digital health technology-based methodologies to support approval of medicinal products*', EMA clarifies that any digital health technology that can be expected to impact, even potentially, on the benefit-risk assessment of an MAA will be subject to regulatory review and hence, sponsors are advised to seek early input from regulators by using the tool of qualification assessment.

However, more detailed guidance and multidisciplinary expert exchange platforms are required. Specifically, guidance should address what data would be required to support statement in the labelling on the compatibility and the clinical relevance (e.g., improving adherence) to be included in the medicine and its companion device labels i.e., Product information/Patient leaflet and Instructions for Use.

3.2. Approval pathways

Approval pathways have not yet been defined. Although the recent EMA '*Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products*' highlights qualification advice as appropriate to obtain agency feedback on a new technology during development, it remains unclear how the conformity assessment of the digital health technology (e.g. a MDSW) will be handled in parallel to the approval process of the medicinal product.

EFPIA point of view: Clarification on the steps and interactions between authorities to achieve co-labelling claims will be needed. The conformity certification for the digital health technology, depending on classification, will be performed by a notified body or via a self-declaration of conformity by the manufacturer (Class I devices). Early alignment between the notified body and competent authority regarding the evidence generation for medicinal product and the concomitantly used digital health technology will be necessary. This in order to gain alignment regarding the acceptability of the generated data package for the MAA in addition to the declaration of conformity. As platforms for these early dialogues, the Innovation Task Force, scientific advice, and qualification advice could be suitable. A prerequisite will be that the right technical expertise (e.g. software) will be able to participate. Notified body representatives, or expert representatives from the national, supervisory, competent authorities, should be part of such integrated platform. In alignment with the EMA 2025 RSS, an integrated review process is supported by EFPIA. Certain enabling amendments to the legal framework might be required.

3.3. Life-cycle management of co-labelled products

Life-cycle management differs significantly between medicinal products and DHTs and there is therefore potential for mismatch. A DHT can be expected to undergo numerous incremental improvements during its lifecycle, including updates to operational systems for connected devices. These changes can and must be implemented quickly. The MDCG Guidance on significant changes should be considered. Lifecycle changes for medicinal products currently take much longer. The latter review timelines, classification and requirements are detailed in the Variation Regulation 1234/2008 and respective Variation Classification Guidance.

The future classification of software as outlined by MDR (Annex VIII, rule 11) ranges from Class I to Class III. However, it is likely that most digital health technologies will fall into Class IIa (software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes, or software intended to monitor physiological processes). For this class, prior approval changes need to be submitted to the notified body (MDR Annex X: change to the approved type or of its intended purpose and conditions of use).

EFPIA point of view: Regulatory reporting requirements for lifecycle changes of digital health technologies, including software, used concomitantly with medicinal products should in principle be determined by their potential to impact the associated benefit-risk for the patient and should be done using a tool/technology-agnostic approach that takes into account updates to algorithms. The framework should also be evidenced-based with the required evidence depending on each case and component quest. The overall impact of the technology change (e.g. data capture, data processing, data architecture, performance, etc.) needs to be evaluated from the standpoint of user interface and data visualization with respect to patient safety.

In case neither treatment decisions, nor the benefit-risk of the medicinal product, is impacted by the digital health technology or software update, there should be no need to notify the competent authority. However, if a technical change or software update does (or may) impact on treatment decisions or the overall benefit-risk of the medicinal product, a procedure for notification of, and

review by, the concerned notified body and the competent authority for medicinal products must be established. A significant change to the DHT may have to be reviewed by the notified body as a prior to implementation and timely notification of the competent authority for medicinal products. Only significant changes should in EFPIA's view be notified to the competent authority, and clear guidance on what is deemed to be a significant change should therefore be established. It is worth noting that in Europe, there are at present no variation categories for significant DHT changes.

An agreement of an upfront comparability protocol outlining nonsignificant and significant changes would be useful. A good example of this in practice is the US FDA's 'Predetermined Change Control Plan' for machine-learning and artificial intelligence. Such an approach enables pre-review of anticipated changes to streamline their implementation post-market. A well-defined integral regulatory procedure is needed for digital health technology lifecycle changes. The respective roles and responsibilities of notified bodies and competent authorities must be clear, and the procedure must accommodate the fast-technological evolution of digital health technologies.

4. List of references

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