Patient Technology

REGULATORY LANDSCAPE TOOL **US & EU**

TransCelerate BIOPHARMA INC.

ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

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1.0 Executive Summary

Over the past several years, digital health technology has made several inroads into the biopharmaceutical environment. Products are now more connected, and data is more accessible than ever before. In the clinical trial environment, which is the focus of this tool, features such as smart packaging, wearable technology, and other adherence tools are becoming more commonly used throughout industry. As the use of digital solutions in the biopharmaceutical industry continues to increase, it may still be unclear what the current regulatory environment around digital solutions is, and what type of regulatory impact these various solutions may have.

This regulatory landscape tool is designed to help address that ambiguity and represents the current state of regulations, guidance, and policy pertaining to how various digital solutions are classified and used within a clinical trial. This tool presents an overview of US and EU regulatory requirements related to patient technology and their use in clinical trials, as well as links to relevant regulations, guidance and intelligence addressing these topics. It helps to draw the line between what types of functionality are considered medical devices, and what types of functionality are not considered medical devices. This distinction is important, because the regulatory requirements for a product classified as a medical device can be significantly higher than the requirements of an unregulated device. These regulatory requirements for medical devices are also provided.

It should be noted that the information in this tool is presented objectively; no analysis was performed, or opinions made on the information. This tool is meant to help inform decisions on the regulatory requirements mandated for various types of technology and tools used in a clinical setting; it should not be used as a sole decision aid*.

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2.0 Scope

This 'Regulatory Landscape Tool' collates US and European policy, regulation and guidance related to digital technologies and their use in clinical trials. This tool incorporates existing Health Authority policy, regulation and guidance up until December 2018.

The scope of this regulatory landscape tool covers existing Health Authority policy, regulation and guidance concerned with:

- Classification of digital technology as a medical device or not and associated requirements for medical devices.
- Related regulations and guidance pertaining to clinical trial conduct that may impact implementation of digital technologies in clinical trials. (Ex. Guidance focused on good clinical practice, patient protection, and electronic data sources).
- Pathways for obtaining Health Authority feedback regarding implementation of digital technologies in clinical trials.
- Policies and initiatives that might reflect or impact Health Authority positions on use of digital technologies (Ex. Guidance focused on collection of real world data/ evidence, clinical trial design, etc.)

The scope of this regulatory assessment *does not* include and *is not* intended to reflect:

- Interpretation of regulatory requirements
- An exhaustive set of device specific guidance that may apply when a digital technology is regulated as a device
- An exhaustive set of trial guidance that may apply to the conduct of a clinical trial
- Specific decision-making recommendations on how to classify a digital solution
- Specific regulatory guidance on digital technologies intended for commercial use

Patient Technology is defined as digital technology with which patients interact to participate in clinical trial activities. Examples of patient technologies include items like wearables, mobile applications, and electronic consent. Policies, regulations, and guidance referenced in this document are not intended to be exhaustive for any specific technology type mentioned in the previous set of examples.

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3.0 Classification of digital technology as a medical device or not and associated medical device requirements

This section provides information about Health Authority regulations and guidance available in the United States and Europe to assist in the regulatory classification of a specific digital technology.

US FDA

21st Century Cures Act — Section 3060

Amended the definition of "device" in the Food, Drug and Cosmetic Act to exclude certain software functions:

- *For administrative support of a health care facility*
- *For maintaining or encouraging healthy lifestyle (general wellness)*
- *To serve as electronic health/patient records*
- *Transferring, storing, converting formats, displaying clinical laboratory data or other device data (Medical Device Data System)*
- *Certain Clinical Decision Support Software (CDSS), that meet the following criteria*
  - *Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal acquisition system*
  - *Intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines)*
  - *Intended for the purpose of supporting or providing recommendations to health care professionals, patients or non-healthcare professional caregivers about prevention, diagnosis, or treatment of a disease or condition*
  - *Intended for the purpose of enabling such health care professionals, patients or non-healthcare professional caregivers to independently review the basis for such recommendations that such software presents so that it is not the intent that the health care professionals, patients or non-healthcare professional caregivers rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient*

Patient Technology products that fall into the above categories will no longer be considered a medical device by FDA, and do not have to comply with any regulatory considerations prior to clinical or commercial use.

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Table 1: Software Regulations from 21st Century Cures Act — Present

Effective Date	Regulation or Guidance
13 December 2016	**21st Century Cures Act — Section 3060** **Exclusion of Certain Software from the definition/requirements of a medical device**
25 October 2017	**FDA Final Guidance — Deciding When to Submit a 510(k) for a Software Change to an Existing Device** *This Guidance will assist industry in determining when a software (or firmware) change to a medical device may require a manufacturer to submit and obtain FDA clearance of a new premarket notification (510(k)). This guidance uses a flowchart and text with considerations and examples to guide manufacturers through the logic scheme recommended to arrive at a decision on whether to submit a new 510(k) for a software change to an existing device.*
8 December 2017	**FDA Draft Guidance — Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act** *This draft guidance provides FDA's current thinking regarding the amended device definition and the resulting effect the amended definition has on FDA's guidances related to medical device software. This guidance details the changes to existing guidance documents related to the regulation of software functions removed from the definition of a medical device with the 21st Century Cures Act.*
8 December 2017	**FDA Draft Guidance — Clinical and Patient Decision Support Software** *This draft guidance identifies the types of decision support software functionalities that:* • *Do not meet the definition of a medical device as amended by the 21st Century Cures Act* • *May meet the definition of a medical device but for which FDA does not intend to enforce compliance with applicable requirements* • *FDA intends to focus its regulatory oversight on*

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Effective Date	Regulation or Guidance
8 December 2017	FDA Final Guidance — Software as a Medical Device (SaMD): Clinical Evaluation *This guidance adopts the internationally converged principles agreed upon by the IMDRF (International Medical Device Regulators Forum) with respect to the clinical evaluation of software as a medical device*
27 April 2018	FDA Draft Guidance — Multiple Function Device Products: Policy and Considerations *Medical products may contain several functions, some of which are subject to FDA's regulatory oversight as medical devices, while others are not. This draft guidance explains FDA's regulatory approach and policy for all multiple function products. Specifically, this guidance clarifies when and how FDA intends to assess the impact of other functions that are not the subject of a premarket review on the safety and effectiveness of a device function that is subject to FDA review. The purpose of this guidance is to identify the principles, premarket review practices, and policies for FDA's regulatory assessment of such products and to provide examples of the application of these policies.*

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Table 2: Additional Information on Digital Products

Effective Date	Regulation or Guidance
9 February 2015	FDA Issues Final Mobile Medical Apps Guidance (See Table 11 in Section 8.4) *This final guidance document informs manufacturers, distributors, and other entities about how the FDA intends to apply its regulatory authorities to select software applications intended for use on mobile platforms. This document clarifies the subset of mobile apps to which the FDA intends to apply its authority. FDA intends to apply its regulatory oversight to only those mobile apps that are medical devices and whose functionality could pose a risk to a patient's safety if the mobile app were to not function as intended. This subset of mobile apps the FDA refers to as 'mobile medical apps'*
29 July 2016	FDA Issues Final Guidance on General Wellness Apps: Policy for Low Risk Devices *This final guidance document provides clarity to industry on the compliance policy for low risk products that promote a healthy lifestyle (general wellness products). General wellness products are defined as products that meet the following two factors:* • *Are intended for only general wellness use (as defined in this guidance)* • *Present a low risk to the safety of users and other persons*

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Table 3: Current Medical Device regulations and guidance

Effective Date	Regulation or Guidance
20 June 1990	Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) 1990 **COUNCIL DIRECTIVE of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (90/385/EEC)** *The **Active Implantable Medical Devices Directive** applies only to active implantable devices. 'Active implantable medical device' means any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure. The Directive has as a first objective the harmonization of the regulatory environment across the European Economic Area, and at the same time, it enables the free movement of goods within the European Union. The Directive sets out the essential safety requirements in terms of function, sterility, material compatibility, marking, 'user' instructions, design documentation and CE marking but also include requirements for type approval, production quality management, clinical investigation and manufacturer registration.*
14 June 1993	Council Directive 93/42/EEC on Medical Devices (MDD) (1993) **COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices** *The **Medical Device Directive** is intended to harmonize the laws relating to medical devices within the European Union. The MD Directive is a 'New Approach' Directive and consequently in order for a manufacturer to legally place a medical device on the European market the requirements of the MD Directive have to be met. Manufacturers' products meeting 'harmonised standards' have a presumption of conformity to the Directive. Products conforming with the MD Directive must have a CE mark applied.* *Currently there are discrepancies between this and national transpositions of this Directive.*

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Effective Date	Regulation or Guidance
27 October 1998	Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDMD) (1998) **DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 1998 on in vitro diagnostic medical devices** *The **In Vitro Diagnostic Medical Devices Directive** applies to in vitro diagnostic medical devices and their accessories. 'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:* • *concerning a physiological or pathological state, or* • *concerning a congenital abnormality, or* • *to determine the safety and compatibility with potential recipients, or* • *to monitor therapeutic measures.* *'accessory' means an article which, whilst not being an in vitro diagnostic medical device, is intended specifically by its manufacturer to be used together with a device to enable that device to be used in accordance with its intended purpose.*
July 2016	In addition, legally non-binding **guidance** documents, MEDDEVs, consensus statements and informative documents pursue the objective of ensuring uniform application of the relevant provisions of the directives within the EU. *Please note that all guidance and implementing measures under the current Directives will be reviewed over the next few years in the light of the texts of the 2 new Regulations.* Key guidance related to Patient Technology include: • MEDDEV 2.1/6 (514 kB) Qualification and Classification of stand alone software. July 2016. *This document defines the criteria for the qualification of standalone software as a medical device when used in the healthcare setting and the application of the classification criteria to such software.*

NEW REGULATIONS: On 5 April 2017, 2 new Regulations on medical devices were adopted, and they entered into force on 25 May 2017. These replace the existing Directives.

The new rules will only apply after a transitional period. Namely, 3 years after entry into force for the Regulation on medical devices (spring 2020) and 5 years after entry into force (spring 2022) for the Regulation on in vitro diagnostic medical devices.

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Table 4: New Medical Device regulations and guidance

Effective Date (Enforcement Date)	Regulation or Guidance
5 April 2017 (April 2020)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC *The new Regulations contain a series of extremely important improvements to modernize the current system.* *The new regulations will ensure:* • *a consistently high level of health and safety protection for EU citizens using these products* • *the free and fair trade of the products throughout the EU* • *that EU legislation is adapted to the significant technological and scientific progress occurring in this sector over the last 20 years*
5 April 2017 (April 2022)	Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU *There are specific features of in vitro diagnostic medical devices, in particular in terms of risk classification, conformity assessment procedures and clinical evidence, and of the in vitro diagnostic medical device sector which require the adoption of specific legislation, distinct from the legislation on other medical devices, whereas the horizontal aspects common to both sectors should be aligned.*
November 2017	Commission Implementing Regulation (EU) 2017/2185 of 23 November 2017 on the codes for the designation of notified bodies in medical devices under Regulation (EU) 2017/745 and in vitro diagnostic medical devices under Regulation (EU) 2017/746. *Implementing measures for the above 2 regulations*

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Table 5: Example European national regulation and guidance on medical mobile applications*

*The below provides one example of guidance by the UK MHRA. Other country examples may also exist and should be consulted based on the countries where the technology will be utilized.

Date	Regulation or Guidance
June 2018 (revision date)	UK MHRA **Guidance: Medical device stand-alone software including apps (including IVDMDs)** Guidance: Medical device stand-alone software including apps ***This guidance is to be used in addition to MEDDEV 2.1/6 and is the UK's interpretation of the guidance.*** *This guidance uses **examples within flowcharts** to show which standalone software and apps meet the definition of a medical device, an in vitro diagnostic device or active implantable medical device and therefore require to be CE marked, and those which do not. For developers of software, including apps, we are also including information on classification, suggestions on how to address the main aspects of the CE marking process and responsibilities for reporting and correcting when things go wrong. For users we offer a few tips on how to decide if the app or software device you are using is a medical device and if so how to ensure it is CE marked along with how to report problems.*

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4.0 Related regulations and guidance pertaining to clinical trial conduct that may impact implementation of digital technologies in clinical trials

US FDA

Table 6: Applicable Clinical Trials Guidance — FDA

Effective Date	Regulation or Guidance
December 2012	Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products *This draft guidance document provides guidance to industry on enrichment strategies that can be used in clinical trials intended to support effectiveness and safety claims in new drug applications (NDAs) and biologics license applications (BLAs). Similar strategies may also be used in studies conducted in earlier stages of development.* *Enrichment strategies fall into three broad categories:* • *Strategies to decrease heterogeneity* • *Prognostic enrichment strategies* • *Predictive enrichment strategies*
September 2013	Guidance for Industry — Electronic Source Data in Clinical Investigations *This guidance provides recommendations to sponsors, Contract Research Organizations (CROs), clinical investigators, and others involved in the capture, review, and retention of electronic source data in FDA-regulated clinical investigations. In an effort to streamline and modernize clinical investigations, this guidance promotes capturing source data in electronic form, and it is intended to assist in ensuring the reliability, quality, integrity, and traceability of data from electronic source to electronic regulatory submission.*

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Effective Date	Regulation or Guidance
23 October 2016	**Final Guidance — Patient Preference Information** *This guidance document provides guidance on patient preference information (PPI) that may be used by FDA staff in decision making related to the approval of submission applications. The objectives of this guidance are:* • *To encourage submission of PPI, if available, by sponsors or other stakeholders to FDA and to aid in FDA decision making* • *To outline recommended qualities of patient preference studies, which may result in valid scientific evidence* • *To provide recommendations for collecting and submitting PPI to FDA* • *To discuss FDA's inclusion of PPI in its decision summaries and provide recommendations for the inclusion of such information in device labeling*
9 November 2016	**ICH E6 (R2) — Integrated Addendum to ICH E6(R1): Guideline on Good Clinical Practice Clinical Trial Conduct** *Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.* *Addendum: this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated*

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Table 7: Applicable Clinical Trial Guidance — EMA

Effective Date (Enforcement Date)	Regulation or Guidance
9 November 2016	ICH E6 (R2) — Integrated Addendum to ICH E6(R1): Guideline on Good Clinical Practice Clinical Trial Conduct *Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.* *Addendum: this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.*
14 June 2017	EMA Guideline for good clinical practice E6 R2 *EMA implementation of ICH E6(R2) — see in particular section 5.5.3 on the use of electronic trial data.*
4 April 2001	EU Clinical Trials Directive 2001/20/EC **DIRECTIVE 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.** *This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice. This Directive does not apply to non-interventional trials.*

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Effective Date (Enforcement Date)	Regulation or Guidance
New — 16 April 2014 (expected to apply Oct 2019)	EU Clinical Trials Regulation REGULATION (EU) No 536/2014 **REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.** *Will replace EU Clinical Trials Directive 2001/20/EC (above) (repeals Directive) — it is currently expected to become application in late 2019.*
27 April 2016 (25 May 2018)	EU General Data Protection Regulation — Regulation (EU) 2016/679 **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, and repealing Directive 95/46/EC (General Data Protection Regulation)** *The General Data Protection Regulation (GDPR) (EU) 2016/679 is a regulation in EU law on data* *protection and privacy for all individuals within the EU and the European Economic Area (EEA). May impact collection and storage of data in Clinical Trials.*
May 2016	European Commission EU Guidelines on Assessment of the Reliability of Mobile Health Applications *This document is intended to capture and describe a set of voluntary guidelines for assessing the validity and reliability of data that mobile health applications collect and process. It has been produced in response to challenges identified within the mHealth market in Europe and, specifically, to address the issues raised as a result of a public consultation in January 2015.*

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5.0 Pathways for obtaining Health Authority feedback regarding implementation of digital technologies in clinical trials

US FDA

Table 8: Pathways for obtaining FDA Feedback

Date	Pathway/Interaction Type
December 2017	**FDA Draft Guidance — Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products** *This guidance provides recommendations to industry on formal meetings between the Food and Drug Administration (FDA) and sponsors or applicants relating to the development and review of drug or biological drug products (hereafter referred to as products) regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). This guidance does not apply to abbreviated new drug applications, applications for biosimilar biological products, or submissions for medical devices.*
December 2017	**FDA Final Guidance — Best Practices for Communication Between IND Sponsors and FDA During Drug Development** *The purpose of this guidance is to describe best practices and procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors and FDA at critical junctures in drug3 development, which may facilitate earlier availability of safe and effective drugs to the American public. This guidance applies to communications between IND sponsors and FDA during the IND phase of drug development, including biosimilar biological product development (BPD). This guidance describes:* • *FDA's philosophy regarding timely interactive communication with IND sponsors as a core activity* • *The scope of appropriate interactions between review teams and IND sponsors* • *The types of advice appropriate for IND sponsors to seek from FDA in pursuing their drug development programs* • *General expectations for the timing of FDA response to IND sponsor inquiries* • *Best practices and communication methods to facilitate interactions between review teams and IND sponsors during drug development* • *Expectations for appropriate methods, including the frequency, of such communications*

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Date	Pathway/Interaction Type
29 September 2017	**FDA Final Guidance — Request for Feedback on Medical Device Submissions: The Pre- Submission Program and Meetings with Food and Drug Administration Staff** *The purpose of this guidance is to provide an overview of the mechanisms available to applicants through which they can request feedback from the Food and Drug Administration (FDA) regarding potential or planned medical device Investigational Device Exemption (IDE) applications or other premarket submissions, such as Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, Evaluation of Automatic Class III Designations (De Novo requests), Premarket Notification (510(k)) Submissions, Clinical Laboratory Improvement Amendments (CLIA) Waiver by Application, and including certain Investigational New Drug Applications (INDs) and Biologics License Applications (BLAs).* *This guidance provides information regarding the logistics for submission, receipt, tracking, and review of/response to these requests.* *The feedback mechanisms addressed by this guidance include Pre-Submissions, Informational Meetings, Study Risk Determinations, Formal Early Collaboration Meetings (i.e., Agreement and Determination Meetings), Submission Issue Meetings, and PMA Day 100 Meetings. For some of these mechanisms, this document largely refers to existing guidance, while for others, this guidance establishes the procedures FDA intends to follow when providing feedback; however, all these feedback requests will fall within the same organizational structure for tracking purposes. These requests for feedback are collectively referred to as "Q- Submissions" or "Q-Subs." FDA believes that the Q-Sub structure provides a convenient and effective way to track these requests.*
7 June 2018	**FDA Draft Guidance — Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program** *The purpose of this guidance is to provide an overview of the mechanisms available to submitters through which they can request feedback from or a meeting with the Food and Drug Administration (FDA) regarding potential or planned medical device Investigational Device Exemption (IDE) applications, Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, Evaluation of Automatic Class III Designations (De Novo requests), Premarket Notification (510(k)) Submissions, Clinical Laboratory Improvement Amendments (CLIA) Waiver by Applications (CW), Dual 510(k) and CLIA Waiver by Application Submissions (Duals), Accessory Classification Requests, and certain Investigational New Drug Applications (INDs) and Biologics License Applications (BLAs) submitted to the Center for Biologics Evaluation and Research (CBER).*

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Table 9: Pathways for obtaining EMA advice/opinion

Date	Pathway/Interaction Type
10 November 2014	Qualification Opinion Qualification of novel methodologies for drug development: guidance to applicants *This guidance describes the EMA qualification process, a voluntary, scientific pathway leading to either a CHMP Qualification opinion or a qualification advice on innovative methods or drug development tools:* • ***CHMP qualification opinion** on the acceptability of a specific use of the proposed method (e.g. use of a novel methodology or an imaging method) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data;* • ***CHMP qualification advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.*
6 August 2014	EMA Innovation Task Force Mandate of the EMA Innovation Task Force (ITF) *The ITF is a multidisciplinary group that includes scientific, regulatory and legal competences. It was set up to ensure coordination across the Agency and to provide a forum for early dialogue with applicants on innovative aspects in medicines development.*
30 June 2017	Scientific Advice EMA Scientific Advice *Scientific advice is when the Agency gives advice to a developer on the appropriate tests and studies in the development of a medicine. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients.* *Medicine developers can request scientific advice from the EMA at any stage of development of a medicine, whether the medicine is eligible for the centralised authorisation procedure or not.* *Scientific advice helps to ensure that developers perform the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing-authorisation application. Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the marketing authorisation. Following the Agency's advice increases the probability of a positive outcome.*

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Date	Pathway/Interaction Type
30 June 2017	**European Medicines Agency guidance for applicants seeking scientific advice and protocol assistance** *This guidance document addresses a number of questions that users of the scientific advice or protocol assistance procedures may have.* *It provides an overview of the procedure to obtain scientific advice or protocol assistance and gives guidance to Applicants in preparing their request. This guidance document also explains the scope and nature of scientific advice and protocol assistance. It will enable Applicants to submit requests which are in conformity with Scientific Advice Working Party (SAWP) requirements and which can be validated and evaluated quickly and efficiently.* *Furthermore, Applicants will be guided through the different steps of the procedure and receive useful information on the preparation of a possible discussion meeting with the SAWP.* **Parallel Scientific Advice with the Food and Drug Administration** The Agency provides scientific advice and protocol assistance in parallel with the United States Food and Drug Administration (FDA): • *General principles — European Medicines Agency-FDA parallel scientific advice* • *Timeline — European Medicines Agency-FDA parallel scientific advice*

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Table 10: Examples of published advice/opinion from EMA on the use of Patient Technology in Clinical Trials

Date	Advice/Opinion
20 September 2018	**Draft qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device** Draft qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy *This report provides a final agreed draft Context of Use for public consultation describing where Stride Velocity measured at the ankle 95th Centile is deemed by CHMP as an appropriate endpoint in studies to support regulatory decision making on medicines for the treatment of Duchenne Muscular Dystrophy (DMD), together with CHMP's scientific consideration of the submission leading to the draft opinion. The document also includes the questions posed by the applicant and also raised by CHMP to the Applicant, and all the data provided by the applicant in support of the Application.*

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6.0 Policies and initiatives that might reflect or impact health authority positions on use of digital technologies

US FDA

Table 11: FDA Initiatives reflecting its position on the use of digital technologies

Date	Advice/Opinion
8 August 2017	FDA Digital Health Innovation Action Plan *The Digital Health Innovation Action Plan outlines FDA's efforts to reimagine their approach for assuring that all Americans, including patients, consumers and other health care customers have timely access to high-quality, safe and effective digital products. This plan lays out the vision for fostering digital health innovation while continuing to protect and promote the public health, including:* • *Issuing guidance to provide clarity on the medical software provisions of the 21st Century Cures legislation* • *Launching an innovative pilot pre-certification program to work with customers to develop a new approach to digital health (FDA Pre-Cert for Software)* • *Building FDA's bench strength and expertise in their digital health unit*
8 August 2017	FDA Digital Health Software Precertification Program *This program will help inform the development of a regulatory model to assess the safety and effectiveness of software technologies without inhibiting patient access to these technologies. This proposed approach aims to look first at the software developer and/or digital health technology developer, which is intended to drive market competition to higher standards of safety and effectiveness. The benefits of the program to a participating organization based on their 'pre-certified' status may include:* • *Ability to market lower risk software as a medical device without premarket review of individual products* • *Ability to participate in a streamlined premarket review* • *Opportunities to collect and leverage real-world post-market data*

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Date	Advice/Opinion
12 September 2018	Statement from FDA Commissioner Scott Gotlieb, M.D., and Center for Devices and Radiological Health Director Jeff Shuren, M.D., J.D., on agency efforts to work with tech industry to spur innovation in digital health *Proposal to create a Center of Excellence for Digital Health that would advance modernizing our regulatory approach to help this industry grow and reach its full potential, while protecting patients.* *This Center of Excellence would help establish more efficient regulatory paradigms, consider building new capacity to evaluate and recognize third-party certifiers, and support a cybersecurity unit to complement the advances in software-based devices. Our Digital Health Innovation Action Plan demonstrates our commitment to spurring digital health innovation and safety. With the creation of a Center of Excellence, the FDA could commit additional resources to helping developers create innovative products that can benefit patients.*

Figure 1: High Level Concept of the Reimagined Approach Using FDA Pre-Cert for Software

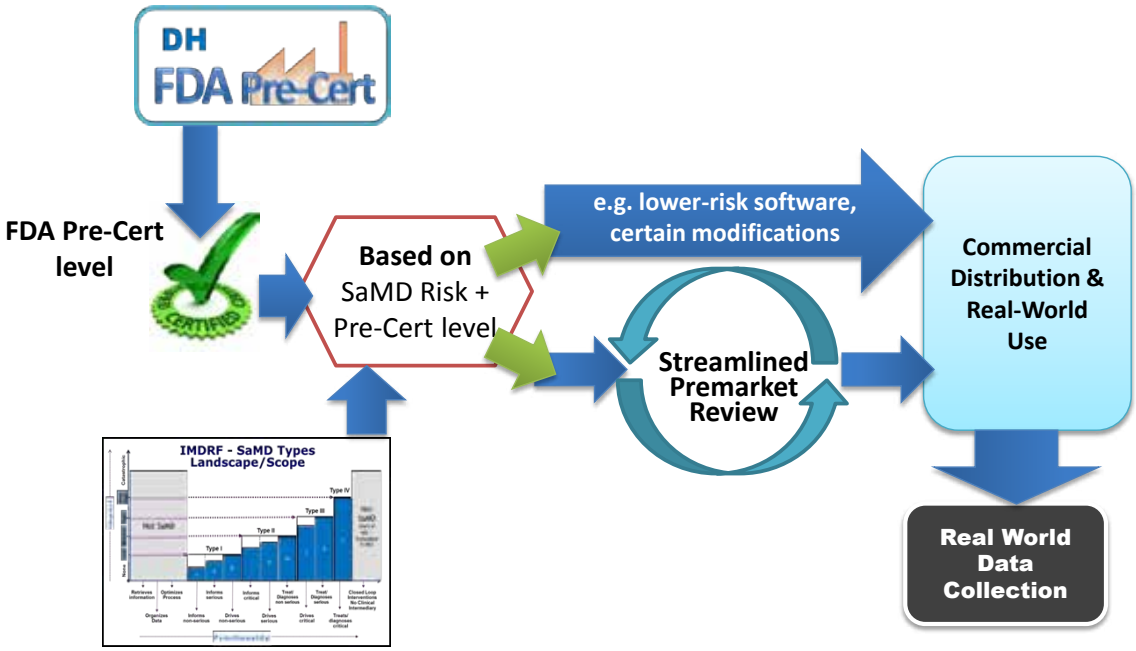

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Table 12: European Commission policies and initiatives reflecting its position on the use of digital technologies

Date	Advice/Opinion
6 December 2012	eHealth Action Plan 2012-2020 — Innovative Healthcare for the 21st Century — *Superseded by Digital Single Market, below* EU Commission overarching Plan.
10 April 2014	**European Commission Green Paper on mobile health ("mHealth")** EC Green Paper on mHealth *On 10 April 2014 the European Commission published a Green Paper on mobile health ("mHealth") which launched a public consultation, open until 10 July 2014, in which it invited stakeholders to provide their views on 11 identified barriers to the uptake of mHealth in the EU.*
May 2015	**European Commission's Digital Single Market (DSM) strategy** *The aim is to create a digital single market where the free movement of goods, persons, services, capital and data is guaranteed — and where citizens and businesses can seamlessly and fairly access online goods and services, whatever their nationality, and wherever they live. The ultimate aim is to develop a cross countries EU health data cooperation network.*

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Date	Advice/Opinion
25 April 2018	**Communication on Digital Transformation of Health and Care in the Digital Single Market** *European Commission published on 25 April 2018 a* Communication on Digital Transformation of Health and Care in the Digital Single Market, *empowering citizens and building a healthier society. These policy documents give direction to EU activities in this field for the coming years.* *It identifies three priorities:* 1. ***Citizens' secure access to their health data, also across borders —*** *enabling citizens to access their health data across the EU;* 2. ***Personalised medicine through shared European data infrastructure —*** *allowing researchers and other professionals to pool resources (**data**, expertise, computing processing and storage capacities) across the EU;* 3. ***Citizen empowerment with digital tools for user feedback and person-centred care —*** *using digital tools to empower people to look after their health, stimulate prevention and enable feedback and interaction between users and healthcare providers.* *Furthermore, the **Communication** provides a concrete set of actions on how each priority can be attained (see the **infographic** for an overview).*

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7.0 APPENDIX

7.1 Key Definitions

Medical Device (FDA FD&C Act):

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals
- intended to affect the structure or any function of the body of man or other animals

and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Medical Device (EU MDR):

The new Medical Device Regulations (MDR) for the EU goes into effect in May 2020. This tool will incorporate the definition from the MDR as current and future products in development will likely be subject to the new requirements.

'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, including organ, blood and tissue donations

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

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M-Health product classified as a Medical Device (EU MDR):

To qualify as a medical device, an M-Health product shall:

- Have a medical purpose
- Perform an action on data (other than just storage) for the medical benefit of individual patients and
- Generate or manage personalized alerts based on monitored patients' vital parameters to drive clinical management or
- Use an algorithm to support or facilitated medical decisions by a healthcare provider.

Standalone software: Software intended to provide information used in diagnostic or therapeutic decisions or to monitor physiological processes is Class IIa. Classification may be higher based on risk.

Artificial Intelligence (FDA)

A device or product that can imitate intelligent behavior or mimics human learning and reasoning. Artificial intelligence includes machine learning, neural networks, and natural language processing. Some terms used to describe artificial intelligence include: computer-aided detection/diagnosis, statistical learning, deep learning, or smart algorithms.

Interoperability (FDA)

A device or product that can exchange and use information through an electronic interface with another medical/non-medical product, system, or device.

Medical Device Data System (MDDS) (FDA)

Hardware or software that can transfer, store, convert data formats, or display medical device data without controlling or altering the functions or parameters of any connected medical device.

Mobile Medical App (MMA) (FDA)

A software application that meets the definition of a medical device. The MMA transforms a mobile platform into a regulated medical device or is an accessory to a regulated medical device.

Novel Digital Heath (FDA)

A device or product that includes new, unfamiliar, or unseen digital health technology never submitted, cleared, or approved by FDA. The technology could potentially be a de Novo, have a new intended use, or have different technological characteristics. This also includes digital health technology or topic areas that have no agreed upon or established definition by industry or FDA

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7.2 Historical Software Regulations from FDA

Table 13: Software Regulations from 2011 – 2016

Effective Date	Regulation or Guidance	Comments
15 February 2011	Final Medical Device Data System (MDDS) Rule — Reclassification from Class III (High Risk Device) to Class I (Low Risk Device) Final MDDS Rule in Federal Register	No longer considered medical device (21st Century Cures Act)
April 2014	FDA Safety and Innovation Act (FDASIA) Health IT Report	Risk based approach to developing software based solutions for healthcare
9 February 2015	FDA Issues Final Guidance on Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communication Devices FDA Final Guidance	No longer considered medical device (21st Century Cures Act)
9 February 2015	FDA Issues Final Mobile Medical Apps Guidance (See Table 11)	Will be amended based on 21st Century Cures Act
29 July 2016	FDA Issues Final Guidance on General Wellness Apps: Policy for Low Risk Devices	ill be amended based on 21st Century Cures Act

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Table 14: Examples of Mobile Medical Apps – Unregulated, Regulated, and Enforcement Discretion

Information taken from FDA Issues Final Mobile Medical Apps Guidance

MOBILE MEDICAL APPS		
Unregulated	**Enforcement Discretion**	**Regulated**
Provide access to electronic copies of medical textbooks Facilitate Patient Access to Information Generic Aids or General Purpose Products such as: • Using a mobile platform as a magnifying glass • Using a mobile platform for recording audio, note- taking • Allowing patients and healthcare providers to interact through email, web- based platforms, video or other communication mechanisms Business Operations in Healthcare Setting Educational Tools for healthcare providers — to be used for medical training or to reinforce training previously received	Help asthmatics track inhaler usage, asthma episodes experienced, location of user at the time of an attack, or environmental triggers of asthma attacks Mobile apps that allow a user to collect, log, track and trend data, such as blood glucose, blood pressure, heart rate, weight or other data from a device to eventually share with a health care provider, or upload it to an online database, personal or electronic health record Mobile apps that record the clinical conversation a clinician has with a patient and sends it (or a link) to the patient to access after the visit Mobile apps that keep track of medications and provide user-configured reminders for improved medication adherence Mobile apps that provide patients a portal into their own health information, such as access to information captured during a previous clinical visit or historical trending	Mobile Apps that are an extension of a medical device by connecting to the device for: • Controlling the device • For use in active patient monitoring • Analyzing medical device data Transform the mobile platform in a regulated medical device • Uses attachments, display screens, or sensors • Includes functionalities similar to those of currently regulated medical devices Mobile apps that perform patient-specific analysis and provide patient-specific diagnosis or treatment recommendations