Biopharmaceutical Digital Health Lexicon

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Digital health is transforming nearly every aspect of our health care system, improving efficiency, expanding access to treatments and technologies, and ushering in increased development of personalized medicine. The transformation of health care during the COVID-19 pandemic has shed light on how these advancements are changing drug development, how care is delivered, and is allowing patients to be involved in managing and developing their care.

The application of digital health tools to biopharmaceutical research and development and the FDA-regulated lifecycle of a product, which we refer to as digital health R&D, is beginning to positively disrupt biopharmaceutical development. Thanks to advancements in science and technology, the biopharmaceutical industry is leveraging digital R&D to improve drug development and deliver value to patients.

One of the foundational elements of a modern digital R&D regulatory framework is a common lexicon and understanding of key terms to orient stakeholders and facilitate conversations related to R&D tools and technologies. PhRMA emphasizes that defining these terms is intended only to facilitate engagement and conversations related to policy. In developing this lexicon, attention was paid to reviewing and incorporating existing terms, definitions, and lexicons where appropriate. It does not suggest any divergent regulatory standard for digital health technology tools as compared to non-digital tools. Below is a list of key terms identified by the biopharmaceutical industry and suggested definitions.

FOUNDATIONAL DIGITAL HEALTH CONCEPTS

Digital Health

Digital Health is defined as the application of **digital technologies** in healthcare, living, and/or society that help deliver and/or provide access to healthcare products and services. The broad scope of **digital health** includes categories such as mobile health (mHealth), and all technologies that allow the utilization of the data generated (e.g., data science and artificial intelligence (AI)), including technologies such as **wearables, telemedicine, software as a medical device (SaMD)**, and health information technology (IT).[1]

Biopharmaceutical Digital Health

Biopharmaceutical Digital Health is defined as the application of **digital technology** within the biopharmaceutical industry. Biopharmaceutical digital health is a subset of **digital health**. It includes the application of **digital health** to foster business operations, patient engagement and outcomes, healthcare provider engagement, research and discovery, biopharmaceutical development and clinical trials, regulatory submissions, post-market pharmacovigilance, and manufacturing.

In stakeholder discussions of specific types of digital health, specific technologies are frequently interchanged or confused with specific applications of those technologies. One technology may be used for multiple divergent purposes. For example, artificial intelligence may be used to discover a new molecule, identify ideal clinical trial patients, or optimize drug delivery logistics. These different applications have very different regulatory implications, and therefore, it is important to distinguish the digital technology for a specific application of it.

Digital Health Research and Development (Digital R&D)

Digital Health Research and Development (Digital R&D) is the application of digital health to the lifecycle of biopharmaceutical products.

Digital Health R&D is a subset of **biopharmaceutical digital health**. It includes the application of **digital health** to research and discovery, biopharmaceutical development and clinical trials, regulatory submissions, post-market data collection, research, and pharmacovigilance, and supply chain management.

Digital Technology

Digital Technology is defined as an electronic method, system, product, or process that generates, stores, displays, processes, shares, purges, and/or uses digital data (signals in zeros and ones). Examples of **digital technologies** include hardware (e.g., wearable sensors, VR headsets, digitally enabled drug delivery devices), **advanced analytics** (e.g., **artificial intelligence, machine learning, sophisticated computation**) and cloud services (e.g., storage, computing, and data processing), and software (e.g., **mobile medical applications, SaMD**). The technology could be a product that includes new, unfamiliar, or unseen digital health technology never submitted, cleared, or approved by the FDA.

Digital Health Technology Tools (DHTT)

Digital Health Technology Tools are defined as electronic technology tools intended for use in clinical investigations (inclusive of clinical trial and post-market settings) or clinical practice. They may, for example, capture data, actively or passively (e.g., measure data and interpret data), educate digitally, or serve as reminders.

Validation (of a digital health technology tool)

Validation is defined as the process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. Elements of validation include, but are not limited to:

- Analytical validation;
- Clinical validation; and
- Software validation.

Digital Therapeutics (DTx)

Digital Therapeutics is defined as **digital health technology applications** with a primary function of delivering software-generated therapeutic interventions directly to patients to prevent, manage, or treat a medical disorder or disease.

CLINICAL TRIALS

Decentralized Clinical Trials

Decentralized Clinical Trials are defined as clinical trials where all or some aspects traditionally completed in the clinic are performed outside of traditional clinical research centers, e.g., in a participant's home or local physician's office, remotely often utilizing **digital technology** to facilitate completion of the activities. Decentralized clinical trials can best be described along the axes of "locality" (where the data is captured) and "method" (how the data is captured). The magnitude of clinical trial decentralization is inversely correlated with the degree of the study's operational dependency on specific sites, such as specialized research facilities (locality), or reliance on intermediaries for data collection (method).

Hybrid Decentralized Clinical Trials are considered Decentralized Clinical Trials. These Hybrid Decentralized Clinical Trials are clinical trials where some, but not all, aspects traditionally completed in the clinic are performed outside of traditional clinical research centers, e.g., in a participant's home or local physician's office, remotely often utilizing digital technology to facilitate completion of the activities. This would also include a trial where some patients go to the site for all visits and assessments and other patients never go to a site.

Digital Endpoint

Digital endpoints are defined as a precisely defined variable intended to reflect an outcome of interest that is statistically analyzable to address a particular research question derived from data captured with a **DHTT**.

Biometrics

Biometrics is defined as a method of verifying an individual's unique identity based on measurement of the individual's physical characteristic(s) or repeatable action(s) where those characteristics and/or actions are both unique to that individual and measurable.[2]

Digital Biomarker

Digital Biomarkers are defined as digital variables that are measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions that can only or should be measured by a validated **DHTT**. Digital Biomarkers differ from digital endpoints in that biomarkers are inherently predictive, diagnostic, or prognostic as opposed to measuring an outcome.

Real-World Data (RWD)

Real-World Data is defined as the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices[3]

Real-World Evidence (RWE)

Real-World Evidence is defined as the clinical evidence regarding the usage and potential benefits, or risks of a medical product derived from the analysis of **RWD**. RWE can be generated by different study designs or analyses, including but not limited to randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).[4]

Passive Monitoring Clinical Outcome Assessment (pmCOA)

Passive Monitoring Clinical Outcome Assessments are defined as a type of clinical outcome assessment with a measurement based on a report that comes from a digital health technology tool after the detection and measurement of activity/function, behaviors, or other manifestations related to a disease or condition. pmCOA measures typically do not require the patient to actively perform a standardized task as in the case of a performance outcome assessment. Rather, they can be obtained passively as the patient goes about their daily life and activities in non-clinical settings (e.g., passive monitoring of falls or sleep quality using wearable instruments).

DATA ANALYTICS

Advanced Analytics

Advanced Analytics is defined as a process (such as an algorithm or set of algorithms) that may leverage a device or product and that can identify, compute, and use big data and large complex data sets from a variety of sources. The process extracts new and relevant information or patterns that can be used for medical purposes. Required for **artificial intelligence** devices. Advanced Analytics may include the use of statistical modeling and analytical techniques that provide insights, predictions, and recommendations based on its analysis. In that respect, devices with embedded algorithms, including Advanced Analytics, may overlap with those, including **artificial intelligence**. However, Advanced Analytics techniques typically analyze large and varied datasets that cannot normally be analyzed by humans without specialized software tools and often discover new patterns in data.[5]

Artificial Intelligence

Artificial Intelligence is defined as 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.[6]

Machine Learning

Machine Learning is used to design an algorithm or model without explicit programming but through the use of automated training with data (e.g., a regression function or deep learning network).[7]

COLLECTION AND SHARING OF DATA

Data Acquisition

Data acquisition is defined as the process of collecting data elements and data sources of health-related and health-research data.

Data Curation

Data curation is the active and on-going management and structuring of data from disparate data sources (e.g., EHRs, sensors, consumers, claims data) through its lifecycle by appropriate authentication, archiving, management, preservation, retrieval and representation to render timely use and re-use over time to enable rapid and sophisticated data analysis.

Cloud

The Cloud is defined as a **digital technology** with internet-based computing that provides computer processing resources and data on demand. The cloud is a shared pool of configurable resources (e.g., computer networks, servers, storage, applications, and services). Computing and data storage resources include servers, operating systems, networks, software, applications, services, and storage equipment.

Examples include:
- **SaMD** being executed in the cloud.
- A mobile colposcope that stores images taken on the cloud for future retrieval and review in the doctor's office.
- A picture archiving and communications system consists of cloud-based, web-accessible software that analyzes cardiovascular images acquired from magnetic resonance (MR) scanners.[8]

Wearables

Wearables are defined as **digital technologies** that users can wear and are designed to collect data related to or to inform users' personal health and wellness.

Sensor

Sensor is defined as a device, module, machine, or subsystem whose purpose is to detect events or changes in its environment, measure outcomes, and send the information to other devices, modules, or subsystems.

Health Telemetrics/Telematics

Health Telemetrics/Telematics involves the use of information processing tools and telecommunications to provide the functional and operational framework that allows for remote capture and transfer of health data.

Telemedicine

Telemedicine is defined as the use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, patient and professional health-related education, public health and health administration.[9]

eConsent

eConsent is defined as the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent.[10].

SOFTWARE

Clinical Decision Support (CDS) software

Software to Support Clinical Decision-making is defined as those software functions that meet the first, second, and third criteria of section 520(o)(1)(E) of the FD&C Act. CDS is not always excluded from the device definition by Cures. Only when a CDS function also meets the fourth criterion of section 520(o)(1)(E), which relates to enabling independent review of the basis for recommendations, is the CDS function excluded from the definition of a device.[11]

Software as a Medical Device (SaMD)

Software as a Medical Device is defined as software intended for one or more medical uses that may run on different operating systems or in virtual environments. Software run on a hardware medical device is a SaMD when **not** part of the intended use of the hardware medical device. Software is not SaMD if it drives or controls the hardware medical device. This can include standalone software that is intended to run on general purpose computers or mobile platforms (e.g., smartphone, tablet).[12]

Software Validation

Software validation is defined as being established by objective evidence, that the software conforms with the user needs and intended use of the device.[13] Software validation is a part of design validation of the finished product. It involves checking for proper operation of the software in its actual or simulated use environment, including integration into the final product where appropriate. Software validation is highly dependent upon comprehensive software testing and other verification tasks previously completed at each stage of the software development life cycle. Planning, verification, traceability, configuration management, and many other aspects of good software engineering are important activities that together help to support a conclusion that software is validated.

Software Verification

Software verification is defined as confirmation that the output of a particular phase of development meets all of the input requirements. Software testing is one of several verification activities intended to confirm that the software development output meets its input requirements.
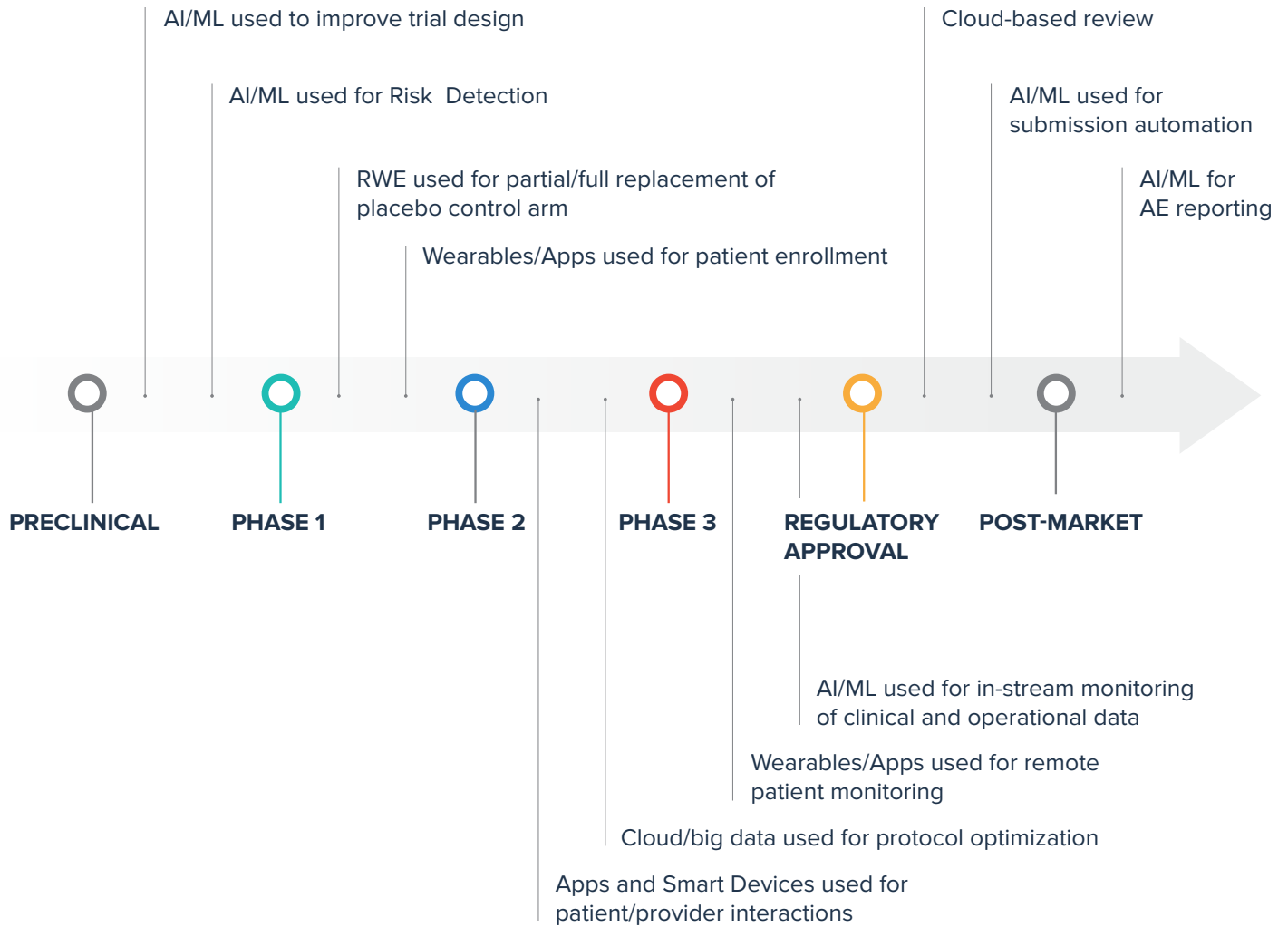
Mobile Medical Applications (MMA)

Mobile Medical Applications are software applications that: (1) can be executed (run) on a mobile platform (i.e., a handheld commercial off-the-shelf computing platform, with or without wireless connectivity), or a web-based software application that is tailored to a mobile platform but is executed on a server; and (2) that are intended for use on mobile platforms that meet the definition of a medical device.[15]

GLOBAL TERMS

While the terms in this lexicon are predominantly based on existing Food and Drug Administration (FDA) terms/definitions, there is an awareness that other global regulatory bodies are also working on defining these terms. For example, Real-World Data, Real-World Evidence, Artificial Intelligence, and Machine learning have already been defined by other global regulatory bodies, as well as FDA.

- **Real-World Data:** Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.[16]

- **Real-World Evidence:** Clinical evidence regarding the usage, and potential benefits or risks, or a medical product derived from analysis of RWD.[17]

- **Artificial Intelligence:** Artificial intelligence refers to systems designed by humans that, given a complex goal, act in the physical or digital world by perceiving their environment, interpreting the collected structured or unstructured data, reasoning on the knowledge derived from this data and deciding the best action(s) to take (according to pre-defined parameters) to achieve the given goal.[18]

- **Machine Learning:** One of AI's sub-disciplines, denoting the ability of a piece of software to learn from its environment or from a very large set of representative data, enabling systems to adapt their behavior to changing circumstances or to perform tasks for which they have not been explicitly programmed.[19]

APPENDIX 1

AI/ML used to improve trial design

AI/ML used for Risk Detection

RWE used for partial/full replacement of placebo control arm

Wearables/Apps used for patient enrollment

Cloud-based review

AI/ML used for submission automation

AI/ML for AE reporting

PRECLINICAL   **PHASE 1**   **PHASE 2**   **PHASE 3**   **REGULATORY APPROVAL**   **POST-MARKET**

AI/ML used for in-stream monitoring of clinical and operational data

Wearables/Apps used for remote patient monitoring

Cloud/big data used for protocol optimization

Apps and Smart Devices used for patient/provider interactions

Endnotes

1   Food and Drug Administration Definition, https://www.fda.gov/medical-devices/digital-health

2   https://www.ecfr.gov/cgi-bin/text-idx?SID=19d1c981d79aeb3767c6870e01a84933&mc=true&node=pt21.1.11&rgn=div5#se21.1.11_13

3   Food and Drug Administration Definition, https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

4   Food and Drug Administration Definition, https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

5   Food and Drug Administration Definition, https://www.fda.gov/medical-devices/digital-health/digital-health-criteria

6   Food and Drug Administration Definition, https://www.fda.gov/medical-devices/digital-health/digital-health-criteria

7   Food and Drug Administration Definition, https://www.fda.gov/medical-devices/digital-health/digital-health-criteria

8   Food and Drug Administration Definition, https://www.fda.gov/medical-devices/digital-health/digital-health-criteria

9   https://www.healthit.gov/topic/health-it-initiatives/telemedicine-and-telehealth

10 Food and Drug Administration Definition, https://www.fda.gov/media/116850/download

11 Food and Drug Administration Definition, https://www.fda.gov/media/109618/download

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14 https://www.fda.gov/media/73065/download

15 Food and Drug Administration Definition, https://www.fda.gov/medical-devices/digital-health/mobile-medical-applications#a

16 Pharmaceuticals and Medical Devices Agency Definition, https://www.pmda.go.jp/files/000226215.pdf

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18 Digital Health Europe Definition, https://digitalhealtheurope.eu/fileadmin/dhe/dhe_documents/dhe_glossary_website_august2019.pdf

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