European Federation of Pharmaceutical Industries and Associations

ACT-EU MSP Methodology workshop: opportunities and challenges in validating digital endpoints

Lada Leyens, Takeda
On behalf of EFPIA

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Validation of Digital Endpoint*

a complex environment at the interface of drug and technology regulatory frameworks

The regulatory requirements and extent/type of evidence depend on:

- **The tool**
- **The Outcome Measure**
- **The Context of Use**

Key stakeholders involved in development and validation

- **Patients**
- **Academia / HCPs**
- **Industry and DHT developers**
- **Regulators (see below)**

Multiple components and evidence with distinct regulatory considerations

The DHT: regulatory identity and documentation?	The Data: quality and clinical operations?	The digital endpoint: meaningful, relevant and robust?
Regulatory identity: Is it a medical device?	Does it comply with privacy, security, GDPR, safety & environmental requirements?	Has it been collected according to GxP principles?
Is the computerised system validated?		Does it represent an outcome that is relevant for patients or is linked to the pathophysiology of the disease and can inform a regulatory decision?
		Is it sensitive to change?

Regulatory Stakeholders

CE Notified Bodies; HMA NCAs; EMA; Ethics Committees	Ethics Committees; HMA NCAs; EMA	EMA; HTA

Relevant Regulatory guidances

Medical Device Regulation Product specific EU legislation (Radio Equipment Directive EMA guideline on Computerised Systems and Electronic Data in Clinical Trials Draft RP on the use of artificial intelligence in the lifecycle of medicines	General Data Protection Regulation Clinical Trial Regulation ICH E6: Good Clinical Practice EU recommendation paper on decentralised elements in clinical trials	EMA Q&A: Qualification of digital technology-based methodologies to support approval of medicinal products ICH E9: Statistical principles for CTs Disease specific guidances for endpoints HTA guidances on endpoints

***Digital Endpoint** = precisely defined variable intended to reflect an outcome of interest that is statistically analysed to address a particular research question, that is derived from or includes a digital measurement (Definition in EMA Q&A) .*
Link to key resources from EFPIA digital endpoints sub-team.

BM= Biomarker COA = Clinical Outcome Assessment; DHT = Digital Health Technology; EC= Ethic Committees; EMA= European Medicines Agency; HTA= Health Technology Assessment Body; NCA= National Competent Authority; CT= Clinical Trial

Important to build on recent workshops, activities and experiences

Outcome and priorities identified at the DHT multistakeholder workshop in 2022

Building on the great momentum in Europe, with initiatives such as ACT-EU or the EMA Regulatory Science Research needs, and advances in IMI projects such as IDEA-FAST or Mobilise-D, EFPIA and a multistakeholder program committee organised a multistakeholder workshop on the use of **Digital Health Technologies (DHTs) in drug development in December 2022**.
Report can be found here.

Identified priority actions from Program Committee to advance the use of DHT in clinical trials

Collaborate and build the science	Build a learning ecosystem	Connected and clear regulatory / access landscape
Action 1: Clarity on Evidence standards	Action 5: A clear Patient involvement path	Action 8: Acceptance by HTA Bodies
Action 2: Unlocking Collaborations	Action 6: Learning ecosystem: how to learn from achievements	Action 9: Regulatory alignment and collaboration (EMA - FDA and others)
Action 3: Terminology alignment	Action 7: Skills development and training (e.g. Ethic Committee)	Action 10: Qualification procedures 2.0
Action 4: Develop data standards		Action 11: Regulatory landscape: Clarity in stakeholders' accountability, mandate, and who are decision makers

Opportunities to increase clarity and streamline procedures

Examples of open questions on the validation and review of digital endpoints

The DHT: regulatory identity and documentation?

- Validation need for **different/updated DHT** for data collection or analysis? bridging studies?
- How to enable a **DHT agnostic** validation of digital endpoints?
- **CSV guidance**: mostly focused on DHTs used for ePROs. Limited for sensors.
- DHT with **AI/Machine Learning** components. Important to align Regulatory guidance.
- DHT **regulatory identity** (medical device?)

The digital endpoint: meaningful, relevant and robust?

- Establishment of **patient relevance** and meaningfulness
- **Comparison to gold standard**: What if they are measuring different CoI?
- Definition of **MCID**
- Validation need in **clinical trial with active treatment**?
- Validation across **other contexts of use**: how to be pragmatic? What data can be re-used?

The Data: quality and clinical operations?

- Data quality: **adherence**, **missing data**: as indication of an event vs Missing at Random. Can we query patients directly?
- **Source data definition**, data flow and investigator oversight (see ICH E6(R3))
- **Data protection and privacy**: reviews by Ethics Committees?

Streamlined ecosystem and procedures?

Clinical Trial Application: documents for submission and training

Acceptance/qualification of endpoints: Need framework that support registrational endpoints acceptance across key HAs (work sharing? Reliance?) and adoption by HTAs when relevant

Pre-competitive collaboration frameworks for more efficient development and validation of novel endpoints

AI= Artificail Intelligence, BM= Biomarker, CoI= Concept of Interest; CT= Clinical Trial ; COA = Clinical Outcome Assessment; CSV: Computer System Validation, DHT = Digital Health Technology; EC= Ethic Committees; EMA= European Medicines Agency; HA= Health Authority; HTA= Health Technology Assessment Body; NCA= National Competent Authority;

3 pragmatic proposals to close the gap

Guidance and optimizations that can simplify this complex environment

Guidance on regulatory framework for Digital Endpoint validation

Develop regulatory principles for validation of digital endpoints in EU (topics from previous slide)

Update current regulatory positions and align them: DHT Q&A, DCT guidance, CSV guidance, ICH E6(R3)

Guidance on what is needed for Clinical Trial Applications

Documentation needed and expectations

Regulatory identity decision tree

Training of regulatory and key stakeholders

Ecosystem optimization and acceleration

Optimize ecosystem that enables **collaborations for development & validation** of digital endpoints

Optimize **regulatory pathways** for acceptance

Enable **alignment of global HAs**

Opportunity to accelerate implementation: test new approaches in pilots and regulatory sandboxes for fast learning and to keep up with this is a fast moving field

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Background

More details on the three proposed pragmatic solutions

Novel methodology /digital endpoint validation guidance

- ❑ Update computer systems/electronic data guidance to include specificities for more complex computer systems
- ❑ Update EMA Q&A on qualification of digital technology-based methodologies (align FDA/EMA terminologies) and/or develop specific guidance with digital endpoints validation requirements

CTA guidance

- ❑ CTCG/MDCG decision tree on whether the tool is considered a medical device or not based on various scenario of COU/IU in the clinical study.
- ❑ Documentation/info related to DHT and digital measure/endpoint
- ❑ Update to computer systems/electronic data guidance to include specificities for sensors

Pre-competitive collaboration frameworks for more efficient development and validation of novel endpoints

Concepts being tested in the EFPIA-EMA-DEEP QoNM pilot

- ❑ Improved framework for pre-competitive multi stakeholder co-creation of standards and novel endpoints with integrated and dynamic regulatory interactions
- ❑ Platform and catalogue to enable reuse of evidence to for example support validation of new DHT or use of a for a qualified digital measure across different contexts of use

CoU : Context of Use; MCID: Minimum Clinical Important Difference; CT= Clinical Trial; HTA= Health Technology Assessment Body; DHT = Digital Health Technology

More detailed representation of pragmatic proposals to close the gap

The DHT: regulatory identity and documentation?

CTCG/MDCG decision tree on whether the tool is considered a medical device or not based on various scenario of COU/IU in the clinical study.

Update to CSV guidance to include specificities for sensors and other more complex computer systems

Update DHT Q&A adding aspect of new/updated DHT

The Data: quality and clinical operations?

Need for CTCG guidance on CA/EC's expectations regarding CTA documentation on the DHT

Ensure alignment ICH E6(R3) annex 2 and updated DCT recommendation paper on data flow, definition of source data and investigator oversight. And have practical examples of application of proportionality for digital endpoints.

Put data standards in practice

The digital endpoint: meaningful, relevant and robust?

Develop new guidance on the validation of digital endpoints beyond the current Q&A to cover all open questions in their validation

Test in a sandbox / pilot the use of reliance / work sharing for qualification across HAs and HTAs

Test in a sandbox / pilot a qualification procedure containing life-cycle management components

Streamlined ecosystem and procedures?

Concepts being tested in the EFPIA-EMA-DEEP Measures QoNM pilot:

- Improved framework for pre-competitive multi stakeholder co-creation of standards and novel endpoints with integrated and dynamic regulatory interactions
- Digital workspaces, ecosystem and catalogue to enable reuse of evidence to for example support validation of new DHT or use of a for a qualified digital measure across different contexts of use