Digital technologies for medicines: shaping a framework for success

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Regulatory agencies can provide advice to support developers of digital technologies for medicines use, but what are the best strategies to maximize the chance of a successful regulatory interaction? Here, EMA and industry representatives comment on the experience so far.

The technological and regulatory landscape for digital technologies in medicines development and use is rapidly evolving, as they are increasingly becoming part of the conduct of clinical trials. Examples include continuous patient monitoring for clinically relevant parameters, electronic data capture of laboratory values, direct data entry by clinicians into clinical record forms and facilitated collection of patient-reported outcomes.

When it comes to using data from such sources for benefit–risk evaluation of medicines, questions often arise about the extent to which digital technologies can be considered to be in line with, more reliable than or less reliable than more established means of data capture. The rational adoption of adequately qualified digital technologies will support novel data collection methods while ensuring their regulatory validity.

The European Medicines Agency (EMA) qualification of novel methodologies is a voluntary scientific procedure to establish the regulatory acceptability for the use of a methodology for the development of medicinal products. Following the assessment of the initial submissions (see Related links), the EMA brought together industry representatives to discuss experience and obstacles encountered in validating and qualifying digital technologies. Here, we provide insights to facilitate the qualification process and discuss issues in the submission of marketing authorisation applications (MAAs) utilizing digital technology to support regulatory decision making.

Maximizing the value of regulatory interactions

Timing. Early interaction between developers and the EMA is crucial, particularly if the use of digital technologies might be relevant to the benefit–risk assessment of medicines for the MAA. Early understanding of the applicant's plans has several benefits. From the procedural standpoint, it allows identification of the most appropriate regulatory interaction channels and timings to achieve the applicant's goal. As the likely complexity of these requests will require assessment by multidisciplinary teams, experts can be identified and involved as needed throughout development, while continuity and knowledge transfer within assessment teams is supported. Furthermore, as the digital technology is likely to evolve during development, early contact maximizes the opportunity for valid and timely data acquisition by defining an appropriate data generation plan and reducing the risk that early data are considered inadequate for regulatory decision making.

Overall, it seems advisable to use an iterative process to establish a proof-of-concept test, followed by more extensive validation to allow use of the technology to support the pivotal data in an MAA. One example is the stepwise approach of the Mobilise-D consortium, a project funded by the Innovative Medicines Initiative to develop a digital mobility assessment system applicable across conditions for which measures of mobility loss can be related to disease progression. Validation is initially planned in Parkinson disease using digital mobility assessment as a disease monitoring biomarker, with the aim to extend to further mobility assessment scenarios as a surrogate, primary or key secondary end point.

Identify a clear research question. It is crucial to identify the components of the digital technologies that would fall within the EMA's remit and those that would not. This does not mean that questions cannot be asked on technology aspects when using scientific advice procedures, but they need to be presented in a way that reflects the EMA's remit and the impact on a medicine's benefit–risk balance.

The concept of interest, a detailed context of use and identification of a clinically meaningful change should form the backbone of the questions to medicines regulators. The benefit of using digital measures over existing methods should be explained, and whether the measure is an alternative to an existing method or intended to measure something intrinsically different. In parallel, documentation should be provided that demonstrates that the technical elements of the digital health technology measure the concept of interest in a reliable, accurate and repeatable manner. The principles of design control should be applied to support this. These aspects are expected to be assessed under the applicable regulatory framework

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for medical devices, and the answers together will provide a more complete picture to assist development decisions.

For example, when qualifying the use of data captured using a wearable device in clinical studies to be evaluated as part of an MAA, the aspects within the EMA's remit include how such data support the benefit–risk assessment (such as end point outcomes, reliability, accuracy, validity, compliance, clinical relevance of the data and data to be reflected in the product information). Technological parameters that are not expected to affect the benefit–risk assessment of medicinal products would be out of scope, although high-level information on the device should be provided in the background to the request. These could include technical aspects related to the performance of the wearable, how to meet the conformity assessment requirements of digital clinical decision support tools and the development of medical devices used to administer medicinal products (but not necessary, and not affecting the benefit–risk balance).

Provide appropriate documentation. The principal mode of action of the digital technology, whether used alone or in combination with a medicinal product, will determine the applicable regulatory framework (for example, either as a medicinal product or as a medical device) and how it will be reflected in the accompanying product information. In this respect, guidance on borderline and classification is being developed as part of the implementation of the new medical devices regulation. For those technologies that are likely to have an impact on the safe and effective use of the product, and are to be reflected in the product information, it is important that the submitted qualification briefing document (see Related links) clearly explains how they are going to be used, and what the potential impact on the use of the medicinal product will be.

The documentation submitted should provide insight into the reliability, repeatability, accuracy, clinical validity, generalizability and clinical applicability of the methodology to be qualified, at a level of detail that is sufficient for assessment, yet not so detailed as to invalidate the qualification when, for example, minor software updates are implemented. Given the speed of evolution of technologies, assessment will focus on how the technology (and its updates) will provide valid and clinically meaningful data, and not on technical specification requirements.

In the MAA, the applicant will be expected to provide a risk assessment of the impact on the validity of the supporting clinical data of any changes introduced to the final digital technology element during development. The risk assessment should be performed in line with the principles of ICH guidelines Q8, Q9, Q10 and Q12 (see Related links). With respect to the impact of changes and software updates, these should be considered under a risk-based approach, conceptually similar to the one taken for manufacturing changes. The impact on the essential performance characteristics, data capture and processing capability, changes in manufacturer, the context of use, and the pivotal or supportive nature of the data are all important in evaluating the degree of risk posed by a given change. Information on the data management, performance management and evaluation protocols and update procedures may be required.

The EMA actively encourages and supports advice being sought by collaborative groups such as consortia and industry trade associations, as data from different sources can be considered in a confidential space to progress an application.

Be mindful of additional requirements. For digital tools that are medical devices, and for in vitro diagnostics, the applicant is expected to ensure that the technology fulfils all other applicable legal requirements at the time of marketing (such as MDR, IVDR, GDPR and ISO). A medical device does not need to have a CE mark during the development stage; however, the applicant needs to ensure that the device has a CE mark, if applicable, by the time of marketing.

Develop a best practice, with input from users. Provide a user guide for implementation in clinical trials for optimal use by patients and/or health-care professionals, or, if not yet developed, explain the key points of the methodology to be used. State whether the measures should be taken for certain periods of time and whether in all environments (for example, at school, at home, outdoor or indoor, clinics, during weekdays and weekends), for how long, what kind of training or support is needed and whether feedback or monitoring will be used. Finally, describe how compliance will be assessed.

Outlook

In this rapidly evolving regulatory landscape, the EMA supports the development of digital tools through openness to discuss a wide range of proposals, even at an early conceptual stage, and endeavouring to widen the expert base, to provide applicants with comprehensive advice on the aspects necessary to ensure safe and effective use of medicines. The implementation of the medical devices regulation and ongoing initiatives at the European level (see Related links) will provide additional clarity on the regulatory framework in the future.

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Competing interests
T.M. is employed by F. Hoffmann-La Roche and owns shares. S.A. is employed by Novartis Pharma and owns shares. J.D. is employed by Alexion and owns shares.

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