

Report from the IMI-EMA-FDA Regulatory Science Summit – Collaborative research through public-private partnership in support to advancing regulatory science

Introduction

The Innovative Medicines Initiative (IMI) held its 6th IMI-EMA-FDA Regulatory Science Summit, organised in collaboration with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) on 3rd and 4th December 2019 in Brussels.

The meeting was attended by over 50 participants representing the regulatory agencies (EMA, FDA, EU national competent authorities, Health Canada), health technology assessment bodies, notified bodies, industry [the European Federation of Pharmaceutical Industry and Association (EFPIA), Vaccines Europe, the European trade association representing the medical imaging, radiotherapy, health ICT and electromedical industries (COCIR)], the European Commission (Directorates General for Research and Innovation, for Health and Food Safety, for Internal Market, Industry, Entrepreneurship and SMEs and for Communications Networks, Content and Technology), the IMI2 Scientific Committee and IMI Programme Office.

The meeting was an opportunity to gather funders, regulators and industry, all having a common interest in advancing regulatory science. More specifically the overall goal of this meeting was to:

- discuss the regulatory science challenges and opportunities that, if unblocked, would be game-changers
 - for the use of digital research and development tools in drug development and for the development of digital health products
 - for the development of advanced therapy medicinal products (ATMPs)
- ensure that the proposed IMI research topics in these areas would deliver tangible results that are relevant from a regulatory perspective to maximise their transformational impact on drug development and on the delivery of innovative products to patients;
- identify scientific gaps that would ideally be worked out collectively and could be addressed in IMI2 JU as well as in a future cross-sectorial public private partnership.

Under the neutral auspices of the IMI and taking advantage of the long term commitment from both the EC and EFPIA in this partnership, the participants discussed openly the challenges and key research questions relevant to regulatory science and public health that could be addressed collaboratively and could be transformative. The boundaries of competitiveness versus non-competitiveness is evolving and such open discussions with the regulators help to define common ground and opportunities for future collaborative research in a public private partnership setting in the areas of ATMPs as well as digital tools in drug development and digital health products.

The key messages resulting from the discussion are outlined below.

Advanced therapies medicinal products

The field of advanced therapies is progressing fast and there is currently a high number of gene/cell therapies products under development and tested in clinical trials. The number of clinical trials in Europe is however low compared to other geographical regions. This might be explained by the complexity of the European regulatory framework, for instance in terms of requirements related to genetically modified organisms (GMOs) that is different in every country, as well as the clinical trials authorisation.

Despite significant advances over recent years, there are still many challenges that could be addressed under IMI. To some extent some of these challenges are linked to the development of products for paediatric and rare diseases. Tackling these challenges would require data sharing, not only to learn from the failures, but also to work together to accelerate development of ATMPs for the benefit of patients. Although not discussed per se, the diversity in ATMPs adds to their complexity and should be kept in mind.

Non-clinical

- There is a need for basic research on the physiopathology of diseases, especially for the ultra-rare diseases.
- Many activities are needed to optimise the translation to first in man clinical trials and to agree on a comprehensive non-clinical data package. In this respect:
 - IMI could help to close the knowledge gap by learning more about failures and by exploring the predictive value of modelling and simulation to extrapolate data (e.g modelling, in vitro system, organ on chips). These tools, if validated, could be used to optimise the animal studies and ultimately reduce, refine and replace them especially in areas where no animal models exist.
 - In terms of animal models, an area of research would be to look at their translational value to public health. IMI could help in defining the situations or the types of gene therapies where juvenile animal studies would not be needed. This could support regulatory convergence on the requirements for such toxicity studies. This is particularly important considering that many ATMPs as potential cure should probably be administered much earlier in children than currently feasible.
- Even if a new ICH Guideline on non-clinical biodistribution studies for gene therapy products (S12) will be released soon, the biodistribution is still an area that could be addressed by IMI. There are remaining knowledge gaps, for instance, to address the need to repeat the biodistribution studies with different vector subtypes (adeno-associated virus serotype 9 (AAV9) as an example).

Clinical

New strategic thinking is needed to optimise the clinical development of ATMPs around the following questions:

- When is the right time to treat?

To define the optimal timing to start treatment, it is important to have disease-based registries or real world data to understand the natural course of the diseases, especially for rare diseases. For this approach, one should consider if it is optimal to go disease by disease, and if there can be other sources of data such as health records. Through IMI effort, there could be an agreement on the useful assessments that could be captured and that could be applicable to different diseases.

Collaboration would need to be explored with the Rare Disease Cures Accelerator Data and Analytics Platform (<https://c-path.org/programs/rdca-dap/>).

- Do we have the right biomarkers?

Biomarkers may be different from those used for more conventional treatment so we may need to develop new biomarkers. However, it is unclear how much evidence would be needed to qualify those biomarkers considering the specific nature of these compounds.

It could be important to look at the regulatory framework that exist or could be developed for ultra-rare diseases, single gene mutations, or scenarios where there are small numbers of patients, or N=1. In particular collaboration and dialogue with regulators would be needed for pilots to look at how a one-patient-trial platform would meet safety, efficacy, and product quality requirements for a highly individualised gene therapy that would treat a different genetic mutation(s) in each patient (e.g., ultra-rare genetic disorder).

- Long-term effects and safety

It is essential to find a better way to capture the long-term safety, including immunogenicity and efficacy (durability of responses) either through real world data, patient registries (rather than product registries) keeping in mind that regulators/HTA bodies may need to use them differently. It is important to capture fit for purpose high quality data.

Manufacturing

Manufacturing of ATMPs is complex, therefore strategic thinking from both the industry and the regulators is needed to ensure the quality of ATMPs products.

- Leveraging prior knowledge for future ATMPs development

ATMP development processes are complex, and leveraging prior knowledge and experience from successful products to future development will bring efficiency. An approach could be to group by product class or by diseases, and apply lessons learned in product development from previous experiences. If this can be led through the IMI structure, the end result may reduce the turnaround time and increase efficiency in the ATMP development. Regulatory convergence will be needed for grouping strategy and regulators should be involved at the get-go. This would require a more in-depth discussion.

- Quality issues/comparability

The product quality which includes quality and stability of raw/starting materials, manufacturing, and quality control testing, is an important issue with ATMPs. An understanding of the critical factors that determine quality during manufacturing and testing is needed. Since manufacturing is global, there should be regulatory convergence on the key aspects that determine product quality and comparability during scale-up steps of manufacturing. During product development, the pace of manufacturing and scale-up should be in line with the clinical development.

A suggestion was made to have a precompetitive technology platform that could be utilised seamlessly for different types of products by academic groups and industry. This would address the broader issue of moving from initial trials (phase I/II) conducted by academic groups using a product manufactured with one process, to a large trial by companies using another manufacturing process including scale-up and scale-out. Having methodology available and standardised would help reduce the need for comparability data, which could be an incentive to industry.

Another challenge that IMI could address that would bring rapidly tangible concrete results is the availability of appropriate assays. For instance for many ATMPs, reliable functional assays that could represent product potency are lacking. In addition, developing rapid and sensitive testing methods using a small amount of sample for cell-based products would facilitate product development efforts in this field.

Education is also an important factor and a curriculum that would support academic research organisations, focusing on ATMPs covering clinical aspects but also manufacturing/quality issues and regulatory aspects would be of value.

Potential synergies and complementarity should be explored to US FDA initiatives in collaboration with groups such as National Institute for Innovation in Manufacturing Biopharmaceuticals (<https://niimbl.force.com/s/>) and Advanced Regenerative Manufacturing Institute (ARMI) (<https://www.armiusa.org/>).

- Supply chain

There are not enough manufacturing sites available for ATMPs. It is important therefore to keep in mind the need to maintain the pipeline and the supply chain for ATMPs. This effort may also include supplies of high-quality critical raw materials such as reagents, excipients, containers, and disposables used in manufacturing and distribution of ATMPs.

Digital tools to optimise clinical data collection, processing and use, including digital diagnostics and endpoints

IMI has already initiated a number of projects in the digital space. However, in order to be transformational and optimise patients' access to innovation, it is important to capitalise on the tools developed, maximise and de-risk their utilisation in drug development as well as to identify potential remaining knowledge gaps that need to be addressed going forward.

- Digital technologies cover a broad range of tools and the pace of development is proceeding at a rapid pace. The regulatory framework is also changing in Europe with the implementation of the two new regulations on medical devices and in vitro diagnostic medical devices in 2020¹. However not all digital tools are medical devices, and there is an important distinction between tools for research purpose and devices for commercial use. It is critical to clearly understand the intended use of the medical device claimed by the manufacturer (that would qualify the device as medical device).
- When looking at digital tools, the different concepts related to the conduct of trials versus the assessment through endpoints should be separated. Some terms like "real world" are used differently and therefore having a glossary would facilitate the discussion among the different stakeholders. Some examples discussed included:
 - Complex trials design: there are some practical questions linked to umbrella trial such as whether it is one study under which there are several trials (i.e one EudraCT² number? One clinical trial application?). These are the points that the new IMI project EU-Pearl could look at.
 - There are also scientific questions such as how to combine the data in umbrella trials and ensure reliability and acceptability for marketing authorisation processes (statistical considerations, data quality standards, fit for regulatory purpose). There is a need for a platform to enable continuous regulatory dialogue on complex trial design especially at the time of submission of the clinical trial application in the different Members States.
 - Use of digital technologies to support communication between investigators and patients: looking at decentralised trials, there are some questions such as the role of the investigators; how to ensure that the interactions between investigators and patients are of high quality and consistent. These issues could be explored in the new IMI project Trials@home.

¹ [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

[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

² European clinical trials database

- Use of medical care data in a clinical trial:
there are many questions about methods used to capture useful data from electronic health records (EHRs) and how this potential form of real world data might be used to inform drug development.

All these aspects would be very important to look at in a short term from a good clinical practice standpoint and it would be useful if IMI could pilot some projects to investigate their potential use.

- Since IMI has already a number of projects it would be important to have a mapping of all the relevant projects (finished or ongoing) and assess their deliverables and tools that support innovative trials. This could feed interaction with the regulators, in particular Head of Medicines Agencies' Innovation Task Force and Clinical Trial Facilitation Group to articulate the research regulatory questions and potentially identify challenges that could be addressed by IMI.
- The proposal from EFPIA on complex design clinical trials to address particular questions and create a digital platform for paediatric and rare diseases was very much supported as a use case. This would support discussion with regulators although ideally it should be indication agnostic rather than disease specific. As there are already many initiatives in the rare diseases space, connecting with notably the International Rare Diseases Research Consortium ([IRDiRC](#)) would be important.

Digital diagnostics and endpoints

- It is important to clarify how digital technologies impact the way clinical trials are conducted (e.g. in terms of outcomes, setting, quality of evidence generated), and how to build on this transformative opportunity without being driven by the technology itself. In terms of outcomes, this means making a clear distinction between new outcomes and standard outcomes measured with digital technologies. It is important to separate the technological aspects from the clinical aspects i.e. what we want to measure that is clinically meaningful for the patient. In this context there is clearly a need for raising the awareness and training of the developers on the new medical devices regulations in Europe.
- The level of evidence will depend of the context of use (fit for purpose).
- Initial exploration of new digital assessment tools should compare side-by-side in clinical trials the new digital assessments with the current clinical endpoints. This can guide future development of digital tools and help improve upon or complement information from traditional clinical scales.
- There is an assumption that these digital diagnostics and endpoints will impact the clinical practice and bring public health benefit. However, to ensure healthcare system readiness for implementation of digital tools, it would be important to engage with doctors and patients to raise their awareness and gain their acceptance. In addition to the implementability aspects, the economic viability should be considered.
- This is a rapidly moving field; therefore, to ensure meaningful development of digital diagnostics and endpoints and to address the regulatory requirements, it would be important to have regulators' driving the stakeholders' engagement towards common understanding and guidance.
- Suggestions for collaborative research include: the setting up of a diagnostic development infrastructure across EU accessible to all stakeholders; the setting up of a regulatory library that could help to identify scientific and technical aspects that need to be tackled globally and be coupled with surveys and testing of acceptance and adoption by end users, healthcare professionals, carers, networks and patients.
- Sustainability and connectivity of the data and infrastructure are critical. In this context further discussion to link with the European Health Space initiative would be important. For instance it would be useful to define use cases that would look at connected data, data exchange and data processing at pan-European level to build confidence in new sources of data.

Digital therapeutics

- This is an evolving field and the challenges appear more related to the application of the new medical devices EU regulations rather than scientific. A lot of initiatives are already ongoing to help with the interpretation of the regulations and a range of guidance documents being developed by the Medical Device Coordination Group to assist stakeholders.
- The digital therapeutics are, as presented, covered by the regulations. An important consideration when developing a digital therapeutic is the intended purpose of the device (claimed by the manufacturer) which defines whether it qualifies as medical device and the level of evidence required.
- There seems to be uncertainty on the regulatory requirements and the roles and responsibilities of developers, notified bodies, etc. In view of the complexity of these innovative technologies, there is a clear need for dialogue to understand the interplay between the regulations and help with the convergence of regulatory requirements on a global level.
- Clinical evaluation of these devices is a newly opened field and standards on how to optimally obtain clinical data and regulatory acceptance are still to be developed. In particular since life cycle management differs from other devices new concepts are necessary. Real world performance could be used as an entry point.
- Communication is essential as many manufacturers are not aware that they are developing devices for health purposes. There is a clear need for raising awareness and training (decision tree) as well as bringing the different stakeholders together (e.g industry, regulators, notified bodies, patients) to change mind-sets.
- In addition to education, potential areas for collaboration include:
 - alignment of HTA requirements across Member States (e.g identify existing HTA methodological guidelines relevant for digital therapeutics, map current reimbursement policies, support development of harmonised approaches, and identify research gaps)
 - interface to raise regulatory science questions on “borderline” products and drug-device combination products
 - develop approaches to generate evidence for combined products that could eventually lead to a system approach (platform for joint learnings for notified bodies and regulators and when relevant HTA bodies).

Conclusions

There are numerous regulatory science challenges and opportunities related to new types of therapeutic interventions such as ATMPs as well as to integration of digital technologies in product development or combinations of medicines and digital products, that – when unblocked - would be game changers for all players. None of these challenges can be addressed by one party in isolation and collaboration is key.

Six recommendations emerged from the discussion:

- Continued scientific and regulatory dialogue and collaborative research mechanisms, such as IMI, are needed to create common understanding of problems, body of knowledge and proof of concepts that would inform the evolution of the regulatory practice. Some questions, such as technology integration, call for a broader multisector collaboration with a neutral broker, as foreseen for instance in the innovative health partnership concept discussed in the framework of Horizon Europe.

- The very competitive field of advanced therapies would benefit from platforms for rapid knowledge and experience sharing and optimisation of preclinical tools. Rare diseases may be a good theme to explore the right time to treat, the right biomarker and the long term effects of treatment.
- Many uncertainties related to interplay between medical devices and medicines regulations require some time to gain experience, but also setting a platform to engage continued regulatory dialogue, and rapid good practice sharing as well as to identify scientific and technical challenges that need to be addressed.
- As far as digitisation of development is concerned, IMI may be the right framework for a project that could surface uncertainties for various stakeholders (regulators, payers, industry, patients, etc.) and try and address them. Some areas, like paediatric development, may particularly benefit from such an approach.
- In addition, it would be important to have a mapping of all IMI projects developing tools, and an assessment of their deliverables and impact to support innovation in public health.
- Finally a dialogue with regulators (e.g. EMA innovation network) would be a good approach to define research questions around various types of novel trial designs and their practical implementation. The result could become a future research project in IMI or in future partnership(s) of a multisector nature.