innovative health initiative

IHI Regulatory Science Summit

27-28 February 2024

Report

COCIR Advancing Healthcare
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MedTech Europe from diagnosis to cure
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Table of contents

Introduction

The Innovative Health Initiative (IHI) held its first Regulatory Science Summit on 27 and 28 February 2024 in Brussels[1].

The hybrid meeting was attended by around 100 participants representing the following stakeholders: regulatory agencies for medicinal products and medical devices (EMA[2], FDA[3], EU national competent authorities, MHRA[4]), notified bodies, health technology assessment bodies, health industry sectors that are members of IHI [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 Association for Bioindustries (EuropaBio), and the European trade association representing the medical technology industries (MedTech Europe), the European Commission (Directorates General for Research and Innovation, for Health and Food Safety, for Communications Networks, Content and Technology), the IHI Science and Innovation Panel, and IHI Programme Office.

The meeting was an opportunity to gather IHI founding members and regulators, that share a common interest in delivering solutions that will facilitate the prevention, diagnosis, treatment and management of diseases, especially in areas where there is an unmet public health need.

More specifically, the overall goal was to:

- discuss regulatory science challenges and opportunities that, if unblocked, would be game-changers in the development of healthcare solutions;
- articulate research areas towards these opportunities that could be addressed in IHI as a cross-sectoral public-private partnership;
- discuss how to maximise regulatory impact of IHI projects, optimise regulatory engagement and the regulatory acceptance framework.

As Europe's public-private partnership, funded and governed by the European Commission and Europe's health industry associations, IHI has a key role as impartial facilitator that creates an environment for open and trustworthy discussions on the challenges and key regulatory science research questions that need collaborative effort to achieve transformative results, by leveraging the long-term commitment of IHI partners within the partnership. Considering the need to embrace the full spectrum of health innovations and the convergence of health technologies, such dialogues with regulators contributed to defining common ground, discussed what science is needed to enable regulatory assessment of tomorrow's innovations and identified opportunities for future collaborative research to drive regulatory science in IHI as a cross-sectoral public-private partnership (PPP). The discussion focused on five themes – rare diseases, paediatrics, real-world data/real-world evidence (RWD/RWE), artificial intelligence (AI), and regulatory sandboxes.

[1] More information about IHI at https://www.ihi.europa.eu/about-ihi

[2] European Medicines Agency

[3] US Food and Drug Administration

[4] Medicines and Healthcare products Regulatory Agency

Rare diseases

Rare diseases present unique challenges and opportunities in the regulatory landscape due mainly to their heterogeneity (over 7 000 rare diseases), often severe manifestations, low number of patients, limited understanding of the diseases, poor diagnosis, and general lack of treatment. While the EU Orphan legislation has stimulated the development of medicines, the revision of the rare diseases legislation, as part of the revision of the EU pharmaceutical legislation[5], aims to steer investment in areas of unmet medical needs. With respect to medical devices, there is no dedicated regulatory pathway for "orphan medical devices" (e.g. criteria, evidence needed pre-market etc.). Together with national regulators and stakeholders, the European Commission (DG SANTE) is developing specific guidance documents for orphan devices to assist the developers to meet the legal requirements. These guidance documents will provide criteria for defining "orphan devices", clarify what is meant by "sufficient level of clinical evidence at pre-market phase", propose support from expert panels and encourage notified bodies to make use of certificates with conditions.

While there are already several initiatives/projects focusing on rare diseases, including IMI/IHI projects, the discussion focused on what else should be done through cross-sectoral public-private collaboration that would be transformational.

The main points made during the discussion are summarised below:

- Many rare diseases do not have defined and globally accepted biomarkers/clinical endpoints. This is a clear gap. The process to develop and validate/qualify biomarkers and/or endpoints can be long and challenging. Therefore, a structured framework should be set up for accelerating biomarkers/endpoints development and validation. The framework should aim to accelerate the development of clinically meaningful endpoints/biomarkers that are acceptable for regulatory purposes and relevant for patients in a reliable way. When talking about endpoints it is important to also consider long term measurement. In addition, there is a need to address 'cluster' and 'personalised'/'individualised' endpoints and therefore a more holistic approach to understand the disease and disease progression should be conceived. Learnings from other fields should be considered, like oncology when it comes to platform trials. Having common biomarkers/endpoints should also be considered even if the diseases are heterogenous as it would help to evaluate biomarkers and products across certain molecular aetiologies. Data on the usefulness of biomarkers/endpoints is often generated during the clinical trials which adds to their complexity, and questions persist on how this could be reconciled with existing data in registries.

- A collaborative mechanism should be in place to stimulate all relevant stakeholders in endpoint development to share data to contribute accelerating the development and ensure global acceptability of biomarkers/endpoints. It was noted that not all surrogate biomarkers in drug development programmes utilise the existing FDA CDER Biomarker Qualification Program. The FDA has established the Rare Disease Endpoint Advancement Program (RDEA) to provide a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process. The RDEA Program encourages engagement with various types of sponsors, including small biotech companies and academia, that are developing novel biomarkers/endpoints, with an important focus on promoting innovation and sharing learnings on novel endpoint development. Comprehensive support for biomarker and endpoint development is also available from the EMA, primarily through Scientific advice procedures.

[5] https://ec.europa.eu/commission/presscorner/detail/en/qanda_23_1844
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52023PC0193

- To accelerate the development of treatments, the possibility of 'clustering' diseases should be explored, although a challenge with rare diseases is to keep up with knowledge generation in parallel with actual development (moving target). The grouping/clustering could be done in different ways, for instance based on common clinical symptoms, genetic causes, or pathophysiology, or their combination. The clustering may depend on the level of knowledge of the disease and of the drug target. A joint system to continually review evolving data and discuss further steps could be helpful for accelerating across multiple stakeholders. Flexibility would still be needed, and clustering should be applied only when relevant.

- Clustering may pose scientific challenges for trial designs such as adaptive trial and basket trial designs, e.g., in terms of answering several scientific questions such as at the level of the target, pharmacodynamics, common and specific clinical effects. In addition, while running a basket trial based on shared aetiology may be scientifically relevant, it might be difficult to reconcile with regulatory requirements for generating data for specific orphan conditions.

- With the advance of genomics, including the increasing availability of genomics data through genomic data infrastructures, diagnosing rare diseases can be done much earlier, even before symptoms may appear (e.g., the case of newborn screening). This creates new challenges yet new opportunities for improvements in disease management and/or treatment paradigms.

- There are many registries in Europe, but they often contain heterogenous data. This is a challenge when registry data cannot be used, for instance to further understand and quantitatively model the natural history of the disease or for post-marketing surveillance because of incomplete data or gaps in comparability between registries. The European research networks (ERNs) offer huge potential for data needs however they may not always be accessible, especially to companies. Agreeing on a common set of minimum data for registries would help to address heterogeneity and thereby increase the availability of good quality data for sharing. Developing rules for engagement for accessing existing data sources by commercial entities would also be warranted.

- With respect to trial designs, there are ongoing discussions at ICH6 level on adaptive trials. Other designs could also be used, like registry-based trials and trials with decentralised elements to optimise the development of medical products for rare diseases. For ultra-rare diseases, there are other challenges to consider (e.g., can 'N-of -1 trial' be justified?). The current IHI call 4 topic 3 address novel approaches to improve clinical trials for rare and ultra-rare diseases.

- Platform trials have a recognised value for rare diseases but to be effective there must be a clear mechanism to support their deployment and ensure their long-term funding in order to keep the infrastructure in place. It is also important to align ethical review criteria to avoid mismatches for clinical trial authorisation. For rare diseases, facilitating multi-national clinical trials are essential and facilitating cross-border participation in clinical trials can be helpful. There is an ongoing initiative to develop recommendations on participating in a clinical trial outside one's home country could be done in practice. In the same way, building trust between hospitals' researchers and ethics committees with the view to facilitate the harmonisation and sharing of data is important. This includes in vitro diagnostic medical devices for rare disease testing as well as for medical devices for orphan and niche indications.

- For medical devices, there are also specific challenges. While a device could address symptoms across several rare diseases, the need to provide self-standing, specific evidence for each of them could be unrealistic. This leads to off-label use and a different approach should be considered to encourage the development of medical devices specifically indicated for rare diseases or conditions. It is important to capture post-market data and novel methodological approaches should be developed to collect such data

[6] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

for post-market surveillance that are feasible to developers, acceptable to regulators and scientifically robust. Modelling/simulation approaches could also be considered.

- The ERNs offer a great opportunity for deeper integrating research and care, and for contributing to an infrastructure supporting development of novel diagnostics, medicinal products and medical devices. It is therefore important to reflect on how they can be better used. In particular, the ‘’regulatory readiness’’ of academic teams needs to be improved to ensure the translation of academic research into products/tools that meet regulatory standards. For instance, there should be a mechanism to support academic and early clinical studies in rare diseases in order to ensure that they are not just an academic exercise but deliver good quality data and provide valuable contributions to advance research and development (e.g., on biomarkers/endpoints).

- Since ultimately the focus of all endeavours is to make solutions accessible to patients, regulatory science should be linked to downstream processes i.e. health technology assessment (HTA) and reimbursement. Therefore, the HTA’s and payers’ perspectives should be considered, including in discussions related to unmet needs versus high unmet needs.

Key takeaways

The field of rare diseases is complex. Nonetheless it is the perfect area to pioneer research that can lead to radical change and ultimately the tools developed could also help to drive personalised medicine. Challenges that could be addressed through public-private collaboration and could be a good fit for IHI include:

- “endpoints factory’’: build a framework for a more systematic approach for identification, development and acceptance of biomarkers/endpoints bringing together all relevant stakeholders including companies, academic, regulators, HTA/payers and patients;

- clustering of diseases (and definitions of diseases): develop a framework that would allow different research approaches e.g., known common symptoms or genomic profiling, to be considered together and to define the subsequent implications of such clustering e.g., design of the studies;

- supporting regulatory readiness and ensuring quality and access to data, in particular regarding registries;

- considerations for cross-sectoriality for the clustering, endpoints to address pharmaceuticals, medical devices and combination products.

Paediatrics

The legal and regulatory frameworks related to paediatric medicines established in the EU and the US in the 2000's have resulted in a significant increase in the number of paediatric development programmes. Still, there are needs and gaps to be addressed. With respect to medical devices and in vitro diagnostics (IVDs), similarly to rare diseases, there is no dedicated regulatory pathway for ''paediatric medical devices", and very few are designed and intended specifically for use in children. The discussion focused on what else could be done through cross-sectoral public-private collaborative research that would accelerate the development of medicines, diagnostics, devices and other interventions specifically fit for children. To this end, the concept of an integrated paediatric research accelerator was one proposal of an approach that would enable an interconnected, data-rich, and resilient research ecosystem in order to expedite paediatric labeling and access to products.

The main points made during the discussion are summarised below:

- To expedite paediatric development and facilitate access to new treatments for children, data generation for regulatory purposes necessitates a strategic and collaborative effort.

- More robust data/evidence are needed and having a paediatric accelerator is attractive to foster development. Nonetheless, the concept would need to be further worked out e.g., who the data curators would be; how to ensure that the data from the curators would be trusted; whether this would require an inspection-type system; access to raw data would still be important for explorative work. Trust in the data is critical and this should be considered when designing such a federated approach for a paediatric accelerator. This entails mechanisms both ways not only to access the data but also to provide feedback to the data owners.

- There may be a need to prioritise the challenges the accelerator could address, e.g., to inform paediatric development, to better understand the natural history of the diseases and treatment responses and to better design clinical trials etc. When it comes to external controls, this is more complex as data would need to be Good Clinical Practices (GCP) compliant. Whatever the priorities are, it is also important not to lose sight of the HTA and payers' perspectives.

- To gather data (real world data) and biospecimens, a federated model (like the one used in IMI project EHDEN) would be favoured as this would also facilitate companies to share their data. A centralised model like the C-Path Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) could also be considered. Data federation is an evolving field and there are learnings to consider when building a new data platform.

- There are challenges linked to somewhat different standards of care in Europe and different cultural approaches to paediatrics that may affect the heterogeneity of data. This should be considered in addition to off-label use. It is also critical not to think about paediatrics from the perspective of adult medicine. Furthermore, there are theoretically a lot of datasets in hospitals, but it is unknown if they hold relevant data that could be harnessed. Since such an accelerator would be broadly used across paediatric diseases, a common data language would be needed.

- There is also an overlap between paediatrics and rare diseases that should be kept in mind.

- In the regulatory practice of EMA and FDA as well as in the proposed revision of the EU pharmaceutical legislation, the concept of the mechanism of action[7] has been introduced to drive the science of research and development of medicines for the paediatric population. *This is a paradigm change, and it would be important to work together to build a framework* looking at the paediatric pathway and *defining* how scientifically such a concept would be applied in practice.

- With respect to medical devices, there is a considerable challenge in paediatrics. Real word device data are scarce in paediatrics, and many elements may be missing to ensure that data are of sufficient quality e.g., a unique device identifier (UDI) may not be captured. There are also far fewer devices developed that are intended for use in children as compared to adults. For instance, wearables cannot be used in children if these are not CE marked for this age group and companies struggle to generate data for children especially for all relevant age groups. This is important in the context of growing children and adolescents. There is a clear need to define approaches to validate device/app uses for paediatric populations, including for research purposes, in particular when the corresponding devices/apps are developed or established for the adult population. Field usability should be tested for each device. So, an integrated approach is needed as well as further research in the science of extrapolation and *in silico* models. This would help in maximising the value of the studies in children.

- The ICH[8] guideline on paediatric extrapolation, ICH E11A, aims to ensure that the necessary data are generated. Therefore, it is also important to understand differences in response to intervention to define what is acceptable and in what context *de novo* trials would be needed.

- There are many aspects that could also be improved like formulation development that respond to children's needs and age-appropriate technologies for blood sampling. Drug utilisation data can inform on the acceptability of paediatric formulations. Developers start using advanced formulation technologies and advanced manufacturing technologies in an ad-hoc and unstructured manner so there is a need for more structured approach to enhance quality innovative paediatric medicines.

- While an integrated approach is very valuable, a one-size-fits-all approach does not work across paediatric therapeutic areas. It is important to look at gaps e.g., specific pathways for neonatology and other underserved paediatric populations. In addition, having a paediatric accelerator without a changing development paradigm may not be enough to shorten the development time of medical products.

Key takeaways

Paediatrics is an area where more public-private collaborative projects and possibly an integrated programme are needed, in order to address specific challenges and be as transformational as IMI projects such as ITCC-P4 and c4c. These include:

- sustainable framework/infrastructure to stimulate and speed up the paediatric development for medicines, diagnostics, and devices; to this end the concept for a paediatric accelerator could be very highly valuable. Scientific robustness will be key;

[7] Under the proposed revision of the EU pharmaceutical legislation, the EMA may impose a PIP based on a mechanism of action when a waiver is sought, that is, where the medicinal product is directed at a molecular target that is *"responsible for a different disease or condition in the same therapeutic area in children"* than the one for which the product is intended for in adults and that does not occur in children.

[8] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- improve the current situation with paediatric medical devices and consider how pre-competitive projects could help with paediatric devices and combination products;

- how to close research gaps that when closed will make necessary investigations much more efficient, for instance to facilitate the implementation of the mode of action mechanism concept as proposed in the revision of the EU pharmaceutical legislation and to address the specific needs in neonatology and other therapeutic areas.

Collaboration is key and a programmatic approach should be considered to advance regulatory science in paediatrics through several complementary projects.

Real-world data / real-world evidence

Real-world data/real-world evidence (RWD/RWE) play an increasing role in advancing research, promoting innovation, and guiding decision-making in the ever-evolving healthcare landscape, although for medical technologies and medicinal products the use of RWE is still evolving. There are already many initiatives/projects addressing RWD/RWE, including a large portfolio of IMI/IHI projects addressing different challenges such as standards and quality of data. Therefore, the discussion focused on what else could be done through cross-sectoral public-private collaborations that could be transformational, especially at the interface of pharmaceutical products and medical devices.

The main points made during the discussion are summarised below:

- In the medtech field, RWE is much discussed although its use is not systematic yet. Currently it is mostly used in post-market clinical evaluation. The post-market surveillance system requires quality data from reliable sources however there are no defined data quality standards yet.

- Although the use of RWE for devices is less mature than for pharmaceuticals, the existing approaches and guidance documents available for pharma can be leveraged, such as the EMA data quality framework as well as the work done by the IMI project EHDEN, which converted data sets to a common data model. This project was a core enabler for DARWIN EU and could also be used for devices data. The FDA published examples of RWE used in medical device regulatory decision-making and a guidance document is currently under revision. So far it has been shown that RWD for many devices are limited and/or insufficient quality. Although it may be difficult to set the bar high in short time for devices, certain standards for data quality as well as guidance for are needed. There are also specificities for diagnostics that should be considered.

- For medicines, the use of what is now called RWE has been established for safety. However, interest is growing to use RWE for effectiveness, and for efficacy. There are already projects looking at the use of RWD including FDA projects like 'RCT-Duplicate' (results published). For devices, there is also an interest to use RWD/RWE in the pre-market phase to accelerate the development (e.g., to evaluate the performance of the device). Therefore, there is merit in considering designing an innovative project that would develop appropriate methodology(ies) for medicines but also medical devices, link causal inference with new tools as well as build a robust framework that is trustworthy to establish the use of RWD for efficacy and effectiveness.

- Health data sharing is key but access to data is still a challenge, although it is expected that the European Health Data Space (EHDS) will enable the sharing of, access to, and use of health data. There is a need to better identify the data sources. The HMA and EMA have launched a public data sources catalogue[9] that could be built upon for devices.

- With respect to registries that offer huge potential for sources of data, there is no agreed minimum of core sets of data fields for registries at EU level, making it more difficult to harness these data and link them to other data. This is a clear gap and having such core sets would be needed that could be relevant for medicines but also devices.

- For most data sources, including registries, exposure to medical devices is not well recorded and there is no systematic identification of the device(s) used. There are also challenges to link the devices with primary care data sources to look at long term outcomes. For medical devices, the risks linked to human

[9] https://catalogues.ema.europa.eu/

factors are also important and therefore a lot of information should be captured regarding the safety aspect. In the UK, the set-up of outcome registries for devices is being considered although this is very complex. Issues around software in medical devices should also be considered (e.g., change criteria). There are therefore lots of opportunities for collaborative research around these questions. The needs of healthcare professionals should be kept in mind to ensure that whatever system is used for collecting data is as simple as possible and user-friendly.

- There is a clear need to improve the data sources and therefore the collection of data. There should be a move from product registries to patient-focused registries where devices should also be recorded (e.g., diseases or interventions registries) although currently the data may not be of sufficient quality.

- It would also be useful to make the care pathway computable in order to look at the performance of devices along this pathway and to help to draw meaningful conclusions on the patients' outcomes. There are already pilots in some fore-front hospitals.

- A topic of considerable importance and complexity, which is highly valuable to address, concerns large simple trials that typically answer only one or two questions in a broader patient population. Developing a support infrastructure and networking to integrate RWD would be crucial in order to facilitate large simple trials/pragmatic trials. To date, Europe has seen limited large-scale, impactful pragmatic trials. This would also serve to bridge the worlds of RWD and clinical trials / clinical investigations.

- There is a cluster of ongoing projects[10] in Horizon Europe focusing on harnessing RWD for regulatory decision-making and for health technology assessment bodies. It would be important to map out all ongoing activities/projects at the EU and US level in this area.

- In paediatrics, RWD has been captured in hospitals for years, but the data cannot be used easily by industry/regulators. Furthermore, data in neonates are not granular enough and lack relevant data fields. These aspects should be fixed to ensure that data collected can be appropriately used.

- HTA bodies and payers are also important decision-makers. The interface between the regulatory decision-making and the downstream decision-making could be looked at so that RWD could be used to support efficacy and for effectiveness and comparative effectiveness.

- The big challenge is data validity, quality, reliability and knowing what level of uncertainty (e.g., on causality, on effect size and duration, on effect modifiers) is acceptable. Improving data standards and ensuring that the data are fit for the different purposes, including for regulatory purposes, are key. Developing good RWE practices for devices and pharmaceuticals could be considered in the same way as Good Clinical Practices.

- Moreover, RWD has predominantly been employed to confirm different hypotheses related to prevalent outcomes with prevalent treatments. However, it is vital to consider that data accumulated over time may influence the hypothesis generated and even lead to a new hypothesis. Also, to what extent data can be trusted to better inform the effectiveness of a product. These are significant issues that necessitate collective deliberation. Trust is of paramount importance. It is also crucial to bear in mind that research questions should guide data and methodology, and HTA bodies should actively contribute to defining these research questions.

- Data access and data sharing remain challenging even if the situation is improving. It would be therefore important to explore how synthetic data could also play a role. Although this approach has already begun to be used, it is important to be able to trust the source data and the modelling. There are already modelling frameworks, but further work is needed – for instance, to understand the regulatory acceptability of such

[10] More-Europa, ONCOVALUE, Real4Reg, REALM, REDDIE and INSAFEDARE

data, to define clear metrics on what high fidelity data are and how we can combine them with other real data to strengthen the evidence.

Key takeaways

This is a complex area that has been discussed for many years and where many activities are ongoing. Nonetheless there is a need for groundbreaking projects that IHI could help with, particularly in the following areas:

- improving quality (globally agreed standards/quality criteria for data sources, core data fields for registries relevant to pharma and medtech);
- building trust and developing robust methodology(ies) to ensure acceptability of RWE and also demonstrating the value of RWE for efficacy as well as for effectiveness;
- facilitating access to data as well as analysis methods used, and leveraging the guidances and data sources (data source catalogues) across sectors;
- building on EHDEN to address additional research questions, for instance to convert health records that are digitalised to a common data model would be highly valuable to make them findable;
- running case studies in areas of common interest that are fit-for purpose.

Artificial intelligence

New artificial intelligence (AI) technologies are developing at a very high pace and will transform healthcare throughout the whole value chain. There are several aspects that need to be considered, such as data-related aspects like quality of data sets, quality and transparency of data sources, data availability, and data access; trust-related aspects, including the risk of bias; data protection, and so on. The discussion focused on what groundwork IHI could do concretely and across sectors to support and demonstrate the application of AI in health while mitigating risks.

The main points made during the discussion are summarised below:

- AI has huge potential, and it is paramount to comprehensively understand the opportunities that AI offers throughout the health product lifecycle.

- There are already many projects in AI, including IHI projects. Mapping existing projects and initiatives would be important to help identify gaps as well as potential synergies. Furthermore, the field is moving so quickly that the time factor should be kept in mind when thinking of what could be done through a research project.

- Global convergence for compliance is needed although this might not fall under the IHI remit, but rather under the ICH frame and/or International Medical Device Regulators Forum (IMDRF). Some work like developing a consensus around medical device regulations is being done under the IMDRF and could be a good forum towards a convergent approach for AI-enabled medical devices.

- So far, lessons learned in the regulatory system are limited as only a few examples of marketing authorisation applications include AI. However, IHI could potentially analyse the stages of the product lifecycle in which AI is currently being used more closely.

- The use of AI in pharmacovigilance (including data processing, signal detection and evaluation) would be a very good case for a PPP, as it is an area of considerable common interest for industry and regulators. For instance, another project like IMI PROTECT that delivered regulatory science solutions (algorithms that are being used) would be welcomed for advancing the development of pharmacovigilance methods using AI with globally relevant approaches.

- AI relies on trust in the underlying data. Confounding and bias in AI are issues to consider (e.g., representativeness of the data, bias of the machine learning (ML) engineer, tuning, bias of training and testing data, algorithmic bias, etc.). When developing AI models, one challenge is the validation of datasets. Work around these aspects could be envisaged in IHI. The potential of using and further optimising synthetic data in this context might also be a further topic to be explored under IHI.

- Besides the use for datasets, AI could also be used to help determine the best way to proceed with product development. For instance, in some paediatric developments AI has been used to optimise the selection of models and simulations for pharmacokinetics.

- AI could help with data discoverability; however, it is important to understand the context as terms can have different meanings. In healthcare we use many ontologies hence semantic engines can help making data discoverable.

- With respect to mapping of legislative frameworks, AI could also help. Firstly, some legislations use the same terms but with different meanings. Hence, a terminology/ontology mapping in the field of AI could be beneficial. Secondly, a complementary initiative could be developing AI for mapping domain-specific terminologies. Both could be an opportunity for IHI to work on this matter with the aim of supporting

advancement of AI in healthcare. They would potentially help all stakeholders, in particular SMEs. If such work was undertaken in IHI, it would be important to have in mind the need to define ownership and the availability of a stable institution to host and maintain such a mapping (referring to the not-so-successful example of a “Rosetta stone”- like efforts created between preclinical and clinical ontologies).

- Applications of AI require a high degree of completeness of datasets. This is a challenge that could be looked at collectively; how regulators could agree on standards or definitions of “completeness” of datasets, with the aim of ensuring that the use of certain datasets is reliable. Completeness is also linked to bias, and to the potential use of synthetic data. It is important to consider that large amounts of data are required to build and validate AI applications.

- Regulatory knowledge on AI is currently limited. In terms of expertise needed, there are technology areas where expertise is already broadly spread or can be scaled up, like for natural language processing. However, there are very innovative areas such as large language models, where expertise is currently limited, and only a few players are prominent the world. Engagement with academia more broadly and is crucial in this fast-developing field.

- It may be important to distinguish Generative AI (GenAI) use and the AI methods primarily used as analytical methods. While the latter may be more established, there is still room for regulatory science to investigate how AI methods could be used for analysis of clinical trials, RWE, etc. Such tools are already deployed for product development, but we miss further insights on how they function exactly.

- To support the use of AI in product development, training on AI and upskilling is a key factor. For instance, there are initiatives at the EMA (Digital Academy, AI Masterclasses, Data Science curriculum) and FDA to support training of staff. There are also initiatives/projects in Europe including an EIT Health initiative on skills partnership with the health industry.

- Clinical evidence is required to use AI for medical devices. There are currently considerable gaps in the knowledge and clinical evidence generation and learning methodology would be needed.

- Another area of interest for a regulatory science project might be on how AI (potentially GenAI) can help in preparing as well as analysing medicines/devices dossiers submitted to regulators. It could also help to generate a common learning path for industry/regulators. There is a grey zone between summarising versus reasoning to be considered.

- Explainability of AI and avoiding bias are two major issues and could potentially be tackled under IHI, also from the technical point of view.

- Success factors for any project to be impactful include the definition of a clear problem, outlining of clear research questions, as well as having the multi-disciplinary expertise and perspectives around the table working together.

Key takeaways

AI is a vast field that is complex and rapidly evolving. Challenges that could be addressed through public-private collaboration and could be a good fit for IHI include:

- common AI terminology/ontology;

- use of AI for mapping domain-specific terminology;

- use of AI in pharmacovigilance;
- use of AI for medical product development;
- use of AI for regulatory assessment processes;
- collecting evidence on how to avoid AI bias and increase explainability.

When progressing ideas for potential future IHI projects, it is important to consider agility and define clear research questions that could be addressed in a project or in several complementary projects to be impactful. Further workshops may be valuable for in-depth discussions.

Regulatory sandboxes

Regulatory sandboxes have been introduced in the proposal for revising the EU's pharmaceutical legislation. This mechanism, although still new in the healthcare and pharmaceutical sector, enables the testing of alternative regulatory approaches for innovations. Although this concept does not exist in the medical devices and *in vitro* diagnostic medical devices Regulations, there is provision in the Artificial Intelligence Act[11] which will enable the use of regulatory sandboxes also for AI-enabled medical devices. The discussion focused on what groundwork could be done through cross-sectoral public-private collaborative research to ensure the safe use of sandboxes for all parties and prepare for a successful implementation of the concept when needed.

The main points made during the discussion are summarised below.

- A shared understanding is needed. Definition of a regulatory sandbox differs between organisations and legislations; purpose, scope and framework need definitions for implementation.
- Research on candidates for sandbox approaches in the regulatory space would be valuable. A holistic view should be taken and horizon scanning activities should be conducted to fully understand the landscape and identify the most promising area to focus on.
- It would be important to define operational aspects for implementation of the sandboxes, in particular a framework for engagement of multiple stakeholders and their different views / utilities concerning potential risks, benefits, mitigations and supervision (e.g., developers, patients, regulators); an impact assessment would also be important to understand the implications on resources.
- In the UK, a regulatory sandbox on medical devices that brings together all the different actors including healthcare systems is being launched so it would be valuable to learn from it.
- In the medtech space, there is already some experience in this field even if not defined under the sandbox terminology. However, the cases have been burdensome since the companies had to generate data under a new pathway while still providing evidence using the traditional pathways for comparison. Therefore, it is important to ensure that the regulatory sandbox approach is attractive for companies.
- Regarding market access, there is also some experience with pilots. The process for using regulatory sandboxes in the context of marketing authorisation would be likely different from the one used for market access.
- It was discussed if sandboxes would be product-specific (or specific for classes of products) and therefore designed for different technologies nonetheless it was noted that an overarching framework on which different scenarios could be adapted could be useful.
- Criteria for applying regulatory sandboxes could include what would benefit most patients and/or the technologies that are the most looked at by companies.
- Enhanced communication and constant dialogue with the developers are critical during the development. Areas like gene therapies could be important for small companies as well as rare diseases, paediatrics diseases or life-threatening diseases. It may be difficult to find a space for companies to work together so

[11] https://www.europarl.europa.eu/doceo/document/TA-9-2024-0138-FNL-COR01_EN.pdf

focusing on simple challenges may be better to ensure that everyone can work together and share the learnings.

- Another point to consider is the need to have appropriate rules for engagement to encourage competitors (companies, innovative academics) to participate in the sandbox, to ensure dialogue and sharing of data while at the same time protecting innovation. This is why in parallel to a project looking at building a framework, pilots to test it would be needed.

- The framework for the sandbox should not be rigid but sufficiently agile to cover innovation coming out in the next decades (think about the unknown). However, a structured loop process should be considered to continuously integrate the learnings from experience (e.g., regulatory innovation during the recent pandemic and regulatory activities).

- During development of regulatory sandboxes it is important to engage with all relevant stakeholders, including HTA bodies and payers.

Key takeaways

There is an opportunity through IHI to prepare for such a regulatory sandbox mechanism and work on areas such as:

- design of a framework for regulatory sandboxes;
- horizon scanning to find the best areas to use the concept;
- multi-stakeholder engagement;
- creation of a safe setting that consider the importance of IP, and the need for testing for scalability.

Roundtable discussion

The round table discussion was an opportunity to gather additional thoughts on where IHI could contribute to advance regulatory science. The suggested areas where collaboration would be beneficial included:

- leveraging tools and existing infrastructures built under IMI rather than developing new ones (e.g., c4c, EHDEN, EUPATI, GetREal) and providing a mechanism to ensure their sustainability (e.g., incubator) as well as avoiding that each project reinvents the wheel;
- conducting further research into vaccine hesitancy, misinformation, impact of aging on vaccines effectiveness;
- ensuring transparency of the data sources and quality of the data as well as the analytical procedures used by researchers – a common thread across all themes discussed;
- improving methodological approaches not only for medical devices for paediatrics and rare diseases, but also for other high-risk devices;
- further strengthening the health system workforce and encouraging young professionals across the EU to be involved in research and development and familiarise themselves with regulatory science;
- promoting education and training for society;
- embedding implementation science in all research projects.

Closing remarks

The meeting offered the possibility for open and trustful discussions between the participants and provided a lot of insights on how IHI, as a cross-sectoral public-private partnership providing a unique multi-stakeholder platform could contribute to regulatory science going forward.

While previous Regulatory Science Summit events were held under the Innovative Medicines Initiative, this was the first experience of the event for IHI, which is cross-sectoral and not focussed on pharma only.

The meeting revealed a shared ambition to transform health by identifying clear research questions that will address public health needs collectively and improve patients' lives. Resources are scarce and duplication of efforts should be avoided across all stakeholders. Collaboration is key to break silos between the different sectors/regulatory bodies to ultimately bring innovation for the benefits of patients and society. In addition, maximising the regulatory impact of IHI projects and optimise regulatory engagement are crucial.

Some of the points discussed will already feed into IHI call topics under consideration, like the regulatory sandboxes topic idea, while others would need further pondering and discussions on how best to design a topic that would deliver transformational results for all stakeholders.

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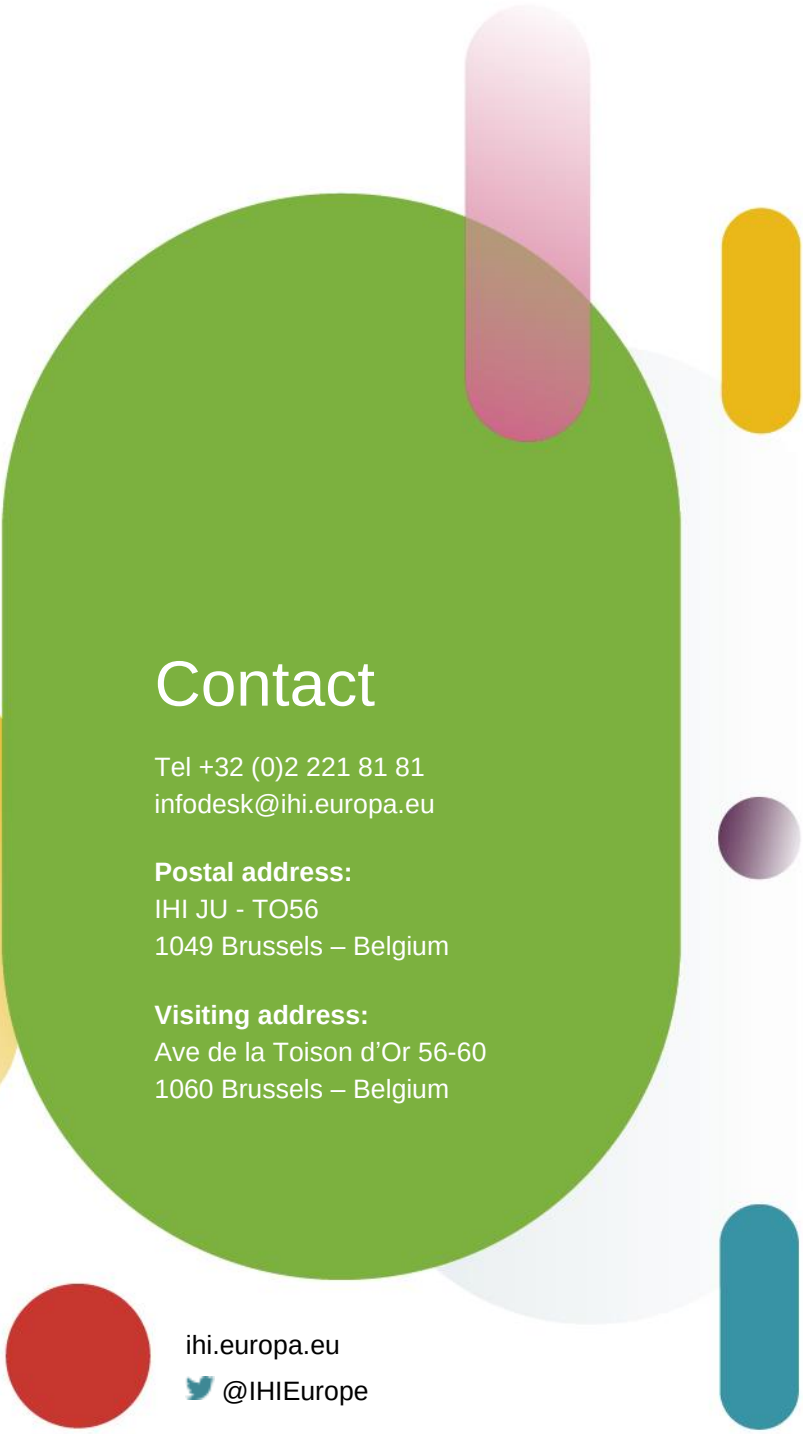

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