Leveraging the value of collaboration - from regulatory science to regulatory innovation

Innovation does not happen in isolation. Collaboration and communication are essential to ensure timely exchange of knowledge, to improve evidence generation, to speed up the drug development process and to close the translational gap from innovation to access. Here, regulatory science plays an important role by leveraging collaboration between different stakeholders and fostering the integration of science and new technology in medicine development and regulatory decision making.

Given an ever-accelerating pace of innovation, a globally aligned approach to accommodate the upcoming challenges is essential. Therefore, the Regulatory Science Network Netherlands (RSNN) organised a workshop titled “Leveraging the value of collaboration - from regulatory science to regulatory innovation”. The workshop was organised virtually on the 17th of November 2020. All relevant stakeholders (patients, academia, industry, health technology assessors, regulators and healthcare professionals) were represented at the event.

The meeting was chaired by Dr. Sabine Straus (Chair of the Pharmacovigilance Risk Assessment Committee at EMA, MEB). Following the opening of the event by Prof. Bert Leufkens (chair of the RSNN), four speakers discussed the current regulatory science ecosystem in Europe and shared their views on the role of collaboration in it. Dr. Tony Humphreys (Head of Regulatory Science and Innovation Task Force, European Medicines Agency, EMA) introduced the EMA Regulatory Science to 2025, while Dr. Marjon Pasmooij (Head of the Science Office, Medicines Evaluation Board, MEB) shared the experience of regulatory science collaboration at a national level. The network dynamics of the innovation life cycle was addressed by Dr. Jarno Hoekman (assistant professor in innovation studies, Utrecht Centre for Pharmaceutical Policy and Regulation, Utrecht University), and Dr. Paul Korte (Director Governmental and External Relations, Janssen Campus Netherlands) shared the industry perspective on the subject. The plenary session was followed by five crosstalks highlighting state-of-the-art regulatory initiatives. During this session, Dr. Liana Gross-Martirosyan (Alternate PRAC member, Medicines Evaluation Board, MEB), Dr. Falk Ehmann (Regulatory Science and Innovation Task Force, European Medicines Agency, EMA), Dr. Rick Vreman (Utrecht University & National Health Care Institute), Tobias Polak (MyTomorrows and PhD student at Erasmus University), and Dr. Delphi Coppens (Dutch Cancer Society) presented prominent case studies of collaboration with evident impact on the regulatory system. The workshop was closed by the plenary discussion and reflection.

This report provides a summary of the key discussion points and most important outcomes from the plenary, crosstalk sessions as well as the discussion session at the end of the workshop.

Regulatory science collaboration and innovation: Where are we now?

Collaboration has been and is in the centre of regulatory science for years. The Innovative Medicine Initiative (IMI), Horizon 2020, and various support tools, such as the Innovation Task Force or early Scientific Advice, are all focusing on bringing stakeholders together to exchange ideas and address the existing challenges. Dr. Tony Humphreys presented five main goals of the EMA 'Regulatory Science to 2025' These goals stress the need for innovation in medicine development and regulatory science, driven by active collaboration between stakeholders while maintaining a patient-centred approach. European Union's intention to boost innovation is also reflected in the various funding programs, the largest one being the Horizon Europe programme that aims to strengthen breakthrough science and improve its impact. At the national level, in the Netherlands, the Medicines Evaluation Board has experience in doing regulatory science for over a decade with different partners. As highlighted by Dr. Marjon Pasmooij, the number of collaborations and joint educational programmes, e.g. PhD or master projects, supported by the MEB is steadily increasing every year. This, and involvement in various national or international initiatives, e.g. IMI, Horizon 2020 projects, make MEB a valuable contributor to the development of new ideas and optimization of the current regulations.

Nevertheless, even though these national or international initiatives certainly yield prominent results, the current regulatory innovation ecosystem still lags behind. This "pacing" or "regulatory readiness" problem, as referred to by Dr. Jarno Hoekman and Dr. Paul Korte, hinders recognition and implementation of new technologies. It is understood – regulation follows science, and it can be reasonably anticipated that this time lag will always exist. But how do we make it as short as possible?

First of all, we need to improve communication and timing of communication between stakeholders. Different stakeholders, such as regulators, industry, academia, patents, funding bodies, have different perspectives regarding human medicine development and regulation. It is important to realize that even though these sometimes result in a certain degree of misunderstanding and attrition, this diversity is the key to progress and contribute to the optimal focus of the development process. Also, very often this misunderstanding comes from the fact that different stakeholders might use and understand (regulatory) language in a different way. To facilitate this dialogue, we need to address these differences in the language that we speak to each other and create a more innovation- friendly ecospace. The key goal of collaboration is to reflect on and connect these various worlds and views, to build trust between different stakeholders.

Secondly, conflict of interest issues that significantly hinders communication can and need to be overcome by full transparency about any interactions between regulators and private or public partners. A more clear and transparent communication will aid in harmonization of rules and regulations across different regulatory spheres, locally as well as globally, that is

pressingly needed. Streamline and proper coordination will facilitate and speed up the implementation of new approaches and technologies.

Further, the best way to embrace changes is to prepare for them. Therefore, we need to scan the innovation horizon and make sure that regulatory infrastructure is ready to accommodate the challenges that are to come. “Prepare for the future”- is the only way to keep up with the speed of life-science development.

All in all, continuous evolution of the regulatory framework, guidelines and tools are essential to ensure the timely support of innovative products and technologies. Regulators have the potential to play a binding role in the communication between different stakeholders and to be the key element in leveraging innovation and its integration in medicine development.

Stretching existing boundaries in regulation

As said, many innovative ideas do not fit within the existing regulatory framework. A certain extent of flexibility and acceptance is required from current regulations to accommodate innovative technologies and tools. During the meeting several examples were mentioned by the speakers, where harmonization and implementation of novel ideas and tools in decision-making is lacking. One well-known examples is the advanced therapeutic medicinal products (ATMP) regulation, addressed by Dr. Delphi Coppens. The innovative nature of these medicines makes it difficult, or even sometimes impossible, to adhere to the strict common regulations. According to Dr. Coppens, an adaptive approach to licensing for ATMPs allows market entry and flexibility for product-oriented commercial development, while regulations that in fact exempt ATMPs from marketing authorization pathways, e.g. the hospital exemption pathways, facilitate availability of ATMPs in clinical practice. More centralized knowledge dissemination and collaborative efforts between regulators, academia, and industry can optimize clinical developments, and together with enhanced transparency, facilitate appropriate use and optimization of regulatory pathways. In this way we can catalyse and speed up the availability of these innovative products for patients on national and global levels.

Tobias Polak put forward another example where the change in regulation and incentives is required – collection of real-world evidence (RWE), and more specifically utilization of the data obtained within the Compassionate Use Programs. There are clear inconsistencies on national and European levels about the collection, quality and use of these data in the decision-making process. The same we can say about biomarkers. Even though biomarkers’ predictive value is recognized, their acceptance in the decision-making process is quite poor. Dr. Falk Ehmann highlighted the value of the early multi-stakeholder dialogue for the future acceptance of novel methodologies in biomarker research and their successful utilization in various stages of the drug-development process. Also, utilization of the innovative trial designs is approaching the next level. The use of combined trials that share a placebo group or using

decentralized clinical trials, where patients are monitored at home, are already foreseen in the near future.

Overall, "We can do better!"- the call heard from all the speakers. We can do better in communicating with each other, in translating new tools to practice, in accepting new ways of evidence generation and thinking. A recent example of an impressive global collaboration between all the parties – academia, industry, regulators, clinicians, public – is the development of medicines against COVID-19. This pandemic raised awareness along with multiple questions: Can we foster regulatory readiness? Can we develop drugs faster? Can a rolling regulatory review that is currently applied for COVID-19 medicines be used for other unmet medical need drugs? Can we communicate with public more openly and in a clear language? How do we assure efficient public engagement in the drug development process? All these will surely have an impact on European regulatory ecosystem and drug development process in general. For example, it is already foreseen that novel mRNA technology that is accepted in the development of vaccines against COVID-19 would be useful for other fields, i.e. oncology.

Patient as a core element of drug development and regulatory science

Another aspect that was clearly stressed during the meeting is the central role of the patient in the whole drug development and decision-making process. Scientific innovations are driven by patients' needs, and patients are the one who should benefit from new treatments. In light of this, we need to realize that regulatory approval of new therapies or technologies does not mean their direct implementation in clinical practice. Usually, accessibility of new treatments for patients relies on their reimbursement. Therefore, as pointed out by Rick Vreman, early and tight collaboration between regulators and Health Technology Assessment (HTA) organizations is crucial to allow timely data exchange and a streamlined drug development process. We need to make sure that the evidence generated during the drug development process is adequate not only for regulatory decision making, but also for HTA assessment and, eventually, to make drug available and affordable to patients.

In general, EMA has a good patient involvement framework at all stages of the drug lifecycle. Patient representatives are regularly present during scientific discussions and their input is valued. Dr. Liane Gross-Martirosyan gave an informative example of a tool that is used by EMA to engage patients and healthcare providers in the regulatory process – i.e. by public hearing. The example of the valproate case clearly showed us that input from different stakeholders – especially healthcare professionals and patients – is needed to optimize risk communication measures by taking into account possible differences in perceiving those risks by stakeholders.

From innovation to implementation

Achieving innovation is not enough; innovations should be implemented for the society and economy to benefit. But how do we facilitate the implementation of innovation?

During the plenary discussion, Prof. Peter Mol (MEB, University Medical Center Groningen), Ivana Silva (Scientific Administrator, EMA), Dr. Larissa de Lannoy (PSC Patients Europe), Aimad Torqui (Director Global Regulatory Policy, MSD), Prof. Joop van Gerven (Central Committee on Research Involving Human Subjects) and Dr. Tony Humphreys, reflected on previous discussions and shared their views on the existing collaborative atmosphere in regulatory science. It was universally agreed that the current regulatory system needs to evolve and prepare to embrace the rapidly changing landscape of innovation – in other words, we need to work on regulatory readiness.

Working with uncertainties is a part of the barging that we probably need to accept. The development and use of many new technologies, such as artificial intelligence, ATMPs, surrogate biomarkers, are still in their infant state and we continuously discover new applications and face new challenges in these areas. Here, training and education of the new generation of scientists that are taught to work with uncertainties and are bilingual in science and policy is essential. In the end, we should stop seeing each other as separate communities – regulators, academics, clinicians –, but as a single scientific community for exchanging knowledge and expertise.

Today, we have already built a regulatory science platform that permits multi-stakeholder dialogue and collaboration. However, the utmost benefits can only be derived when we share learnings and experiences in the most transparent and open-minded way, in a language that is understood by everyone. Transparency, harmonization, and continuous education are essential to increase knowledge and improve scientific data quality. At the same time, in an endeavour to ensure proper evidence generation and regulatory preparedness, we should keep in mind that in the end the impact on regulatory decision making, public health and patient benefit is what counts. Therefore, Collaboration, Innovation, Implementation – are the three steps that will bring us forward, make EU an innovation-friendly environment and give the right value to what we do. The Regulatory Science Network Netherlands (RSNN) and its partners are prepared to deliver here. All in all, we have one shared commitment – to meet patient expectations and needs.