RAPPORT RSNN EXPERT MEETING

REGULATORY READINESS LEVELS AS A TOOL TO DRIVE REGULATORY INNOVATION

On the 29th of June 2021, the RSNN expert meeting 'Regulatory Readiness Levels as a tool to drive regulatory innovation' was organised. Eighteen experts affiliated to academia, industry, and government bodies were invited to discuss this topic. The invited experts introduced a broad spectrum of knowledge and contributed on personal title under the Chatham House Rule. This report provides a concise summary of the discussion.

1. THE 'REGULATORY READINESS'-PROBLEM

The motive for this meeting was triggered during the RSNN-EMA workshop in November 2020, when the problem was highlighted that a significant delay exists between the high pace of regulatory innovations and their implementation in the regulatory framework. Regulatory authorities have the complex task to ensure protection of public health while facilitating access to the best possible healthcare interventions in a timely and affordable manner. This necessitates an adaptive regulatory framework that is 'ready' to incorporate innovations in medicinal product development as well as the regulatory science methods to assess these products. Although national and international collaborations to date in regulatory science (such as the Innovative Medicine Initiative and Horizon 2020) yield prominent results, there is a perception that the current regulatory innovation ecosystem still follows technological innovation rather slowly. As highlighted during the RSNN-EMA 2020 workshop: "Achieving innovation is not enough; innovations should be implemented for the society and economy to benefit" (Korte, 2020). This 'regulatory readiness'-problem hinders recognition and implementation of new technologies. It is understood – regulation follows science and technology, and it can be reasonably anticipated that this time lag will always exist (Korte, 2020). But how do we make it as short as possible? To answer these and other questions, this expert meeting was organized.

Before novel medicinal products can be implemented, new regulatory science methodologies (e.g., methods, tools, pathways, and approaches) fit to evaluate these products need to be developed. These regulatory methodologies need to be based on convincing evidence while performed as a collaborative effort between the various key players involved, such as regulators, industry, academia, patients, and funding bodies. Each of these stakeholders have different perspectives regarding medicine regulation. While this sometimes result in a certain degree of misunderstanding and attrition, diversity is key to progress and contribute to the optimal focus of the development process. Therefore, various criteria are deemed important while developing regulatory science methodology, including: 1) information collection and validation, 2) stakeholder involvement and alignment, and 3) compliance with the requirements of the regulatory system to minimize potential risks. How can we enable stakeholders to achieve these criteria?

Outside the regulatory field, tools have been designed to assess the maturity of projects to guide them from the phase of explorative research up to the level of implementation into practice. In the field of technology, the Technology Readiness Levels (TRL)-system was developed by NASA during the 1970's to mature projects (aircrafts) from innovation to proven for implementation (flight qualified) (Héder, 2017). This system has received gradual diffusion to other sectors. Since 2014, the European Commission has adopted this system as a tool for innovations in project management, progress planning, and resource allocation in the Horizon 2020 program (European Commission Decision C,

2015)(see table 1). The TRL system is a stage-gated concept of maturity progression based on risk reduction through information collection and validation. The various stages of the TRL system are divided in three higher levels: 1) the research stage, 2) the development stage, and 3) the deployment-phase. Would it be possible to design a concept assessment tool that accelerates maturation of new regulatory methodology that evaluates medicinal products and their evolution into more complex fields, such as personalised medicine? If so, could we base it on the existing TRL-method?

Table 1: Technology Readiness level (RRL) based on (European Commission Decision C, 2015)

Level	Definition	Phase
1	Basic Principles Observed	RESEARCH
2	Technology concept formulated	
3	Experimental Proof of Concept	
4	Technology validated in lab	DEVELOPMENT
5	Technology Validated in relevant environment	
6	Technology demonstrated in relevant environment	
7	System prototype demonstration in operational environment	DEPLOYMENT
8	System complete and qualified	
9	System proven in operational environment	

Research questions:

- What causes the delay in implementation of novel regulatory methodology?
- What is needed to shorten the lag in implementation of regulatory methodology?

The experiences from the experts in innovation endorsement were discussed to identify commonalities and bottlenecks in the implementation process. A plethora of cases were presented, varying from remote patient monitoring, cell and gene therapy, artificial intelligence, chemistry manufacturing control, to patient-derived organoids. For each case, the perspectives, roles, incentives, and expectations were considered for each stakeholder involved. First, the important question arose: 'What is the driver of developments in regulatory methodology? The present experts all agreed that innovations in regulatory methodology are being developed in response to societal demand, more specifically unmet medical need. Within the broad range of presented cases, common actions and steps could be identified to achieve regulatory endorsement of methodology, including:

- Access to patients
- Societal demand for regulatory innovation.
- Conceptualisation.
- Explorative research.
- Technical and clinical validation.
- Defining the regulatory requirements to prove benefit under acceptable risk.
- Review by authorities against regulatory requirements

The shared experiences were characterized by a lengthy and complex procedure, marked by common bottlenecks. First, regulatory authorities have the fundamental responsibility to deal with uncertainties that are associated with implementation of novel regulatory methodology. Novel regulatory requirements for proven benefit under acceptable risk are defined by the regulator to protect the targeted population. For developers (being academia and/or industry) these requirements may not be clear or may not yet be in place for newly developed methodology. Second, the magnitude of science required to reach a level of convincing data meeting the regulatory requirements

necessitates a collective effort and goes beyond the capabilities of individual academic groups or companies. Early involvement of industry and regulators as partners is fundamental to align expectations and requirements.

Increased multi-disciplinary interaction may help to overcome both challenges. Open dialogue may aid regulators to define or adjust the regulatory requirements for proven efficacy and safety, while developers will gain knowledge concerning the evidence necessary to comply to the governing requirements. Furthermore, increased transparency concerning the regulatory methodology invites for multi-disciplinary consortium building. In summary, the attending experts agree that the delay in implementation is not the result of a lack of incentive of the regulator or inadaptability of the regulatory framework. The limited amount of (early) multi-disciplinary interaction between the various stakeholders is an important cause of delayed implementation. This becomes particularly important in the domain of personalised medicine, Advanced Therapy Medicinal Products and/or medical devices, each of which undergo different methods of regulatory scrutiny.

Research questions:

- Can a concept tool to assess the 'readiness' of novel regulatory methodology help to establish (early) multi-disciplinary interaction?
- If so, could this concept be based on the existing TRL-system?
- What are the similarities and differences in the implementation process between technological and regulatory innovation?

2. THE CONCEPT OF THE 'REGULATORY READINESS LEVELS'-SYSTEM

During the expert meeting, it was proposed to draft a concept for a so-called 'Regulatory Readiness Levels (RRL)'-system to assess readiness of regulatory methodology and to facilitate multi-disciplinary interaction to accelerate implementation. It was decided that the focus of the proposed RRL-system is, not the medicinal products themselves, but the regulatory methodology evaluating the quality, benefits, and risks of medicinal products (e.g., procedures, guidelines, and methods). As mentioned before, an important cause underlying the regulatory readiness-problem is the misunderstanding between the various players involved as a result of using and understanding distinct (regulatory) languages. Open dialogue and transparency about the applicable standards for efficacy, quality and safety are a necessity to overcome delayed implementation. The proposed concept RRL-tool could potentially facilitate dialogue within the regulatory ecosystem on which steps have to be taken by which stakeholder to achieve endorsement of novel methodology. Risk aversion by means of later endorsement of regulatory methodology may not always be beneficial. The RRL-system may help to identify specific situation in which increased risk due to early adoption of methodology is justified. This could for example be the case in a disease setting where alternative treatment is missing. The RRL-system may help to engage societal stakeholders in early phases of methodology development. During this phase, the expected effects on society of early adoption of specific methodology, associated with increased uncertainty, need to be compared with late endorsement with a decreased risk.

The field of technology may contain parallels to the regulatory field. From the shared experiences we could identify that, in general, the high-level phases in the TRL system (research, development, and deployment) may also apply easily and well to achieve regulatory endorsement. Another similarity is that mainly academia plays a leading role during the initial research-phase while mainly industry

directs the deployment phase. In between both phases there is a crucial but challenging stage of collaboration between both.

Although similarities may exist, clear discrepancies in innovation maturation between the field of technology and regulation have been identified. First, it was emphasized that regulatory methodology applies to a broad range of innovations, varying from pharmaceuticals to devices. Drafting a concept describing the same readiness levels for all innovations is challenging. Second, the TRL system is a stage-gated concept based on a linear concept of technology development. During the meeting it was questioned if the assumption of a linear maturation can be translated to the field of regulatory readiness. Third, technologies will be received by the regulator mainly at the end of the TRL-scale when a high level of maturity is reached. In the situation of regulatory methodology, it would be maximally advantageous when regulators are involved at an early stage.

A pilot assessment using the RRL-system

The experts concluded that a pilot assessment of a novel regulatory methodology using the RRL-system could be performed to bring the concept of RRL-system further. Several key considerations need to be made to design and perform a successful pilot assessment. First, since societal demand plays a crucial role in driving innovations, the method should be applied in a field with clear unmet medical need. Second, risk minimization is an important limiting factor for regulatory endorsement. Therefore, a methodology where its implementation is associated with a minimal amount of uncertainty is preferred. Third, such a methodology should be formulated in a pre-competitive space. During this pilot assessment, it is important to determine the added benefit for society when adopting the methodology earlier with increased risk, in comparison with later adoption and decreased risk. Could lives have been saved in a situation of earlier adoption?

Research questions:

- Which regulatory methodology and corresponding disease domain is suited for the pilot assessment using the RRL-system?
- Which level of readiness can be identified for this specific regulatory methodology?
- Which activities need to be performed to bring this method closer to regulatory endorsement?
- What is the effect on society of early adoption associated with higher risk, in comparison with later adoption and lower risk?

CONCLUSIONS

From this meeting, we can conclude that the high-speed developments in the field of medicinal products and novel methodology are being pursued by adaptations of the regulatory framework. Key bottlenecks identified that may delay the implementation of novel regulatory methodology include:

1) The challenging task of regulators to define regulatory requirements for proven efficacy under acceptable risk for novel regulatory methodology,
2) The magnitude of the science required to reach a level of convincing data meeting the regulatory requirements necessitates a collaborative effort of academia, industry, and societal stakeholders.

The proposed RRL-system may help to overcome these hurdles by facilitating early multi-disciplinary interaction. Open dialogue may help to define the regulatory requirements and to communicate these to developers. The RRL-system invites for timely partnership establishment to collect convincing data meeting the regulatory requirements. Furthermore, this system may also help to perform risk

assessment and to identify situations where early endorsement of novel methodology with increased risk outweighs the effect of late endorsement with decreased uncertainty. The findings of this meeting will be taken on by our RSNN partners and will be included in future research agendas.

REFERENCES

European Commission Decision C. (2015). Horizon 2020 Work Programme 2014-2015. 8621.

Héder, M. (2017). From NASA to EU: the evolution of the TRL scale in Public Sector Innovation. *The Innovation Journal: The Public Sector Innovation Journal, 22*(2), 1-23.