PORTFOLIO INTERVIEW **REGULATORY INNOVATION**

The Lygature Regulatory Innovation Portfolio: improving the regulatory system through collaboration

An interview with:

Pieter Stolk, PhD

Pieter Stolk, PhD

Program Manager at Lygature

"Collaboration is a means to an end. Only by understanding the views and interests of all partners can success be achieved."

Current projects in this portfolio:

- Regulatory Science Network Netherlands (RSNN)
- Health Innovation Netherlands (HI-NL)
- Non-Biological Complex Drugs Working Group (NBCD)

Completed projects in this portfolio:

- ADAPT-SMART
- The Escher Project

In the second in a series of interviews that highlight the added value of Lygature, we shine a light on our Regulatory Innovation portfolio. Senior Program Manager Pieter Stolk shares his vision and goals for regulatory innovation partnerships and explains what the role of Lygature is in fulfilling this vision.

Can you introduce Lygature's Regulatory Innovation portfolio?

An effective and efficient regulatory system serves everybody's interests. It speeds up innovation, improves resource allocation, and helps to make new products and services available and affordable. The Regulatory Innovation portfolio is a broad portfolio and has historically evolved from work done within TI Pharma, one of Lygature's pre-merger organizations, in projects like the Escher Project. Regulatory Innovation focuses on how new health innovations are assessed and on the regulatory system as a whole.

On the methodology side, it is about the methods and techniques used to assess whether a new therapy, treatment or device is safe, effective, and of good quality. Are the methods and techniques we are currently using the right ones? Do they provide the right knowledge, and do we apply them properly?

At the system level, it is about the regulatory system as a whole. Society wants safe, functional health innovations that are of high quality, delivered as quickly as possible,

and available at the lowest possible price. At the same time, it must be ensured that there are sufficient incentives in the system to make innovation and investment in (new) medical therapies attractive.

Different stakeholders in the system have competing needs and wishes. Companies on the supply side (pharma and medical device manufacturers) want their products to come to the market as smoothly as possible and they want to be able to sell them at a good price.

On the demand side there are the patients, who want access to innovations as quickly as possible but also want them to be safe and effective. From society at large you see additional wishes: that innovations come at acceptable cost and that they are the ones needed. This requires a constant discussion about the most pressing unmet medical needs.

The regulatory system must establish a balance between these different needs and wishes. A good example is the current pandemic, which suddenly created an urgent need for certain types of innovation. It is up to the regulatory system to play a mediating role in balancing the wishes of the various parties out there.

RSNN
Regulatory Science Network Netherlands

HEALTH INNOVATION NETHERLANDS

Non-Biological Complex Drugs working group

ESCHER THE TI PHARMA PLATFORM FOR REGULATORY INNOVATION

ADAPTSMART

The current projects in the Regulatory Innovation portfolio are the Regulatory Science Network Netherlands, Health Innovation Netherlands, and the Non-Biological Complex Drugs working group.

Regulatory Science Network Netherlands (RSNN) focuses on providing a neutral platform for stakeholders from different backgrounds to discuss regulatory science. The shared ambition is to advance an efficient and effective regulatory system that supports medicines development, marketing authorization, access, and appropriate use of medicines.

Health Innovation Netherlands (HI-NL) is based on the proven fact that early dialogue between innovators and relevant stakeholders improves the value and effectiveness of health innovations. By bringing all relevant innovators and stakeholders together in one place through the HI-NL Round Table service, comprehensive well-structured guidance can be provided to accelerate the introduction of innovations that directly meet end-user needs.

Non-Biological Complex Drugs (NBCD) is a multi-stakeholder consortium promoting the development of globally harmonized, science-based approval and post-approval standards for complex drugs to ensure patient safety and benefit.

Regulatory Innovation is ultimately about the most essential and relevant questions surrounding health innovation. How does society deal with these innovations? Where do they have their place? How do you ensure that they reach the right patient at the right time?

Within Lygature, my focus is on how the regulatory framework was designed, which trade-offs are being made, and how you make those trade-offs. There is no area of medical innovation that does not ultimately involve regulation around market authorization and the tensions that come with it. That's what makes the regulatory field both important and interesting.

What is Lygature's and your role in this portfolio?

Except for NBCD, I have always been closely involved both in the completed and on-going projects in this portfolio. As a program manager, my role in these projects is to help shape Lygature's efforts. Lygature contributes knowledge from projects in all its portfolios about how health innovations can take the next step towards implementation.

Lygature has expert knowledge and experience related to interaction with regulatory authorities and health technology assessment (HTA) organizations and their corresponding processes. For example, if at some point you want to go to the European Medicines Agency (EMA) for scientific advice regarding an innovation, you need to start preparing for that a year in advance. Companies often have little experience working in research consortia, so Lygature can help them with our specific expertise in that area.

Lygature has expert knowledge and experience related to interaction with regulatory authorities and health technology assessment organizations and their corresponding processes.

I think Lygature has the ability to play a neutral role in a lot of sensitive discussions throughout the portfolio. This is strongly reflected in RSNN, which is a good example of Lygature being a neutral facilitator between companies, academia, and authorities. Moreover, Lygature has research expertise to answer specific research questions. This was demonstrated in many public-private consortia that we have managed in the past, such as the Escher projects.

What are currently the main challenges in Regulatory Innovation?

I think the main challenge today is how to deal with the multitude of innovations in different scientific domains that increasingly intermingle. Traditionally for pharmaceuticals, the involvement of the EMA and the types of question they dealt with were well defined. Now it's becoming more complex and technologies from other scientific fields are becoming relevant. Artificial Intelligence and machine learning are good examples.

Interestingly, the way of thinking in the fields of pharmaceuticals and medical devices has become similar. The medical devices field was traditionally an area where risk classification was extensively used, with the level of regulation focused on the risk associated with a medical device or product. The regulation of pharmaceuticals was very different. Within Europe, for example, you now see increasing discussion about how to make the regulation of pharmaceuticals more risk-driven, and how we can collect the necessary evidence before a product comes onto the market, depending on the level of risk. When the risks are relatively small, preliminary market admission could potentially be given sooner.

This issue was already relevant in the ADAPT SMART project, where a discussion took place about to give patients early access to an urgently needed new therapy when you can reduce the negative risks.

While the regulation of pharmaceuticals increasingly embraces the risk assessment typical of medical devices, process standardization in the medical device domain means that in some respects medical devices are now starting to resemble pharmaceuticals. For example, the concept of Health Technology Assessment (HTA), which has been established in pharma for a long time, is finding its way more and more into the world of medical devices.

There are many different cross connections here but I doubt it will become one system any time soon. You do get more and more issues around responsibility, for example, how is the EMA going to pass judgment on a very complicated AI algorithm, if they are not currently equipped for it?

What do you think will be the main themes in the Regulatory Innovation field in the coming years?

The European Commission's Pharmaceutical Strategy discusses the balance between incentives for innovation, fast access for patients, sufficient guarantees, and reasonable costs. These are important themes that Lygature can contribute to, as in the case of RSNN. I think the challenges posed by new technologies will be an important theme in the coming years.

Another hot topic will be matching incentives to unmet needs. COVID-19 has shown us the need for pandemic preparedness, but what about Antimicrobial Resistance (AMR) for example? How do we get the necessary innovations we need in that field? And finally, how do you ensure that the functioning of the system is examined properly? These are more strategic themes.

On an operational level there is also an enormous desire for cooperation in the field, which is new. Ten years ago, something like RSNN was very hard to imagine. Now the concept is increasingly emerging from the European Commission. How do we ensure that things are affordable and how do we ensure that they remain competitive? How do we ensure that we also get the products we need? Collaboration plays an important role in all of that.

How do you safeguard the interests of patients and how do you involve them?

What matters in research is that you ask patients for input on the research at an early stage. For example, ask them what the research should focus on. Furthermore, you should follow up on that and let patients know what has been done with the information they provided.

Far too often, patients are asked for their opinion but afterwards they never hear anything from the consortium again. In other situations, this is done as a kind of tokenism - i.e. a project has to have patient involvement, so it convenes a patient panel. Yet nothing actually gets done with it.

Articulating patients' demands is highly desirable but at the same time very challenging. How does a patient or patient group formulate their wishes? How do you do it right? You can start with one person, but what does that one person represent? Those questions are difficult to get properly answered.

I think patient involvement is already promoted well by Lygature in projects such as HI-NL and RADAR-AD. RADAR-AD has shown that it can indeed work very well even in challenging patient groups such as people with Alzheimer's disease or mild cognitive impairment. You are also dependent on how strong the patient associations are in certain disease areas. Alzheimer Europe is an example of a very well-organized patient organization. Stating in advance that a given patient group is too challenging is something to avoid. In the RADAR-AD project, early patient involvement worked well and valuable information was obtained by asking patients for input about which aspects of the disease were most stressful for them.

For Lygature, patient involvement is an important topic and a major challenge throughout all its portfolios. This is also true for health research in general: how do you ensure that the voice of the patient is incorporated properly and how do you make sure that those patients are actually involved and really have a proper dialogue?

What is your vision for the Regulatory Innovation Portfolio, and what role could Lygature play to contribute to that vision?

The regulatory system should become as adaptive as possible, in the sense that it should be able to mold itself to the type of innovation it is presented with. Also, more adaptive in the sense of what kind of evidence is needed and when. In short, the end goal is a system that is very flexible depending on the case and not one that can only perform one action. We should try to move towards a system that is more adaptive regarding the level of evidence needed before you can give patients access.

The patient should also have a clear role in that system. You cannot leave everything to a patient, but when you are talking for example about adaptivity in terms of an acceptable degree of risk for patients you can make much more use of patients' knowledge and experience.

The next step for Lygature towards reaching this more adaptive system is expanding its mediating role, making the connection between innovators/consortia and the regulatory system in order to consolidate and strengthen it. Within RSNN that is already happening, but it must be further consolidated. The Future Affordable and Sustainable Therapies (FAST) initiative may play a major role in that.

Lygature's visibility in the regulatory field as a knowledge and expertise center should also be strengthened. Lygature, and more specifically its Regulatory Innovation team, which includes recognized experts like Sjaak Bot and Bert Leufkens, can offer a network, a neutral platform, and knowledge about engagement from regulators, industry, and patients. Lygature's substantive knowledge about the regulatory system through research is one of its important assets. Lygature is always happy to make contact with new and existing research consortia to discuss pioneering medicine together.