

# Scientific Advisory Board

Report of the Third Meeting

Utrecht, The Netherlands, September 27, 2019



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# 1. Introduction

This document details the Scientific Advisory Board's discussions in September 2019 regarding the scientific strategy of Lygature. It comprises three parts:

1. Task and composition of the Lygature Scientific Advisory Board (SAB) and the agenda of the meeting (page 2-3)
2. Summary of the conclusions of the discussion sessions (page 4-5)
3. Detailed write-up of the discussions during the entire meeting (page 6-11)

This report is made publicly available through the Lygature website to inform all Lygature stakeholders.

## Task and composition

On Friday, September 27, 2019, the third meeting of the Scientific Advisory Board (SAB or 'the committee') was held.

The SAB is appointed by the Lygature Board of Directors. Its task is threefold:

1. On an annual basis, to advise on the coherence of Lygature's project portfolio, provide feedback, and identify opportunities for cross fertilization between projects in the various domains
2. To provide input on the development of new public-private initiatives from an international perspective, building on the strengths of the Dutch life sciences and health sector
3. On an ad hoc basis, to review project proposals that will be submitted by Lygature to various consortia funders (e.g. Bill & Melinda Gates Foundation, Japanese GHIT fund)

The members of the SAB together span all dimensions of Lygature's activity: scientific discipline (medtech, pharma), geographic scope (national, international), organizational structure (public, private), etc.

In 2019, Tomas Salmonson was welcomed as a new member of the Scientific Advisory Board. The current (September 2019) members of the SAB are:

- Daan Crommelin (Chair), Professor Emeritus of Biopharmaceutics at Utrecht University
- Rob Williams PhD, Chief Drug Development Scientist at the Centre for Drug Development, Cancer Research UK
- Matthias Gottwald PhD, Head of R&D Policy and Networking at Bayer AG Pharmaceuticals Division
- Laurent Degos MD PhD, Professor Emeritus of Hematology at University of Paris, Diderot Hospital Saint Louis, Paris, founder and first President of Haute Autorité de Santé, and past Vice President of the Pasteur Institute and Curie Institute
- Sjaak Deckers PhD, CEO of GTX Medical
- Tomas Salmonson PhD, partner at Consilium Salmonson & Hemmings, former chair of the Committee for Human Medicinal Products at the European Medicines Agency

Both Matthias Gottwald and Rob Williams were unable to attend the meeting in person. Their input for the discussions and feedback on the write-up is incorporated in this report.

## Agenda

The meeting was divided into three discussion sessions:

- 1 Overall discussion and progress since last year
- 2 Presentations on newly started or starting initiatives facilitated by Lygature
- 3 Discussion session on trends and developments

Bert Leufkens, Alexander Duyndam and Jorg Janssen from Lygature joined the entire Scientific Advisory Board meeting. Various other Lygature staff members joined the discussion sessions: Tale Sliedrecht (Biologics Factory), Wim-Jan Koot (MOMENTUM), Irene Kanter-Schlifke (Hii~Holland and afternoon discussion), Kevin Klein and Janneke Boere (afternoon discussion).

## 2. Conclusions

The three sessions resulted in the following conclusions being drawn:

### Overall discussion and progress since last year:

- The committee complimented the progress made since the last SAB meeting. Lygature's added value has become more visible and there is clearly more focus in its overall project portfolio. In addition, medtech is clearly better addressed – a recommendation made in last year's meeting.
- Lygature can be described in two words: partnership management. It is now sharp and clear what Lygature is about. At the same time, it is a great think-tank for new ideas.
- While recognizing that modesty and discreetness are essential elements in Lygature's role as a facilitator, the committee expressed the opinion that Lygature should claim a degree of credit for partnership successes. This remains an ongoing balancing act.
- A return-on-investment factor of more than 12 for the transition funding was impressive, and the Netherlands should grasp the opportunity to be part of Lygature's success. The SAB concluded that the Dutch government is missing a chance if they do not invest in Lygature or its portfolios.
- The importance of addressing four essential aspects of the data infrastructure domain were discussed: cyber safety, privacy protection, access and quality assurance. It is good to see the professional level with which these aspects are addressed by Lygature, within the Health-RI initiative and other projects.

### Newly started or starting initiatives:

#### **MOMENTUM:**

- Set up as a large multicenter study for radiotherapy guided by magnetic resonance imaging, the MOMENTUM project is very strong in terms of being able to assess the health economics. Using the same protocol at each of the seven sites is a very good approach.
- Interpretation of the data in terms of added clinical value will likely only be possible when matching control groups are available. The need for an independent enabler is clear and the SAB is pleased to see Lygature fulfilling a key role in this consortium.

#### **Biologics Factory:**

- The goal of the Biologics Factory is to enable the development of novel biologic therapeutics by Dutch academics through collaboration with three major Dutch biotech companies. Under Lygature's guidance, the consortium will focus on establishing the rules of the game.
- The committee recommended that other disease areas should be explored, and that the scalability of the initiative should be looked at.

#### **Health Innovation Infrastructure (Hii~Holland):**

- The committee complimented Hii~Holland for its unique setup, which involves all stakeholders including payers. Their participation in round tables, in which proposed health innovations are discussed, definitely adds value.
- The committee indicated that changes related to the MDR should preferably be dealt with at European level, but since this is currently lacking, it is great to see a national initiative embracing the challenge in a positive way.
- The committee concluded that the initiative is very valuable not only for innovators, but also for the investors behind it and the healthcare system in general.

## Discussion session on trends and developments:

- Finding out how patients can be supported as users of new therapeutic solutions has become an essential element of innovation. The experience so far is that questions asked by patients often drive new developments in the research projects. Additionally, the committee stressed the value of the human factor getting more attention.
- The committee stressed the importance of nurturing the inclusive dialogue mindset, and the approach taken in the area of regulatory innovation. It is clear that Lygature is uniquely positioned to facilitate these types of networks and discussions, helping to translate ideas and concepts into practical approaches. In this way, real impact is created. More case studies are needed in this field and the possibility of starting new projects in this area should be explored.
- With the EMA (market approval) now relocated to Amsterdam, the strong presence of the Netherlands in the HTA space (i.e. ZIN, EuNetHTA) and the positioning of Lygature, the Netherlands has a unique opportunity to make a difference in the two stages of assessment: market approval and HTA.

## 3. Detailed write up

### 3.1 Overall discussion and progress since last year

The meeting started with an overview of the current status of Lygature and developments in the past year. The strategy of focusing on four portfolios and providing general partnership management support to adjacent initiatives was explained.

Highlights of the past year included the Lygature Partnerships MeetUp on November 1st, 2018, which attracted 200 attendees and included parallel sessions on scientific topics and ingredients for partnership success, a keynote speech by Tomas Salmonson on regulatory challenges, and ample time for networking and discussion. Furthermore, various projects were extended during the year, including the IMI-funded ESCulab project, which builds on the success of the European Lead Factory. Last year was also a crucial year for Health-RI, with various projects and initiatives in data and biobanking consolidating into this national Health Research Infrastructure. In addition, new initiatives were started, such as GNA-NOW which aims to deliver clinical development candidates against Gram-negative bacteria, and an extension of the scope of the RADAR (Remote Assessment of Disease and Relapse) platform with Alzheimer's disease. Two other new initiatives, MOMENTUM and Hii~Holland, were also on the agenda of the SAB meeting and are further expanded on in this report.

A brief update was provided on the focus on personal development in Lygature's human resource policies. The committee applauds the approach and would like to be updated in more detail during next year's meeting.

The final meeting to close the 'TTI transition funding' period was held in June 2019 with several government representatives. A return-on-investment factor of more than 12 for the transition funding was impressive, and the Netherlands should grasp the opportunity to continue co-investing to mobilize European funding.

A concept presentation to communicate the essence of the four portfolios on which Lygature's activities focus was discussed. While some are easy to explain, such as the pipeline in the neglected disease portfolio, others need more explanation and rework to fully grasp the coherence of the portfolio as well as the added value of Lygature. While recognizing that modesty and discretion are essential elements in Lygature's role as a facilitator, the committee expressed the opinion that Lygature should claim a degree of credit for partnership successes. This remains an ongoing balancing act.

The data infrastructure portfolio is a major area of interest for Lygature. Clearly, a knowledgeable 'honest broker' and program management organization that bridges stakeholder interests is crucial in this portfolio. The importance of addressing four essential aspects of the data infrastructure domain were discussed: cyber safety, privacy protection, access and quality assurance. It is good to see the professional level with which these aspects are addressed by Lygature, within the Health-RI initiative and other projects. Data stewardship and reproducibility is still an issue and should be high on the agenda. Adherence to the defined standards is essential and learning from projects needs to be further incorporated in all projects whenever possible. A suggestion made by the committee during the discussion was stratification of projects according to their use of data.

### 3.2 New or starting initiatives

During the past year, several new initiatives started and some running projects were extended and/or expanded. New projects included the IMI-funded RADAR-AD and GNA-NOW consortia, the international multi-center MOMENTUM project, and the Dutch Health Innovation Infrastructure: Hii~Holland. In addition, three running projects were extended: the core of the European Lead Factory continues via an IMI grant for the ESCulab project; the Health-RI initiative with support from the NFU and UMCs; and a follow up partnership agreement was signed for the Non-Biological Complex Drugs (NBCD) working group.

#### 3.2.1 MOMENTUM

Wim-Jan Koot presented [MOMENTUM](#) (Multiple Outcome Evaluation of Radiotherapy Using the MR-linac), a large international study that focuses on creating one big dataset to measure the impact of the MR-linac, which allows

radiotherapy guided by magnetic resonance imaging. The complexity of this study in terms of combining two advanced technologies, the number of sites involved both in Europe and North America, the many different tumor sites for which the MR-linac will be used, and the two patient data sources (technical and clinical), makes Lygature's role in this study very valuable. Starting with a cohesive observational study is already a strong point, and the plans for various future clinical studies that utilize the IDEAL ([McCulloch et al., 2009](#)) and R-IDEAL ([Verkooien et al., 2017](#)) evaluation frameworks are ambitious and essential to demonstrate the clinical value of MR-linac technology.

The MR-linac approach also needs to be compared with both proton therapy, for which the clinical benefits still have to be proved, and Hi-FU (high intensity focused ultrasound) therapeutic solutions. For the latter, the French experience in how to deal with body elasticity should be looked at.

Various challenges were discussed, including developing a framework on how to measure value based on registry data. Using the same protocol at each of the seven sites is a strong approach. Interpretation of the data in terms of added clinical value will likely only be possible when matching control groups are available. Set up as a large multicenter study, the project is very strong in terms of being able to assess the health economics. However, the data gathering is likely to be impacted by Brexit, which means the UK should be considered as a separate region next to Europe and North America.

The need for an independent enabler is clear and the SAB is pleased to see Lygature fulfilling a key role in this consortium. The committee wonders whether MOMENTUM, or at least the efforts by the Dutch groups active in this study, could be used as a case study to show the benefits of Health-RI.

### 3.2.2 Biologics Factory

The concept of the Biologics Factory and the progress made since last year's meeting was explained by Tale Sliedrecht. The goal of the Biologics Factory is to enable the development of novel biologic therapeutics by Dutch academics through collaboration with three major Dutch biotech companies. In a truly collaborative effort, interesting fundamental projects will be developed via co-creation from bench to proof-of-principle. While the core of the consortium in its current stage is relatively small, it provides many interesting challenges for the Lygature team and an excellent opportunity to showcase the expertise and experience housed within Lygature. The consortium will need to agree on a multitude of sensitive topics such as IP ownership and access, target clearance and logistics, to name but a few. Under Lygature's guidance, the consortium will focus on establishing the rules of the game. If successful, this will allow for significant expansion of the consortium. A major launching partner in a specific disease area has already been identified and a term sheet will be generated in the coming months with the aim of launching the Biologics Factory in early 2020. The committee recommended that other disease areas should be explored, and that the scalability of the initiative should be looked at. Various suggestions on how to approach this were provided in the discussion.

### 3.2.3 Health Innovation Infrastructure

Professor Carl Moons from the University Medical Center in Utrecht introduced the Health Innovation Infrastructure, Hii~Holland. This initiative focuses on the surge in the number of medtech and eHealth innovations on the one hand, and the challenges in proving benefit for users and the healthcare system on the other. Hii~Holland aims to create bridges to avoid the two 'valleys of death' innovators can experience: from development to commercialization, as well as the next step of roll out in the healthcare system. Hii~Holland stimulates health innovations that are safe, have a proven health benefit and are cost-effective. By involving all relevant stakeholders at early stages of the innovation process, its multidisciplinary approach focuses on accelerating the uptake of impactful innovations into healthcare budgeting policies and the substitution of existing care where needed. Its ambitions are high and are reflected in the fact that the initiative positions itself as an infrastructure to serve health care innovators.

One of the triggers for setting up Hii~Holland is the upcoming Medical Device Regulation (MDR) and the lack of applicable standards. The committee indicated that changes related to the MDR should preferably be dealt with at European level, but since this is currently lacking, it is great to see a national initiative embracing the challenge in a positive way. Hii~Holland could also help to alter the perception that the MDR is purely an instrument focused on preventing innovations entering the market. The number of devices, including apps, that are currently on the market and that must adhere to the new MDR standards number several hundred thousands, which will put an enormous pressure on the system.

Next to a handful of large companies, Hii~Holland focuses on serving small and medium sized companies, accounting for around 95% of the players involved. In addition, academia-driven innovations that could form the basis for new startups are included in the Hii~Holland approach. The connect with various national programs in the Netherlands aimed at the more effective use and evaluation of healthcare complements the scope of this initiative. The committee complimented Hii~Holland for its unique setup, which involves all stakeholders including payers. Their participation in round tables, in which proposed innovations are discussed, definitely adds value. For example, this has become evident in the ADAPT-SMART project, in which the European Medicines Agency (EMA) and Lygature led a partnership to discuss medicines adaptive pathways to patients (MAPPS) for drugs.

The difference between regulatory pathways for medical devices and those for drugs was alluded to. Firstly, regulations for devices can, given their diversity, never be as prescriptive as those for drugs. Secondly, effectiveness is not included in the current CE mark approval process for devices. Coming into effect more or less at the same time as the MDR, the value that Hii~Holland adds is evaluation of the value of a solution – is it as effective/safe/cheap as is claimed. Furthermore, Hii~Holland advises on the method for testing effectiveness. The committee concluded that this makes the initiative very valuable not only for innovators, but also for the investors behind it and the healthcare system in general. The SAB recommended also to take stock of all the lessons learned (including the failures) in pharma regulation and informed landing of new innovations.

In the discussion, the difference between Europe and the United States was put forward. Companies are already moving from Europe to the US, especially in the area of Class 3 devices, due to the uncertainties and complexities the MDR entails. Hii~Holland is connected to the US initiative [Excite International](#), which includes amongst others the US Food & Drug Administration (FDA). This allows the two initiatives to learn from each other, for example, on evidence gathering. Connecting with Excite is clearly an advantage, especially given the size of the markets involved.

The suggestion was made to use a subset of devices, such as the Class 3 implants, to start a pilot on a European scale instead of a country by country effort. Pragmatism is needed here, and learnings should be taken from initiatives like EUnetHTA and ADAPT-SMART, because this is a complex topic to which the European dimension adds to the complexity. For instance, a European common effort could be made to assess the comparative effectiveness research leaving to the member state authorities the choice of reimbursement and pricing. Both the French ('forfait innovation') and Norwegian approaches to medical technology approval and reimbursement may provide inspiration or potential connects for collaboration.

### 3.3 Discussion session on trends and developments

During the afternoon session, two topics in which Lygature plays a pioneering role were presented by Lygature staff members. Irene Kanter-Schlifke introduced on-going efforts in the area of patient engagement and Lygature's ambitions for the future in this area. Kevin Klein, together with Janneke Boere, presented Lygature's work in its regulatory innovation portfolio and possible directions for the future. The session continued with a discussion based on input by the SAB members on trends and developments as seen from their perspective.

#### 3.3.1 Patient Engagement

Irene Kanter-Schlifke gave a presentation on how Lygature involves patients in various research projects and its ambition to increase future activities in this area. Overall, the board was enthusiastic to see Lygature taking an active role on the topic.

In relation to patient involvement, the naming and framing of activities is important. For example, the RADAR-AD project is positioned as engaging 'people living with Alzheimer's', recognizing that people affected by the disease are first of all human beings rather than categorizing them as 'patients'. Furthermore, it acknowledges the fact that their partners and/or other care givers are involved in the research.

Lygature focuses on enabling patients to take up roles in projects by contributing the knowledge and expertise they have gained through both their experience of a disease and the therapy choices involved in treating it. Their input provides valuable lessons for deciding the research direction in a project as well as practical solutions, for example, in drafting protocols for clinical studies. Their active involvement is pioneering, representing the next level beyond being purely regarded as a 'study object' or simply being informed about an ongoing study. It is about patients fully participating in research consortia and co-directing the research. Patient advisory councils now attend consortium meetings as full members. In the past their role had to be stressed. Today it should be viewed as perfectly normal and an integral part of all research projects, now and into the future.

The experience so far is that questions asked by patients often drive new developments in the research projects. Additionally, the committee stressed the value of the human factor getting more attention. Finding out how patients can be supported as users of new therapeutic solutions has become an essential element of innovation.

### 3.3.2 Regulatory Innovation

Kevin Klein introduced the various initiatives worked on in the regulatory innovation portfolio. A strong niche in which impact is being created is the area of non-biological complex drugs. This class of molecules, which are neither biologicals nor small molecules, lack a properly defined regulatory pathway. This clearly represents an unmet regulatory need for which a joint understanding of the issues via science-based discussion is valuable, not only to enable this class of medicines to reach patients but as a blueprint for how to regulate future advanced therapies.

A third area presented was the future of medicines adaptive pathways to patients (MAPPs). Within the completed ADAPT SMART project, the concept was discussed with all stakeholders involved. The learnings and results are publicly available via an [infographic](#) on the ADAPT SMART website. The approach, which involves all stakeholders sitting round the table, is essential for these types of topics. The ADAPT SMART set-up employed a unique and valuable approach that could, for example, be used for discussions on how to arrive at post-approval standards.

With regard to national initiatives, the Regulatory Science Network Netherlands (RSNN) is a very strong national example of having all stakeholders at the table – one that illustrates the Dutch mindset of collaboration. The input provided by the RSNN to the regulatory science agenda of the EMA earlier this year proved the value of the network. By scanning and critically evaluating the current landscape of regulatory science in the Netherlands, the RSNN sets the agenda for further discussion in the field.

In the committee's discussion, some additional regulatory topics were raised. For example, the issue of regulatory approval after a Phase 2 trial. There are no regulations yet for approval, nor for reimbursement. In addition, another question is how to assess the value of the so-called 'plateaus in survival or quality of life' – situations in which the clinical result is much better than a permanent decline of survival. Frameworks are needed to decide on the benefit-risk for the vast number of new and advanced therapies in the pipeline, while not knowing their long-term effects. More methodological research is therefore needed in regulatory science. Early assessment and conditional approval continue to be important areas, not least because of the increase in orphan drug regulation, which has become a victim of its own success. A public-private partnership on conditional coverage is needed.

The committee stressed the importance of nurturing the MAPPs and/or RSNN mindset of inclusive dialogue, and the approach taken. It is clear that Lygature is uniquely positioned to facilitate this type of network and discussions, helping to translate ideas and concepts into practical approaches. In this way, real impact is created. More case studies are needed in this field and the possibility of starting new projects in this area should be explored. With the EMA (market approval) now relocated to Amsterdam, the strong presence of the Netherlands in the HTA space (i.e. ZIN, EuNetHTA) and the positioning of Lygature, the Netherlands has a unique opportunity to make a difference in the two stages of assessment: market approval and HTA.

### 3.3.3 Trends, developments & overall conclusions

To prepare for the meeting and as input to the discussion, the members of the committee were asked to think about the three most important trends from their perspective in their own field of expertise. Many of the trends discussed, such as patient engagement, data, and more broadly, the need to involve all stakeholders, are included in specific sections of this report above. The remaining topics and some of the committee's overall conclusions are noted in this section.

Two topics not covered earlier in this report that were touched upon are artificial intelligence (AI) and the identification of biomarkers. AI is being widely discussed as having transformational potential in wide ranging aspects of healthcare and medical research, from target identification to the interrogation of clinical data sets. Pharma is investing heavily and there is a lot of tech activity. Cancer Research UK has a group currently looking at the potential utility of AI and how Cancer Research UK can get involved. Being clear about what questions you are trying to answer and what issues need to be solved is important, otherwise a lot of time and resources may be needlessly wasted. It is good to see a session on AI ('without the hot air'), aimed at connecting the regulatory network with the data experts, listed in the program of the Partnerships MeetUp 2019. The identification of biomarkers predictive of the therapeutic activity of drugs is an issue that impacts on the efficiency of trial design in drug development, and the approval/reimbursement of drugs down the line. In

oncology, the paradigm of mutations in driver pathways predicting the activity of drugs modulating growth pathways is not being translated into the immunotherapy field. Understanding what determines responsiveness in the minority of patients that respond is not well understood, and much research is focused on pathological examination of biopsies and the concept that only ‘hot’ inflamed tumors are primed to respond to checkpoint inhibitors.

A meeting like this one cannot ignore the debate on the cost of medicines, despite it being difficult. Discussions on pricing are needed at an early stage in drug development. The blockbuster model is broken, but what is replacing it looks even worse. Prices paid for startups and the valuation of biotech companies somehow have to be paid as investors demand an adequate return on investment. An ethical paragraph in contracts could provide direction or legal agreement on topics such as anti-shelving and sustainable pricing.

Wrapping up, the committee complimented the progress made since the last SAB meeting. Lygature’s added value has become more visible and there is clearly more focus in its overall project portfolio. In addition, medtech is clearly better addressed – a recommendation made in last year’s meeting.

Lygature can be described in two words: partnership management. It is now sharp and clear what Lygature is about. At the same time, it is a great think-tank for new ideas. For example, the concepts being developed in the strategic asset sharing portfolio, such as the Biologics Factory, are really unique. However, finding a suitable business model to recover the investment needed to get these ideas off the ground remains challenging.

Internationally, the MOMENTUM project is an excellent example of Lygature’s added value as an international partnership management organization. The committee suggests developing this project into a showcase study to explain Lygature’s role.

With respect to the European landscape, the fact that there has been no EU commissioner appointed for research is worrying. How the balance between research and innovation will develop remains to be seen. However, they definitely need each other, which may open up new opportunities. Lygature is uniquely positioned in Europe as an independent enabler for research and innovation to create impact. By focusing on strengths in its four portfolio areas it is clearly more strongly positioned, especially compared to commercial and general project management/administration companies.

On a national level, the SAB concluded that the Dutch government is missing a chance if they do not invest in Lygature or its portfolios. They should grasp the opportunity to be part of Lygature’s success.

