CBG MEB

MEDICINES EVALUATION BOARD

# Towards Tomorrow

**A status update on the Medicines Evaluation Board Science Policy 2020 - 2024**

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## A status update on the Medicines Evaluation Board Science Policy 2020 - 2024

Medicines Evaluation Board

# Contents

# 1 Introduction

This brochure describes the scientific activities that have occurred in the last few years concerning MEB Science Policy 2020–2024 and the regulatory science research we are currently undertaking. Our aim is to improve the assessment of medicines, their proper usage and people's trust in them.

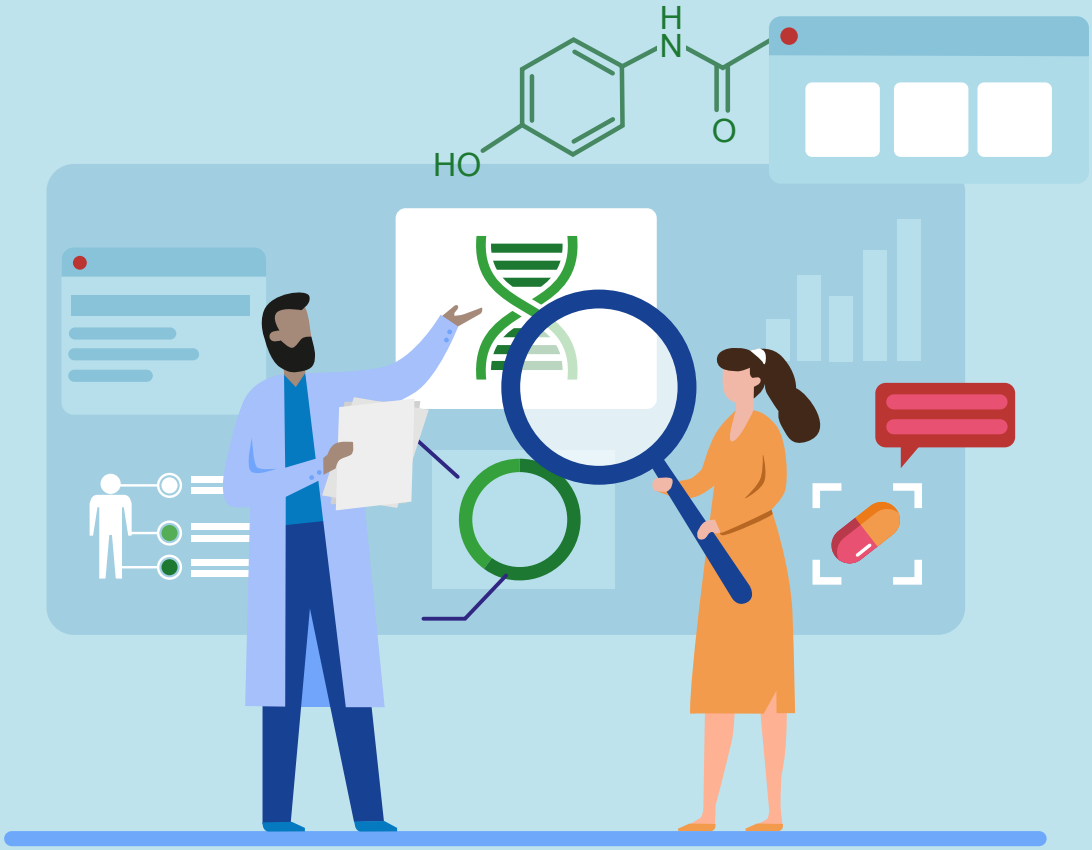
The MEB's scientific activities serve several purposes:

- To continue ensuring the availability and accessibility of medicines for patients via the latest scientific insights, innovations, tools and expertise for the high-quality assessment of medicines
- To innovate and improve our regulatory system through continuous assessment of internal regulations while influencing international guidelines and policy
- To make the organisation future-proof by anticipating and contributing to new, innovative developments
- To anchor and secure knowledge in our work by translating scientific insights and results into daily (assessment) practice
- To inspire and help (potential) employees develop, enabling them to combine research, supervision and educational activities with their primary (assessment) work
- To contribute to a robust (inter)national scientific and regulatory network by combining our expertise with the knowledge and expertise of academic groups and other knowledge institutes while strengthening our partnerships.

We adopted eight main themes within the Science Policy 2020–2024 "Regulating with the Knowledge of Tomorrow". These cross-dossier themes are linked to societal developments, such as the replacement, reduction and refinement of animal tests (3Rs), personalised medicine and the influence of big data on the assessment of medicines. Many of the themes are relevant for developing medicines for humans and animals. In this brochure, we zoom in on the progress we have made for each of these themes. Furthermore, based on developments in the last few years, we describe progress in other areas, such as male/female differences and sustainability. Lastly, we highlight two specific projects: STARS (Strengthening Training of Regulatory Science in Academia) and the European Medicines Regulatory Database.

Many scientific activities were performed in collaboration with bachelor's, master's and PhD students. This brochure includes interviews with all PhD students. If you are interested in contacting one of them, or interested to hear more about other research projects, please email science@cbg-meb.nl.

> **Regulatory science** is an applied science which, via various scientific disciplines, assesses internal regulations and policies concerning the assessment of the entire lifecycle of medicines. New insights contribute to "evidence-based regulatory practice", answering questions such as, "Are we doing things properly, do adjustments need to be made based on new knowledge, and are we prepared, based on our current knowledge and expertise, for change and innovation?" Regulatory science also aims to develop and improve instruments, standards and methods used to assess medicines concerning the efficacy, risks and quality to improve and innovate the system as a whole.




# 2 Regulatory Science at the MEB

## 2.1 The start of regulatory science at the MEB

The MEB has fostered regulatory science for over 15 years. Emeritus Professor Bert Leufkens (former chair of the MEB 2007–2017) and Dr Christine Gispen-de Wied (head of the Science Office 2011–2018) were instrumental in incorporating regulatory science in the organisational structure by starting the Science Office in 2011. This foundation of a strong network with academic partners and other stakeholders has been extended in the last years, working on Science Policy 2020–2024. We are currently collaborating with most universities in the Netherlands and the Copenhagen Centre for Regulatory Science (University of Copenhagen, CORS).

MEB representatives engage in multiple national collaborations, such as in the drafting of the Royal Netherlands Academy of Arts and Sciences (KNAW) report on “Efficiency Gains Through Innovation in Medicines Development: How Can Science Contribute?” and meetings with academic technology transfer officers to share knowledge about regulatory science requirements to stimulate interaction between the Agency and Dutch academic researchers.

Finally, the MEB is also active in international projects like the International Rare Diseases Research Consortium (IRDiRC), which expedites drug development in areas of unmet needs.

## 2.2 Regulatory Science Network Netherlands

Exemplary for multi-stakeholder collaboration is the Regulatory Science Network Netherlands (RSNN), a neutral platform for various stakeholders (i.e. industry, academia, regulators and patient representatives) to discuss regulatory science topics from various perspectives. RSNN was started in 2015 by the MEB, the TI Pharma Escher project and the Dutch Society of Pharmaceutical Medicine. Currently, Steering Committee members include the MEB, the Association of Innovative Medicines (VIG), the University Medical Centre Groningen (UMCG), Utrecht University (UU) and Lygature. Both universities have Professors of Drug Regulatory Science, Prof Peter Mol (UMCG/MEB) and Prof Marieke De Bruin (UU).

The RSNN organises annual workshops and expert meetings on important themes. For instance, in 2023, a workshop on Innovation in the Regulatory System is planned, linked to the new pharmaceutical legislation. Moreover, the RSNN has changed and developed itself further. Since 2022, the RSNN has closely collaborated with FAST (Future Affordable and Sustainable Therapies). RSNN is actively working on a prototype for a helpdesk mainly targeting academic drug developers, start-ups and small and medium-sized enterprises. Furthermore, in 2023, the RSNN will conduct a research project for FAST on pandemic preparedness focusing on four aspects: 1) advanced therapy medicinal products (ATMPs), 2) remote monitoring technologies, 3) drug repurposing and 4) pharmacovigilance.

## 2.3 Patient perspective

With the new Science Policy 2020–2024, emphasis has been given to incorporating the patient perspective in our research activities. Discussions have taken place in the meetings held between the MEB and patient organisations on optimally incorporating the patient perspective. Each research project proposal has included an assessment of relevance and feasibility from the patient's perspective. Active patient participation has been especially included in the research projects focusing on weighing benefits and risks (patient preferences), risk communication and recalls.

## 2.4 Funding

The MEB values sustainable and suitable financing for all its work; the same applies to our scientific activities. The research budget is a structural element of the MEB's annual budget, and the scientific activities are explicitly included in the organisation's annual plan. The funding level for the science activities from the MEB has not changed since 2019. However, in the last few years, we have invested more in acquiring external funding and have also succeeded in participating in IMI (Innovative Medicines Initiative) and Horizon Europe-funded projects. For example, IMI EPND develops a biomarker platform for neurodegenerative diseases, PRIME-CKD develops biomarkers in chronic kidney disease, More-EUROPA focuses on real-world data for regulatory decision-making by regulators and health technology assessors, and ONCODE-PACT aims to accelerate preclinical development in oncology. The PRIME-CKD and ONCODE-PACT have only recently been funded and initiated, so the PhD students who will work on these projects have not been included yet in this brochure.

## 2.5 Independent position

IMI projects are public-private partnerships in which academic research groups, pharmaceutical companies and other stakeholders collaborate. Through the internal MEB Science Committee, the MEB ensures that the scientific research projects in which the MEB participates are non-competitive and intended to help improve the regulatory system as a whole. In the context of these multi-stakeholder projects, the role of a regulatory authority like the MEB is important to ensure that the research project developments align with the regulatory requirements.

## 2.6 Regulatory impact of scientific output

The MEB's regulatory science research outcomes have directly and indirectly led to policy changes intended to improve regulatory efficiency and the product lifecycle. Examples include research on biosimilars and risk communication, which affected the regulatory position statement on switching biosimilars and how important safety information should be communicated to healthcare professionals (HCPs) via direct healthcare professional communication (DHPC). Likewise, research on the generic drug principle's validity has helped formulate a list now included in the *Leidraad Verantwoord Wisselen Medicijnen* ("Guideline Responsible Exchange of Medicines"), which different health-related stakeholders published in 2022. Moreover, the MEB supported research on the need for extensive reproductive and developmental toxicity testing which resulted in revising the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S5 guideline, which has led to a major change where the number of animals for developmental toxicity testing is restricted to the bare minimum.

# 3 Regulatory Science in Numbers

## 3.1 Bachelor's and master's internships

Since 2011, the number of bachelor's and master's students who intern at the MEB has grown from about 10 to 25 students annually in recent years (Figure 1). Almost all students intern for at least five months, with some internships extended up to nine months. Students are mainly from master's programmes such as pharmacy, drug innovation, biomedical sciences, and "management, policy analysis and entrepreneurship in health & life sciences".

In addition, last year, we collaborated with two groups of bachelor's students from Utrecht University in informatics, on the European Medicines Regulatory Database project. These students did not formally intern at the MEB, so they were not included in the numbers above. They helped develop the database and dashboard. Since artificial intelligence (AI) and natural language processing is taking flight, we envision that in the coming years, more bachelor's and master's students will intern at the MEB with knowledge of AI, programming and modelling capabilities.

## 3.2 PhD defences

In the last two years (2021 and 2022), there have been nine PhD defences (Figure 2), which will continue in 2023, as there were already five PhD defences in the first three months. See Appendix 2 for more details on each of these PhD projects.

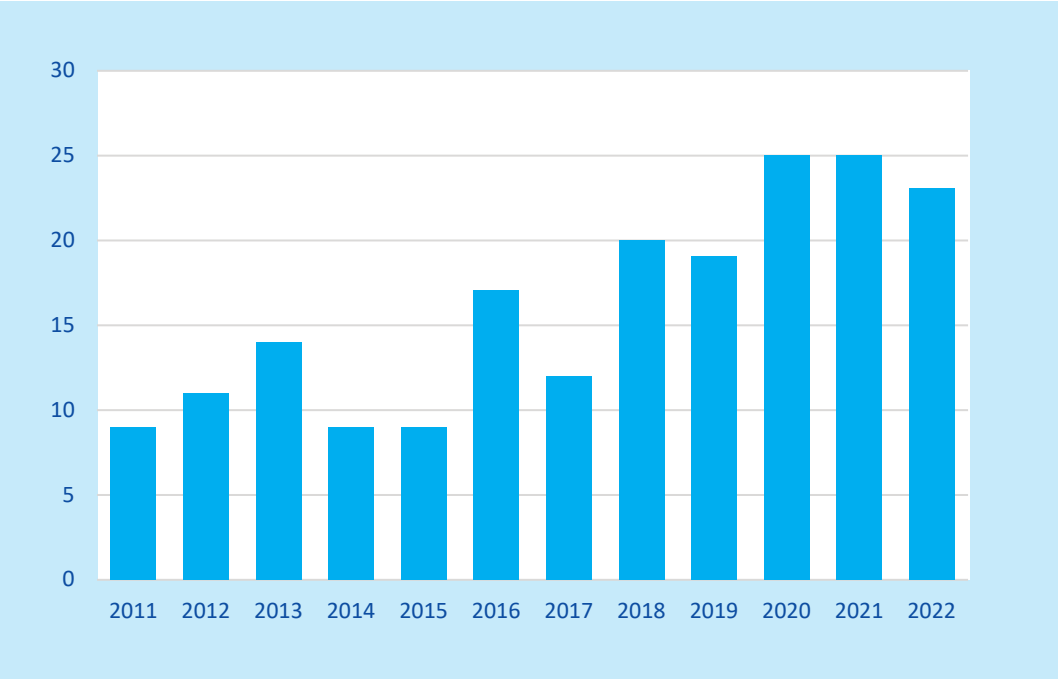



**Figure 1 Bachelor's and master's students per year**

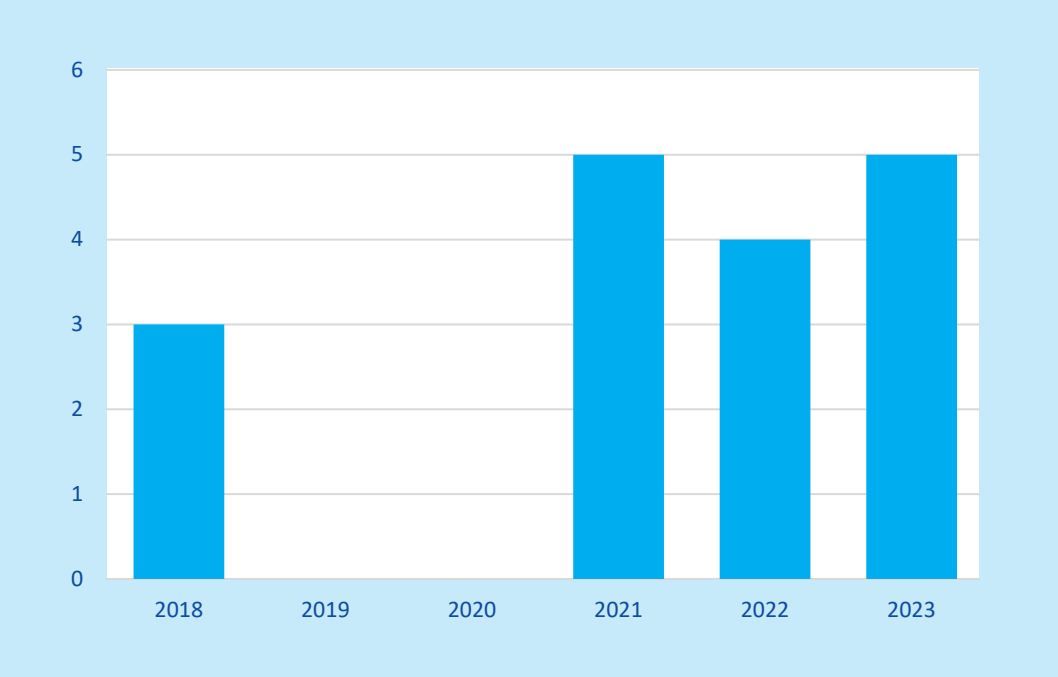



**Figure 2 PhD defences per year**

## 3.3 Scientific publications

The MEB aims to publish all our regulatory science research in international peer-reviewed scientific journals with open access, making the publications available within the regulatory network and to other stakeholders, such as patients, companies and academia, to stimulate discussions. As seen in Figure 3, the number of publications rose after establishing the Science Office in 2011, increasing to 40–60 publications per year.

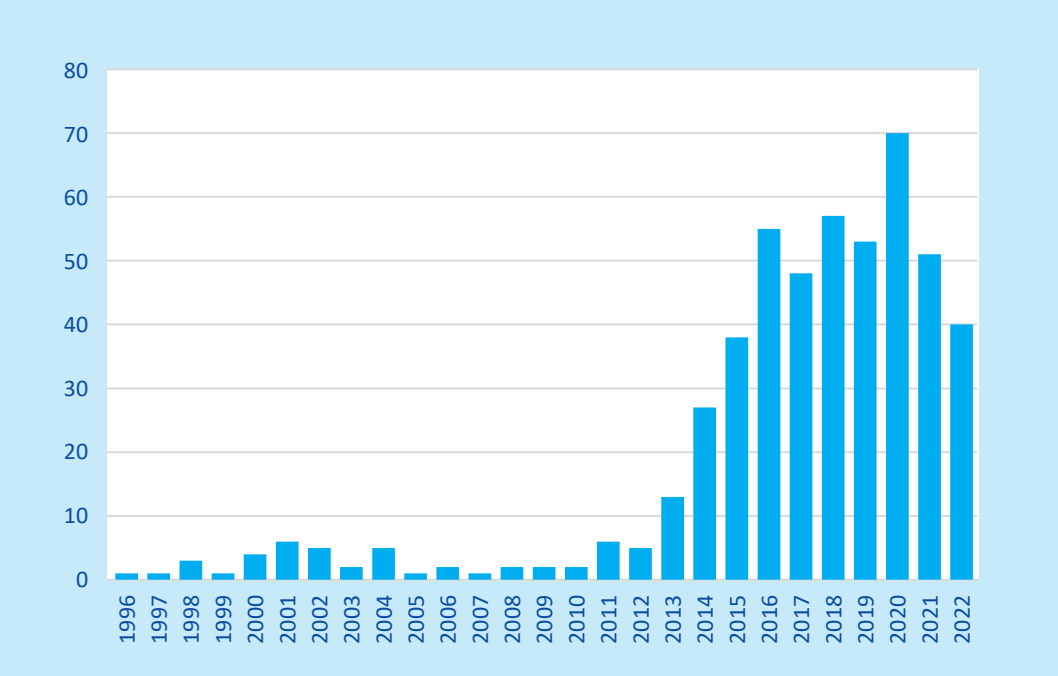
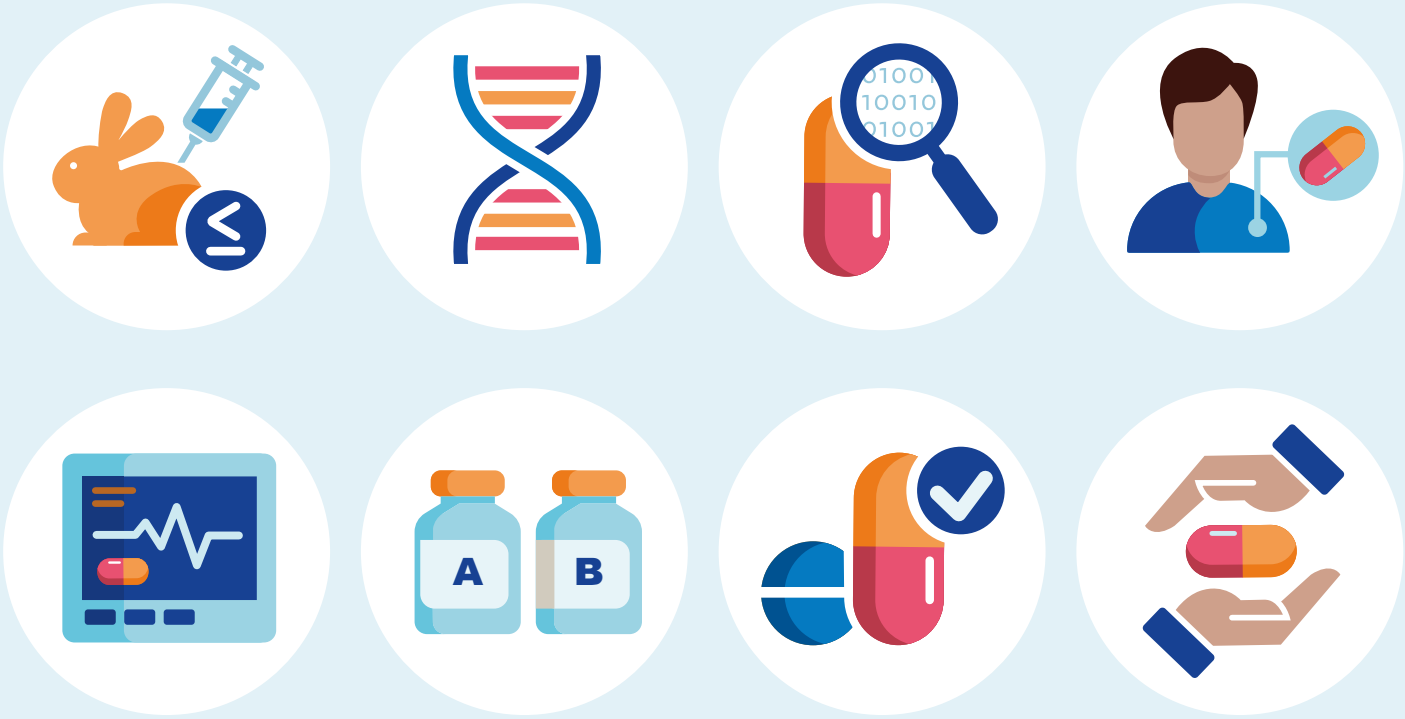



**Figure 3 Publications per year with MEB affiliation**




# 4 Themes

Science Policy 2020–2024 comprises eight main themes based on the MEB's daily work aligned with the entire lifecycle of medicines:

1. **Replacement, reduction and refinement of animal tests (3Rs)**
2. **Advanced therapy medicinal products (ATMPs)**
3. **Data-driven assessment**
4. **Personalised medicine and biomarkers**
5. **Medical devices**
6. **Generics**
7. **Medicines used better**
8. **Safety and effectiveness after authorisation**

Below is an update of activities occurring since the start of the Science Policy 2020–2024 for each theme, including the vision for subsequent years. A list of all current regulatory science projects where the MEB is involved appears in Appendix 1. Furthermore, an overview of finished PhD projects in 2020–2023 is displayed in Appendix 2.

## 4.1 Replacement, reduction and refinement of animal tests (3Rs)

Developing medicines goes hand-in-hand with animal research in the early development phase (before testing on people) and during the clinical phase. The MEB critically evaluates the added value of animal research in drug development because current evidence suggests that data from animal studies cannot always be translated to humans. Hence, we contribute to research on the applicability of alternative models of efficacy and safety in drug development, evaluating the need for animal studies in international guidelines. We are also working to identify the most efficient way of assessing the safety of new classes of medicines based on as few animal studies as possible (or with non-conventional studies). Therefore, animal testing will only be conducted if a real added value exists. We aim to create a future where alternative methods replace these tests as much as possible.

The MEB is represented in the European Medicines Agency (EMA) nonclinical working party, the EMA 3Rs working party and several ICH expert working groups. This representation allows us to disseminate the science generated at the MEB while furthering the appropriate use of animal studies in drug development while implementing sound 3Rs principles in regulation. In addition, we are using the results of the 3Rs research in the scientific advice procedure when companies or academic groups ask questions about their development plan for medicine and the use of animal studies in the process.

The MEB is involved in several projects to further the 3Rs:

- Together with the European Partnership for Alternative Approaches to Animal Testing (EPAA) and the National Centre for the Replacement Refinement and Reduction of Animals in Research (NC3Rs), we evaluated the regulatory requirements for animal testing for monoclonal antibodies (mAbs) in non-human primates (NHPs). We showed that the safety profile for monoclonal antibodies was well-defined, while novel toxicity critical for humans was infrequently identified in studies beyond six months (Chien et al., 2023). A newly developed weight-of-evidence approach can be useful in identifying products for which a six-month study may not be necessary.
- The MEB similarly evaluates the need for testing developmental toxicity with mAbs applied for a marketing authorisation application (MAA). The aim is to determine in which cases an enhanced prenatal and postnatal study could be waived in the future.
- The MEB collaborates with the Health and Environmental Sciences Institute (HESI) Developmental and Reproductive Toxicity (DART) technical committee to investigate the need for NHP studies on reproductive toxicity, specifically to investigate the fertility of small molecules and mAbs.
- In a previous collaboration with HESI-DART and the National Institute for Public Health and the Environment (RIVM), the MEB constructed a database with all available developmental toxicity studies in rats and rabbits submitted as part of an MAA. This data showed that for 80% of compounds, testing in one species adequately described the developmental risk. These data were subsequently used to support 3Rs discussions that led to far-reaching changes in ICH S5(R3).
- Currently, the MEB is updating this database by adding more than a decade of data from new MAAs, including additional endpoints for all compounds to determine the need for testing in two species.
- Together with the RIVM, the MEB has explored and evaluated opportunities to minimise the number of studies needed to evaluate the safety of ATMPs through discussions and (international) workshops with stakeholders in the field.

- However, the 3Rs are not only crucial in safety. Many drugs in development fail in the clinic despite promising efficacy results due to poor selection of animal models of efficacy. In collaboration with the MEB, Utrecht University developed a tool to identify human-relevant animal models of efficacy, allowing better estimation of the potential clinical efficacy of drugs, which has been evaluated for several models, applicable in industry labs and academia.
- Moreover, in the ONCODE-PACT, the role of organoids in drug development will be studied.
- Our involvement in multiple steering committees and advisory groups, including the ZonMW *Meer Kennis met Minder Dieren* (More Knowledge with Less Animals) scientific committee, the NXTGenhightech project and the Virtual Human Project, underlines the MEB's strong interest in 3Rs research.

> "As a next step towards animal-free drug development, more responsible use of animals for scientific purposes can be achieved"

## Selection of Animal Models for Drug Efficacy

*Désirée H. Veening-Griffioen*[1]
*Promotors: Prof Ellen H. M. Moors*[2]*, Prof Huub Schellekens*[1]
*Co-Promotors: Dr Peter J. K. van Meer*[1,3]*, Dr Wouter P. C. Boon*[3]

1. *Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*
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3. *Medicines Evaluation Board (MEB), Utrecht, The Netherlands*

*February 2018 - March 2023*

*Désirée completed her PhD thesis and successfully defended it in March 2023.*

Désirée Veening-Griffioen completed her master's degree in molecular life sciences. She is a passionate all-around scientist with expertise in in-vivo and in-vitro work in applied immunological and pharmacological research, as well as (bio)safety and security. She has substantial experience in academic, pharmaceutical and food-industry environments. "Data" inspires her the most. This PhD project, funded by the Ministry of Health, Welfare and Sport (VWS), the Ministry of Agriculture, Nature and Food Quality (LNV), and the MEB, has contributed to her inspiration.

**Your project focuses on the efficacy of animal models. Can you elaborate on that?**
“A major hurdle in drug development is the limited benefit of efficacy data in animals for use in the clinic. For each patient (sub)group or disease, many different animal models exist to provide insight into drug efficacy. However, it is often unclear how predictive the outcomes of drugs tested in these models are for the clinic and on what basis researchers select a specific model”, Désirée explains.

The main goal of this thesis is to gain insight into the selection of animal models for drug efficacy. Désirée offers, “We studied the extent of the low value of animal models for predicting efficacy. Then, we analysed the underlying causes of this low value. To this end, we studied the role of different stakeholders in the selection process, such as researchers, local and national ethics committees, and funding agencies. Finally, we presented an instrument that supports the evaluation of similarities between animal models and patients: the Framework to Identify Models of Disease (FIMD)”.

The FIMD provides a solution to assess the value of animal models for efficacy. Thus, Désirée continues, “We applied the FIMD to validate two animal models of cow’s milk allergy in young children. We demonstrated that the instrument contributes to validating animal models for drug efficacy and thus can facilitate the appropriate animal model selection. When applied, this instrument provides a scientific basis for policy recommendations and changes, which can lead to the more responsible use of animals in drug development”.

**What will this lead to?**
“As a next step towards animal-free drug development, more responsible use of animals for scientific purposes can be achieved”, Désirée states. “This can be done by selecting animal models that will be more predictive for the targeted patient group”.

“Besides that, although patient participation is not included in this project, this research will benefit patients for which new treatment options are tested and likely result in less ‘waste’ of animals used for scientific purposes”.

"Toxicological risk assessment techniques are undergoing a shift from animal-based approaches to human tissue culture-based approaches capable of providing detailed dose-response profiles"

## Nuclear Hormone Receptors in Drug Safety

*Britt Duijndam[1,2]*
*Promotor: Prof Bob van de Water[1]*
*Co-promotors: Dr Jan Willem van der Laan[2], Dr Tineke van den Hoorn[2]*

1. *Division of Drug Discovery and Safety, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands*
2. *Medicines Evaluation Board (MEB), Utrecht, The Netherlands*

*September 2015 - July 2023*

Britt Duijndam holds a bachelor's degree from the University of Applied Sciences in Rotterdam and a master's in biopharmaceutical sciences from Leiden University. During her graduate studies, she interned at the Division of Drug Discovery and Safety, LACDR, Leiden, studying the motility of breast cancer cells to identify possible targets for therapeutic interventions. Following a Regulation of Drug Safety course, she was introduced to the MEB and the regulatory perspective of drug development. After an internship at the Karolinska Institutet in Stockholm, Sweden, she was invited back to the Division of Drug Discovery and Safety at the LACDR for this PhD project. During her PhD, Britt was also trained as a nonclinical assessor at the Section on Pharmacology, Toxicology and Kinetics at the MEB, where she is currently employed.

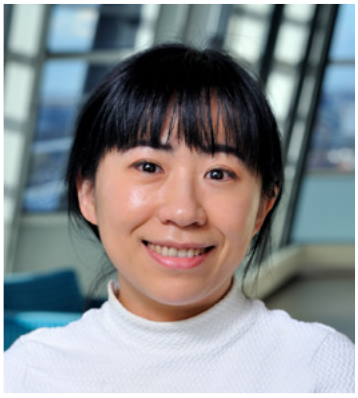
**Your PhD project focuses on the reduction of animal studies. Can you explain the main focus?**
"The regulatory standard assay for the detection of carcinogenic compounds is a two-year bioassay in rodents. However, these rodent bioassays are expensive, time-consuming, not able to describe the molecular mechanism and have poor translatability", Britt explains. "Also for ethical reasons, toxicological risk assessment techniques are undergoing a shift from animal-based approaches to human tissue culture-based approaches capable of providing detailed dose-response profiles".

To date, several non-animal alternatives to the rodent bioassay have been globally accepted or are currently under review by the Organisation for Economic Co-Operation and Development (OECD). Britt explains, "These alternatives primarily focus on the detection of genotoxic carcinogens while leaving the non-genotoxic carcinogens undetected. A well-known non-genotoxic carcinogen mode of action is the overactivation or deregulation of the oestrogen receptor alpha (ERα). In this project, we've developed a human cell-based reporter platform to identify and characterise compounds with oestrogenic activity, which can lead to cell cycle progression and proliferation of cells, which can ultimately culminate in tumour formation" (Duijndam et al., 2022).

**How is this research relevant in the current international working field?**
Recently, the ICH has released the ICH S1B(R1) addendum (ICH, 2021), describing an additional approach for assessing the carcinogenic risk of small molecule pharmaceuticals. Britt continues, "Emphasis is given to the human relevance of the potential carcinogenicity. Our reporter platform is expected to provide essential information for this weight-of-evidence approach by identifying key events in pro-proliferative ERα pathway activation. Considering the need for novel high-throughput screening platforms, we believe our technology represents a valuable asset. In addition, this reporter platform can provide spatial and temporal pathway activation dynamics on a single cell level, which can be incorporated in a quantitative adverse outcome pathway modelling framework, improving carcinogen risk assessment with a more mechanistic approach".

**What is the impact of your work on the industry and regulators?**
"My project contributes to the reduction, refinement and replacement of animal testing (the 3Rs principle), which is one of the focus areas of the MEB. It also demonstrates the usefulness of new approach methods (NAMs) in pharmaceutical development, which is important for both the industry and regulators".

> "Conducting animal studies is actually time- and resource-consuming"



## Regulatory Opportunities and Challenges to Improve Nonclinical Requirements in Drug Development

*Hsiao-Tzu Chien[1,2]*
*Promotor: Prof Frans G. M. Russel[1]*
*Co-promotors: Dr Peter T. Theunissen[1,2], Dr Peter J. K. van Meer[1,2]*

1. *Department of Pharmacology and Toxicology, Radboud University Medical Centre, Nijmegen, The Netherlands*
2. *Medicines Evaluation Board (MEB), Utrecht, The Netherlands*

*July 2021 - June 2026*

Hsiao-Tzu Chien obtained her Doctor of Veterinary Medicine in Taiwan. After specialising in veterinary anaesthesiology, she applied for a master's programme in the biology of diseases at Utrecht University. During the programme study, she interned at the MEB, where she continued a research project after completing her master's. Currently, Hsiao-Tzu is a PhD candidate conducting research on regulatory sciences at the Radboud University Medical Centre (Radboud UMC) and a nonclinical assessor at the MEB.

**What is the focus of your research topic?**
Before an investigational new drug is tested in human trials, it is often necessary to conduct animal studies for safety and efficacy reasons. These animal studies are guided by (inter)national guidance and legislation.

“It is increasingly being debated and questioned whether animal data could truly inform clinicians of safety and efficacy”, Hsiao-Tzu explains. “With the emergence of drugs that are of new chemical modalities such as monoclonal antibodies (mAbs), cell therapies or gene therapies possessing high target and/or species specificity, opportunities to implement 3Rs principles to the drug development are driven and coming to light. Furthermore, the re-evaluation of regulatory guidance (a 4th R) can prevent unnecessary animal testing that provides information irrelevant to humans”.

Hsiao-Tzu’s research projects focus on identifying 3Rs opportunities during the development of medicinal products without compromising human safety. “These include developing a weight-of-evidence approach to carry out a risk assessment and help determine whether a chronic toxicity study is required for a therapeutic mAb intended for long-term administration”.

“Furthermore, a weight-of-evidence approach will be developed to determine the need for a developmental toxicity study for a therapeutic mAb that may be given to pregnant women. Other projects include determining the nonclinical requirements for the assessment of antisense oligonucleotides and the need for testing embryo-foetal developmental testing in two species for specific pharmaceutical classes”.

**Can you elaborate on the relevance of your research for regulatory processes?**
“The results of my research could provide scientific evidence supporting the re-evaluation of current regulatory guidance”, Hsiao-Tzu explains. “Also, these results could assist nonclinical assessors in decision-making on the nonclinical requirements for certain investigational new drugs in submission for registration, leading to a meaningful assessment with a minimal number of regulatory animal studies”.

**Who benefits from these insights?**
“As I mentioned before, animal data on safety and efficacy may not be as informative as we thought before. For ethical and scientific reasons, the conduct of animal studies that are not informative should be stopped”.

However, that is not all. “Conducting animal studies is actually time- and resource-consuming”, Hsiao-Tzu continues. “Once I complete my research, I envisage that we could provide scientific evidence for policy recommendations and change, achieving the scientifically-justified reduction of animal studies in drug development”.

Hsiao-Tzu hopes this research will facilitate the whole drug development pipeline, which should benefit public health by reducing costs, increasing drug accessibility and driving the development of alternative methods that are more human-relevant than animal testing to inform scientists of safety and efficacy.

> “In the end, this could reduce animal studies, lower the costs, and shorten the process of drug development, while safeguarding the risk assessment”

## Evaluating the Need for Animal Studies in Developmental and Reproductive Toxicity Testing

*Puck Roos*[1]
*Supervisors: Dr Peter J. K. van Meer*[1,2,3]*, Dr Peter T. Theunissen*[1,2]

1. *Medicines Evaluation Board (MEB), Utrecht, The Netherlands*
2. *Department of Pharmacology and Toxicology, Radboud University Medical Centre, Nijmegen, The Netherlands*
3. *Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*

*February 2022 - February 2024*

Puck Roos studied pharmaceutical sciences and obtained a master’s degree in drug innovation at Utrecht University. During a course about drug development and regulation, she became acquainted with the work of the MEB. As a result, she applied for an internship at the MEB, and afterwards, she received the opportunity to stay at the MEB. Since February 2022, Puck has worked as a junior researcher at the MEB. From February 2024 onwards, she will be employed as a PhD student with the ONCODE-PACT project, which aims to accelerate preclinical development.

**Your research is about reducing animal testing. What exactly are you focusing on?**
“My research is focused on evaluating the need for animal studies in the field of developmental and reproductive toxicity (dart) testing”, Puck explains. “Before new drugs can enter the market, potentially harmful effects on fertility, during pregnancy and embryo-foetal development must be evaluated. This is done in animal studies. Over the past years, there has been increasing interest in replacement, reduction and refinement of animal studies: for scientific reasons (animal studies are not always predictive of human toxicity) and ethical concerns”.

One of Puck’s projects involves embryo-foetal development studies. “In these studies, drugs are administered to pregnant animals to investigate adverse effects on the pregnant female and the developing foetus. These studies are usually performed in rats and rabbits. Our aim is to evaluate whether it is necessary to conduct these studies in two species or whether one species would be sufficient. To do this, we looked at the type of effect, clinical indication, involvement of maternal toxicity and animal-to-human exposure margins”.

Another project involves reproductive toxicity studies in non-human primates (NHPs). Puck explains, “Over the past decades, more biopharmaceuticals have entered the market. These compounds are often not pharmacologically active in conventional test species, such as rodents, only in NHPs.

Therefore, there has been an increase in the use of NHPs for risk assessment of these compounds. However, this brings along ethical and practical concerns. In this project, which we perform in collaboration with the HESI-DART technical committee, we aim to analyse the use of NHPs for dart assessment to identify opportunities to minimise the use of NHPs".

**What does this research bring to the MEB?**
"Nonclinical assessors at the MEB evaluate the toxicology studies that are conducted by industry for marketing authorisation of a novel drug compound. In regulatory decision-making, the 3Rs have also gained more attention. My research could provide a scientific basis for updating current regulatory guidelines to include 3Rs opportunities".

**How can this help reduce animal testing?**
"There is increasing interest in reducing the number of animal studies conducted during drug development. My research could provide scientific evidence for this. In the end, this could reduce animal studies, lower the costs and shorten the process of drug development while safeguarding the risk assessment".

## 4.2 Advanced therapy medicinal products (ATMPs)

Advanced therapy medicinal products (ATMPs) hold great promise. However, their development is complex at multiple levels; manufacturing often differs fundamentally from chemicals and the more traditional biologicals. Therefore, the manufacturing processes are often not fully mature, the mechanism of action of these products is multi-focal and quite complex, and the field is relatively young and evolving quickly. Moreover, while the treatment effect may be intended to last lifelong and be irreversible, the long-term consequences of treatment with an ATMP can often not be fully predicted (e.g. in the case of some gene therapies).

Consequently, developing these complex products is associated with higher uncertainty than less innovative products. However, at the same time, many ATMPs are game-changing products offering a cure or effective treatment for conditions where no other treatment is available, so withholding or delaying promising treatments to patients is not prudent. Because of this ambiguity, the regulation of ATMPs is challenging. It requires continuous adaptation or flexibility to accommodate the development of these products while maintaining a delicate balance between fostering their development and early access and ensuring that patients are not exposed to unacceptable risks. Therefore, the MEB invests in setting up projects and building a network of expertise with the scientific community to follow and support the development of safe and effective ATMPs to aid the patient.

Studied questions include the following:

- How can we identify the critical quality attributes of ATMPs?
- How can we relate these critical quality attributes (in particular potency) to clinical outcomes?
- How can we control the quality of highly variable autologous products?
- Which regulatory requirements contribute to high production costs, and how can they be managed or changed?
- How can nonclinical studies give insight into and predict the activity and safety of ATMPs, and how can we translate the acquired nonclinical data?

Besides scientific questions, regulatory issues may appear due to the complexity of the products, for example, how to balance the anticipated (and unknown) risks of irreversible treatment to the expected or shown benefits of treatment or how to cope with the (inherent) uncertainties associated with these products (see Anne Taams' PhD project).

The research projects on ATMPs aim to acquire insights into the development issues for these products to allow adequate assessment of data submitted with marketing authorisation applications. Moreover, they seek to support and facilitate companies by giving appropriate scientific advice during development. These projects include the following:

- Investigating the relationship between product characteristics (especially potency testing) of chimeric antigen receptor (CAR) T-cells and the antitumour response in vivo
- Analysing the European regulatory view on the need for dedicated biodistribution and in-vivo tumorigenicity studies for (genetically modified) cell therapy products
- Deducing the common practice in advising for genotoxicity studies for gene therapeutic medicines
- Reviewing the scientific literature and regulatory information to provide an overview of potency assays for immune cell-based ATMP
- Investigating the manufacturing costs of cell-based products by interviewing companies producing ATMPs and collaborating with academic cell therapy facilities

In addition, a PhD project will start later in 2023 in collaboration with several academic partners to identify critical factors of gene-editing methods influencing the safety and efficacy.

Furthermore, the MEB organises three meetings on ATMPs annually with all national stakeholders (academia, industry organisations and regulators) to stimulate discussion and collaboration with partners such as the RIVM, the Central Committee on Research Involving Human Subjects (CCMO) and the National Health Care Institute (ZIN), as well as the embedment of investigations supporting the development of ATMPs within the broader national ATMP network. Furthermore, several MEB ATMP experts participate in different committees and networks to ensure efficient coordination and integration of the gained knowledge:

- European: The Committee for Advanced Therapies (CAT), the EU Innovation Network (EU-IN) gene-editing subgroup, Agora, DARE-NL
- Global: HESI Cell Therapy - TRAcking, Circulation, & Safety (CT-TRACS) and the CASSS Cell and Gene Therapy Products meeting.

To summarise, the MEB aims to ensure that the assessments and scientific advice procedures are of high quality and based on state-of-the-art science. Moreover, the MEB aims to contribute substantially to national and international discussions on this subject in the coming years to facilitate better and faster access to this type of treatment for patients who need it.

"By understanding and consistently discussing important uncertainties during drug regulatory processes, establishing the benefits and risks of innovative medicinal products may become less challenging"

## Mapping and Managing Uncertainty for Innovative Medicinal Products in Drug Regulatory Processes

*Anne C. Taams*[2]
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*July 2022 - July 2027*

After her bachelor's study in biopharmaceutical sciences at Leiden University, Anne Taams was trained as a pharmaceutical scientist, specialising in drug regulatory processes at Utrecht University. During this master's programme, she researched in Singapore for the Health Sciences Authority and the MEB. She joined the MEB as a pharmacovigilance assessor in 2020. Currently, she performs assessment work 50% of the time, combined with internal MEB projects, such as guidance for assessments of medical devices. The other 50%, Anne focuses on this PhD project at the Division of Pharmacoepidemiology & Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS).

**Your research focuses on uncertainties around innovative medicines. What exactly are you studying?**
"The drug regulatory system consists of authorities such as the EMA or, at the national level, the MEB. The main objective of these authorities is to promote and protect public health by evaluating and monitoring medicines. Regulators do so by continuously weighing treatment effects", Anne explains.

Assessment of innovative medicinal products such as gene therapy or immunotherapies may be complex. Anne continues, "That is due to uncertainties stemming from, for example, their manufacturing methods, (unknown) mechanisms of action, uncertainties associated with a small study population or an uncontrolled or externally controlled trial design". These make it possibly increasingly challenging for regulators to establish benefits and risks (BR) of innovative medicinal products. "In order to facilitate regulatory decision-making, increase the predictability of regulatory decision-making for applicants and understanding by physicians and patients, uncertainties of innovative medicinal products require further evaluation".

Anne's research project aims to identify uncertainties related to innovative medicinal products during the entire drug regulatory lifecycle. "We're assessing how regulatory authorities, including trial regulators assess and address uncertainties from the early clinical (phase 1) to the post-authorisation phases (phase 4)".

**What is the relevance of that research question?**
"Drug regulatory authorities continuously monitor the BR balance of medicinal products. For medicinal products with several important uncertainties, the evaluation of the BR may be challenging. My research aims to provide a better understanding of uncertainties that may occur during the lifecycle of medicinal products in order to facilitate regulatory decision-making". Eventually, this may lead to the development of guidance "on how to assess, manage and communicate about uncertainties to facilitate increased consistency of uncertainty assessments, predictability of uncertainty management and improved communication about uncertainties to other stakeholders such as patients, HCPs, applicants and health technology assessment bodies that are responsible for reimbursement decision-making", Anne explains.

**What will the impact be on establishing BR ratios for these kinds of medicines?**
"By understanding and consistently discussing important uncertainties during drug regulatory processes, establishing the BR of innovative medicinal products may become less challenging. Therefore, our research may impact those who evaluate innovative medicinal products in the drug regulatory field, such as assessors of the MEB or reimbursement authorities".

**How will it impact healthcare providers and patients?**
The research could overall have a multi-stakeholder impact. As Anne explains, "HCPs (doctors, pharmacists) could make more informed decisions by providing them with additional information on uncertainties".

"The objective of one of the research projects within this PhD research is to review the perspectives of patients and patient representatives on the identified uncertainties, their classification and how they are communicated. Do we as a regulator identify and weigh the uncertainties similarly as patients do"?

## 4.3 Data-driven assessment

The scientific analysis of data forms the basis for our medicine assessments. Medicine dossiers contain a considerable amount of data, and the nature, sources and possibilities for applying this data are developing continually.

### Real-world and big data

Together with the University of Groningen (RUG), the MEB conjointly supervises a PhD project (Stefan Verweij) studying the use of real-world evidence (RWE) in regulatory decision-making. The project aims to build a dossier that contributes to the (non-)acceptability of RWE as a supplement to – or substitute for – evidence obtained from randomised controlled trials (RCTs) in regulatory procedures. In addition, the project contains a network meta-analysis to observe to what extent effect estimates from observational studies differ from those obtained from RCTs and target trial emulation approaches. Real-world data (RWD) is included in many dossiers submitted to the EMA (Flynn et al. 2022, Eskola et al. 2022). However, their contribution to the actual decision-making is still limited for new applications and extensions of indications. To reach this conclusion, Lysbeth Bakker (UMCG) interned at the EMA and dove deep into European Public Assessment Reports to identify how the Committee on Human Medicinal Products appreciated the RWE to support efficacy claims (Bakker et al., 2023). In contrast, RWD remains an important component for the lifecycle management of authorised medicines, with,

for instance, important lessons learned on the safety of COVID-19 vaccines during the pandemic in near real-time.

The EMA has invested heavily in access to RWD sources and increasing its capability to analyse RWD. The Erasmus Medical Centre (Erasmus MC, University Medical Centre Rotterdam) is the coordinating centre of the DARWIN EU project, where EMA has invested to perform over 100 RWD studies annually addressing questions raised in one of EMA's committees on drug safety and effectiveness, disease epidemiology and the impact of regulatory interventions, for example. While the pharmacovigilance risk assessment committee is currently driving study requests in DARWIN EU, the expectation is that questions other than safety will be increasingly investigated.

The MEB is monitoring these developments and will initiate a combined PhD-assessor trajectory with Erasmus MC and UMCG (supervisors: Prof Peter Mol, Dr Katia Verhamme, Dr Sabine Straus) to increase the knowledge and experience with state-of-the-art methods to analyse these data. The project will also focus on barriers and facilitators to using these RWD in daily practice while providing guidance on how assessors should appreciate RWD presented in regulatory dossiers. This project will be aligned with the More-EUROPA project, led by Peter Mol at the UMCG, and intends to establish the value of registry-based RWD in augmenting RCT data and to enable the more effective and ethical use of registry data to support patient-centred regulatory and HTA decision-making.

The More-EUROPA project is one of five Horizon Europe-sponsored projects (EUR 35 million total EC budget) that aim to establish a better understanding and appropriate adoption of RWD in the European Union approval and reimbursement discussions. Through this project and various other activities and alliances, with, for example, the GetReal Institute, the Dutch Institute for Clinical Auditing, Professor Olaf Klungel as an RWE expert in EMA's methodology working party, the Heart4Data project and ONCODE-PACT, the MEB will ensure it stays on top of developments on the proper integration of RWE in future regulatory dossiers.

### Data strategy

The MEB is currently developing a research environment with advanced analytical tools. In Q1 2023, the MEB will start a pilot within this research environment to ensure its analytical facilities become future-proof, considering the ten recommendations made by the Big Data Task Force of the EMA. The pilot's findings will be considered when creating the MEB data strategy.

The MEB also addresses research questions related to AI, modelling, simulation and extrapolation. Together with Leiden University and the Swedish Medical Products Agency, a PhD trajectory will start as part of the ONCODE-PACT project on AI. It is a topic of major interest, yet many unknowns exist regarding regulatory guidance. The PhD student will start with a review of the use of AI in a regulatory setting based on the literature, including reports from scientific advice, qualification advice/opinions and innovation task force meetings.

Another project with the University Medical Centre Groningen (UMCG), RUG and Radboud UMC investigates the potential use of modelling and simulation studies for generic medicinal products (see Esther Lubberts' PhD project, Theme 6: Generics). The development of complex generic medicinal products, such as long-acting injectables (LAIs), is often hampered by the unfeasibility of the EMA Guideline recommended clinical trials. For example, multiple-dose studies with LAIs administered once monthly or longer will take years to conduct. This project will investigate whether modelling and simulation can optimise the clinical trial design for generic medicinal products. In addition to the PhD project on generics, modelling, simulation and extrapolation techniques are also used by applicants who apply for paediatric marketing authorisation. Several projects are being conducted by master

students that aim to evaluate the role of modelling and simulation in paediatric drug development. We will also explore whether modelling and simulation analyses, as specified in the Paediatric Investigation Plan (PIP), contribute to regulatory decision-making in marketing applications for paediatric indications.

> "The estimands framework can impact all healthcare stakeholders at different levels"

## Estimands in Clinical Drug Development: From Design to Regulatory Assessment


*Marian Mitroiu[1,2]*
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*October 2017 - December 2022*

*Marian completed his PhD thesis and successfully defended it in December 2022.*

Marian Mitroiu was born in 1988 in Buzău, Romania. In 2007, he started his pharmacy studies at the UMF Carol Davila Faculty of Pharmacy in Bucharest. Then, he specialised in clinical pharmacy, completed a pharmacovigilance master's programme at Iuliu-Haţieganu University in Cluj-Napoca and grew an interest in signal detection. While working in pharmacovigilance, he pursued a biostatistics degree at the University of Bucharest. During a traineeship at the EMA in London at the Biostatistics and Methodology Office, he learned more about regulatory statistics and drug development in the European Union (EU)/European Economic Area (EEA). Marian had the fortunate, unique opportunity to support the ICH E9(R1) Expert Working Group that developed the estimands addendum. In 2017, Marian started his doctoral studies at the Julius Centre, UMC Utrecht and Utrecht University. He worked in parallel at the Methodology Group at the MEB, where he consulted for scientific advice procedures focused on estimand methodology and was a statistical assessor for centralised procedure scientific assessment. Marian combined his estimand research with the postgraduate master programme in epidemiology at Utrecht University, graduating in 2021 with a specialisation in medical statistics. Marian joined Biogen as a biostatistician in August 2021 and continues the estimand methodology research, implementation and application in clinical drug development as a member of various estimand-related working groups.

**What exactly has your work focused on?**
For a new drug to enter the market, efficacy and safety must typically be demonstrated in randomised trials. “It is often not clear which question the trials address and how the corresponding treatment effects should be interpreted”, Marian explains. “For instance, when investigating the efficacy of antibiotics for sore throat treatment, it is important to account for painkiller use when measuring the outcome. A pain score of 7 while using painkillers means something different than the same score without taking any painkillers. Factors impacting the interpretation or measurement of the outcome should be considered and accounted for in a trial design. This can be done in a structured way by defining a clinical question using the estimand framework. An estimand is defined as a precise description of the treatment effect reflecting the clinical question posed by the trial objective”.

In Marian’s thesis, a review of current practice showed the need to start with precise descriptions of targeted treatment effects and align trial design and analysis. Marian offers, “There is a mismatch between the targeted effect and the effect obtained with the analysis method used. Our findings emphasise that estimands should be prespecified because when retro-fitting estimands, there is no 1-to-1 mapping between common analysis methods and estimands”.

Marian proposes a few technical solutions to help plan and design trials implementing the estimand framework: “Multidisciplinary collaboration and healthcare stakeholder interaction are needed to align trial objectives, data collection, analyses, interpretation and communication of trial results, employing the estimands framework at every stage”.

**Where in the drug development process does this research add the most value?**
“The entire process”, Marian responds. “Implementation of estimands can be helpful from the design of clinical trials to communicating treatment effects to patients. The results of my thesis can help the implementation and application of the estimands framework by using an explicit structure of estimands constructs, helping to estimate formulated estimands while understanding what treatment effects can correspond to formulated estimands”. The estimands framework can impact all healthcare stakeholders at different levels (e.g. the MEB through scientific advice/protocol assistance procedure for clinical trials designed using the ICH E9(R1) estimand framework).

**What impact does it bring, and for whom?**
“The proposed data-generating models (DGMs) are powerful tools for evaluating estimands and understanding possible ways to model the association between outcomes and intercurrent events. This can provide valuable insights into the way they impact the targeted estimands. The estimands framework can impact all healthcare stakeholders at different levels, depending on the role and timing of their involvement in the lifecycle of medicinal product development. For instance, it can impact patients and caretakers because they ultimately receive the clinical benefit and are best positioned to judge whether the estimands are meaningful for them”.

> "Hence understanding the value of the evidence from observational studies is very important when it comes to regulatory approval of a pharmaceutical product, for both regulators and the pharmaceutical industry, but eventually also for the patients"

## Efficacy Results Obtained from RCTs Translate to Effectiveness Data From Observational Studies

*Stefan Verweij*[1,3]
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*February 2022 - February 2027*

Stefan Verweij studied biotechnology and bioinformatics at Wageningen University, focusing on programming and machine learning. As a data scientist at the Leiden Bioscience Park, he used artificial intelligence in the field of protein engineering. After switching to the MEB, he has combined his role as a data scientist with a part-time PhD project on using real-world data in regulatory decision-making at the University of Groningen.

**What is the focus of your research topic?**
"There has been growing interest in the evidence generated from observational studies in recent years, especially in areas where the application of RCTs is less feasible, for example, due to ethical limitations of assigning a patient randomly to a placebo", Stefan explains. "Therefore, the MEB is interested in how it can assess the evidence from observational studies for the authorisation of pharmaceutical products. My project aims to build a dossier with cases of how the MEB could use this evidence as a substitute for – or supplement to – evidence from RCTs in regulatory decision-making".

**What is your main research question?**
RCTs are the gold standard in regulatory decision-making when estimating a treatment's efficacy. Due to randomisation and blinding, forms of bias are largely avoided. These biases can distort the causal inference of the effect of treatment X on disease Y.

Stefan explains, "In real-world (or observational) studies, the effect of treatment X on disease Y in the real-world population is studied, and no randomisation nor blinding takes place, distorting the inference of causal effects. Hence, evidence obtained from observational studies, real-world evidence (RWE), is often argued to be less acceptable in regulatory decision-making as opposed to evidence obtained from RCTs".

"My PhD project aims to study how and when RWE is acceptable enough to act as a supplement to – or substitute for – evidence obtained from RCTs in regulatory decision-making by building a framework that identifies the criteria RWE has to meet". The differences in effect estimates between real-world studies and RCTs will be observed using network meta-analyses (NMAs). "Once these differences (or similarities) have been observed, we will try to simulate RCTs in real-world populations (e.g. disease registries) using target trail emulation approaches to examine if these approaches can 'upgrade' the quality of evidence obtained from real-world data sources".

**How is patient participation included in your research?**
"In a later stage, qualitative research will take place among regulatory experts and patient organisations". Stefan explains, "We'll try to gather opinions on the conditions RWE has to meet to be used as an acceptable substitute for – or supplement to – evidence gathered from RCTs. Expert opinions from patient organisations will help to build a qualitative framework to identify what criteria RWE has to meet to act as an acceptable substitute for – or supplement to – evidence obtained from RCTs for regulatory decision-making".

**What will be the impact once your research is completed?**
"Understanding the value of evidence from observational studies", Stefan says. He mentions the EMA, which is building a research centre for executing observational studies, called DARWIN EU. "There is an ongoing trend in using evidence from observational studies in the marketing authorisation procedures both within Europe as well as globally. Hence, understanding the value of this kind of evidence is very important when it comes to regulatory approval of a pharmaceutical product, for both regulators and the pharmaceutical industry, but eventually also for the patients".

> "By evaluating whether extrapolation is possible, the need for a full program with specific studies may no longer be necessary to support an extension of the anti-seizure medication to use in other age groups, seizure types or syndromes"

## Exploring the Possibilities to Support a Change in the Labelling of Anti-Seizure Medication Through the Use of Existing Data


*Loes den Otter[1,2]*
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5. *Maastricht University Medical Centre+, Maastricht, the Netherlands*


*May 2022 - May 2027*

Loes den Otter always had the ambition to conduct research related to medicines for brain disorders. Accordingly, she completed a Neuropsychology and Research Master's in Fundamental Neuroscience at Maastricht University. Since 2017, Loes has worked as a clinical assessor at the MEB, specialising in evaluating the efficacy and safety date of medicines for neurological and psychiatric disorders. As of May 2022, she combined this function with work as a part-time PhD student at Maastricht University.

**What exactly are you researching in your PhD project?**
Anti-seizure medications (ASMs) are the drugs of choice to treat epilepsy, a common brain disorder characterised by the occurrence of seizures. ASMs are usually approved for treating a specific seizure (sub)type or epilepsy syndrome. However, when a pharmaceutical company wants to expand the treatment setting in which the ASM can be used, additional clinical studies are considered necessary. "These studies", Loes explains, "are often difficult to conduct, costly and time-consuming. An alternative route could be the use of data from existing clinical studies through the so-called extrapolation exercise. This method uses existing information derived from one patient (sub)

population to make inferences about another. A well-known example is the extrapolation of efficacy obtained in adult patients down to children of a certain age".

In her PhD project, Loes intends to explore to what extent the extrapolation exercise can be used to support changes to the product information of ASMs. "In epilepsy, extrapolation of efficacy data has been accepted by the EMA from adults to children aged four years with a specific type of seizures", Loes adds. Part of her research will focus on whether this assumption is still valid or whether an update (e.g. younger children) is warranted. "My project also intends to evaluate if extrapolation can be used to support the addition of new seizure types or epilepsy syndromes to the product information of ASMs based on data from clinical studies performed in a different epilepsy patient population".

**How does this project help in assessing these medicines?**
"We could help identify situations in which the extrapolation exercise could provide an alternative route to support the extension of the indication of an approved ASM", Loes explains. "The knowledge of whether extrapolation is possible within the epilepsy setting will provide better guidance for clinical assessors on the clinical development programme of new ASMs, and it could contribute to the further optimisation of the regulatory decision-making process".

**So that helps the regulatory process? Who else will benefit?**
"Currently, specific studies are considered warranted to support the addition of a new patient subpopulation or seizure type to an approved ASM. By evaluating whether extrapolation is possible, the need for a full programme with specific studies may no longer be necessary to support an extension of the ASM to use in other age groups, seizure types or syndromes", Loes explains, "and this could motivate pharmaceutical companies to generate the data needed to support the extension of the indications of their respective ASMs".

In addition, the results from the project can increase prescribers' ability to make confident decisions. Loes adds, "It helps them decide whether they should initiate a specific ASM treatment in their patients, even when the ASM has not yet been approved for the patient's specific situation (for example, "off-label" treatment)".

At the moment, patient participation is not yet included in this project. Loes explains, "There are plans to involve the Dutch Epilepsy Patient organisation (EpilepsieNL) in the PhD project at a later stage".

## 4.4 Personalised medicine and biomarkers

"Precision medicine" has become a topic of key interest in the scientific, regulatory and public domains. Due to rapid advances in science and specifically understanding disease pathophysiology, underlying biological pathways and specific molecular targets, a more targeted approach to diagnostics and treatment is possible. The concept of precision medicine aims to identify early-in-development investigational medicinal products with a promising treatment effect along with the patients who would respond to treatment.

In addition, precision medicine refers to subjects who may not respond to treatment but suffer from severe or rare adverse events. Finally, dose-finding can be facilitated by the current understanding of molecular targets and pharmacogenomics. Regulatory flexibility is required to stimulate the development and expedite the authorisation of promising medicinal products intended to treat life-threatening diseases.

> Biomarkers are biological markers indicating that someone is sick, which can predict how serious an illness will be or show whether a treatment is working. One example of this is PDL-1 protein expression for immunotherapy in the context of oncology.

In line with these developments, the MEB has included a theme in the regulatory science strategy specifically intended to support research on the development of personalised medicine for the authorisation of medicines for even more specific groups of patients. Several research projects are dedicated to different aspects of the precision medicine concept. For instance, there is a need for knowledge of new methodologies, the validation of biomarkers, alternatives in drug development pathways, such as innovative trial design and analytical methods, and the possible use of real-world evidence. Different collaborative PhD projects are ongoing in personalised medicine:

- Jorn Mulder (MEB/UU) defended his thesis "The Authorisation of Anticancer Medicinal Products" successfully in January 2023 (see Jorn's PhD project). First, he investigated the difficulties and challenges of approving anticancer medicinal products. Different aspects were studied, starting with early drug development and regulatory tools supporting promising medicinal products. Then, moving to the challenges in the approval phase, two aspects were investigated – the experience and regulatory perspective of the evidence generated in single-arm clinical trials and the role of different stakeholders in evidence generation for targeted treatments in oncology and regulatory pathways. Finally, a comparative analysis of the postmarketing measures for medicines registered for tissue agnostic indications provided data on the regulatory challenges in the postmarketing phase (Mulder et al., 2022).
- Lysbeth Bakker (UMCG, IMI Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt-DKD) project) investigated the challenges of introducing personalised medicine approaches in a chronic disease area, diabetic kidney disease, from a regulatory science perspective.
- Sonia Roldan (UMCG, Marie Curie co-funded PROMINENT project) investigated how the patient's perspective can be used to personalise a treatment approach or appreciation of drug efficacy and safety.
- The MEB is involved in an advisory setting in the Horizon 2020 initiative "A New Intervention for the Implementation of Pharmacogenetics in Psychiatry (PSY-PGx)". The goal is to investigate the potential of implementing pharmacogenetics in existing clinical practice, particularly in treating patients with certain psychiatric disorders (major depression, anxiety spectrum and psychotic disorders). All data collected will be combined with an artificial intelligence methodology to develop an algorithm for personalising patient medication prescriptions to reduce side effects and increase pharmacotherapy's effectiveness.
- Another project with MEB involvement is the EPHOR, which stands for **E**xpertisecentre **PH**armacotherapy in **O**ld pe**R**sons. Its mission is to improve appropriate prescribing to old frail patients, mainly > 75 years of age. EPHOR collects information about the effectiveness of medicinal products in the elderly and side effects especially relevant for older patients, such as anticholinergic effects, dizziness and risk of falling. This information has been published via the website, the EPHOR app and Farmacotherapeutisch Kompas.
- Recently, two new European research projects have been initiated (IMI EPND and PRIME-CKD) in which the MEB participates as a full partner to address questions around the implementation of personalised medicine approaches in drug development and evaluation, specifically focusing on biomarkers in neurodegenerative diseases (see Audrey Hermans' PhD project) and chronic kidney disease (PhD student Renske Grupstra will start mid-2023).

> "If these medicines fulfil an unmet medicinal need, expedited approval may be warranted"

## The Authorisation of Anticancer Medicinal Products

*Jorn Mulder*[1]
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*May 2017 - January 2023*

*Jorn completed his PhD thesis and successfully defended it in January 2023.*

After Jorn Mulder received his master's degree in biomolecular sciences, he applied for a job at the MEB, becoming a part-time clinical assessor and PhD candidate. After finishing his PhD, Jorn continued working as an MEB assessor, focusing on cancer products.

**You are examining how novel anticancer medicines are assessed. Can you explain what you are focusing on?**
A better understanding of tumour biology has led to the development of precision medicine. "These medicines use novel approaches to target the tumour and may show promising or even dramatic antitumour activity early during clinical development", Jorn explains. "If these medicines fulfil an unmet medicinal need, expedited approval may be warranted".

Jorn points out that regulatory agencies have implemented programmes to facilitate earlier access to beneficial medicinal products. "This, however, requires flexibility from regulators (and other stakeholders). A reflection on regulatory decision-making with regard to the authorisation of promising anticancer medicinal products is needed in our opinion".

Jorn offers, "In this project, the difficulties and challenges related to the authorisation of anticancer medicinal products were discussed".

**How does your research connect to the MEB?**
"This project focuses on topics that concern the approval of new anticancer medicinal products, such as 'single-arm trials' or 'histology-independent drug development'. The research directly connects to the work conducted at the MEB, as, yearly, numerous anticancer medicinal products receive marketing authorisation in the European Union", Jorn explains.

Jorn continues that insights from this project can facilitate future decision-making and may be useful for updates to existing regulatory guidelines: “The findings of this research will be valuable for regulators (and potentially other stakeholders) with regard to regulatory decision-making”.

> “Preference studies contribute to well-founded decisions because they explore how the trade-offs are distributed among the populations, and they can provide grounds to set thresholds”

## Stakeholder Preferences in the Medicines Lifecycle

*Sonia Roldan Munoz*[1]
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*September 2018 - December 2022*

After obtaining her Master of Pharmacy in 2015 at Alcala de Henares University (Madrid, Spain), Sonia Roldan Munoz worked as a pharmacist in the United Kingdom for one year. From 2016 to 2018, she joined the EMA, where she worked on a project evaluating safety information from pregnancy registries and assessing new medicines for the paediatric population. In 2018, Sonia started her PhD project in Groningen on eliciting different stakeholder preferences. Since January 2023, she has worked as a clinical assessor at the MEB.

**What exactly have you researched in this PhD project?**
Sonia Roldan Munoz’s PhD project explored the preferences of various stakeholders concerning the effects of medicines and their preferences for communicating health-related information. “Also, we assessed several factors contributing to preferences heterogeneity”, Sonia adds. “We’ve conducted studies among patients, caregivers, the general population and regulators. Various factors, such as age, gender and beliefs about medicines, explained heterogeneity in identified preferences in several of our

studies. For instance, beliefs about medicines partly explain medication use for chronic diseases during pregnancy" (Roldan Munoz et al., 2020).

In addition, concerning what people were willing to accept to delay the progression of Alzheimer's disease and the preferences of European regulators for the communication of certain safety issues, she noted, "We also examined the effect of country, which was a determining factor of heterogeneity in the preferences of Dutch and Turkish people with type 2 diabetes".

The final project of Sonia's thesis tried to move the elicitation of preferences to clinical practice. "We conducted a pilot study about the usability of a decision aid in daily clinical practice to assist patients and doctors when choosing among treatments for diabetes. The decision aid included a preference elicitation exercise that resulted in a ranking of their preferred treatment effects and the most suitable drug classes according to their preferences".

**Can you highlight the relevancy?**
"Multiple decisions need to be made through the medicines lifecycle", Sonia explains. "Specifically for regulators, whether the benefit-risk of a medicine is positive or whether to communicate certain safety information are frequent questions. However, these decisions might not always be unified; for instance, a certain risk can be tolerable for one person but too high for another. Preference studies contribute to well-founded decisions because they explore how the trade-offs are distributed among the populations, and they can provide grounds to set thresholds".

In this specific thesis, Sonia demonstrated the existence of subpopulations with different needs, emphasising the importance of understanding and acknowledging the heterogeneity of these preferences when making regulatory decisions.

**Does this project appear to have a broad impact?**
"Absolutely. Since it is of interest to all stakeholders taking decisions in the medicines lifecycle, patients can benefit from this research because their opinions are more and more explored and incorporated when taking medical and regulatory decisions. HCPs and regulators can use the information elicited from preference studies for benefit-risk assessments, communication and shared decision-making".

**Speaking of patients, how is their participation included?**
"Most of our studies consisted of cross-sectional surveys. Patients were involved in the survey development. For instance, for our study about treatments for Alzheimer's disease, we conducted focus groups in which patients discussed the most important aspects of the progression of the disease, relevant clinical outcomes, adverse events, and, among others, the wording, length and difficulty of the survey. This ensured that the information was understandable to the participants and that the study outcomes were actually of interest for patients themselves".

> "Alternatively or additionally to using biomarkers to generate evidence for authorisation of new precision medicines, real-world evidence may be used as a source"

## Alignment of "Precision Medicine" Drug Development Trajectories With Regulatory Decision-Making Needs

*Lysbeth Bakker*[1]
*Promotors: Prof Peter G. M. Mol*[1,2]*, Prof Hiddo J. H. Lambers Heerspink*[1]
*Co-promotor: Dr Viktoriia Y. Starokozhko*[1,2]

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*September 2019 - June 2023*

Lysbeth Bakker studied at the University of Groningen. She started with a Bachelor of Life Science and Technology, finishing in the biomedical sciences and behaviour and neuroscience tracks. During her bachelor's, she minored in pharmacy, which caused her to continue in the direction of medicines. After obtaining her bachelor's degree, she started a Master in Medical Pharmaceutical Sciences with a Pharmacoepidemiology track. In the second year of her master's, she interned at the MEB, mostly in the office in Groningen, under the supervision of Peter Mol. In September 2019, Lysbeth started a PhD under Peter Mol's supervision in regulatory science. She worked closely with MEB and EMA colleagues on several of the projects.

**What is the topic of your PhD?**
Precision medicine aims to provide patient-centred health care by providing therapy tailored to stratified or precise populations. However, traditional randomised controlled trials usually need large patient numbers and may not be suited to study these precision medicines. Therefore, a shift towards a more precise approach is needed.

"One way to accomplish this is to use biomarkers to select the trial population that is, for example, most likely to benefit from treatment. Biomarkers can also be used to predict disease progression in a certain population or to predict the effect of a medicine on a clinical endpoint", Lysbeth explains. "Regulatory endorsement of biomarkers, for example through a qualification procedure, may provide medicines developers with validated biomarkers to be used in the development of new treatments". Lysbeth also mentions the use of real-world evidence: "Alternatively or additionally to using biomarkers to generate evidence for authorisation of new precision medicines, real-world evidence may be used as a source".

Lysbeth explains that her PhD thesis comprises several projects, including

- How and how often biomarkers are currently used in clinical studies of recently approved medicines
- Recent biomarker qualification procedures identifying commonly raised issues around biomarkers (Bakker et al., 2022)
- The use of real-world evidence for regulatory decision-making in recent MAAs.

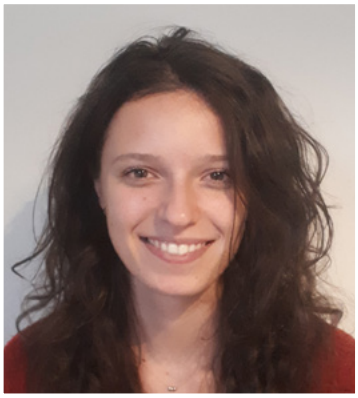
“Additionally, we studied the value of including a generic quality of life questionnaire as a patient-reported outcome in trials studying medicines for chronic kidney disease. These projects together aim to explore the current integration of precision medicine in regulatory processes and ways for further implementation, as well as potential hurdles”.

**What is the relevance of your project to the field and the MEB?**
“Regulatory authorities, such as the MEB and the EMA, agree on the need to support developments in precision medicine, including biomarkers, to enable more patient-centred health care”, Lysbeth explains. “The projects in this thesis provide insights about the current practices around precision medicine in drug development and regulatory decision-making by thoroughly reviewing regulatory documents, including marketing authorisation and biomarker qualification dossiers”.

**What impact will this research have once it is completed?**
Lysbeth: “The information gathered can be built upon by regulators and drug developers to improve the implementation of precision medicine, leading to more targeted treatments and perhaps advancing the development of new treatments in areas with an unmet medical need”.

**Finally, how is patient participation included in your research?**
“Patients and patient advocates were one of the stakeholder groups participating in a consensus-building meeting among diabetic kidney disease stakeholders”, Lysbeth says. “This meeting was held to identify their perceived benefits, obstacles and potential solutions to the obstacles related to precision medicine”.

> "Biomarkers can help earlier diagnosis, select the right treatment for a patient, and monitor treatment effects better"



## Biomarkers in the Development of Treatments for Neurodegenerative Diseases in the European Union

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*August 2022 - August 2027*

Audrey Hermans obtained a Bachelor in Science and Innovation Management at Utrecht, where she focused on innovation in healthcare. During her master's (Management, Policy Analysis and Entrepreneurship in the Health and Life Sciences) in Amsterdam, she focused on the impact of policy and regulation on healthcare practice. This two-year master's included one year of conducting research internships. Her second internship was at the MEB in collaboration with Utrecht University on the impact of the European Union In-Vitro Diagnostics Regulation (EU IVDR) on the practice of diagnostic laboratories in hospitals. After finishing her studies, she started this PhD project at the MEB.

**What is the relevance of focusing on these biomarkers in your PhD project?**
Audrey investigates how biomarkers are used to develop treatments for neurodegenerative diseases, a diverse group of diseases and a common cause of cognitive impairment and motor skill issues, like Alzheimer's disease, Multiple Sclerosis, Parkinson's disease, Huntington's disease and Spinal Muscular Dystrophy. "Biomarkers can help earlier diagnosis, select the right treatment for a patient, and monitor treatment effects better", Audrey clarifies. "That is why it is important to improve access to patients' clinical data and biosamples so that researchers can discover new biomarkers".

The EPND tries to make collaborating and sharing these data easier to stimulate the discovery of relevant biomarkers in neurodegenerative diseases. "Previous research has clarified how often EMA's qualification procedure has led to the qualification of biomarkers. It has also provided insight into different characteristics, such as who applies for a qualification procedure, which kinds of diseases and what issues are frequently brought up during the qualification procedure" (Bakker et al., 2022).

Audrey explains little is known about how biomarkers affect regulatory advice and decision-making in neurodegenerative diseases: “That is why we try to learn more about how often and in which way different types of biomarkers are used in the development of treatments for neurodegenerative diseases. We want to learn more about the role of biomarkers in the field of neurodegenerative diseases and what challenges the use of biomarkers in drug development and clinical practice”.

**Can you describe the link to the MEB and how this will impact stakeholders?**
The MEB is involved as one of the partners of the IMI-funded EPND. Audrey elaborates, “The task of the MEB involves increasing the impact of the EPND on the regulatory validation of biomarkers. The first study of the project creates a report on the qualification of samples for regulatory biomarker approval. The research will provide insight into how the EPND can impact the regulatory validation of biomarkers. Ultimately this will help with the development of treatments or diagnosis of patients with neurodegenerative diseases so that availability of treatments and care can be improved”.

**Has patient participation been considered in this project?**
“In this first study, we did not include patient participation”, Audrey says. “However, patient organisations are involved in the work package that we are part of. Our research will ultimately impact patients by hopefully improving the availability of treatments and care for patients with neurodegenerative diseases”.

## 4.5 Medical devices

Medical devices and in-vitro diagnostics are being used more frequently in a personalised approach to healthcare, individually and in combination with medicines. The category featuring a combination of medicines impacts the work at the MEB. In 2021 and 2022, two European directives came into force: the Medical Device Regulation (MDR) for medical devices and the In-Vitro Diagnostic Medical Devices Regulation (IVDR) on in-vitro diagnostics. The MDR and IVDR aim to achieve greater consistency in the assessment of medical devices in the EU in terms of product quality and patient safety, while the certification requirements for in-vitro diagnostics are being brought more in line with the importance of the test when it comes to treating a patient and the consequences of misclassification.

Concerning in-vitro diagnostics, a major change compared to the current situation is that clinical evidence must be supplied for companion diagnostics (in-vitro diagnostics linked to a medicine). In principle, a notified body is responsible for assessing companion diagnostics. However, because the benefit-risk balance of the medicine can depend on the companion diagnostic, close cooperation between the EMA, national agencies and the notified bodies is required. In a regulatory-science approach aimed at preparing for this new task, the MEB has researched the points raised during discussions in recent years in centralised marketing authorisation procedures and European scientific recommendations concerning companion diagnostics present in the dossiers for the medicinal product (Maliepaard et al., 2022). Furthermore, the consequences of the new IVDR for the current practice in The Netherlands were investigated. The results indicated that the MEB and EMA have already gained experience assessing companion diagnostics and advising on their development. In the field, worries were expressed about the consequences of the IVDR on the use of in-house testing widely used in the Netherlands (Hermans et al., 2022).

Furthermore, in the EU-Innovation Network the MEB is in the lead of the Horizon Scanning exercise for companion diagnostics.

## 4.6 Generics

More than 75% of the prescribed medicines issued by public pharmacies in the Netherlands are generic medicines used by large numbers of patients. However, research has shown that changing medicines, as often occurs in the case of generics, affects patient trust. To challenge and potentially optimise the current requirements for registering generic medicines in the EU, the MEB is researching the interchangeability of generics to establish which differences are acceptable (see Pieter Glerum's PhD project) and which risk minimisation measures must be taken in the event of differences. Our overall aim is to contribute to patient trust in generic medicines.

The Ministry of Health, Welfare and Sport also commissioned the MEB, to put together an overview of medicines for which changes are undesirable, for example, because incorrect changes of these products can lead to serious health issues. The result became the backbone of the list now included in the Leidraad Verantwoord Wisselen Medicijnen ("Guideline Responsible Exchange of Medicines"), which various health-related stakeholders published in 2022.

Current generics-related investigations at the MEB focus on the potential use of modelling and simulation techniques (i.e. physiology-based pharmacokinetics [PBPK] and population-pharmacokinetics [popPK] modelling) to generate supportive data for the registration of generic medicinal products. This project aims to investigate if using such methodologies may facilitate the development of generic medicines (see Esther Lubberts' PhD project).

> "It is the responsibility of the regulator to review their methodology and requirements on a regular basis in order to confirm that the most suitable regulatory system is in place"

### Generic Interchangeability: Between Science and Regulation

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*October 2014 - March 2023*

*Pieter completed his PhD thesis and successfully defended it in March 2023.*

Pieter Glerum has a background in biomedical sciences from Utrecht University. During his master's programme in biomedical sciences, he performed a research internship at the Laboratory of Experimental Cardiology of the University Medical Centre Utrecht (UMCU) on the mechanisms of human cardiomyocyte progenitor cell differentiation, where he gained experience with cell cultures and several genomic and proteomic techniques. Pieter completed his second internship under the supervision of Dr Christine Gispen-de Wied at the MEB, analysing the content of one of the decision-making bodies of the MEB. Pieter wrote his master's thesis on the modernization of medicine evaluation under the supervision of (former) MEB chair Prof Bert Leufkens.

**You are studying "generic interchangeability"; please elaborate.**
"This research aims to study generic interchangeability issues in clinical practice and challenge the robustness of the current bioequivalence requirements", Pieter explains. "In the first part of this research, we investigated patient-reported clinical discomfort using a systemic approach. Therefore, we studied the number of adverse drug reactions (ADRs) related to drug switches. We placed these into perspective by identifying the number of people switching between (generic) drug products".

Pieter and his colleagues also studied the frequency of drug switches in the Netherlands for 20 active substances for which switch-related ADRs are most often reported. "We analysed the reported ADRs concerning the number of drug switches. Additionally, we investigated the reasons for generic drug switching in the Netherlands in a pilot study".

The robustness of the applied bioequivalence methodology was investigated in the second part of this research. "Using modelling and simulation, we investigated whether a conclusion of bioequivalence in a healthy population held for a vulnerable patient population with altered pharmacokinetic characteristics. We built a non-parametric pharmacokinetic model of gabapentin based on the exposure data for gabapentin, following the administration of the originator and three generic drug products in healthy subjects. With the model, we performed simulations to possibly identify patient subpopulations for whom aberrant pharmacokinetic profiles were more likely to occur upon switching to or between bioequivalent generic drug products" (Glerum et al., 2022).

**For which stakeholders is this topic most relevant?**
"Generic interchangeability is a highly relevant topic for most stakeholders; patients, prescribers, regulators and scientists. Patients should be able to trust the quality, safety and efficacy of the drugs they use – in the case of this research, generics in particular. Challenging the current regulation of demonstrating average bioequivalence only to the originator drug is of particular importance. It is the responsibility of the regulator to review their methodology and requirements on a regular basis in order to confirm that the most suitable regulatory system is in place".

**Do patients participate in this research?**
"The main focus of this research was on population-level data on the frequency of generic drug switching, related adverse drug reactions and on the bioequivalence methodology", Pieter explains. "However, we did gather patient-related data at several different pharmacies in the Netherlands on the reasons for a patients' generic drug switch".

**What will the impact be?**
"We have aided in the discussions amongst different stakeholders on the total number of drug switches and how drug switching could be performed responsibly in Dutch pharmaceutical practice with this research", Pieter concludes. "Furthermore, this research can support building trust in the regulatory system and generic medicines in general, as our results (considering their limitations) support generic interchangeability and the regulatory requirements for generic drug approval".

> "This research would ultimately contribute to maintaining the availability of good medicines based on state-of-the-art science"

## The Potential of Modelling and Simulation as an Alternative for Clinical Pharmacokinetic Studies in Generic Marketing Authorisation Applications

*D. Esther Lubberts[1,2,3]*
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*Co-promotors: Dr Jeroen V. Koomen[1,3], Dr Laurens F. M. Verscheijden[3]*

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3. *Medicines Evaluation Board (MEB), Utrecht, The Netherlands*

*October 2022 - October 2027*

Esther Lubberts obtained a bachelor's degree in biopharmaceutical sciences and a master's degree in pharmacy (Leiden University). Her master's thesis consisted of developing a population-based pharmacokinetic model at the Department of Clinical Pharmacology at the Karolinska Institute in Stockholm, Sweden. After applying for a PhD position in Pharmacometrics at the Department of Anaesthesiology at the UMCG, Esther received an offer to combine a PhD project with hands-on experience as a pharmacokinetic assessor at the MEB.

**What is your PhD research about?**
"I'm exploring the potential use for modelling and simulation (M&S) as an alternative for clinical pharmacokinetic (PK) studies to facilitate and strengthen generic MAAs", Esther explains.

The first potential use of M&S is for the MAA of generic long-acting injectables (LAIs). "LAIs require demonstration of bioequivalence after single- and multiple-dose administration. We expect that the

degree of accumulation at steady-state is predictable, based on single-dose PK data of the new generic product and the principle of superposition. Therefore, using single-dose data submitted in the electronic drug dossiers, the predictive value of population-based pharmacokinetic (popPK) models for the multiple-dose PK of LAIs will be evaluated".

The second potential use of M&S focuses on waiving proton pump inhibitor (PPI) interaction studies for specific immediate-release generic products using physiology-based pharmacokinetic modelling (PBPK). Esther: "We expect that a PBPK model is able to quantify the influence of PPIs on in vivo pH. Subsequently, using physiochemical properties of a medicinal product, the influence on solubility and pharmacokinetic profile could be predicted".

Lastly, Esther will explore the potential to waive food-effect studies for modified release products using PBPK M&S. "The food-effect on PK is expected to be influenced by multiple mechanisms such as gastric pH, gastric volume and intestinal bile salt concentrations. The rate-limiting steps incorporated in these mechanisms may be comparable and thus predictable through PBPK model simulations".

**How does this connect to the MEB work?**
Esther shares, "Increasing the knowledge on the use of M&S in generic MAA is expected to improve regulatory decision-making and reduce the exposure of healthy volunteers to generic test drugs. The outcomes of this research will be published in scientific journals and potentially contribute to updated EMA guidelines. For example, the number of marketed generic LAIs is limited, so lowering the boundary to develop these generics by providing more workable guidance for MAA is desirable. This research would ultimately contribute to maintaining the availability of good medicines based on state-of-the-art science".

**What will this research lead to, eventually?**
"The ultimate aim is to validate the use of M&S to optimise and partially replace clinical PK studies in generic MAA", Esther explains. "As a result, the development of generic drugs could become more efficient by accelerating the developmental process and reducing the exposure of healthy subjects to the generic test drug. Subsequently, this could lower the boundary to produce complex generic drugs and reduce social costs".

## 4.7 Medicines used better

The MEB aims to encourage the proper use of medicines by making its information on medicines more accessible and understandable. This goal concerns information to care providers (e.g. summary of product characteristics [SmPC] and risk minimisation materials) and patients (e.g. package leaflets and packaging). We also help tailor medicines information to a certain target group, such as elderly patients. Providing information that is easier to understand and more accessible will help increase medication safety, improve therapy compliance, reduce wastage and improve shared decision-making.

Scientific research on this theme relates to activities carried out throughout the organisation. For example, we use research outcomes to improve the package leaflets and other information on medicines, including information on specific categories of medicines, such as heavy pain medication, to reduce misuse. Other activities are to improve the accessibility of the MEB website with information on medicines (geneesmiddeleninformatiebank.nl) and technical options for the reuse of the MEB information on medicines. To emphasise the importance of this theme, the MEB established the Team Use of Medicines (Team *Geneesmiddelgebruik*) with a primary focus on these topics.

The Team Use of Medicines has coordinated several projects. For instance, based on research data, the team was responsible for introducing a new policy allowing four warning pictograms on medication

packages. This set of pictograms brought vital warnings to the attention of the user. The pictogram subjects were about using medication in combination with alcohol, driving, pregnancy and breastfeeding. Using these pictograms on the packaging is non-mandatory, so the marketing authorisation holder (MAH) can choose to use them. In addition, the MEB is exploring the value of enabling the use of standardised pictograms in the package leaflet to help patients find and understand information more easily. This topic has also been discussed at the EU level.

Furthermore, MEB research was conducted by the Netherlands Institute for Health Services Research (NIVEL) regarding the general public's trust in medicines and vaccines. The results identified themes where the MEB could improve information on medicines to increase the public's trust in medicines and vaccines.

Besides creating policies about pictograms and coordinating research, the Team Use of Medicines also has created supplementary medicine and vaccine information complementary to the patient information leaflet (PIL). An example is "Vaccine in Short" for COVID-19 vaccines, which contains essential comprehensible information about the vaccine on one page, accompanied by pictograms. Research was conducted to test the comprehensibility of "Vaccine in Short". The research also tested to what degree the general population rated its trustworthiness. The research demonstrated that "Vaccine in Short'" is perceived as comprehensible and trustworthy.

## 4.8 Safety and effectiveness after authorisation

Five current and two recently concluded PhD projects have addressed topics on post-licensing evidence generation on medicinal effects, both harmful and beneficial. In the concluded PhD project of Carla Jonker (MEB, UMCU Julius Centre, UMCG), she argues that "rare disease registries are a must for regulatory decision-making" to follow-up medicinal products after and partially before approval. Most projects have focused on the efforts regulators and MAHs have made to optimise the benefit-risk balance post-licensing. Remy Francisca (MEB, Erasmus MC) showed in his thesis, "Investigating Additional Risk Minimisation Measures for Medicines in the European Union", that additional risk minimisation measures (aRMMs) are frequently implemented, but impact assessment and optimal adoption by HCPs and patients need more effort (see Remy Francisca's PhD project). Moreover, Esther de Vries (UMCG) investigates the DHPC, a key regulatory risk communication tool, and makes recommendations to align the distribution of these DHPCs to fit with Dutch hospitals' practices to ensure the safe use of medicines (see Esther de Vries' PhD project; De Vries E et al., 2022).

Medicine shortages are an increasing problem. Doerine Postma (KNMP, UU) studies the impact of shortages (Postma et al., 2022) and the timing of the identification of shortages by authorities, pharmacists and the public.

Frequent product recalls due to quality issues with the manufacturing of medicines may reduce the trust of patients and HCPs in medicine supply. Pieter Annema (Jeroen Bosch Hospital, Amsterdam University Medical Centre, Amsterdam UMC) investigates the impact of drug recalls on patients and healthcare providers. His research will provide feedback to regulators on how best to communicate and reassure users of medicinal products in the Netherlands (see Pieter Annema's PhD project).

Sharon Essink (MEB, UU) provides a more general picture of risk management and minimisation measures during a product's lifecycle, building on the work of Remy (see Sharon Essink's PhD project). Moreover, Nafise Ghalandari (Erasmus MC) expands the work initiated by her colleague Ineke Crijns investigating how pregnancy prevention programmes contribute to the safety of medicines by identifying biologicals exposure levels in pregnancy and lactation (see Nafise Ghalandari's PhD project).

Finally, PhD student Aleksandra Opalska (European Commission) focuses on antimicrobial resistance – an area of major unmet need – where scarce new medicinal products must be safeguarded from inappropriate use, an area receiving much attention in the new 2023 EU pharmaceutical legislation. Post-authorisation evaluation of safety and effectiveness are clearly in the scope of the MEB. The described research primarily focuses on the regulator's toolbox to ensure its optimal use after a medicinal product is authorised so that the benefit-risk balance remains optimal.

> "The EMA and other regulatory agencies may use my findings to inform guideline development"

## Investigating Additional Risk Minimisation Measures for Medicines Authorised in the European Union

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*August 2015 - January 2023*

*Remy Francisca completed his PhD thesis and successfully defended it in January 2023.*

Remy graduated with a degree in medicine in 2013, after which he began working as a physician at Maasstad Hospital in Rotterdam in the Internal Medicine, Gastroenterology, Pulmonology and Cardiology Departments, along with the Emergency Room and Intensive Care Unit. Following two very instructive years, Remy successfully applied to become a doctoral researcher at the Erasmus MC Department of Medical Informatics under Prof Miriam Sturkenboom and Drs Sabine Straus and Inge Zomerdijk. In 2020, Remy began his training to become an internist. He worked briefly at IJsselland Hospital before transferring to Sint Franciscus Hospital to complete the non-teaching hospital portion of his training. He applied for the PhD position at the Erasmus MC, having always been interested in pharmacotherapy.

**What is your research topic?**
"Medicines are authorised in the EU when the benefits of taking the medicine outweigh the risks (the possible side effects that may occur). Sometimes, medicines may be associated with serious risks for

which aRMMs may be needed to reduce how often the risks occur or to reduce the risks' effects on the patient", Remy explains. "This is achieved by

- helping prescribers select patients in which the risks are less likely to occur
- helping prescribers and patients use the medicine as intended to prevent medication errors
- helping prescribers and patients to recognise early signs of the risks' occurrence
- helping prescribers manage the risks adequately once they have occurred".

**What are your main research questions?**

Remy investigated the following:

- How often aRMMs were needed at the time of authorisation, how often they were needed after authorisation and how often they became obsolete
- Which risks were most often minimised through additional measures
- How the risk of medication errors can be minimised
- How the effectiveness of aRMMs is assessed for medicines authorised with additional measures.

**How does your research connect to the MEB?**

"The MEB, in conjunction with the other regulatory agencies in the EEA and the EMA, is responsible for determining when aRMMs are needed and whether they are effective", Remy explains.

**Who will benefit from your research?**

Remy: "My research has contributed to the further understanding of additional risk minimisation. The EMA and other regulatory agencies may use my findings to inform guideline development".

> "To mitigate the impact of medicine shortages on patients, early identification is considered critical"

## Medicine Shortages

*Doerine J. Postma[1,2]*
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*November 2015 - December 2023*

After studying pharmacy in Groningen, Doerine Postma worked from 2004–2018 at the Royal Dutch Pharmacists Association (KNMP) Farmanco. KNMP Farmanco is the website providing pharmacists with up-to-date information on medicine shortages in the Netherlands. During this period, she became intrigued by the phenomenon of medicine shortages. Therefore, Doerine started as a professional PhD student. She currently works at the Dutch Foundation for Pharmaceutical Statistics (SFK), developing systematic searches for pharmacists to enhance the proper use of medicines.

**What are you focusing on in this research project?**
Medicine shortages are increasing all over the world, also Europe, also in the Netherlands. With increasing numbers of shortages, identifying shortages having high-patient impacts may help mitigate the impact of shortages on patients in a timely manner.

Doerine continues, “Medicine shortages impact patients. Due to shortages, patients may need to switch to another label with the same active substance, switch to medicines containing another active substance, postpone treatment or have treatment denied. These changes directly impact patients”. Doerine also explains the indirect impact of medicine shortages: “Indirect impact is due to HCPs having less time for medical care, as they redirect their time to solve medicine shortages. Furthermore, medicine agencies and other authorities must increase their capacity for preventing and mitigating the effects of medicine shortages”.

Whereas the direct impact on patients is clear, the indirect impact on health care and society is often overlooked. “We created a broad framework to assess the impact of shortages with different perspectives in mind, covering both the direct and indirect impact on patients”, Doerine explains.

Doerine offers, “To mitigate the impact of medicine shortages on patients, early identification is considered critical. We studied the timing of identification by authorities (before the Dutch Medicine shortages and Defects Notification Centre), Dutch pharmacists (KNMP Farmanco) and the public at large (Twitter)”.

**How would you describe the relevance of your research project?**
Medicine shortages affect the availability and accessibility of medicines for patients. Therefore, the Dutch authorities launched the Medicine Shortages and Defects Notification Centre in 2017. This notification centre is accompanied by a roadmap describing the various potential solutions for identifying and mitigating the impact of shortages and the roles of various actors (government, manufacturer, wholesale supplier, pharmacist and health insurer).

“Together, the notification centre and the roadmap aim to quickly identify and resolve shortages. The KNMP has a similar aim to the website KNMP Farmanco. By combining the world of the regulators (the MEB in particular) and pharmacists (KNMP), a unique cooperation in this field of research, a broader perspective is given on this topic”, Doerine explains.

**What impact will your research have on patients once it is done?**
“Various actors are trying to mitigate the impact of medicine shortages on patients. With increasing numbers of shortages, efforts should target those shortages with the highest patient impact for effective mitigation strategies”, Doerine explains.

"Women suffering from immune-mediated inflammatory diseases have a dilemma between stopping the biologics versus continuing them"

## Safety of Biologics During Pregnancy in Women With Immune-Mediated Inflammatory Diseases

*Nafise Ghalandari[1,4]*
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4. *Medicines Evaluation Board (MEB), Utrecht, The Netherlands*

*June 2017 - February 2023*

*Nafise completed her PhD thesis and successfully defended it in February 2023.*

Nafise Ghalandari obtained a Doctor of Medicine at the Tehran University of Medical Sciences in Tehran (Iran) in 2016. She graduated after a research project at the Departments of Neurology and Nuclear Medicine on the potential diagnostic value of 131I-MIBG myocardial scintigraphy for discrimination of Alzheimer's disease and Lewy-body dementia. Interested in clinical research, she joined the Rheumatology Department of the Erasmus MC in Rotterdam to conduct doctoral research on the use of biologicals during pregnancy. She combined her PhD project with working as a clinical assessor at the MEB, where she assessed the benefit-risk profile of new medicines (or new indications). As an extra challenge, from 2017 to 2021, she simultaneously completed a part-time master's degree in pharmacoepidemiology.

**What is the main focus of your PhD project?**
"When planning to become pregnant, women with immune-mediated inflammatory diseases (IMIDs) face many challenges", Nafise explains. "Due to lack of data, use during pregnancy is prohibited for many effective treatments (such as most biologics). Only a few treatment options are authorised to be used during pregnancy, but these options might not control the disease".

"Before authorisation, pregnancy data cannot be collected (as it is unethical to expose unborn children to unauthorised medications). Regretfully, thereafter, many of the MAHs fail to gather reliable evidence with respect to safety during pregnancy".

Women suffering from IMIDs have a dilemma between stopping the biologics versus continuing them. Nafise continues, "The outcome is either risk a flare of the disease or the lack of knowledge of the

consequences for the foetus". In her dissertation, Nafise attempts to fill in the knowledge gaps on using biologics during pregnancy in women with IMIDs.

**Who does this work impact? How is patient participation accounted for?**
The work done in this project impacts women of childbearing age suffering from IMIDs, "but it also impacts the work of rheumatologists, gastroenterologists, dermatologists, gynaecologists and regulators". In her project, Nafise uses retrospective and prospective data to answer her research questions through pharmacovigilance databases (EudraVigilance) and inclusion in a pregnancy cohort in Erasmus MC (PreCARA study).

**What is the relevance of your work?**
Based on current regulations, at least 300 prospectively collected pregnancies with no increased risk of congenital malformations (CMs) compared to the general population (around 3%) are needed to receive conditionally approved use during pregnancy. "Acquisition of this amount of prospective data will go together with high costs and requires time and resources", Nafise describes. "It will take years for some biologics to gather this amount of prospective pregnancy data".

Nafise and her colleagues also have noticed that, even if unintended pregnancy cases occur during phase 3 RCTs or the initial years of the postmarketing period, information on the outcomes of these pregnancies is not reflected in the SmPCs. Nafise elaborates, "Considering the crucial need for treatment in pregnant women with IMIDs and the consequences of active disease for mothers and their offspring, an earlier update of SmPCs, even with lower numbers, is advised. It is not implicated that lower numbers are needed for conditional approval to use during pregnancy, but this is an attempt to update the SmPCs as soon as possible with any amount of data available. Regulations regarding reflecting pregnancy data from periodic safety update reports (PSURs) into SmPCs, can add important information for clinicians, especially in earlier phases of the postmarketing period".

"It also appears that more collaboration is needed between physicians, regulators and MAHs to enhance the usability and transparency of pregnancy data in PSURs for clinical practice".

> "It became clear that the direct health-care professional communication (DHPC) is an important tool to inform healthcare professionals about new important safety issues of medicines. However, both studies also showed that actions following the DHPC were rare"

## Communicating Risks in a Hospital Setting, the Direct Healthcare Professional Communication in the Netherlands

*Esther de Vries[1,2]*
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2. *Medicines Evaluation Board (MEB), Utrecht, The Netherlands*

*November 2017 - June 2023*

Esther de Vries studied biomedical sciences, earning a Master in Infection and Immunology at the University of Amsterdam (UvA). While working as a researcher in driving safety studies, she stumbled upon a vacancy at the MEB that discussed combining a PhD project with working as a pharmacovigilance assessor. This combination of working activities spoke to her, and although it can be challenging sometimes, she describes it as really rewarding.

**What is the research topic of your PhD?**
After medicines are registered, new important safety issues can be identified. In order to minimise these important safety issues, regulators can choose to inform HCPs. "This form of communication is called a DHPC. To continue to use the medicine in a safe (and efficacious) manner, it is important a DHPC is effective. Unfortunately, studies have shown this is not always the case", Esther explains.

"In order to improve DHPCs' effectiveness, it is important to gain a better understanding of what happens when HCPs receive the DHPC and their preferences. Since HCPs working in hospitals are the biggest group of receivers of the DHPC, we focused our studies on hospital-based HCPs", Esther says.

She explains that the research aimed to gain insight into the procedures and practices of handling new drug safety information in Dutch hospitals. Esther continues, "In addition, we used hypothetical communications to increase our understanding of how specific characteristics of the safety issue influence the communication preferences and the behaviour of hospital-based HCPs. It became clear that the DHPC is an important tool to inform HCPs about new important safety issues of medicines. However, both studies also showed that actions following the DHPC were rare".

Esther says that the limited number of actions can partly be explained by a well-known point of criticism that the clinical implication of the reported safety issues in DHPCs are unclear or not made: "Based on our study results, we made recommendations on how to improve these clinical implications in future communications. Our recommendations will be further developed together with relevant stakeholders in a Regulatory Science Networks Netherlands expert meeting".

**You are nearly finished with your research. What impact do you think your research will have once it is complete?**
Esther: "Hopefully, our research will be the starting point of an optimised way of communicating new safety issues of medicines better aligned with the preferences of HCPs. This way, the impact of the communication will improve, and the burden DHPCs sometimes are for HCPs, will decrease".

**How does your research relate to the work of the MEB, and how is patient participation included?**
"As a regulatory agency, the MEB is involved in the process of the DHPC on a European and national level", Esther explains.

"In our first studies, we did not include patients since the communication was not intended for them, and we tried to gain a better understanding of how DHPCs were handled by their current receivers. In our final studies to improve our recommendations, a patient representative will be included", Esther explains. "Although the DHPC does not target the patient directly, it can reach the patient through (social) media, and it does concern medicines patients might take".

> "Eventually, effective risk minimisation will reduce the occurrence and/or severity of adverse events and will thus benefit patients"

## Risk Management and Risk Minimisation Measures During the Lifecycle of a Product

*Sharon C. M. Essink*[1,2]
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*December 2021 - December 2026*

In 2021, Sharon Essink obtained her master's degree in biomedical sciences at the Radboud University in Nijmegen. During her master's, she focused on epidemiology and clinical pharmacology/toxicology. Shortly after graduation and a temporary job at the Nationaal Vergiftigingen Informatie Centrum, Sharon came to the MEB and Utrecht University to start a PhD project. She also works as a pharmacovigilance assessor at the MEB (50% of the time).

**What are you researching for your PhD project?**
The European Union Risk Management Plan (EU-RMP) is important in the proactive life cycle management of medicines and facilitates identifying, characterising, monitoring and minimising risks. "Within the EU-RMP, the risk minimisation plan describes the measures that aim to prevent the occurrence and/or severity of adverse drug reactions (i.e. risk minimisation measures)", Sharon explains. Routine risk minimisation measures, such as product information, are in place for all medicines. Sharon offers, "Some medicines may be associated with important risks for which aRMMs are needed to ensure a positive benefit-risk balance. Examples of aRMMs are educational materials and pregnancy prevention programmes".

Sharon elaborates that evaluation of the effectiveness of aRMMs is needed to determine whether risks are sufficiently minimised when the medicine is used in clinical practice and whether aRMMs may be stopped or amended. "Both quantitative and qualitative research can be used in these evaluations. The overall aim of this PhD project is to provide insight into effective risk minimisation measures during the lifecycle of medicines".

The first study within this project focuses on the duration of aRMM effectiveness evaluations (e.g. the time needed from MA to the final recommendation by the Pharmacovigilance Risk Assessment Committee [PRAC]).

**How does your PhD project connect to the work of the MEB?**
Sharon: "The topic of my PhD project is closely linked to the pharmacovigilance department of the MEB. The results of my PhD project may give insight into how to improve future aRMMs and aRMM effectiveness studies". She explains that the results may be used to improve various good pharmacovigilance practices (GVP) guidelines on risk management and risk minimisation.

**Your research focuses on risk minimisation. What impact will your research have on the field once it is complete?**
"Insight into effective risk minimisation is beneficial for regulators. As stated before, the results of my research may be of added value in the regulatory field and give additional knowledge for improving the GVP guidelines. Eventually, effective risk minimisation will reduce the occurrence and/or severity of adverse events and will thus benefit patients", Sharon explains.

**Is it already clear if you will include patient participation in your research?**
Sharon explains that how and whether patient participation can be included in a substudy of the PhD project should still be discussed. She gives an example where survey data of patients may be used to make suggestions for improvement of aRMM in clinical practice.

"Through finding out what patients consider important about a drug recall and what kind of information they want to receive and from whom they want to receive that information, drug recalls can be tailored more to patients"

## Impact of Drug Recalls on Patients and Healthcare Providers

*Pieter Annema[1,2]*
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*January 2022 - December 2026*

Pieter Annema studied pharmacy in Groningen and then worked at the Medical Centre Leeuwarden for one year. In 2021, he started his pharmacy residency at the Jeroen Bosch Hospital and the Radboud MC. During the first year of his residency, he developed several research ideas, which ended up in a PhD project in collaboration with the MEB and Health and Youth Inspectorate (IGJ).

**Your research focuses on drug recalls. Can you elaborate on that?**
"The production of drugs is subject to strict quality controls to prevent patients from being exposed to defective or contaminated drugs. If a product defect is discovered in a batch of drugs that is already distributed and in use by patients, the drug may be recalled", Pieter explains. "We don't really know what the impact of drug recalls is on patients and healthcare providers".

Publicity and actions surrounding a drug recall may positively or negatively influence patient confidence in drugs. Pieter explains, "An increase or decrease in drug confidence may lead to a change in medication adherence which in turn impacts clinical outcomes. Moreover, a drug recall impacts healthcare providers such as pharmacists and physicians and requires a significant amount of their time and money ultimately paid for by society". Pieter says that drug recalls' potential benefits and risks should therefore be carefully weighed. "Research into these dilemmas is relatively absent".

**What does this mean for the MEB?**
Pieter explains that the IGJ and the MEB receive notification of a product defect from MAHs in the Netherlands. “The inspectorate consults with the MEB if and how a drug recall should be performed”. Pieter points out that by recalling drugs from the market, both parties aim to protect patients against defective products and thereby increase the public’s trust in pharmacovigilance by the government.

“With this research project, we want to determine the impact of drug recalls on patients and healthcare providers. The results of this project could aid the Inspectorate and the MEB in decision-making surrounding drug recalls in the future”.

**How would your research eventually help patients?**
Pieter had said that the Inspectorate and MEB could use the results of their research to improve decision-making surrounding drug recalls: “Through finding out what patients consider important about a drug recall and what kind of information they want to receive and from whom they want to receive that information, drug recalls can be tailored more to patients”, Pieter adds. “By doing so, patient trust in drugs and medication adherence could improve. Ultimately this research can impact patients, healthcare providers and policymakers”.

**Is patient participation also included in the research?**
Pieter: “The impact of drug recalls on patients will be analysed through qualitative research. In one study, we are designing and performing focus groups with patients. In a follow-up study, we will use the results from the focus groups to develop an online questionnaire sent to a large patient panel. In another study, we try to quantify the acceptance level between drug efficacy and safety through discrete choice experiments with patients”.

## 4.9 Other developments

### 4.9.1 Male/female differences

Attention to sex differences is increasingly important in drug development, treatment and monitoring. Initially, the discussion focused on whether women are underrepresented in clinical trials, as this might explain why women report more adverse reactions than men after marketing authorisation has been granted. Currently, the focus of the discussion is shifting towards recognising sex differences in the pathophysiology of diseases and addressing that so-called non-specific symptoms may be specific indeed in women. A better understanding of these differences is paramount to improving diagnosing and treating both men and women, which may positively affect (personalised) pharmacotherapy in the future.

The regulator’s task is to ensure that effective and safe medicines are available for all patients, irrespective of sex. Thus, the evidence from studies with an experimental drug should be assessed with this in mind. Meanwhile, in establishing the benefit-risk ratio, it remains challenging to determine which data are important for healthcare practitioners and how to best present them in the label and the public domain while considering legislative consequences. It is essential that this discussion occurs with all stakeholders based on solid scientific evidence.

In the past two years, the MEB initiated or participated in the following research projects:

- *Sex Proportionality in Preclinical and Clinical Trials: An Evaluation of 22 MAA Dossiers Submitted to the EMA*. This study aimed to assess to what extent women were included in all phases of drug development for various diseases (e.g. hepatitis C, HIV, heart failure, diabetes mellitus) using the information in the MAA dossiers. We additionally assessed whether information on efficacy and

safety was available per sex and explored whether women and men differed in the efficacy and safety of the various drugs (Dekker et al., 2021).

- *Attention to Sex in COVID-19 Trials: A Review of Regulatory Dossiers.* This study is similar to the one mentioned above, conducted among the COVID-19 treatments and vaccines (De Vries S et al., 2022).
- *Methodology for Sex-Specific Safety Analysis by Thoroughly Analysing the Case of Denosumab (a Treatment for Osteoporosis).* Considering that women report more adverse events than men, even when treated with a placebo, this master's thesis aimed to describe a method for identifying adverse drug reactions with a clear sex difference. The methods may also be suitable for other patient groups, such as those based on ethnicity.

Currently, the following projects are ongoing:

- *Selective Serotonin Reuptake Inhibitor (SSRI) Treatment for Patients with Obsessive-Compulsive Disorder: Optimising Clinical Trials and Treatment Response.* Within this project, sex differences in response to treatment with selective serotonin reuptake inhibitors (SSRIs) are examined in patients with obsessive-compulsive disorder (OCD) using individual patient data meta-analysis.
- *Gender Differences in Pivotal Registration Trials in Antipsychotic Medications for Schizophrenia and Acute Mania.* This project examines whether gender and menopausal status moderate the response to antipsychotic medication in patients with schizophrenia and acute mania, using individual patient data meta-analysis (Storosum et al., 2023).
- *Sex Differences in the Safety Profile of New Medicines Recently Approved by the EMA.* This study uses a methodology for sex-specific safety analysis recently developed by the MEB to evaluate if adverse drug reactions with a clear gender bias can be identified in recently approved products.

In the future, the MEB intends to move towards more personalised medicines research, simultaneously considering the patient's unique individual characteristics, including age and ethnicity, to contribute to the optimal choice of individualised therapy for each person.

"Appropriate enrolment of women and people of all ethnicities in these clinical trials and specific analysis of data on both gender and ethnicity may be critical for the expected efficacy, dosing and safety of therapeutic agents"

## Marginalised Groups in Registration Trials of Antipsychotics and Mood Stabilisers for Schizophrenia and Acute Mania

*Bram Storosum[1]*
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5. *Arkin Institute for Mental Health, Amsterdam, The Netherlands.*

*July 2019 - October 2024*

Bram Storosum obtained his master's degree in medicine in 2019. He is interested in the optimal evidence-based uses of psychotropic medication, which led him to start his PhD project at the MEB alongside his residency in psychiatry at the Amsterdam UMC, combining clinical practice and research.

**What is your research topic, and what are your main research questions?**
Schizophrenia and acute mania are the leading causes of disability worldwide, affecting both genders and all ethnicities. "In schizophrenia and acute mania, although gender differences in incidence per age category are found, there is no gender difference in the various prevalence measures. Similarly, these disorders have equal prevalence across different ethnicities. Antipsychotic medication and mood stabilisers have been proven effective in pivotal clinical trials for these disorders", Bram explains.

However, women are underrepresented in pivotal drug trials conducted on patients with schizophrenia, which are not powered to infer reliable gender-specific similarities or differences in effect. Bram continues, "In acute mania, there are indicators for differences between genders, for example, in aetiology and course of the disease. However, differences in the effect size of antipsychotic

medications remain underinvestigated. There are also indicators that ethnicity impacts the effect size of antipsychotics and mood stabilisers. In the public domain, pivotal drug trials are inconsistent in reporting subjects' ethnicity, making it impossible to perform ethnicity-specific analysis".

"Appropriate enrolment of women and people of all ethnicities in these clinical trials and specific analysis of data on both gender and ethnicity may be critical for the expected efficacy, dosing and safety of therapeutic agents. Furthermore, specific analyses concerning gender and ethnicity may yield valuable information for clinical practice", Bram adds.

**How does this work connect to the work of the MEB?**
In recent years, there has been an increased societal interest in the subjects of gender and ethnicity, especially in the context of the treatment of women and ethnic minorities. "The MEB is interested in investigating to what extent it is recommended that women and ethnic minorities should be specifically researched in registration trials in this field", Bram explains. "The aim of this project is to explore the difference in effect size between men and women and people of different ethnic subgroups suffering from schizophrenia and acute mania through individual patient data meta-analysis of placebo-controlled registration trials for antipsychotic medication and mood stabilisers".

Bram: "Where applicable, steps for the assessment of future clinical trials and regulatory studies, with regard to gender and ethnicity, will be recommended".

**What impact will your research have, and for whom?**
Bram's research is based on individual patient data obtained between 1991 and 2004. Through this research, suggestions may be made regarding the guidelines for treating schizophrenia and acute mania. "This project furthers the understanding and awareness of gender and ethnic differences both in regulatory science and clinical practice", Bram explains. "Therefore, it might also impact patients".

"Approximately 50% of patients fail to respond adequately to initial first-line pharmacological treatment, even with the best available treatments"

## SSRI Treatment for Patients With Obsessive-Compulsive Disorder: Optimising Clinical Trials and Treatment Response

*Sem E. Cohen*[1]
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*December 2021 - December 2025*

Sem Cohen studied medicine at the UvA/Amsterdam UMC and has been working as a psychiatrist in training for three years. His area of research was previously on machine learning for response prediction, but he grew very curious about how large clinical trials are conducted and how study characteristics influence study outcomes. The Amsterdam UMC has some experience collaborating with the MEB, as they have worked together on PhD projects from multiple earlier PhD candidates. Their work intersected with his topics of interest, and after exploring possible avenues for a new collaboration, Sem and his co-promotors decided to take up his current project.

**What is the topic of your PhD?**
Selective serotonin receptor inhibitors (SSRIs) were established as the first-line pharmacological treatment for obsessive-compulsive disorder (OCD) in the 1990s following a large number of double-blind, randomised controlled trials (RCTs). "Despite evidence that key demographic and clinical variables can influence clinical response and dropout, trials all included patients with OCD regardless of symptom profile and without any meaningful stratification", Sem explains. "From a clinician's perspective, treatment selection for OCD patients is based on trial and error, with no possibility to reliably predict an individual's response to a certain treatment". Sem explains that, consequently, patients are regularly exposed to multiple failed treatments and can wait months to years for successful treatment for their OCD symptoms.

Sem: "While associations between demographic and clinical factors and SSRI treatment outcomes have been shown, datasets from individual trials are too small to allow generalisable conclusions. In this PhD

project, we will conduct individual participant data meta-analyses (IPDMA) pooling SSRI trial data to address this limitation". According to Sem, this analysis will enable the improvement of treatment outcomes by identification of markers of treatment success which, before treatment commencement, can inform clinicians of the chance of responding to a particular treatment. "Furthermore, we will identify whether study characteristics such as the number of intervention arms and the use of placebo run-in impact the shown efficacy".

**What is the relevance of your project?**
Sem: "Approximately 50% of patients fail to respond adequately to initial first-line pharmacological treatment, even with the best available treatments. The findings of our research could shorten illness duration by guiding treatment regimens and could facilitate efficiency and lower costs of clinical drug development for OCD patients". Sem also explains that they will use anonymised data from participants from placebo-controlled OCD trials.

**How does this connect to the work of the MEB?**
Sem explains that due to its task, the MEB has appropriate and important data and documents required for his research. The result of his research contributes to improving and updating the development of medicines by the industry and the assessment of those medicines by the authorisation authorities, like the MEB.

**What impact do you think this research will have once it is done?**
"With our project, we aim to extract clinical biomarkers from placebo-controlled RCTs for OCD medication to positively impact the standard of care in patients suffering from OCD", Sem says. "The conclusions of my research on the influence of study characteristics on efficacy could hopefully be incorporated in the next EMA guideline", he adds.

### 4.9.2 Sustainability

Protecting the environment is important in every way, including preserving biodiversity, combating climate change and preventing unintentional exposure to substances potentially harmful to humans, flora and fauna. Therefore, the MEB investigates where it can contribute to a healthier living environment, focusing on medicines that eventually end up in the environment through use or waste. To this end, the internal Working Group Medicines and Environment was established at the end of 2022. The working group members represent various scientific and regulatory disciplines and are all highly motivated to think through environmental issues while providing input on the issues at stake.

The Environmental Risk Assessment (ERA) is part of the dossier for medicinal product applications received by the MEB. In cases where a more in-depth assessment (phase II) of the ERA is needed, the MEB collaborates closely with the RIVM, which performs the assessment.

Last year, in collaboration with Utrecht University, different perspectives of multiple stakeholders on the ERA were investigated. The ERA is currently not decisive in concluding whether to issue a marketing authorisation for the medicinal product. Therefore, the project will also highlight possible regulatory options to increase the relevance of the ERA. In addition, the newly proposed EU pharmaceutical legislation will strengthen the environmental aspects of the ERA related to manufacturing.

Furthermore, the MEB has an advisory role in the NWO (Top Sector Water & Maritime) project PsychoPharmac'eau (UvA /Wageningen University & Research [WUR]/Netherlands Institute of Ecology [NIOO]). This project studies the possibilities of reducing emissions and effects of psychopharmaceu-

ticals in water through improved regulation, developing environmentally friendly alternatives and providing a better understanding of ecosystem effects and mitigation through water treatment and nature-based solutions.

### 4.9.3 STARS: Strengthening Training of Academia in Regulatory Science

STARS was a three-year project, including most of the European national competent authorities (NCAs) and the EMA. The goal of STARS was to advance academic drug development by improving the interaction and knowledge exchange between academics and regulators. Four surveys laid the foundation for understanding the awareness and utilization of support tools offered by European regulators and identified researchers' regulatory challenges and support needs. The surveys targeted four main European stakeholders in academic medicines research, who responded in unprecedented numbers: 706 academic research groups, 99 academic research centres, 49 funding organisations and 22 medicines agencies (Kallio et al., 2023). As a result, STARS has made 21 recommendations in five strategic areas (Starokozhko et al., 2023). These recommendations address the main gaps and barriers identified in the current regulatory support system, and aim to optimise the interaction between academic drug developers and EU regulatory authorities:

- A lack of communication between regulators and academia
- A lack of awareness and use of regulatory support tools by academia
- Insufficient regulatory knowledge among academics
- Suboptimal alignment of regulatory support with the needs of academia
- Suboptimal downstream interaction with industry

Within the Heads of Medicines Agencies (HMA)-EMA EU Innovation Network, regulatory agencies will continue implementing the recommendations of the STARS project. For example, the STARS project findings will be fed into the Accelerating Clinical Trials in the EU (ACT EU) Accelerating Clinical Trials in the EU (ACT EU) | European Medicines Agency (europa.eu) project, launched in 2022 by the European Commission, HMA and the EMA. This project aims to integrate regulatory scientific advice activities and downstream (health technology assessment) and upstream (clinical trial approval) bodies to create a competitive EU trial landscape, particularly for investigator-initiated (academic) trials.

### 4.9.4 European Medicines Regulatory Database

Data about drug regulation are of great value to stakeholders – drug developers, regulatory scientists, HCPs, patients and regulators – to aid consistent decision-making. However, in Europe, data about regulated drugs are dispersed over various websites and numerous documents per medicine, which are often highly technical due to the complex legal and regulatory framework. Consequently, stakeholders can poorly access, understand and use these data. In collaboration with Utrecht University, the MEB is developing the European Medicines Regulatory Database (EMRD): an up-to-date, website-based dashboard that centralises and contextualises data about authorised medicines and orphan designations (ODs) granted by the EMA since its establishment in 1995. The EMRD combines data scraped from the EMA website and the European Commission's Union Register of medicinal products and a broad array of legal and regulatory documents on these websites. These documents include all drug labels, legal decisions and assessment reports ever published for each drug. Up to 31 December 2022, the EMRD's algorithms had accessed over 60,000 documents and extracted almost 70 variables (i.e., drug, disease, legal and regulatory characteristics) of 1,648 drugs and 292 ODs. The dashboard explains these characteristics, their legal and regulatory history, and options to download, visualise or analyse selected data or upload additional user-generated data. We will make the EMRD openly available in 2023 and are confident that it will enhance accessibility, understanding and the (consistent) use of European regulatory data.

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This reference overview is not a complete overview of all MEB-related publications. For a full list of references with the involvement of the MEB, click here.


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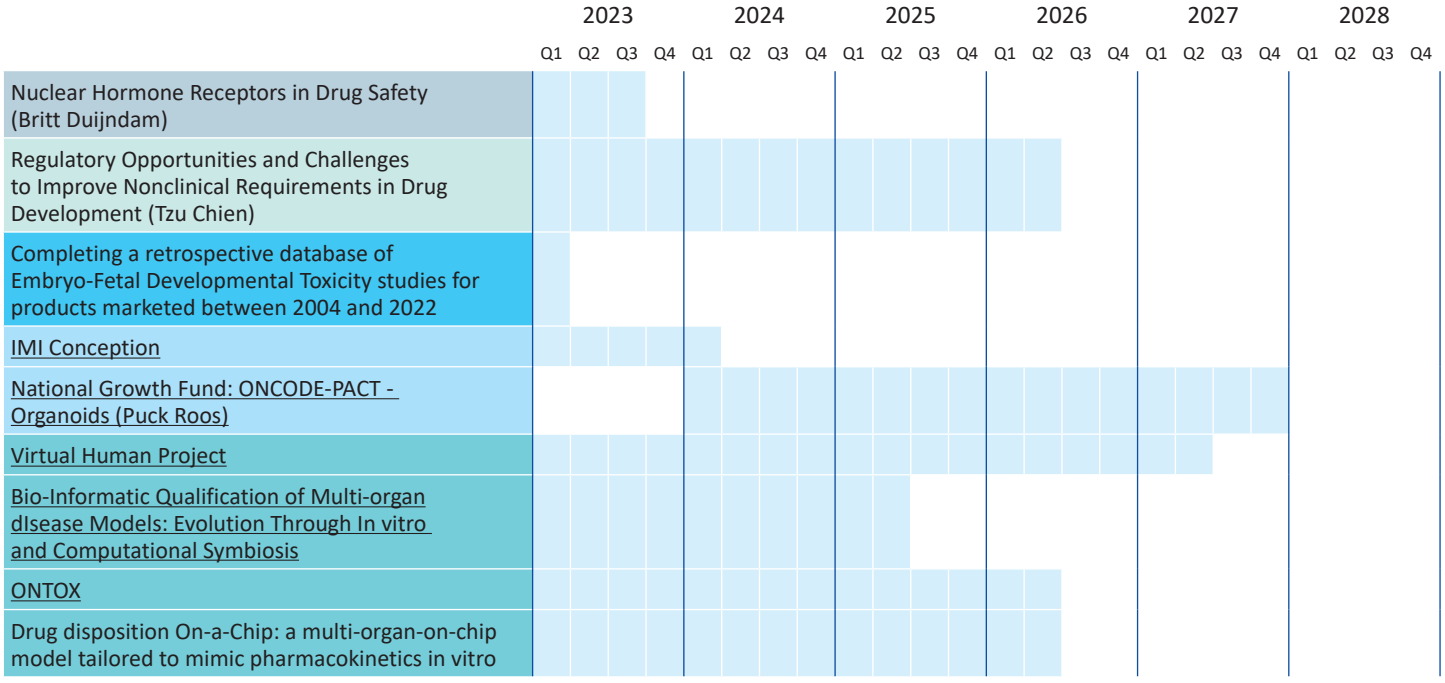
# Appendix 1
# Overview of Regulatory Science Projects

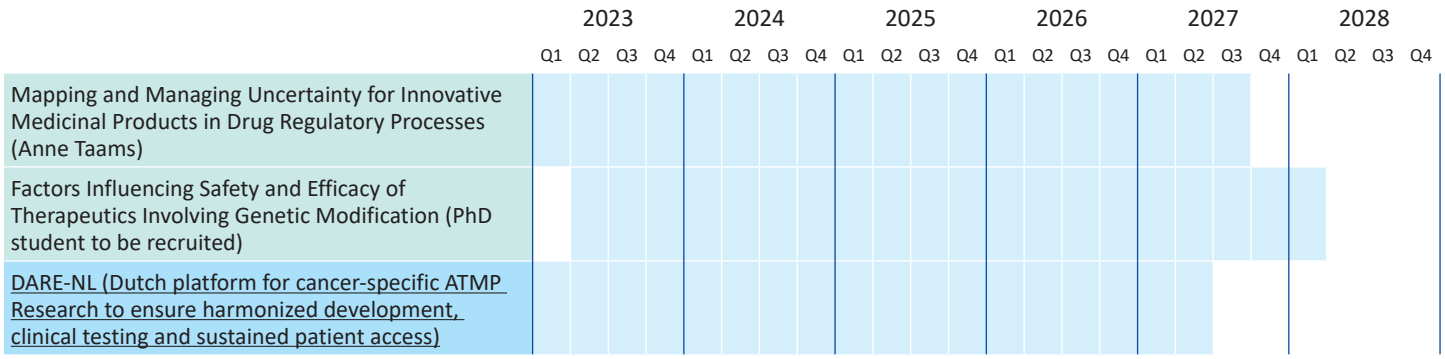
### Legend

| |
|---|
| MEB PhD-trajectory |
| Contract MEB PhD-trajectory has ended, promotion ceremony has yet to take place |
| External PhD-trajectory, MEB is involved as a supervisor |
| MEB research |
| Project with external financing |
| Participation in advisory board |
| Miscellaneous |

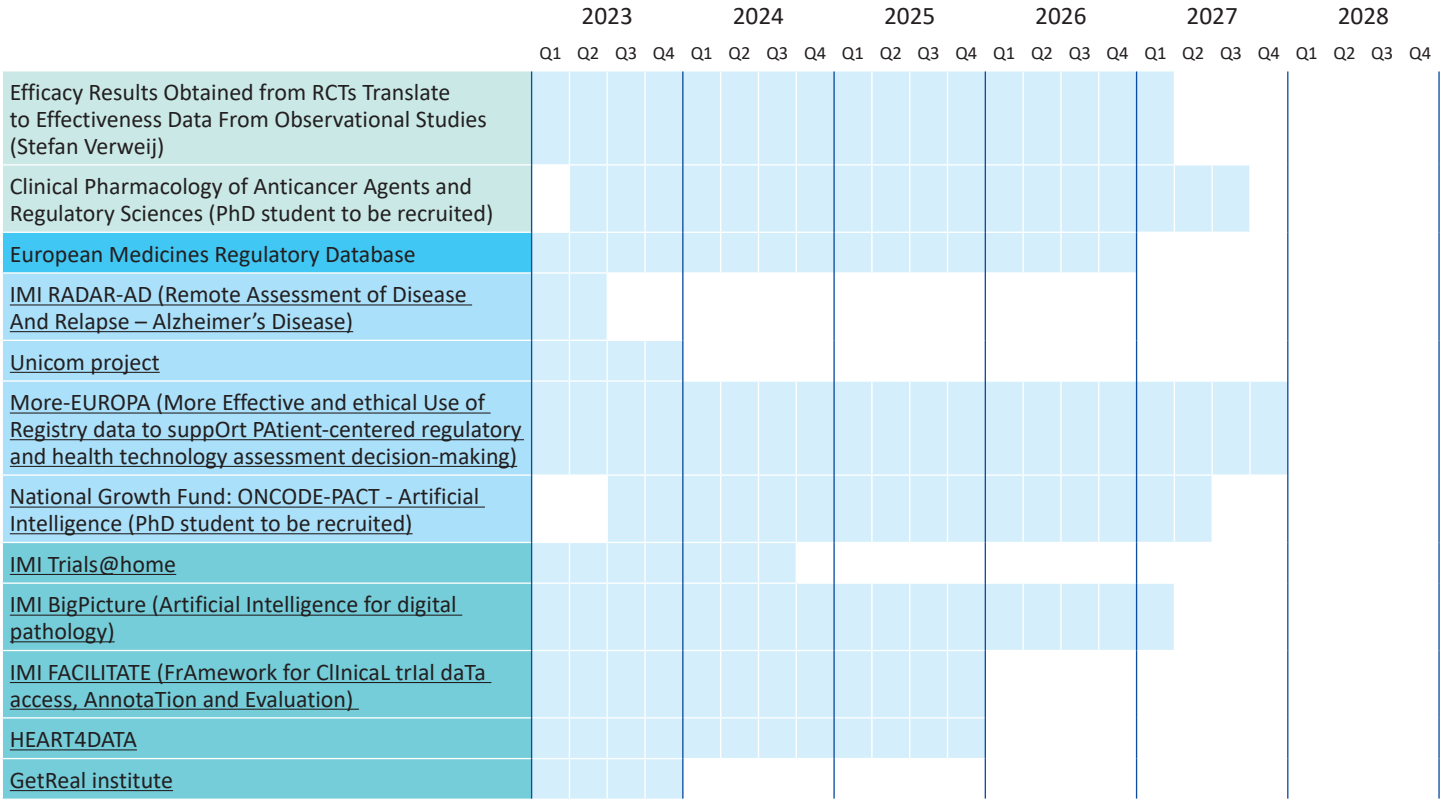
### Theme 1: Replacement, reduction and refinement of animal tests (3Rs)



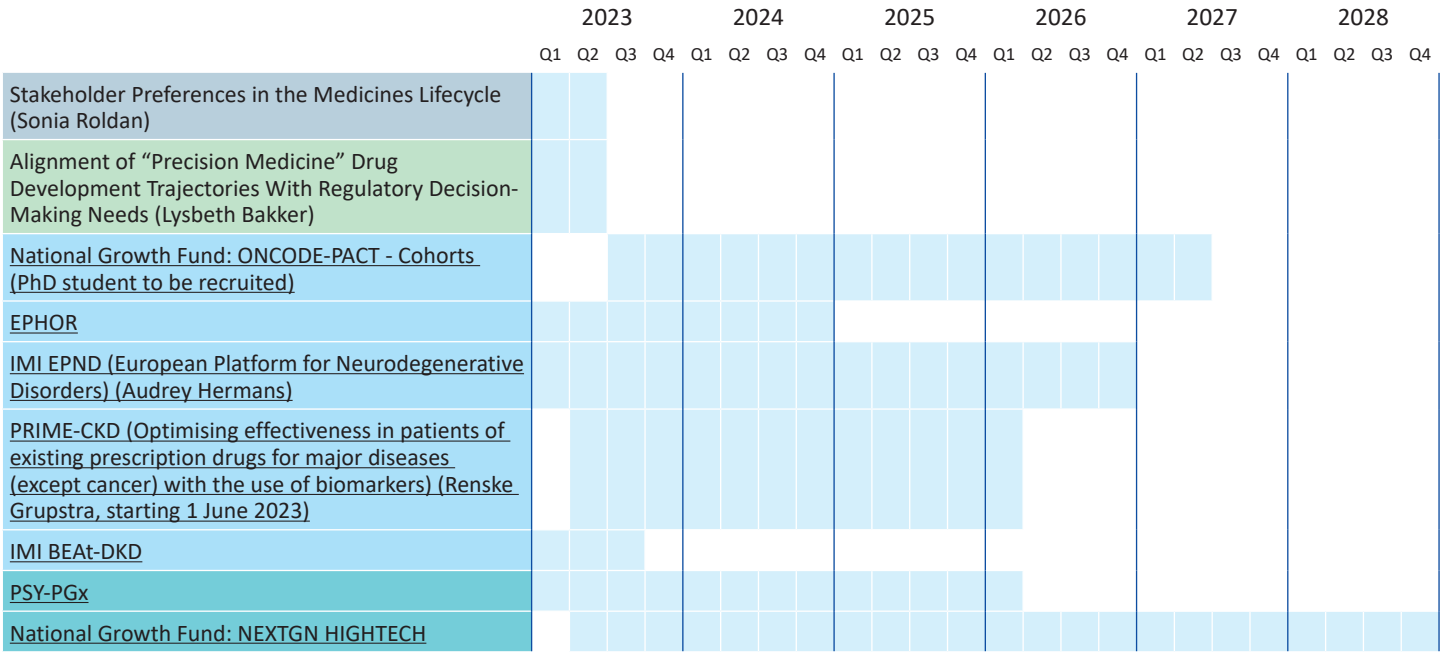

### Theme 2: Advanced Therapy Medicinal Products (ATMPs)



## Theme 3: Data-driven assessment



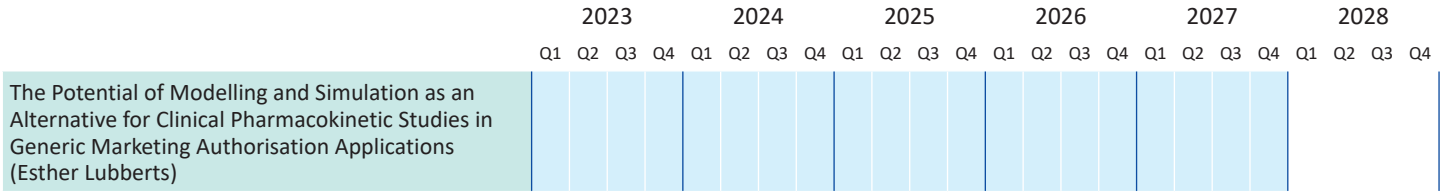

## Theme 4: Personalised medicine & biomarkers



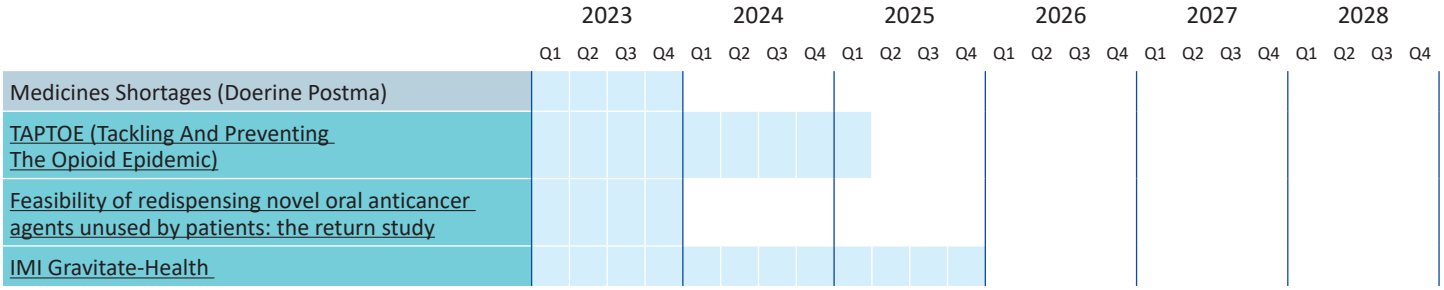

## Theme 5: Medical Devices

No dedicated regulatory science projects are conducted at the current time.

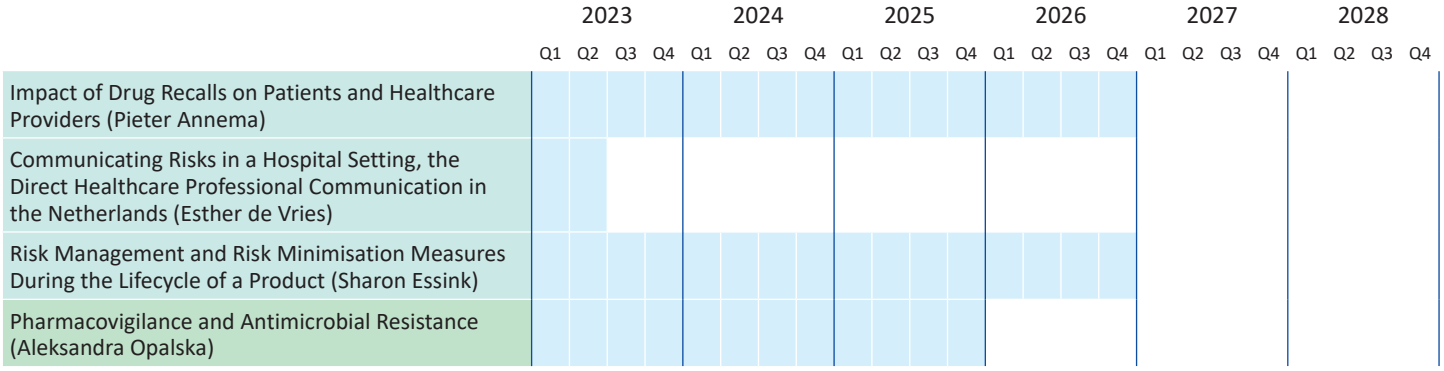
## Theme 6: Generics



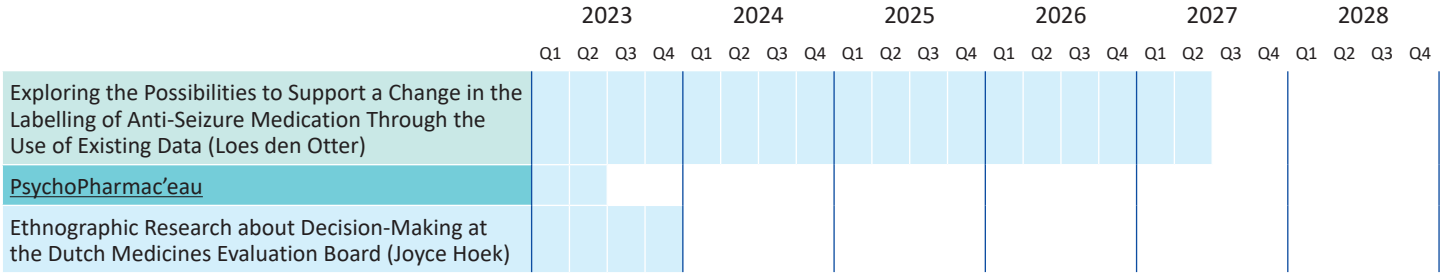

## Theme 7: Medicines Used Better



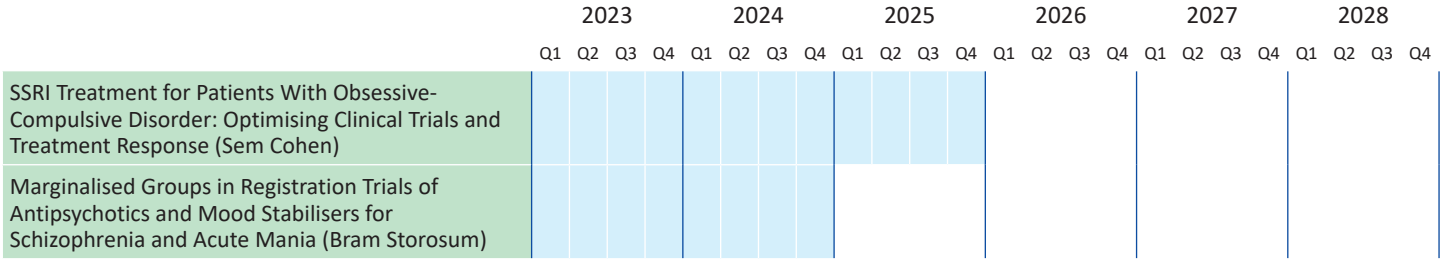

## Theme 8: Safety and effectiveness after authorisation




## Other developments




## Male/female differences



# Appendix 2
# Overview of PhD Theses

| PhD-Student | Title | Affiliation | Supervisors | Date of defence |
|---|---|---|---|---|
| **Pieter Glerum** | Generic interchangeability: between science and regulation | *Maastricht University* | Prof C. Neef, Prof D. M. Burger, Dr M. Maliepaard | 3/29/2023 |
| **Désirée Veening-Griffioen** | Selection of animal models for drug efficacy | *Utrecht University* | Prof E. H. M. Moors, Prof H. Schellekens, Dr P. J. K. van Meer, Dr W. P. C. Boon | 3/17/2023 |
| **Nafise Ghalandari** | Safety of Biologics during Pregnancy in Women with Immune-mediated Inflammatory Diseases | *Erasmus University Rotterdam* | Prof J. M. W. Hazes, Prof E. P. van Puijenbroek, Prof R. J. E. M. Dolhain, Dr H. J. M. J. Crijns | 2/23/2023 |
| **Jorn Mulder** | The authorisation of anti-cancer medicinal products; Clinical benefit, precision medicine and regulatory flexibility | *Utrecht University* | Prof A, de Boer, Prof E. E. Voest, Dr V. V. Stoyanova-Beninska, Dr A. M. G. Pasmooij | 1/25/2023 |
| **Remy Francisca** | Investigating additional risk minimisation measures for medicines in the European Union | *Erasmus University Rotterdam* | Prof M. C. J. M. Sturkenboom, Dr S. M. J. M. Straus, Dr I. M. Zomerdijk | 1/17/2023 |
| **Marian Mitroiu** | Estimands in clinical drug development: from design to regulatory assessment | *Utrecht University* | Prof K. C. B Roes, Dr K. Oude Rengerink, Dr S. Teerenstra | 12/12/2022 |
| **Christel Hoeve** | Medication Errors - Through the eyes of the regulator and governmental bodies | *Erasmus University Rotterdam* | Prof M. C. J. M. Sturkenboom, Dr S. M. J. M. Straus | 9/28/2022 |
| **Rawa Ismail** | Real-world data in cancer treatment - Bridging the gap between trials and clinical practice | *Utrecht University* | Prof A. de Boer, Prof M. W. J. M. Wouters, Dr D. L. Hilarius, Dr M. van Dartel | 5/18/2022 |
| **Carla Jonker** | Rare disease registries: A must for regulatory decision making | *Utrecht University* | Prof A. W. Hoes, Prof P. G. M. Mol, Dr H. M. van den Berg | 2/15/2022 |
| **Lourens Bloem** | Evidence generation on benefits and risks of medicines and its impact on regulatory and downstream decision-making | *Utrecht University* | Prof A. K. Mantel-Teeuwisse, Prof O. H. Klungel, Dr. J. Hoekman, Dr M. E. van der Elst | 11/24/2021 |
| **Lotte Minnema** | Post-marketing safety learning for biologicals: regulatory and clinical insights | *Utrecht University* | Prof H. G. M. Leufkens, Prof A. C. G. Egberts, Dr T. J. Giezen, Dr H. Gardarsdottir | 6/28/2021 |
| **Renske ten Ham** | Development, market authorization and market access of gene and cell-based therapies | *Utrecht University* | Prof O. H. Klungel, Prof H. G. M. Leufkens, Dr J. Hoekman, Dr G. W. J. Frederix | 6/4/2021 |
| **Guilherme Ferreira** | Tools to enable animal to human translation: Assessing the value of disease models | *Utrecht University* | Prof H. Schellekens, Prof E. H. M. Moors, Dr P. J. K. van Meer, Dr W. P. C. Boon | 1/22/2021 |
| **Jeroen Koomen** | Pharmacokinetic insights in individual drug response: A model-based approach to quantify individual exposure-response relationships in type 2 diabetes | *Groningen University* | Prof H. J. Lambers Heerspink, Prof P. G. M. Mol, Dr J. Stevens | 1/18/2021 |
| **Charlotte de Wolf** | Regulating the regulators - Monitoring immune mechanisms in targeted therapies | *Utrecht University* | Prof W. van Eden, Prof F. Broere, Dr M. H. N. Hoefnagel | 10/11/2018 |
| **Alexandra Pacurariu** | The role of signal detection in Pharmacovigilance | *Erasmus University Rotterdam* | Prof M. C. J. M. Sturkenboom, Dr S. M. J. M. Straus | 7/6/2018 |
| **Yvonne Schuller** | Mind the gap - Bridging the difference between efficacy and effectiveness of orphan drugs | *University of Amsterdam* | Prof C. E. M. Hollak, Dr M. Biegstraaten, Dr V. V. Stoyanova-Beninska | 7/4/2018 |

# List of abbreviations

| | |
|---|---|
| **3Rs** | replacement, reduction and refinement of animal tests |
| **ACT EU** | accelerating clinical trials in the EU |
| **ADRs** | adverse drug reactions |
| **Amsterdam UMC** | Amsterdam university medical centre |
| **aRMM(s)** | additional risk minimisation measure(s) |
| **ASM** | anti-seizure medication |
| **ATMPs** | advanced therapy medicinal products |
| **BR** | benefits and risks |
| **CAR** | chimeric antigen receptor |
| **CAT** | committee for advanced therapies |
| **CCMO** | central committee on research involving human subjects |
| **CKD** | chronic kidney disease |
| **CMs** | congenital malformations |
| **DART** | developmental and reproductive toxicity |
| **DGMs** | data-generating models |
| **DHPC** | direct healthcare professional communication |
| **EEA** | European economic area |
| **EMA** | European medicines agency |
| **EMRD** | European medicines regulatory database |
| **EPAA** | European partnership for alternative approaches to animal testing |
| **EPHOR** | expertise centre pharmacotherapy in old persons |
| **EPND** | European platform for neurodegenerative diseases |
| **ERA** | environmental risk assessment |
| **Erasmus MC** | Erasmus medical centre |
| **Erα** | oestrogen receptor alpha |
| **EU** | European union |
| **EU-IN** | EU innovation network |
| **EU IVDR** | European union in-vitro diagnostics regulation |
| **EU-RMP** | European union risk management plan |
| **FAST** | future affordable and sustainable therapies |
| **FIMD** | framework to identify models of disease |
| **GVP** | good pharmacovigilance practices |
| **HCPs** | healthcare professionals |
| **HESI** | health and environmental sciences Institute |
| **HMA** | heads of medicines agencies |
| **ICH** | international council for harmonisation of technical requirements for registration of pharmaceuticals for human use |
| **IGJ** | health and youth inspectorate |
| **IMI** | innovative medicines initiative |
| **IMIDs** | immune-mediated inflammatory diseases |
| **IPDMA** | individual participant data meta-analyses |
| **IRDiRC** | international rare diseases research consortium |
| **IVDR** | in-vitro diagnostic medical devices regulation |

| | |
|---|---|
| **KNAW** | royal Netherlands academy of arts and sciences |
| **KNMP** | royal Dutch pharmacists association |
| **LACDR** | Leiden academic centre for drug research |
| **LAIs** | long-acting injectables |
| **LNV** | ministry of agriculture, nature and food quality |
| **MAA(s)** | marketing authorisation application(s) |
| **mAbs** | monoclonal antibodies |
| **MAH(s)** | marketing authorisation holder(s) |
| **MDR** | medical device regulation |
| **MEB** | medicines evaluation board |
| **M&S** | modelling and simulation |
| **NAMs** | new approach methods |
| **NCAs** | national competent authorities |
| **NC3Rs** | national centre for the replacement, refinement and reduction or animals in research |
| **NHPs** | non-human primates |
| **NIOO** | Netherlands institute of ecology |
| **NIVEL** | Netherlands institute for health services research |
| **NMAs** | network meta-analyses |
| **OCD** | obsessive convulsive disorder |
| **OD** | orphan designation |
| **OECD** | organisation for economic co-operation and development |
| **PBPK** | physiology-based pharmacokinetic(s) |
| **PIL** | patient information leaflet |
| **PK** | pharmacokinetic(s) |
| **PopPK** | population-pharmacokinetic(s) |
| **PPI** | proton pump inhibitor |
| **PRAC** | pharmacovigilance risk assessment committee |
| **PSURs** | periodic safety update reports |
| **Radboud MC** | Radboud university medical centre |
| **RCTs** | randomised controlled trials |
| **RIVM** | national institute for public health and the environment |
| **RSNN** | regulatory science network Netherlands |
| **RUG** | university of Groningen |
| **RWD** | real-world data |
| **RWE** | real-world evidence |
| **SFK** | foundation for pharmaceutical statistics |
| **SmPC** | summary of product characteristics |
| **SSRI(s)** | selective serotonin receptor inhibiter(s) |
| **STARS** | strengthening training of regulatory science in academia |
| **UIPS** | Utrecht institute for pharmaceutical sciences |
| **UMCG** | university medical centre Groningen |
| **UMCU** | university medical centre Utrecht |
| **UU** | Utrecht university |
| **UvA** | university of Amsterdam |
| **VIG** | Dutch association of innovative medicines |
| **VWS** | ministry of health, welfare and sport |
| **WUR** | Wageningen university & research |
| **ZIN** | national health care institute |

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