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Drug Regulatory Science
Collaborate to improve drug development and evaluation

Inaugural lecture

25 November 2022

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Inaugural lecture by

Prof. dr. Peter G.M. Mol

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On acceptance of the post of professor of

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Dear Members of the University Board,
Dear colleagues, friends and students,

Today, I have the pleasure to talk to you about Drug Regulatory Science. I will explain why science of drug regulation is important, and how collaboration between multiple stakeholders and scientific disciplines can contribute to more efficient drug development, appropriate assessment of drug effects, and transfer of knowledge to enable appropriate use.

Weighing the evidence

When we, drug regulators, tell about our work, we move our hands in a gesture suggesting to weigh two objects. And, that is the essence of our job, to balance benefits and risks of drugs. If the benefits outweigh the risks we allow the medicinal product on the market, if not then we don't. This seems like a simple enough job. You may ask yourself: "do we really need a field of regulatory science, and a professor at the University Medical Center Groningen (UMCG) to improve this work?"

But, as I learned early, weighing is a specialist job, and different tools are used to weigh different things. I vividly remember working in my father's bakery during the university holidays. I was weighing pieces of dough so my father could shape them into loafs of bread when he reprimanded me that it was to be about 800 grams. The 'about' may have been +/- 25 grams, or more. A shock for the first year pharmacy student who had just mastered the milligram balance. Who now understood his skills were not appreciated nor needed. He was just way too slow!

I will come back to the regulator's tools and speed of work a bit later but, first let me start with the complexity of the objects being weighted, i.e., comparing the proverbial 'apples and oranges'. The apples are the benefits or as we call these in the European Public Assessment Reports, the favourable effects of the drug. The oranges are the risks or unfavourable drug effects. We often laugh when non-English speakers refer to 'apples and pears' translating literally their e.g., Dutch expression of comparing 'appels en peren' Actually, this is a not so wrong, as the unfavourable effects can be any adverse effect that emerges in a trial, predefined or not, i.e., oranges, pears or any non-apple type of fruit. So, how do you compare that a vaccine prevents patients being hospitalised due to COVID19, but that this puts them at risk for rare but serious adverse events like myocarditis or blood clots. Then you may begin to understand the regulator's job is more complex.

Moreover, what I or you, find acceptable and which trade-off in benefits and risks we make may differ. The trade-off, you could argue, may also differ between regulators and patients that will have to take the drug, or the health care professional who is prescribing the drug. This is what Arna Arnardottir investigated in a so-called discrete choice experiment, where we asked patients with diabetes, regulators and physicians to choose

from two hypothetical diabetes drugs.[1] These hypothetical drugs differ in their impact on favourable and unfavourable outcomes. And, we found that regulators, patients and physicians favoured similar outcomes equally. However, patients attached more weight to symptomatic adverse events like hypo's and gastrointestinal discomfort in their treatment choice. These type of 'patient preference studies' are currently receiving more attention in an increasingly patient-centered drug development and evaluation. Our study was performed in the context of the Escher project that aimed to develop a more efficient and effective regulatory system (https://www.lygature.org/escher). It is in that context that we philosophised whether one day drug regulation could be moulded like the Anglo-Saxon legal system. Regulators would lay out the evidence, benefits and risks of the drug, and a 'jury' of patients (and or relevant healthcare professionals) would decide on approval. Exact terms of drug use – like the sentencing in the legal system – would then be worked out by the regulator and laid down in the Summary of Product Characteristics (SmPC; i.e., the information for the healthcare professional) and the Patient Information Leaflet.

1 Mol PG, Arnardottir AH, Straus SM, de Graeff PA, Haaijer-Ruskamp FM, Quik EH, Krabbe PF, Denig P. Understanding drug preferences, different perspectives. Br J Clin Pharmacol. 2015;79(6):978-87.

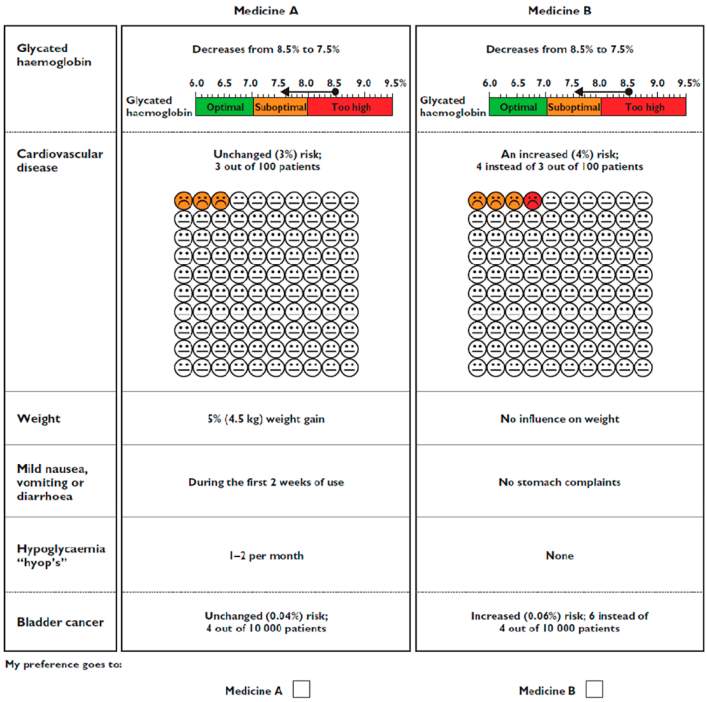

Figure 1. Example of a discrete choice task.
Reproduced from Mol. et al. Understanding drug preferences, different perspectives. Br. J Clin. Pharm. 2014. DOI:10.1111/bcp.12566

The EU regulatory system

But, before changing the system drastically let me briefly explain how we currently regulate drugs in Europe. The CBG-MEB, representing the Netherlands, provides together with the 26 other EU member states the experts that perform the work in various committees and working parties that are hosted by the European Medicines Agency (EMA). The EMA is primarily responsible that the process runs smoothly, and steers the poli-

cy-oriented direction of travel to ensure an agile future-proof EU regulatory system. In the EU regulatory system the Netherlands are known to 'punch beyond its weight' to quote former United States of America president Barack Obama. The CBG-MEB is in the top 5 of all procedures.[2] For buy-in and support of decisions it is vital, however, that member states feel heard and involved in the decision-making. This is important as decisions for 'centrally approved products' lead to market approval in the whole of the EU.

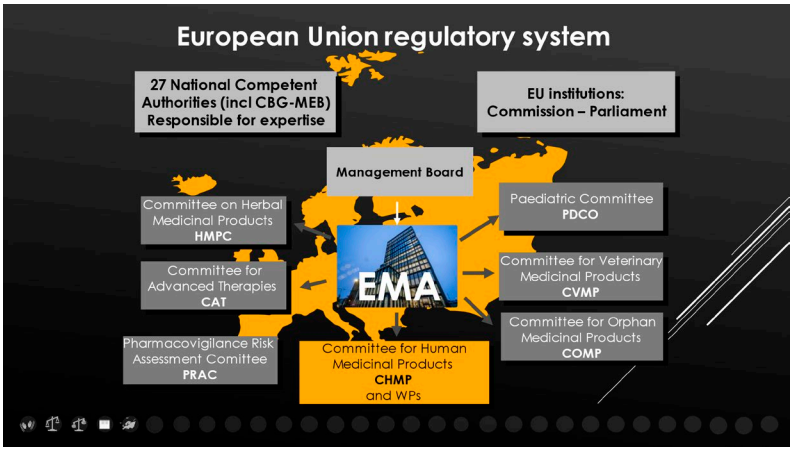

Figure 2. The Dutch Medicines Evaluation Board in the European Union Regulatory Network

A structured template for the assessment – 'clinical overview' – report in which facts and uncertainties around demonstrated

2 Dutch Medicines Evaluation Board (CBG-MEB). *CBG Jaarverslag 2021: De blik vooruit*. Available online at: https://www.cbg-meb.nl/actueel/nieuws/2022/05/10/cbg-jaarverslag-2021-de-blik-vooruit. (assessed November 22, 2022).

favourable and unfavourable effects are summarised, and that includes a summary table of the main drug effects provides a level playing field that guides the benefit-risk discussion at the Committee on Human Medicinal Products (CHMP).[3] This semi-structured evaluation streamlines the discussion in the CHMP – where the decision to approve will ultimately have to be agreed on by the majority of the EU member state representatives. But as Sonia Roldan showed when expanding our earlier patient preference study, weighing of drug effects may be different across countries. While, Dutch diabetes patients considered multiple favourable and unfavourable effects in their drug choice, the choice of Turkish patients was solely determined by the drug's effect on cardiovascular disease.[4] Also, between EU member states, the 'apples and oranges' may be weighed differently, and an iterative – although, in principle time-limited – process is foreseen to support that a joint conclusion is reached. Currently, the power of argumentation is not to be underestimated in steering the decision. Professor Pieter de Graeff, my regulatory educator, made it very clear "You have to make a

3 European Medicines Agency. Day 80 assessment report – Overview and D120 LOQ template with guidance – Rev.08.21. https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.ema.europa.eu%2Fen%2Fdocuments%2Ftemplate-form%2Fday-80-assessment-report-overview-d120-loq-template-guidance-rev0821_.docx&wdOrigin=BROWSELINK (accessed 12 December 2022) .

4 Roldan Munoz S, Postmus D, de Vries ST, Arnardottir AH, Dolu İ, Hillege H, Mol PGM. Differences in importance attached to drug effects between patients with type 2 diabetes From the Netherlands and Turkey: A preference study. Front Pharmacol. 2021;11:617409. DOI: 10.3389/fphar.2020.617409.

choice and then follow through and defend that choice." With Professor Hans Hillege and Douwe Postmus we currently work on integrating preference data in the regulatory decision process. Perhaps, integrating these preferences in their ADDIS-tool (https://mcda.drugis.org/) may one day support a quantified – and predictable – benefit-risk decision based on the drug effects summary table.

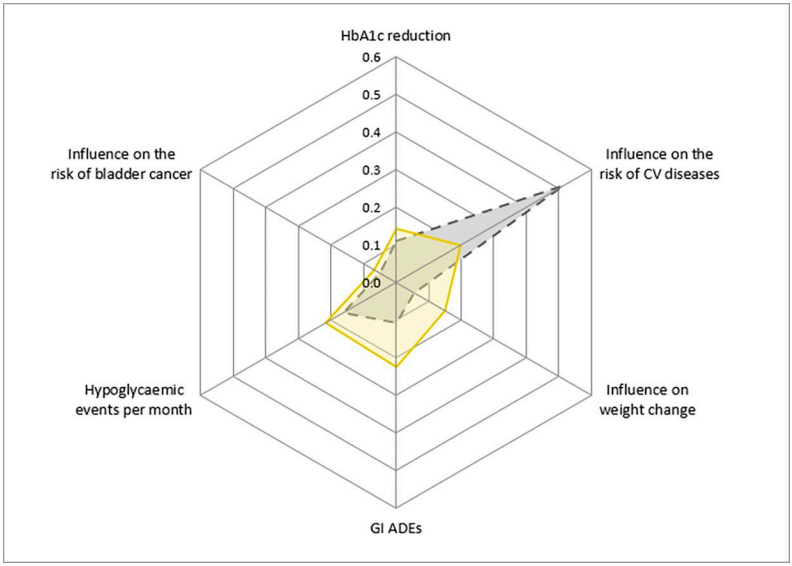

Figure 3. Relative weight scores of preferences towards the drug attributes of A Dutch and B Turkish patients.
Reproduced from Roldan Munoz et al. Differences in importance attached to drug effects between patients with Type 2 Diabetes from the Netherlands and Turkey: a preference study. Front Pharm. 2021. DOI: 10.3389/fphar.2020.617409

Different decisions across the Atlantic

While the iterative regulatory review process has a formal 210 day assessment timeline the EU process has been criticised to be the slowest among global regulators.[5] Clearly, it is important to review what causes the delay. The complexity of the EU system with multiple member states may be one reason. Another cause for the different review times, and approvals per se, may be the different weighing of benefits and risks, and differences in evidentiary standards, i.e., acceptance of uncertainty by different global regulators. The 21st Century Cures Act allows the United States of America Food and Drug Administration (FDA) more liberty in terms of evidence required to support drug approval.[6] An important example is the recent approval by the FDA of aducanumab for treatment of Alzheimer's disease.[7] CHMP, however, denied approval of the product in the EU as clinical efficacy in terms of cognition was not adequately (conflicting trial results) nor convincingly (impact had borderline clinical relevance) demonstrated and that treatment was accompanied by considerable potential risk in the form of amy-

5 Downing NS, Zhang AD, Ross, JS. Regulatory Review of New Therapeutic Agents — FDA versus EMA, 2011–2015. NEJM 2017; 376:14 DOI: 10.1056/NEJMC1700103

6 US Food and Drug Administration (FDA). https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act (accessed December 12, 2022)

7 US Food and Drug Administration (FDA). FDA's decision to approve new treatment for Alzheimer's disease. 2021. Available online at: www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease. (accessed November 22, 2022).

loid-related imaging abnormalities.[8] The FDA, acknowledging the weak demonstration of clinical benefit, based its approval primarily on the observed effect on changes in a so-called biomarker; i.e., resolution of amyloid plaques. As Alzheimer's Disease is an area of unmet need, the FDA considered an accelerated approval based on the biomarker they labelled a '*reasonably likely surrogate of benefit'* justifiable. Although, the approval sparked hope among patients and caregivers, there was also controversy if the FDA's choice had been made independent of unduly industry influence.[9]

Biomarkers

Clearly, biomarkers play a crucial role in drug development.[10] They can accelerate access to new treatments as treatment effects can be observed much faster than having to wait for clinical events to occur. For instance, blood pressure is an established biomarker, or surrogate outcome, therefore antihypertensives are approved based on their blood pressure lowering effects, which are much earlier detected than clinical events

8 European Medicines Agency (EMA). Aduhelm: Withdrawal of the marketing authorization application. Available online at: https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/aduhelm. (accessed November 22, 2022).

9 Walsh S, Merrick R, Milne R, Brayne C. Aducanumab for Alzheimer's disease? BMJ 2021;374:n1682 DOI:10.1136/bmj.n1682.

10 FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet] (Food and Drug Administration (US) and National Institutes of Health (US), Bethesda (MD), Silver Spring, MD, 2016). <https://www.ncbi.nlm.nih.gov/books/ NBK326791/ (accessed December 12, 2022)

(e.g., myocardial infarction or stroke). In addition, 'prognostic' biomarkers can also be used to select patients most in need of treatment, because their disease is progressing rapidly. 'Predictive' biomarkers are indicative of a druggable target, e.g., a tumour expressing a certain protein, that can be silenced or remedied with a drug that is specifically targeted (precision medicine) to this protein-expressing tumour. Biomarkers may therefore greatly expedite drug development and may identify patients most in need for, and responsive to certain drug interventions. This supports designing innovative and efficient trials and personalised medicine. In the Innovative Medicines Initiative (IMI) Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt-DKD) project my colleague Professor Hiddo Lambers-Heerspink and international colleagues search for novel biomarkers with the "aim to improve prevention and management of DKD and establish a new paradigm for precision medicine in DKD" (https://www.beat-dkd.eu/).

In which case, however, it may be acceptable to approve a drug based on a novel biomarker-guided development program is where regulatory science can help.

Regulatory science

The CBG-MEB and the EMA define regulatory science as: *"The science of developing new tools, standards and approaches to evaluate the efficacy, safety, quality and performance of medical prod-*

ucts in order to assess benefit-risk and facilitate a sound and transparent regulatory decision-making."

Christine Gispen-de Wied and Professor Bert Leufkens added the importance of the

"...analysis of regulatory frameworks itself..."

as a key component of regulatory science.[11] They argued important lessons could be drawn from previous regulatory decisions.

"Collaborate to improve drug development and evaluation" would be my addition to the definition of regulatory science. I lead a work package in BEAt-DKD that is focused at the implementation of precision medicine in regulatory but also clinical practice. Through a series of stakeholders meetings Lysbeth Bakker investigated what was needed to strategise a way forward in implementing precision medicine in DKD.[12] This year our work culminated in a qualification of novel methodologies procedure

11 Gispen-de Wied CC, Leufkens HGM.From molecule to market access: drug regulatory science as an upcoming discipline. Eur J Pharmacol. 2013;719(1-3):9-15. DOI: 10.1016/j.ejphar.2013.07.021.

12 Bakker E, Mol PGM, Nabais J, Vetter T, Kretzler M, Nolan JJ, Mayer G, Sundgren AK, Heerspink HJL, Schiel A, de Vries ST, Gomez MF, Schulze F, de Zeeuw D, Pena MJ; BEAt-DKD Consortium. Perspectives on a way forward to implementation of precision medicine in patients with diabetic kidney disease; Results of a stakeholder consensus-building meeting. Front Pharmacol. 2021;12:662642. DOI: 10.3389/fphar.2021.662642.

with EMA's Scientific Advice Working Party (SAWP) to seek regulatory acceptance of the PRE score, i.e., a panel of biomarkers to guide drug development and select patients most in need of treatment.

The Day job – the candy store of applied regulatory science

My 'day job' at the CBG-MEB, for the past ten years, has been to provide scientific advice, primarily to pharmaceutical companies.[13] For this reason I have traveled on a monthly basis to London, then since 2019 due to Brexit and the move of the EMA, to Amsterdam. In 4-day meetings we discuss between 70-100 new drug development programs. The aim of the scientific advice is to guide development programs that once they are completed should provide adequate data to support a marketing authorisation application and allow a robust evaluation of benefits and risks by the CHMP. The advice given is based on scientific principles of drug development. Importantly, the advice is also informed by regulatory science, i.e., what we learned from previous regulatory decisions. The Scientific Advice procedure is a legal obligation for the EU regulator, and the advice remains confidential until the company has received

13 European Medicines Agency (EMA). Scientific Advice Working Party. Available online at: https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/scientific-advice-working-party (accessed November 22, 2022). And European Medicines Agency (EMA). Scientific advice and protocol assistance. Available online at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance (accessed November 22, 2022)

market approval of its compound. Safeguards have been put in place to assure advice from SAWP is separated from decision-making by the CHMP.

For me personally, attending the SAWP meeting is like visiting the ***candy store*** with my best friends. In the SAWP store of applied regulatory science the newest ideas are showcased; e.g., gene therapies addressing hitherto untreatable devastating afflictions, innovative trial methodologies, including, novel ways of evaluating treatment outcomes, and, the possibility to use data from non-trial settings, so-called 'real world data'. The SAWP is also where the 'qualification of novel methodologies' procedures,[14] such as for the mentioned PRE score, take place. Understandably, in case of the PRE score, the boundaries of my Conflict of Interest were reached, and I could not take part at either side of the table in the qualification discussions at the EMA.

Ultimately, the SAWP documents provide a rich source I tap into for an '*analysis of regulatory frameworks'.* The confidential data when aggregated can provide unique insights in the latest development in regulatory science and regulatory requirements.

14 European Medicines Agency (EMA). Qualification of novel methodologies for medicine development. Available online at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0. (accessed November 22, 2022).

Collaborate to improve drug development and evaluation

I intend to stimulate collaboration between regulators and relevant stakeholders, emphasising drug regulation that focuses on what matters to patients. There is an intense but delicate relation with industry, where we interact under carefully regulated circumstances. Though, occasionally we do collaborate in pre-competitive research activities through public private partnerships like the mentioned BEAt-DKD project. Realising that advanced drug therapies – like gene therapy – are increasingly developed in academia, I see it as an important task to bring regulators in closer contact with the academic field, and vice versa. For example, in the COFUND PROMINENT programme of the Research Institute for Drug Exploration (GUIDE) (https://umcgresearch.org/w/prominent) and the German regulator-led EU-funded STARS project (https://www.csa-stars.eu/) the emphasis was on collaboration between academic research and the regulator. Through interactive training programs academic researchers were introduced to regulatory science and made aware of regulatory requirements that should facilitate translation of their research to public health solutions in the future. The interactive training sessions and additional surveys and stakeholder meetings performed in STARS, stimulated much needed two-way communication.[15] This led to regulators'

15 Starokozhko V, Kallio M, Kumlin Howell Å, Mäkinen Salmi A, Andrew-Nielsen G, Goldammer M, Burggraf M, Löbker W, Böhmer A, Agricola E, de Vries CS, Pasmooij AMG, Mol PGM; STARS consortium. Strengthening regulatory science in academia: STARS, an EU initiative to bridge the translational gap. Drug Discov Today. 2020:S1359-6446(20)30434-7. DOI: 10.1016/j.drudis.2020.10.017.

improved understanding of academic researchers information needs and their perspectives about regulatory science and regulatory requirements. The key message, as also emphasised in a 2021 Royal Netherlands Academy of Arts and Sciences (KNAW) report is that academic researchers and regulators interact early.[16] An important component of my chair will therefore be on providing education on regulatory science to stimulate collaboration between researchers and regulators and help close the translational gap of academic research and its ultimate adoption in public health.

My ***educational*** activities start by explaining first year pharmacy and medical students about the basics of drug development. In master or post-master courses, like Drug Discovery respectively clinical pharmacology, I can dive a little deeper in drug regulation. A number of these students find their way to doing internships at the CBG-MEB and write a master thesis on a regulatory science topic. Future prospects are to offer sandwich training in regulatory science, with industry, regulatory and academic internships.

Another topic where collaboration needs strengthening is that between EU authorities (regulators, clinical trial approval, and inspectors) and drug researchers to facilitate so-called 'repur-

16 KNAW (2021). Efficiency gains through innovation in medicines development: how can science contribute?, Amsterdam.

posing' studies, where approved drugs are investigated in new indications. The most famous example is perhaps asprin. Asprin was initially marketed to relieve pain, but was later discovered to prevent cardiovascular disease. Repurposing studies are often initiated by academic researchers, and can lead to important discoveries. During the Pandemic, the UK-based RECOVERY and NL-based REMAP-CAP platform trials, demonstrated the value of already marketed drugs dexamethasone respectively tocilizumab in the treatment of severe COVID-19 infection.[17][18] Bringing the information on label, i.e., include the information in the SmPC when the innovator company no longer is involved proves challenging.[19] The use of a so-called Article 5(3) procedure by CHMP to pro-actively assess the RECOV-

17 RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704. DOI: 10.1056/NEJMoa2021436.

18 REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. 2021;384(16):1491-1502. DOI: 10.1056/NEJMoa2100433.

19 Gispen-de Wied CC, Weemers J, Boon J, Mol PGM, Stolk, P. Future of the drug label; perspectives from a multistakeholder dialogue. Br J Clin Pharmacol. 2019; 1-4. DOI: 10.1111/bcp.14070

ERY trial results and propose SmPC wording to be included by all dexamethasone producing manufacturers deserves further consideration as a regulatory tool to maximise impact of drug repurposing programs. However, it was sobering to learn that less than 10% of patients in the trials that supported COVID-19 vaccines and treatments approvals originated from Europe. Therefore, the EC decided to initiate the Accelerating Clinical Trials in the EU (ACT EU) joint action project to transform how clinical trials are initiated, designed and run in the EU (https://www.ema.europa.eu/en/news/accelerating-clinical-trials-eu-act-eu-better-clinical-trials-address-patients-needs). In the past years I have been working on a new global International Conference on Harmonisation (ICH) E19 guideline on a selective approach to safety data collection in late-stage clinical trials.[20] This guideline aligns with the recently implemented European Clinical Trials Regulation (EU) No 536/2014, which provides the possibility to define in the study protocol that for some adverse events systematic collection may not be necessary.[21] Together, they will facilitate conducting 'pragmatic tri-

20 European Medicines Agency (EMA). ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials – Scientific guideline. Available online at: https://www.ema.europa.eu/en/ich-guideline-e19-selective-approach-safety-data-collection-specific-late-stage-pre-approval-post. (accessed November 22, 2022).

21 European Medicines Agency (EMA). Clinical trials regulation. Available online at: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation#:~:text=The%20Clinical%20Trials%20Regulation%20harmonises,Economic%20Area%20(EEA)%20countries. (accessed November 22, 2022).

als' like RECOVERY and REMAP-CAP. Collaboration through the Regulatory Science Network Netherlands (RSNN) with FAST, the centre for Future Affordable Sustainable Therapy development, will also nationally contribute to an improved trial landscape. At a smaller scale researchers in the UMCG can touch base through a monthly regulatory consultation hour and receive some initial thoughts on how to navigate the regulatory system and receive some high level developmental feedback.

My research

My research is rooted in what I learned from my scientific mentor and first PhD-supervisor Prof Dr Flora Haaijer-Ruskamp. Together with professor Petra Denig she educated me in implementation research. I follow their careful path to implementation, using qualitative and quantitative research techniques to understand the target population's needs and perspectives, followed by the selection and/or adaptation of the intervention based on these needs. Both, however, taught me also that 'if you don't know where you are going, you don't know if you have arrived'. Therefore, they trained me as a drug utilisation researcher who identifies the data needed to evaluate the impact of an intervention, and suitable techniques to analyse the data. The pictorial developed by the ISPE Special Interest Group on Benefit Risk Assessment, Communication and Evaluation that I co-founded displays the continuous cycle of thinking that applies specifically to my regulatory science research

agenda.[22] At various stages of the drug life cycle an assessment of the benefits and risks needs to be made and communicated to relevant audiences. Towards, the end of the cycle to guide continued development and improvement the impact of these activities needs to be evaluated.

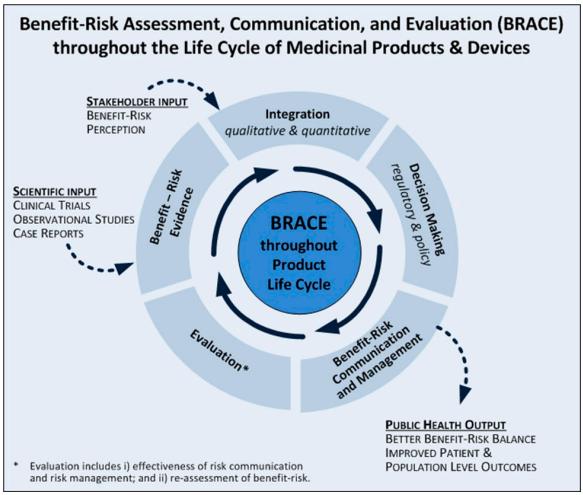

Figure 4. BRACE cycle.
Reproduced from Radawski et al. Benefit–Risk Assessment, Communication, and Evaluation (BRACE) throughout the life cycle of therapeutic products: overall perspective and role of the pharmacoepidemiologist. Pharmacoepidemiology and Drug Safety. 2015. DOI: 10.1002/pds.3859

22 Radawski C, Morrato E, Hornbuckle K, Bahri P, Smith M, Juhaeri J, Mol P, Levitan B, Huang HY, Coplan P, Li H; BRACE Special Interest Group. Benefit-Risk Assessment, Communication, and Evaluation (BRACE) throughout the life cycle of therapeutic products: overall perspective and role of the pharmacoepidemiologist. Pharmacoepidemiol Drug Saf. 2015;24(12):1233-1240.

In the coming years my research agenda will revolve around regulatory drug knowledge transfer, personalised medicine, and real world evidence. I will work on (co)developing new tools in these research areas. In addition, I will apply my just described research skills to contribute to the implementation of these novel tools in regulatory and clinical practice.

Knowledge transfer

In my first regulatory science project I studied a major regulatory tool – the Direct Healthcare Professional Communication (DHPC), which was and partly still is a paper-based letter to inform healthcare professionals about newly identified drug safety issues. The DHPC functions suboptimal as a tool to transfer new safety knowledge. Too many DHPCs end up – unread – in the wastebin of the healthcare professional they are sent to. The key paper in Sigrid Piening's PhD project, published in 2012, was a survey among 1,200 Dutch healthcare professionals.[23] It became instrumental to support the notion that trust in the sender is key and that industry as sender of a DHPC was not well received.

23 Piening S, Haaijer-Ruskamp FM, de Graeff PA, Straus SM, Mol PG. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. Drug Saf. 2012;35(11):1061-1072. DOI: 10.1007/BF03261992.

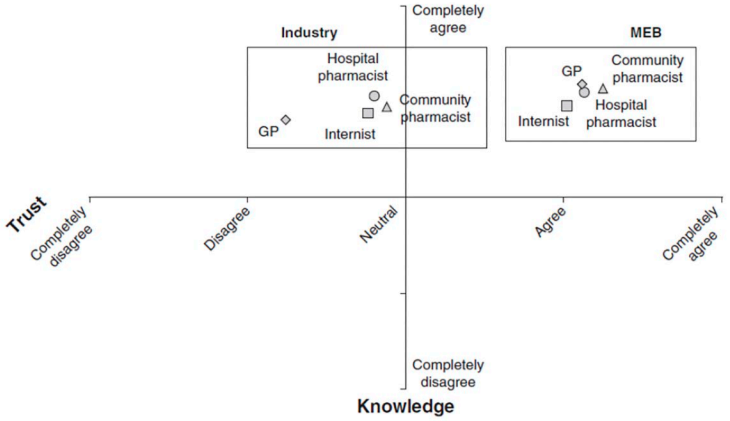

Figure 5. Trust (and knowledge) attributed to the Dutch Medicines Evaluation Board/pharmaceutical industry.
Reproduced from Piening et al. Healthcare professionals' self-reported experiences and preferences related to Direct Healthcare Professional Communications. A survey conducted in the Netherlands. Drug Saf 2012; 35 (11): 1061-1072. DOI: 10.1007/BF03261992

We concluded that regulators should take a more active role in sending this information. In subsequent projects, IMI WEB-RADR and in the SCOPE joint action program, we expanded our work on DHPCs and regulatory safety knowledge transfer into Europe.[24] [25] Currently, we are back to studying in-depth how

24 Pierce CE, de Vries ST, Bodin-Parssinen S, Härmark L, Tregunno P, Lewis DJ, Maskell S, Van Eemeren R, Ptaszynska-Neophytou A, Newbould V, Dasgupta N, Wisniewski AFZ, Gama S, Mol PGM. Recommendations on the use of mobile applications for the collection and communication of pharmaceutical product safety information: Lessons from IMI WEB-RADR. Drug Saf. 2019;42(4):477-489. DOI: 10.1007/s40264-019-00813-6.

25 de Vries ST, van der Sar MJM, Coleman AM, Escudero Y, Rodríguez Pascual A, Maciá Martínez MÁ, Cupelli A, Baldelli I, Šipić I, Andrić A, Michan L, Denig P, Mol PGM; SCOPE work package 6. Safety communication tools and healthcare professionals' awareness of specific drug safety issues in Europe: A survey study. Drug Saf. 2018;41(7):713-724. DOI: 10.1007/s40264-018-0643-5.

new drug safety knowledge transfers into Dutch hospitals using 'mixed-methods' approaches, combining qualitative and quantitative research.[26]

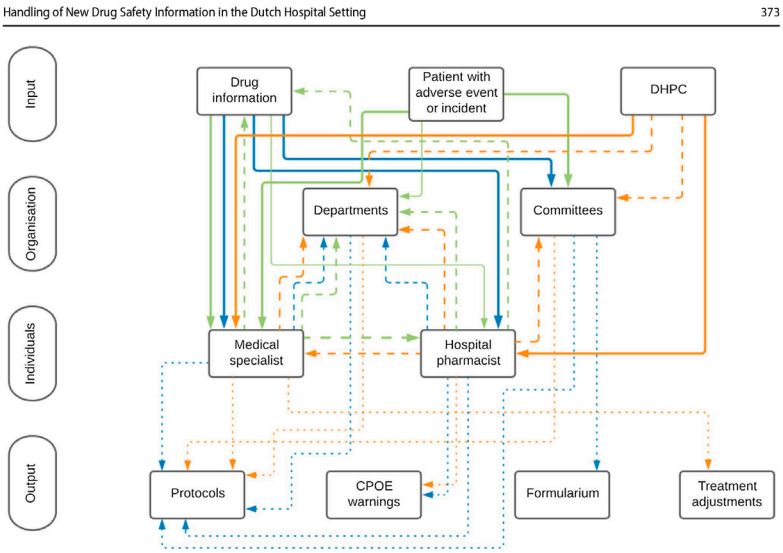

Fig. 1 Handling of drug safety information within Dutch hospitals. Blue: drug safety information, Green: adverse events and incidents, Orange: DHPC. Continuous line indicates fixed information flow, dashed line indicates possible information flow, dotted line possible output. Of note, the DHPC is not directly sent to departments or committees, the dashed line represents that DHPCs are input as a fixed agenda item. In addition, the thickness represents the importance or how often the information flow was mentioned; however, this is an interpretation of the data and not a quantification of the data. *CPOE* computerised physician order entry, *DHPC* Direct Healthcare Professional Communication. Program used: Lucidchart

Figure 6. Handling of new drug safety information in Dutch hospitals. Reproduced from de Vries et al. Handling of new drug safety information in the Dutch hospital setting: A mixed methods approach. Drug Saf 2022. https://doi.org/10.1007/s40264-022-01149-4

26 de Vries E, Bakker E, Francisca RDC, Croonen S, Denig P, Mol PGM. Handling of new drug safety information in the Dutch hospital setting: A mixed methods approach. Drug Saf. 2022;45(4):369-378. DOI: 10.1007/s40264-022-01149-4.

Esther de Vries combines her role as a pharmacovigilance assessor at the CBG-MEB with a PhD project, with the aim to improve the routing of DHPC and drug safety information in Dutch hospitals. This part of my research is primarily dedicated to improve the regulatory science toolbox. However, some part of this work will remain focused on the 'evaluation of the regulatory framework'. Such as, the study we recently performed to understand what factors make EU regulators want to communicate about drug safety issues related to SGLT2-inhibitors, a class of diabetes drugs. We found that regulators' concern was influenced by characteristics of the safety issue as well as demographic characteristics (e.g., sex, region) and attitudes (e.g., risk-taking behaviour).[27] Employing diverse groups of experts regarding such factors would thus ensure that various views are incorporated in risk communication decision-making. The increased attention to benefit and risk communication by the CBG-MEB through e.g., the 'Programma Goed Geneesmiddel Gebruik', and collaboration with important 'partners in the Netherlands, such as the Dutch Pharmacovigilance Center Lareb, the healthcare institute Netherlands (ZIN.NL), and the Royal Dutch Society of Pharmacists (KNMP) should result in better transfer of drug knowledge.

27 Roldan Munoz S, Postmus D, de Vries ST, Gross-Martirosyan L, Bahri P, Hillege H, Mol PGM. What makes EU regulators want to communicate about drug safety issues related to SGLT2-inhibitors; an online survey study. Drug Saf. (in press)

Another aspect, where I believe future work will be necessary is around unlocking information that is now 'hidden' in the European public assessment reports and industry's marketing authorisation dossiers. As I mentioned earlier, certain information may be perceived as missing, such as specific information of a drug's effect in (sub-)populations of interest. Most noticeably, perhaps, is the idea that drugs are not studied in women. Considering the societal interest, we initiated several studies to review how drugs had been studied in women.[28] [29] We observed that women were actually included in all phases of clinical drug research, however, the included number of women was not always proportional to disease prevalence rates. Moreover, while sex-specific information was available in all dossiers, this information was not always available to the general public. Furthermore, although efficacy was mostly similar between women and men, adverse events were reported more often by women. Interestingly, both in the active as well as placebo arms. Additional work to disclose this type of information are required to address public needs. With my colleagues Patrick Vrijlandt, Sieta de Vries, and backed by the CBG-MEB focus

28 Dekker MJHJ, de Vries ST, Versantvoort CHM, Drost-van Velze EGE, Bhatt M, van Meer PJK, Havinga IK, Gispen-de Wied CC, Mol PGM. Sex proportionality in pre-clinical and clinical trials: An evaluation of 22 marketing authorization application dossiers submitted to the European Medicines Agency. Front Med (Lausanne). 2021;8:643028. DOI: 10.3389/fmed.2021.643028.

29 de Vries ST, Starokozhko V, Schellens IMM, Wijnans L, Enzmann H, Cavaleri M, Mol PGM. Attention for sex in COVID-19 trials: a review of regulatory dossiers. BMJ Glob Health. 2022;7(3):e008173. DOI: 10.1136/bmjgh-2021-008173.

group on Gender we will continue working on disclosing this information to professional and lay audiences. Finally, truly different favourable and unfavourable drug effects – so called effect modification – are sometimes observed between women and men. These will receive our full attention also.

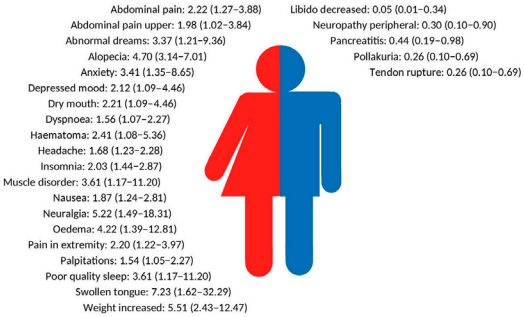

FIGURE 2 Odds ratios with 95% confidence intervals of adverse drug reactions with higher odds for women (left side) or for men (right side) of β-hydroxy β-methylglutaryl-CoA reductase inhibitors

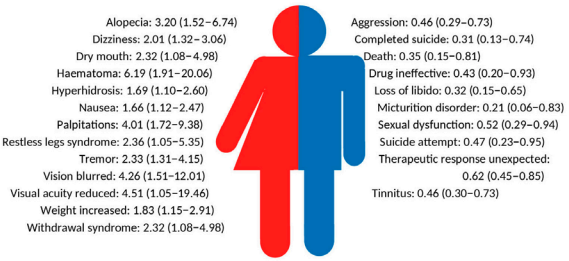

FIGURE 3 Odds ratios with 95% confidence intervals of adverse drug reactions with higher odds for women for (left side) or for men (right side) of selective serotonin reuptake inhibitors

Figure 7. Sex differences in reported adverse drug reactions. Reproduced from de Vries et al. Sex differences in adverse drug reactions reported to the National Pharmacovigilance Centre in the Netherlands: An explorative observational study. Br J Clin Pharm 2019. https://doi.org/10.1111/bcp.13923

Personalised Medicine

Personalised medicine is reshaping drug regulation, and it is where my day job in the 'candy store of applied regulatory science' and my research are most closely interacting. More targeted approaches will result in smaller treatment populations, for which new trial designs, statistical methodologies, including borrowing Bayesian techniques, and use of external trial or real world data (RWD) controls will see the light. Moreover, personalised patient-centered development will also see us move away from traditional outcomes, with larger attention to patient reported outcomes and digital mobility outcomes that are collected 24/7 by wearable devices.[30] These devices hold great promise, as they capture much more granular data than the traditional endpoints of cardiometabolic trials.

Therefore, personalised medicine comprises for me both targeted therapies and attention to more patient-centred and value-based health outcomes. These capture much more detailed the impact of diseases and drug effects on a patient's life. Techniques, like patient preference studies, as I described earlier, can be used to identify outcomes that matter to (individual) patients. Adoption of new approaches will, however, require a thorough understanding of strengths and weaknesses of these approaches and anchoring to outcomes we understand and

30 Cohen AB, Mathews SC. The digital outcome measure. Digit Biomark. 2018;2(3):94-105. DOI: 10.1159/000492396.

trust. Through the EMA 'qualification of novel methodology' procedure a thorough review of these approaches is possible, and once a positive opinion is given the tool will be publicly endorsed on EMA's website.

Currently, with Marjon Pasmooij the head of the CBG-MEB's scientific office, and Viktoriia Starokozkho a Groningen-based CBG-MEB colleague we run a similar implementation work package in the IMI European Platform for Neurodegenerative Diseases project (EPND; https://epnd.org/). 'Our' PhD student Audrey Hermans will perform a number studies around the implementation of the novel methodologies developed by our EPND colleagues. In addition, we will run a similar work package in the HORIZON EUROPE-funded PRIME-CKD project that will start January 2023. This project is led by my colleague professor Hiddo Lambers Heerspink, and is a follow-on project from BEAt-DKD. The continued collaboration both shows the importance attached to regulatory input in the implementation of academic-led biomarker research, it also exemplifies the fruitful collaboration between the department of clinical pharmacy and pharmacology and the CBG-MEB.

Real World Evidence

The final chapter in my lecture will be dedicated to the regulatory utility of RWD and the evidence derived from it, i.e., Real

World Evidence (RWE). The tried and tested randomised control trial (RCT) is the cornerstone for drug development. Rob Hemmings – former SAWP chair – compared the RCT with a car that while not being a new concept, with its four wheels and a steering wheel, has proven a valuable means of transportation. Still, as drug utilisation researcher I could not resist joining EMA's Patient Registry Initiative in 2015. In the years that followed I would collaborate closely with Xavier Kurz and his EMA registry team, and with Carla Jonker, a CBG-MEB case manager who started her PhD project on registries at the same time. In these two projects we laid foundations on how patient registries could inform regulatory decision-making better. We worked using the power of the European context in bringing all relevant stakeholders around the table. Thereby, mending the broken triangle where regulators talked to the industry, and the industry spoke with registry owners but with no direct talk between regulators and registry owners. The fact that regulators now were able to speak directly with registry owners, resulted in a better – two-way – understanding of the possibilities and impossibilities of what data can be collected in patient registries and which regulatory questions can be answered with these type of data. The work resulted in the publication of the impactful Guideline on registry-based studies, in the midst of an ongoing Pandemic. I am still proud that our paper "Patient Registries: An Underused Resource for Medicines Evaluation" published in 2019 is the most tracked paper from

the Drug Safety journal of that period.[31] Combined, the Patient Registry Initiative and Carla's thesis set the mark for future work on maximising the use of registry-based RWD to support regulatory decision-making.[32]

EMA is investing heavily in the promise of RWD and commissioned among others 52 million Euro to the DARWIN center at the ERASMUS Medical Center in Rotterdam to coordinate and perform 100 RWD studies annually.[33] Although, the amount sounds impressive it pales in comparison to investments made by industry, where e.g., Roche acquired the American Flatiron health data set for roughly two billion dollars.[34] Through initiatives like the European Health Data Space and the 'Regie op Registers' initiative of the Dutch Ministry of Health led by our national health technology assessment body ZIN.NL access to health data will improve.

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31 McGettigan P, Alonso Olmo C, Plueschke K, Castillon M, Nogueras Zondag D, Bahri P, Kurz X, Mol PGM. Patient registries: An underused resource for medicines evaluation : Operational proposals for increasing the use of patient registries in regulatory assessments. Drug Saf. 2019;42(11):1343-1351. DOI: 10.1007/s40264-019-00848-9.

32 Jonker C. (2022). Rare disease registries: A must for regulatory decision making. [PhD thesis, University of Utrecht].

33 European Medicines Agency (EMA). Data Analysis and Real World Interrogation Network (DARWIN EU). Available online at: https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu. (accessed November 22, 2022).

34 Flatiron. Roche to acquire flatiron health to accelerate industry-wide development and delivery of breakthrough medicines for patients with cancer. (Press release). Available online at: https://flatiron.com/press/press-release/roche/. (accessed November 22, 2022).

My future activities in the field are two-fold. *First*, I will work with people understanding the methodology, such as professor Eelko Hak, Maarten Bijlsma, and Katrien Oude Rengerink, and data scientists like our PhD student Stefan Verweij. We will utilise and fine-tune state-of-the-art analytical techniques to understand how RWE holds up against evidence derived from trials. There are exciting prospects with the ERASMUSMC, and in a separate project with the Dutch Institute for Clinical Auditing (DICA) to further study the robustness of RWE across different disease areas. *Second*, and most excitingly, I am in the very lucky position to have obtained a HORIZON EUROPE grant myself. Together with Sieta de Vries, my trusted right-hand (or perhaps for the GoT-fans, I should just say 'the hand') and a lot of help of Professor Kit Roes from the RadboudMC and chair of EMA's methodology working party we secured funding to work the next five years on the More-EUROPA project. In the More-EUROPA project we will work with 14 partners from seven EU countries, 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 health technology assessment decision-making. Among others, we will investigate, if we can address the concerns on the generalisability of RCTs incorporating RWD to estimate drug effects in important subgroups while building on the RCTs strength to isolate drug effects. Perhaps, I am personally most excited about the possibility to collaborate with methodologists, regis-

try owners, patient representatives and the target groups of regulators and health technology assessment staff to share new knowledge that will enable the uptake of RWE to the fullest possible. Importantly, market authorisation does not equal market access, and our More-EUROPA case studies on (cost-) effectiveness of multiple sclerosis drugs, impact in heart failure subgroups and case studies in lung cancer may contribute to change the way these patients live with their disease. Strengthened collaboration between health technology assessment and payors, with regulators and drug researchers should lead to drug development programs including RWE that satisfy knowledge needs of all stakeholders.

Finally, I am excited that through my chair of drug regulatory science I can contribute to further collaboration of the wider European regulatory network, professional societies, industry and academic researchers to advance regulatory science. I would like to emphasise the fantastic and perhaps unique collaborative Regulatory Science Network Netherlands (https://www.rsnn.nl/) in which academia, industry and the Dutch regulator contribute to advancing the field of drug regulation. Perhaps, the Network rooted in the Netherlands 'punches above its weight', and I am certain it will be the catalyst to advance regulatory science on a European scale to the benefit ultimately of public health.

Then, a few words of thanks. First to the Groningen Universiteits Fonds, and the Department of Clinical Pharmacy and Pharmacology for installing my chair of drug regulatory science. Second, to my dedicated team of researchers, including my PhD candidates (Jasperien van Doormaal, Jeroen Koomen, Derbew Berhe, and others mentioned earlier). Some of whom are employed by the department of clinical pharmacy and pharmacology, the CBG-MEB or by both (my Groninger CBG colleagues). Third to my colleagues in the SAWP (the candy store kids) and other regulatory colleagues for inspiring me. And last but never least, as Amy Winehouse sang, a big thanks to my darling wife and my dearest family and friends who never ceased to support me.

'Ik heb gezegd'

Peter Mol is professor of drug regulatory science at the University Medical Center Groningen (UMCG). His research focus is on developing new tools to support regulatory decision-making and the exchange of knowledge between regulatory authorities, health care professionals and lay people.

He is a senior assessor at the Dutch Medicines Evaluation Board and a long-standing member (vice chair 2016-2022) of the European Medicines Agency Scientific Advice Working Party. He has coordinated over 300 European and national scientific advice procedures.

Peter obtained his PhD at the UMCG and his pharmacy degree (PharmD) from the University of Utrecht. He has worked previously in a community pharmacy in Amsterdam, as a regional pharmacist in Namibia, and as a veterinary pharmacist in Utrecht.