Utrecht University

CBG MEB

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Evolution of regulatory science in the Netherlands

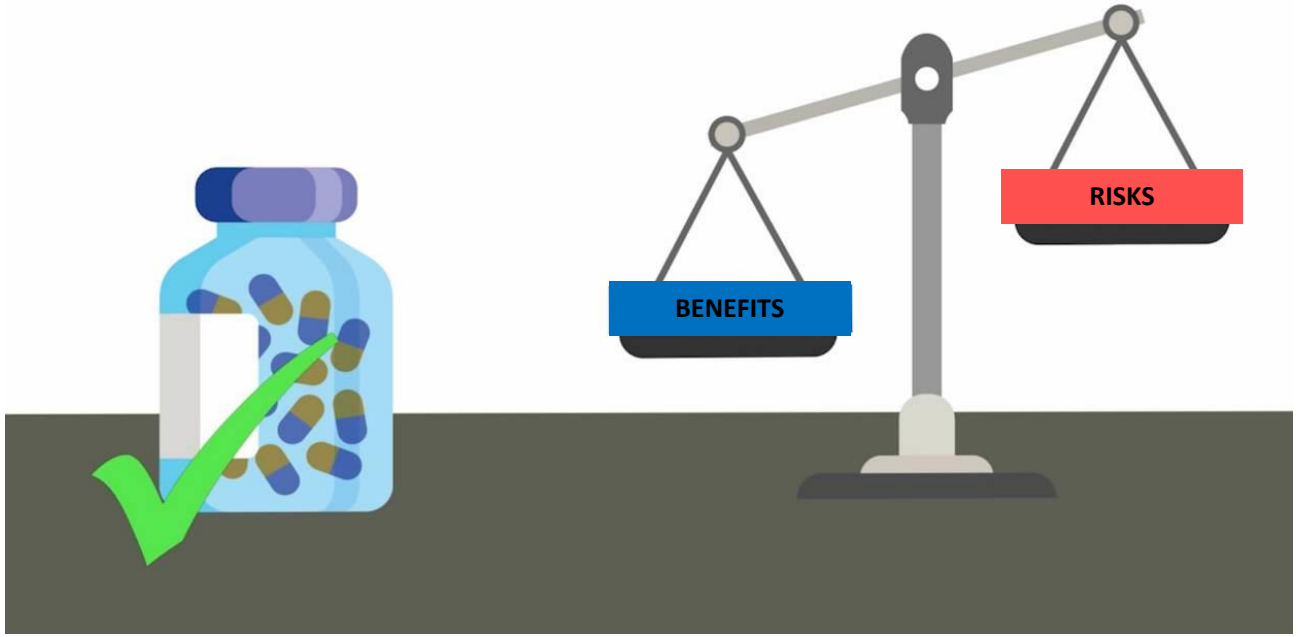
Marjon Pasmooij

Advancing Regulatory Science Research – 18 November 2024

Dutch Medicines Evaluation Board

Core values:

1. Scientific
2. Vigilant
3. Connected



Regulatory Science Programme (2011 - now)

Eight themes

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

Regulatory Science Research

Two principles:

1. **System improvement**
2. **Innovation**

"Involves answering questions such as:
Are we doing things properly?
Do adjustments need to be made on the basis of new knowledge?
Are we prepared, based on our current knowledge and expertise, for change and innovation?"

24 PhD students across different universities in NL

Naam
Lysbeth Bakker

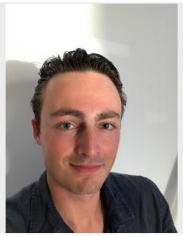
Naam
Njeri Kamau

Naam
Noa Rosenberg

Naam
Pieter Annema

Naam
Anne Taams

Naam
Audrey Hermans



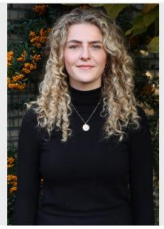
Naam
Bram Storosum

Naam
Britt Duijndam

Naam
Christine van Hattem

Naam
Doerine Postma

Naam
Donya Moslemzadeh



Naam
Esther Lubberts

Naam
Fabian Windführ

Naam
Geeske Grit

Naam
Loes den Otter

Naam
Loes Maton

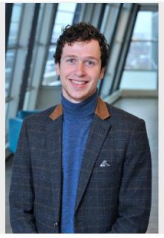
Naam
Puck Roos

Naam
Rafaella Buzatu

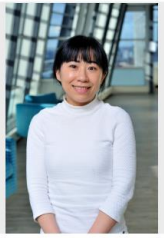
Naam
Renske Grupstra

Naam
Sem Cohen

Naam
Sharon Essink



Naam
Stefan Verweij

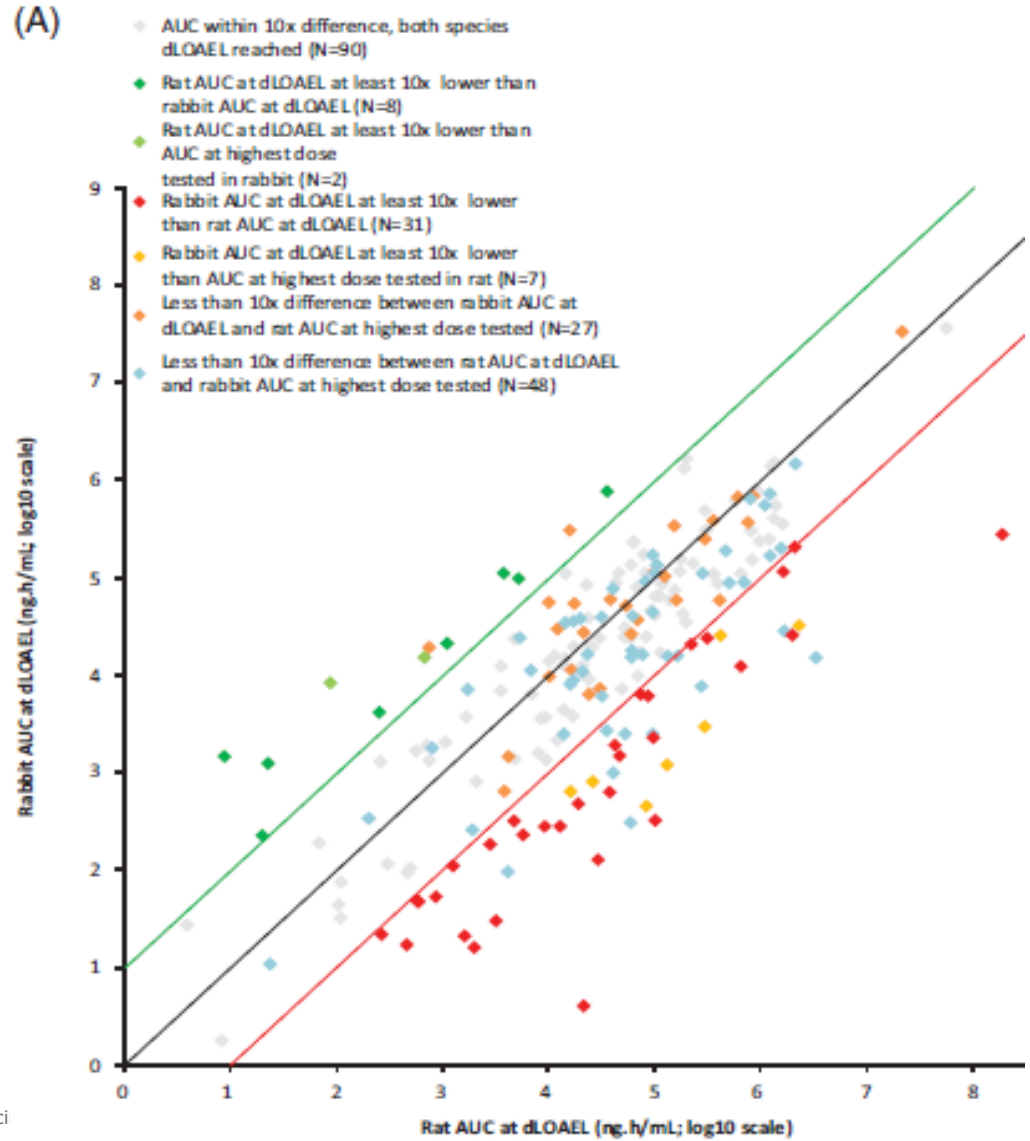


Naam
Tzu Chien

Naam
Lucina-May Nollen

ICH S5: Rat and rabbit developmental toxicity testing. Do we need both?

- Since thalidomide, 2 species reproductive toxicity testing is required (rat+rabbit).
- **Are both species needed?**
- **From phase 1 onwards, ICH S5** requires a EFD DRF, later embryofetal development in both species
- Analysis of ~380 pharmaceuticals with rat and rabbit data (including failed products)
- Rat and rabbit are relatively equal in sensitivity (NOAEL, LOAEL and HED).
- Also severity incidence is similar



Theunissen et al. Crit Rev Toxicol. 2016 Nov;46(10):900-910
Theunissen et al. Crit Rev Toxicol. 2017 May; 47(5):402-414

ICH S5: Rat and rabbit developmental toxicity testing. Do we need both?

- If they are comparable, you should be able to use just one species
- New ICH S5R3 revision proposes exactly that!
- **1 species DRF + (advanced) in vitro studies are sufficient before phase 3 + safety measures in phase 1/2**

deVolkskrant

Hundreds of thousands less laboratory animals are needed

CRITICAL REVIEWS IN TOXICOLOGY
2024, VOL. 54, NO. 9, 619–633
https://doi.org/10.1080/10408444.2024.2374281

Taylor & Francis
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REVIEW ARTICLE

OPEN ACCESS Check for updates

Evaluation of rat and rabbit embryofetal development studies with pharmaceuticals: the added value of a second species

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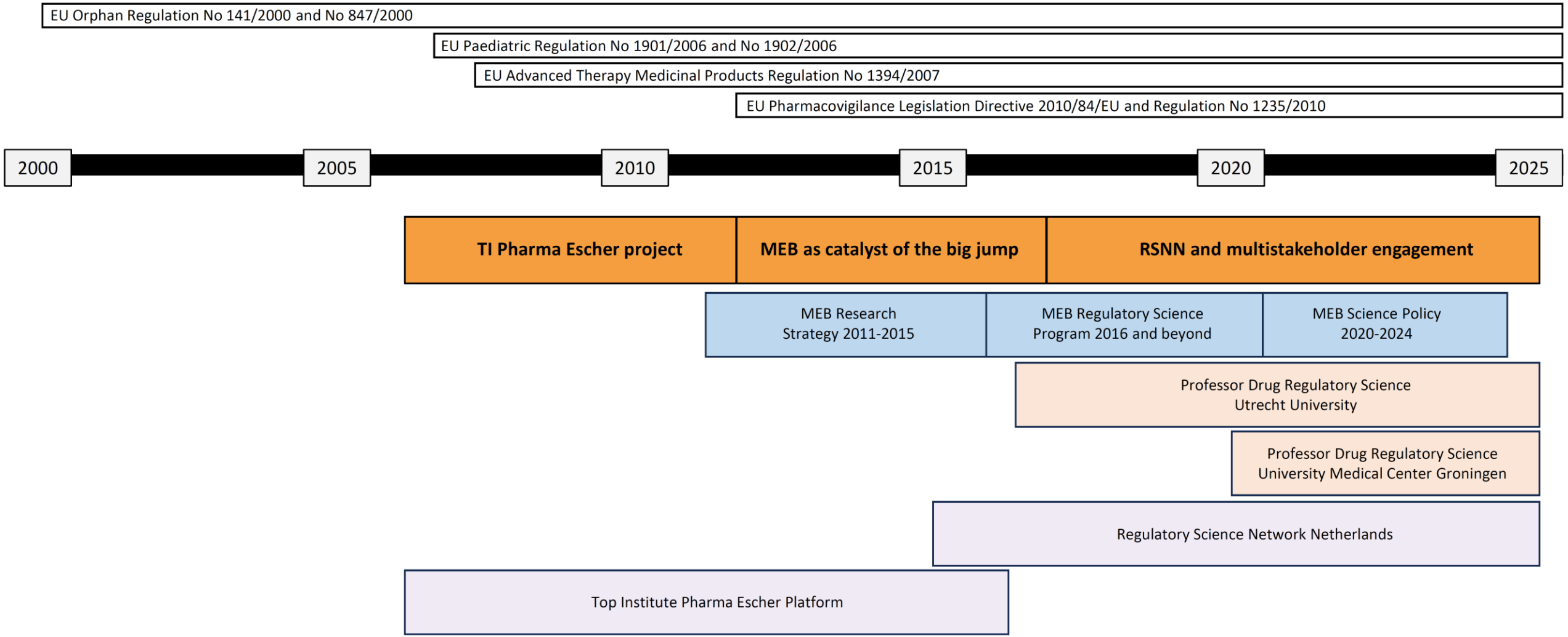
Three pivotal episodes



Pasmooij et al., 2024, CPT

TI Pharma Escher project (2007 – 2012)

- Multistakeholder (academia, industry, patients and regulators) platform
- National public-private program
- Identifying, evaluating and removing regulatory barriers for bringing efficacious and safe medicine to patients
- Wide array of research topics
- More than 15 regulatory science projects
- Many regulators at EMA and MEB were engaged

- Paved in a transdisciplinary research setting the route to a modernized regulatory landscape

Dutch Medicines Evaluation Board as catalyst of the big jump (2012–2017)

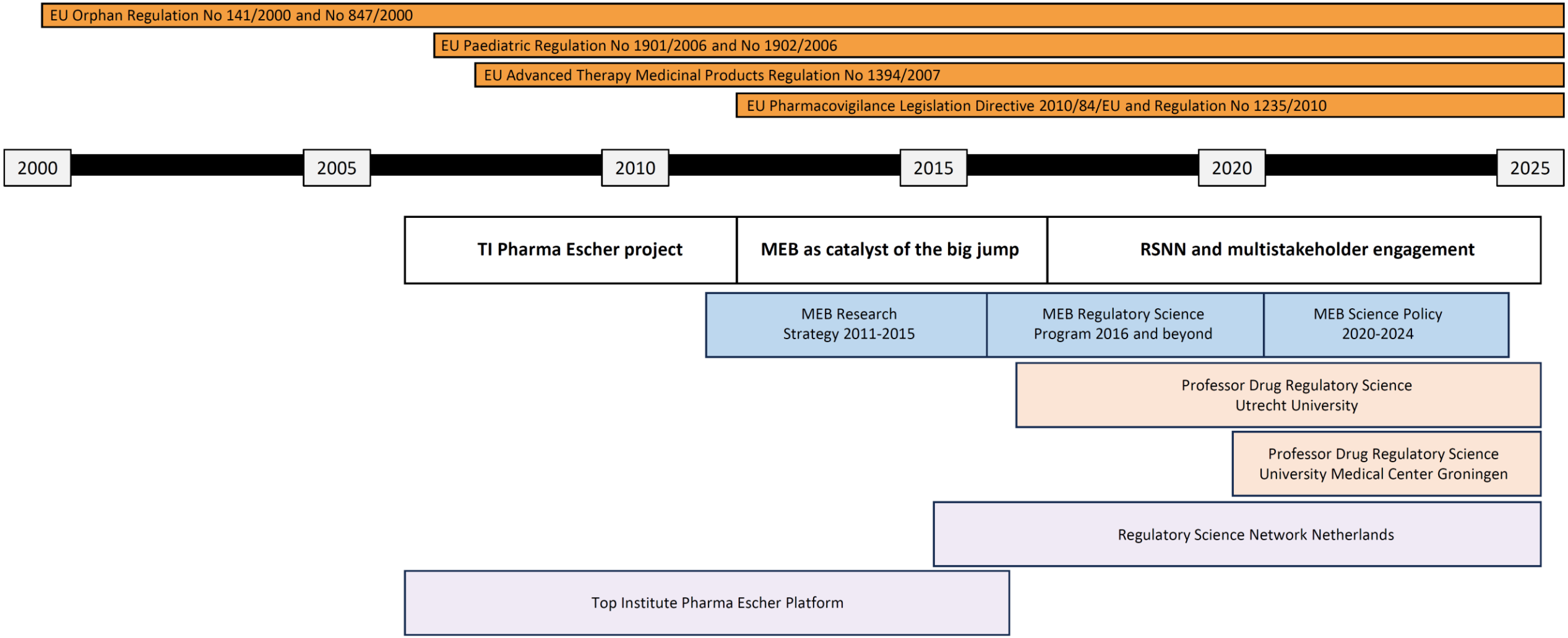
- Investing in more in-depth interactions with academia, clinic and other stakeholders
- Network of PhD and master students, partly with MEB funding
- Model of PhD students – 50% PhD trajectory / 50% assessor or expert at MEB
- Strong interaction between daily regulation and regulatory science
- Role of MEB as (co)rapporteur for centralized European procedures, scientific advice procedures or national procedures

- Experts exposed to scientific discussions - sustained critical thinking

RSNN and multistakeholder engagement (2017–now)

- Network of experts from government bodies, academia, patient representatives and industry
- 3 co-chairs (Marieke De Bruin, Sjaak Bot, Marjon Pasmooij)
- Workshops, expert-meetings
- Special Interest Group on Advanced Therapies (Lourens Bloem, Renske ten Ham)
- www.rsnn.nl

Key EU medicinal product legislation changes



Pasmooij et al., 2024, CPT

Regulatory Science Research topics

Domain	Research topics
Quality/ CMC	Quality attributes for biosimilars, child/elderly friendly formulations, drug shortages, quality by design, bedside manufacturing/ATMPs
Non-clinical	Preclinical data as predictor for clinical outcomes, 3Rs in animal studies, PK/PD modelling, informative animal free toxicology models such as better toxicology models/ organ on a chip and organoids, special populations (ICH S11), diagnostics and screening, data science
Clinical	Clinical evidence generation (small populations, high medical need), trial design (basket, platform), non-inferiority studies, biomarkers, endpoints
Post-approval	Risk management plans, safety communication, risk minimisation, alignment with HTA, pharmacovigilance strategies, registries/RWD
System	Benefit–risk, decision making, scientific advice, expedited/adaptive pathways, access to medicines, ethics/human rights, patient preference

Pasmooij et al., 2024, CPT

Evolution continues...

- Regulatory Science to improve the system and/or to enhance innovation
- Willingness to share learnings and experiences
- Talks started with EMA in 2022 for a European Platform for Regulatory Science Research

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