RSNN Regulatory Science Network Netherlands

Welcome

Special Interest Group (SIG) Advanced Therapies workshop

Programme

09:30 – 09:35 – Welcome & introduction chair

09:35 – 09:45 – Introduction RSNN

09:45 – 10:00 – Introduction RSNN SIG

10:00 – 10:45 – Assessment current challenges in ATMP landscape

10:45 – 11:45 – Appraisal challenges, stakeholder roles and needs

11:45 – 12:00 – ATMPs and the new Pharmaceutical Legislation

12:00 – 12:15 – Takeaways from break-out sessions

12:15 – 12:30 – Wrap-up

12:30 – 13:00 – Lunch & potential transition to RSNN afternoon program

Goals current meeting

- To facilitate and enhance interaction between stakeholders

- To identify and assess current challenges in the ATMP lifecycle
  - Pre-clinical and clinical development, regulatory assessment, reimbursement, and market and patient access
  - Multistakeholder fashion

> Assess the top challenges in more detail in break-out sessions

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Introduction RSNN

Special Interest Group Advanced Therapies

Marjon Pasmooij

Vereniging Innovatieve Geneesmiddelen

CBG MEB

umcg

RSN Holland BIO

Universiteit Utrecht

lygature pioneering medicine. together.

Regulatory Science Network Netherlands (RSNN) was founded in 2015 as a Multistakeholder* Platform

- **Why?** Facilitate knowledge exchange about the **regulatory system and science** to stimulate access to new, effective, and safe therapies
- **What?** Contribute to an **efficient** and **effective** regulatory system for the development, marketing authorisation, access, and appropriate use of medicines.
- **How?**
  - **Bundling** expertise
  - Knowledge **exchange** and **dissemination**
  - **Agenda-setting** for regulation and regulatory science
  - **Involved** in relevant (inter)national regulatory science discussions
  - **Catalyzing** regulatory science

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*Academia, Regulators/Authorities, (Bio)Pharmaceutical industry, Patient Organizations

All stakeholders together set the RSNN agenda

Vereniging Innovatieve Geneesmiddelen

CBG MEB

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Holland BIO

ccmo

Steering Committee

Sjaak Bot
Janssen Biologics

Marjon Pasmooij
Medicines Evaluation Board (CBG-MEB)

Peter Mol
UMCG/Medicines Evaluation Board (CBG-MEB)

Carla Vos
Vereniging van Innovatieve Geneesmiddelen (VIG)

Peter van Meer | Vice-chair
Medicines Evaluation Board (CBG-MEB)

Marieke De Bruin
Utrecht University

Sophie Huiskes-Berends
Program Manager

Pieter Stolk | non-voting
Lygature

The entire regulatory ecosystem is connected

Advisory Board

- Francisco Hernandez, Pfizer, Chair
- Dr. Peter Bertens, VIG
- Carine Besselink, Eupati fellow
- dr. Helga Gardarsdottir, UU
- Prof. Dr. Joop van Gerven , Centrale Commissie Mensgebonden Onderzoek
- Marit Heblij, HollandBIO
- Dr. Jarno Hoekman, Utrecht University
- Dr. Agnes Kant, Lareb
- Prof. Dr. Aletta Kraneveld, Utrecht University
- Marlous Kooijman, FAST
- Dr. Larissa de Lannoy, PSC Patients Europe, patient advocate
- Evelien Minten, Medicines Evaluation Board (CBG-MEB)
- Connie van Oers, UniQure/RegNed
- Huib Scheijbeler, Bayer
- Lonneke Timmers, ZIN
- Aimad Torqui, Medicines Evaluation Board (CBG-MEB)
- Pauline Walstra, Astellas
- Just Weemers, Janssen
- Wieteke Wouters, HollandBIO

Multistakeholder Regulatory Dialogue activities: *RSNN Annual workshop*

- **Why?** Sharing knowledge regarding regulatory topics relevant to all players in the field, identifying new research questions, and stimulating networking.
- **How?** Annual workshop (100-150 participants)
- **Impact?** Identification of new topics for regulatory dialogue, initiation of collaborations, meeting reports, and responding to needs within the regulatory field.
- **Examples?**
  - *Pharmaceutical legislation – Highway to innovation (This afternoon)*

Multistakeholder Regulatory Dialogue activities: *RSNN Annual workshop*

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RSNN ANNUAL WORKSHOP 2022 REPORT

Patient preferences: towards a more structural incorporation in the regulatory pathway

Medicine regulators have the role to assess the benefits and risks of medicines in order to ensure that only those medicines that have proven efficacy and safety (positive benefit-risk balance) enter the market and are available for the population. Assessing this balance is, however, sometimes challenging due to the heterogeneity of these two elements. Since 1965 medicine medicine regulations have been evolving, aiming to provide harmonization and guidance for this assessment. However, these assessments still require certain value judgments, which translate as the importance (value) given to the observed drug effects. These values are difficult to quantify, and might vary from person to person and among

Received: 1 March 2019 | Revised: 29 May 2019 | Accepted: 28 June 2019
DOI: 10.1111/bcp.14070

SHORT REPORT

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Future of the drug label: Perspectives from a multistakeholder dialogue†

Christine C. Gispen-de Wied[1] | Just Weemers[2] | Wouter Boon[3] | Peter G.M. Mol[1,4] | Pieter Stolk[5]

[1] Medicines Evaluation Board, Utrecht, Netherlands
[2] Pfizer Netherlands, Capelle aan den Ijssel, Netherlands
[3] Department of Geosciences, Copernicus Institute of Sustainable Development, Utrecht University, Utrecht, Netherlands
[4] Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands

Regulating drugs does not end when market access has been granted. Monitoring drugs over the life cycle has become state of the art, inherent to evolving legislation and societal need. Here, we explore how the drug label could move along in a changing playing-field and become a sustainable label for the future. A dialogue between academia, government, the pharmaceutical industry and patient/societal organizations was organized by the Regulatory Science Network Netherlands. This is their view.

Multistakeholder Regulatory Dialogue activities: *FIGON Dutch Medicines Day – Regulatory session*

- **Why?** Increasing regulatory awareness and strengthening the connection with the drug development field within the Netherlands.
- **How?** Organizing a multistakeholder session regarding a regulatory topic regarding drug development
- **Impact?** Articulation of regulatory questions, reports, and scientific publications.
- **Examples?**
  - *Regulatory pandemic preparedness (September 2023)*
  - *Academic drug development across Europe, regulatory challenges and learnings (June 2022)*

Multistakeholder Regulatory Dialogue activities: *Rapid Response Expert Meetings*

- **Why?** Multistakeholder discussion regarding present day regulatory hurdles and possibilities
- **How?** Personal invitation of topical experts (n=10-15) discuss under the Chatham House Rules.
- **Impact?** Focused output such as concrete regulatory science research questions, supported statements, (scientific) papers, and reports.
- **Examples?**
  - *Facilitating human relevant safety assessment of medicinal products: towards implementation of new approach methods (NAMs) - May 2023*
  - *Direct Healthcare Professional Communication: Recommendations to improve impact - April 2023*
  - *Regulator-initiated Studies for Regulatory Decision-Making: Scenarios and Learnings – Oct 2022*
  - *Regulatory Readiness Levels as a Tool to Drive Regulatory Innovation – June 2021*
  - *How to bring Advanced Therapy Medicinal Products from bench to bedside: The local Hospital Exemption procedure versus EMAs' centralised authorisation? – March 2021*

Multistakeholder Regulatory Dialogue activities: *Rapid Response Expert Meetings*

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RAPPORT RSNN EXPERT MEETING

25 October 2022

REGULATOR-INITIATED STUDIES FOR REGULATORY DECISION-MAKING: SCENARIOS AND LEARNINGS

On the 25th of October 2022, an RSNN expert meeting took place to discuss the topic "Regulator-initiated studies for regulatory decision-making: scenarios and learnings". For several years, regulators have requested Marketing Authorisation Holders (MAHs) to conduct post marketing studies, which made use of real world data (RWD). These studies have been mostly related to pharmacovigilance. However, over the past years, drug developers have displayed a growing interest to use RWD in the pre-marketing phase as well, for example when experimental study designs such as randomized controlled trials are deemed impossible or unethical. On a European level, the European Medicines Agency (EMA) is exploring the use of high quality RWD in decision-making for instance through the Data Analysis and Real-World Interrogation Network (DARWIN EU®). DARWIN EU® includes a coordination center that is

frontiers in Medicine

PERSPECTIVE
published: 09 December 2021
doi: 10.3389/fmed.2021.790782

Check for updates

Extension of Indication for Authorised Oncology Products in the European Union: A Joint Effort of Multiple Stakeholders

Jorn Mulder[1], Robin Verjans[2], Ciska Verbaanderd[3,4], Elias Pean[3], Just Weemers[5], Hubert G. M. Leufkens[6], Francesco Pignatti[3], Anthonius de Boer[1,6], Emile E. Voest[7,8], Violeta V. Stoyanova-Beninska[1] and Anna M. G. Pasmooij[1]*

[1] Dutch Medicines Evaluation Board, Utrecht, Netherlands, [2] Lygature, Utrecht, Netherlands, [3] European Medicines Agency, Amsterdam, Netherlands, [4] Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [5] Janssen Biologics BV, Leiden, Netherlands, [6] Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands, [7] Department of Molecular Oncology and Immunology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [8] Oncode Institute, Amsterdam, Netherlands

OPEN ACCESS

After marketing authorisation, the development of a medicinal product often continues with studies investigating new therapeutic indications. Positive results can potentially lead to changes to the terms of the marketing authorisation, such as an extension of

Multistakeholder Regulatory Dialogue activities: *Rapid Response Expert Meetings*

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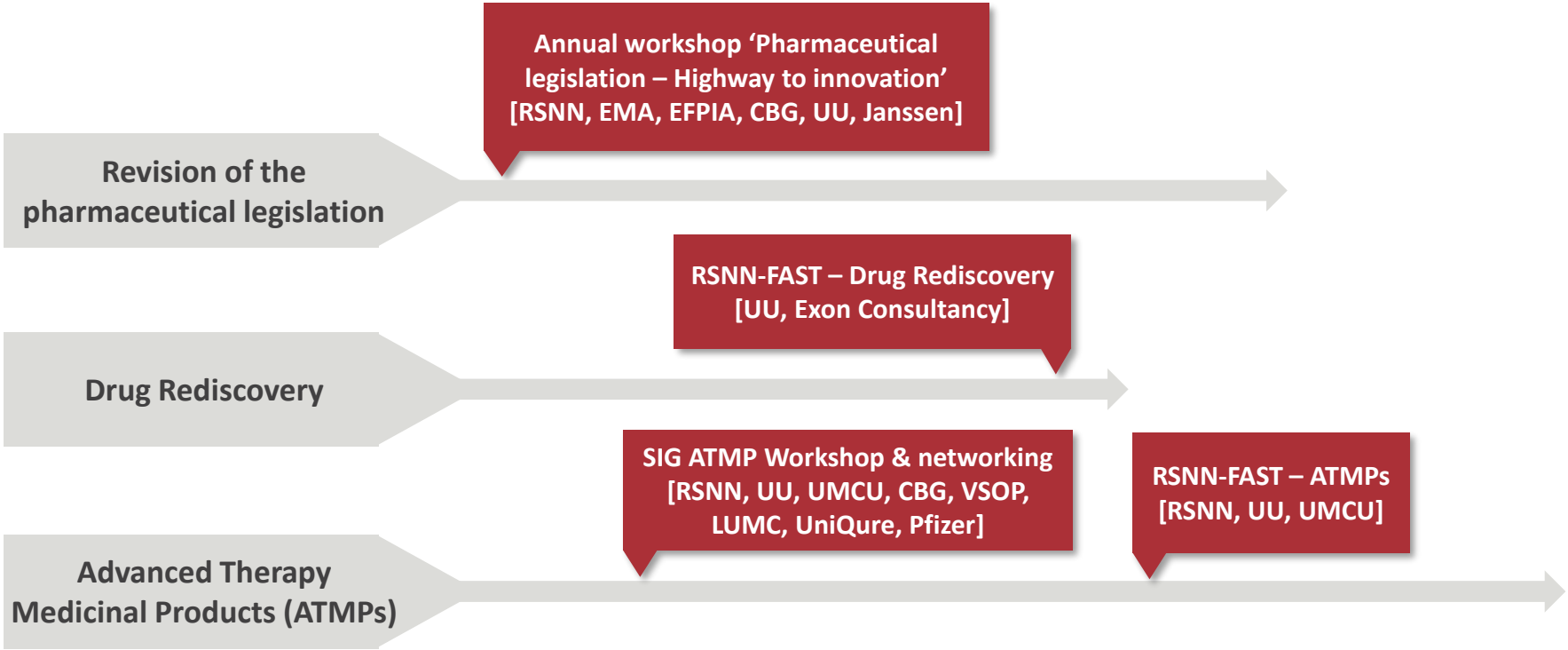
  - *How to bring Advanced Therapy Medicinal Products from bench to bedside: The local Hospital Exemption procedure versus EMAs' centralised authorisation? – March 2021*

RSNN Special Interest Group: Advanced Therapies

- **Why? -** Advanced therapy medicinal products (**ATMPs**) such as gene and cell-based therapies are highly innovative medicines that provide new opportunities to treat conditions with **high unmet medical need**. ATMPs experience several **regulatory challenges**, more so than conventional medicinal products.
- **What? -** Identify **knowledge gaps** and **actions** to address regulatory and access challenges perceived by stakeholders in ATMP **development** and **assessment**.
- **Who?** Special Interest Group Core members include:
  - **Lourens Bloem** – UU
  - **Renske ten Ham** – UMCU
  - **Babs Fabriek** – CBG
  - **Annemieke van der Waal** – ZIN
  - **Mariette Driessens** – VSOP
  - **Pauline Meij** – LUMC
  - **Connie van Oers** – UniQure
  - **Francisco Hernandez** - Pfizer

Planned activities addressing current and future regulatory bottlenecks through dialogue



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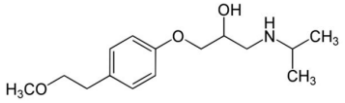
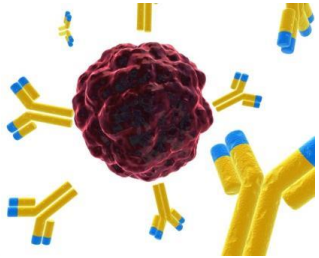
SIG
Advanced Therapies

RSNN Presentation by Renske ten Ham & Lourens Bloem

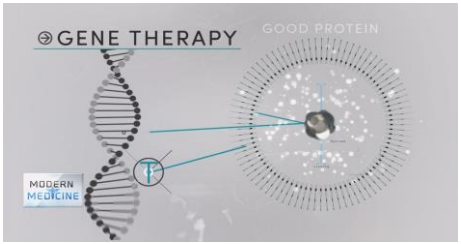
SIG Advanced Therapies: Why?



Small Molecules

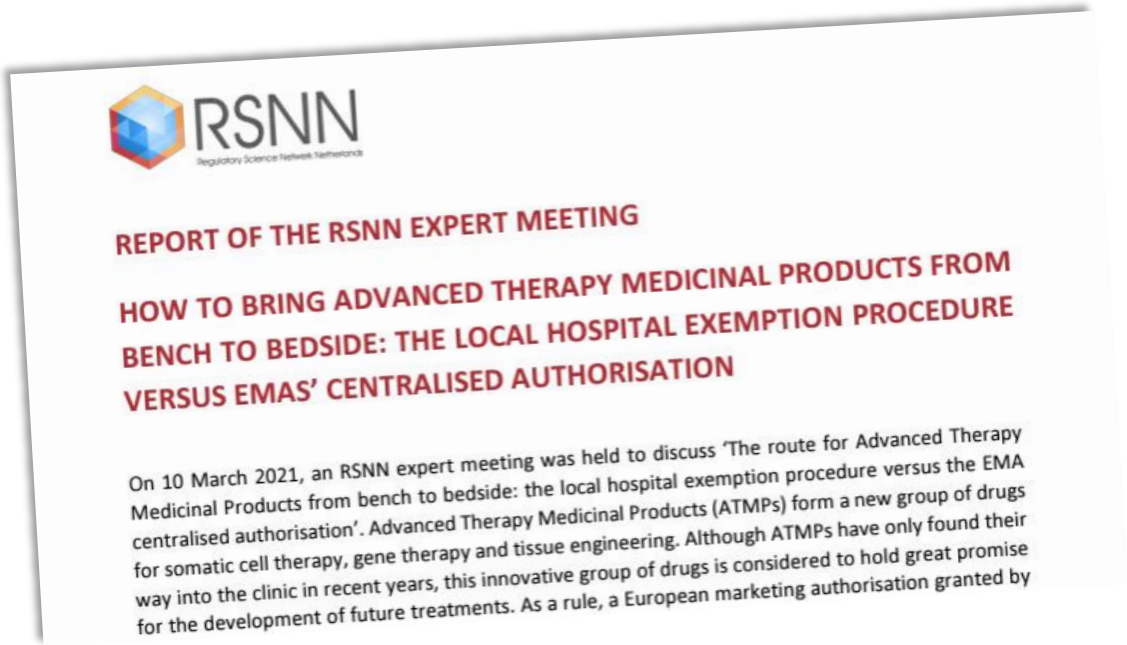


Biologicals



Advanced Therapies

SIG Advanced Therapies: Why?



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REPORT OF THE RSNN EXPERT MEETING

HOW TO BRING ADVANCED THERAPY MEDICINAL PRODUCTS FROM BENCH TO BEDSIDE: THE LOCAL HOSPITAL EXEMPTION PROCEDURE VERSUS EMAS' CENTRALISED AUTHORISATION

On 10 March 2021, an RSNN expert meeting was held to discuss 'The route for Advanced Therapy Medicinal Products from bench to bedside: the local hospital exemption procedure versus the EMA centralised authorisation'. Advanced Therapy Medicinal Products (ATMPs) form a new group of drugs for somatic cell therapy, gene therapy and tissue engineering. Although ATMPs have only found their way into the clinic in recent years, this innovative group of drugs is considered to hold great promise for the development of future treatments. As a rule, a European marketing authorisation granted by

Mission & Vision

- To facilitate and enhance interaction between stakeholders involved in all stages of development, assessment, and access of ATMPs

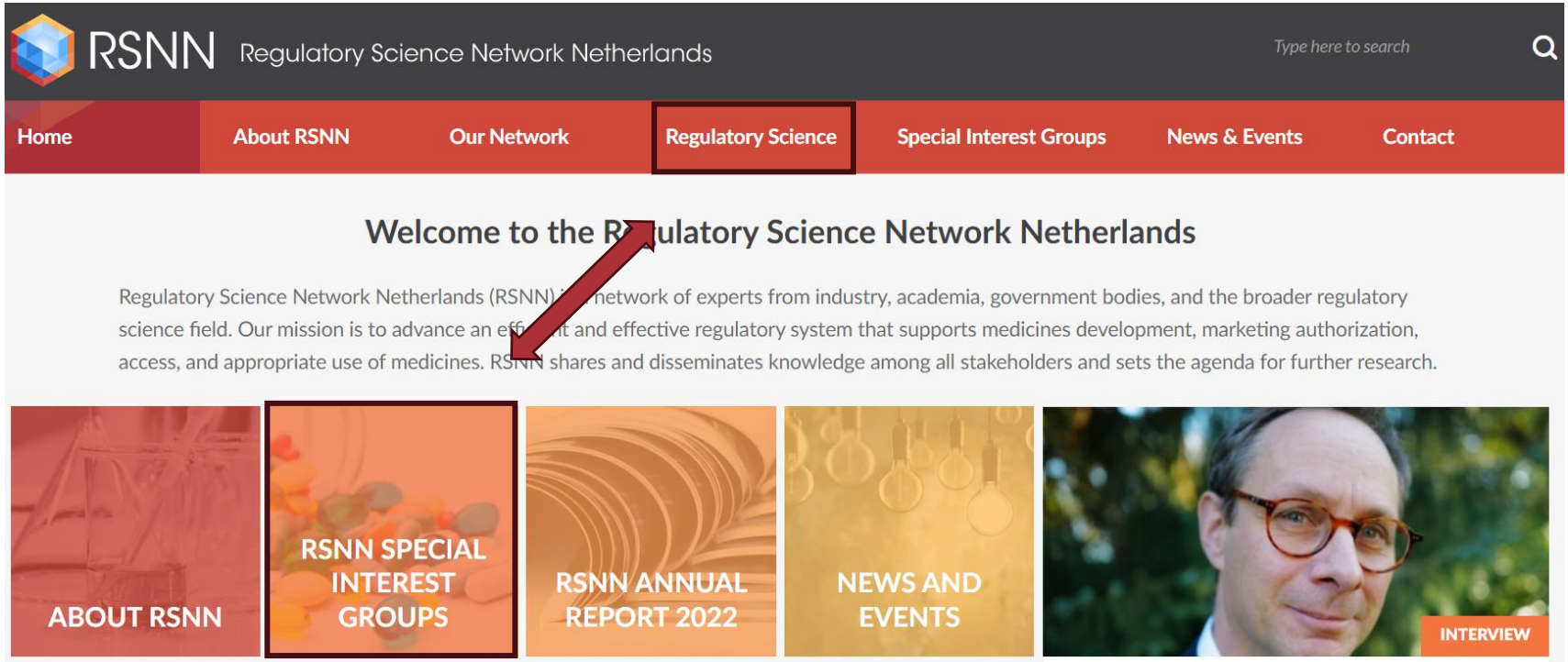
- To identify knowledge gaps and actions to address regulatory challenges perceived by stakeholders in a multistakeholder fashion

The objectives of the SIG Advanced Therapies are met if these products have become an integral part of the drug development landscape

Activities & Deliverables

- Website is assembly point for network, information & documentation
- Meet twice a year around a specific topic
- Discussions are data driven
- Outcomes:
  - Research questions to address specific challenges
  - Actionable next steps

More information






Governance

The governance of the RSNN SIG Advanced Therapies is as follows:

- Dr. **Lourens Bloem,** Assistant Professor Clinical Therapeutics at the Division of Pharmacoepidemiology and Clinical Pharmacology; Utrecht Institute for Pharmaceutical Sciences; Utrecht University (**Co-Chair**)
- Dr. **Renske ten Ham,** Assistant Professor Health Technology Assessment at the Department of Healthcare Innovation & Evaluation and Medical Humanities; Julius Center; University Medical Center Utrecht (**Co-Chair**)
- More SIG Advanced Therapies-members will be published in the nearby future.

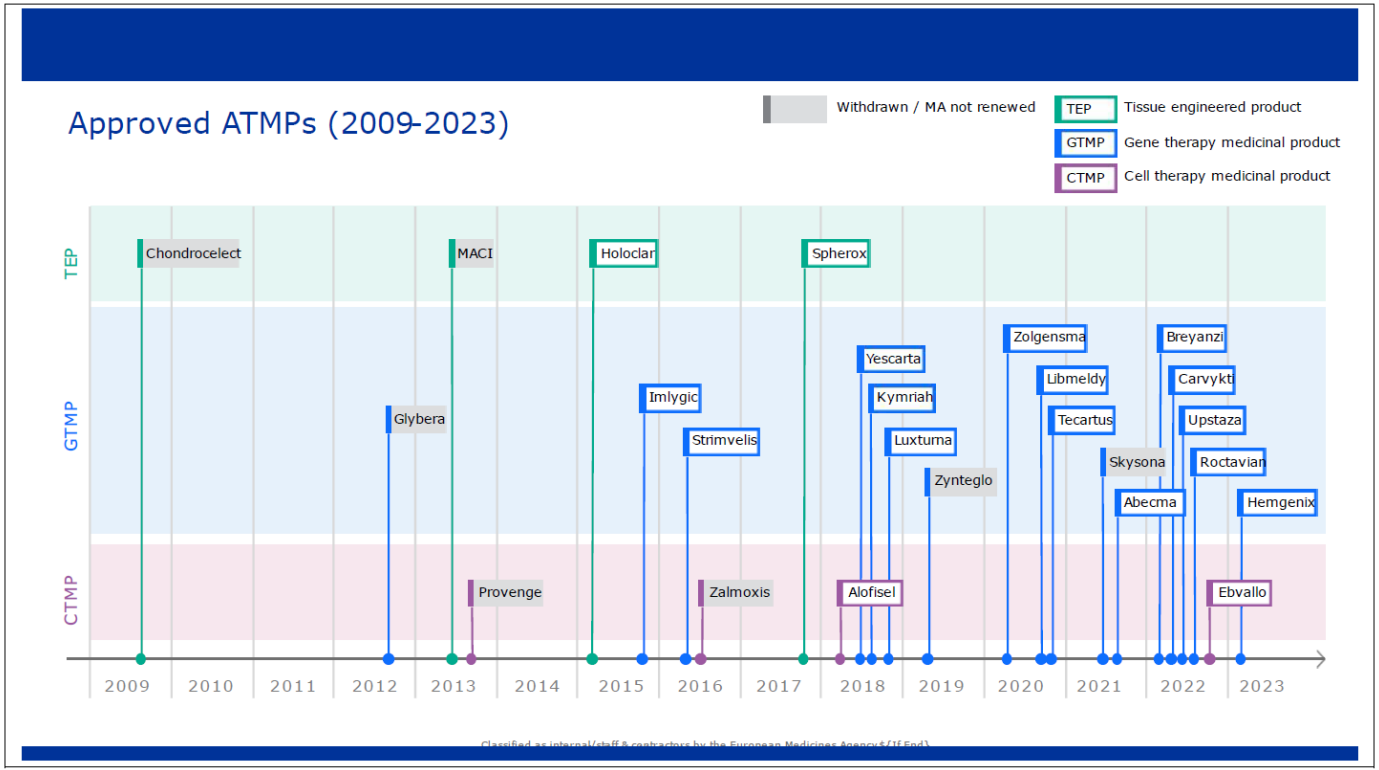
Core Members

- **Mariette Driessens** – VSOP
- **Babs Fabriek** – CBG-MEB
- **Francisco Hernandez** – Pfizer
- **Pauline Meij** – Leiden University Medical Centre
- **Connie van Oers** - uniQure
- **Annemieke van der Waal** – Zorginstituut Nederland

RSNN SIGs are open and inclusive initiatives and subject to continuous development. Are you interested in contributing? Please contact info@RSNN.nl.




Current landscape



2009 – April 2023:

25 authorized
- 19 orphan
- 7 withdrawn

Last 5 years (*N* = 15)
- 14 gene therapy
- 14 orphan
- 11 regulatory support (PRIME)

1 under review

Current landscape

Approved therapies until 31/12/2023 for selection of countries:

- EU: 24 (of which 7 withdrawn)
- US: 20 (and 8 hematopoetic progenitor cell products)
- Japan: 17
- Australia: 6
- China: 4, including first two worldwide (2004, 2005)

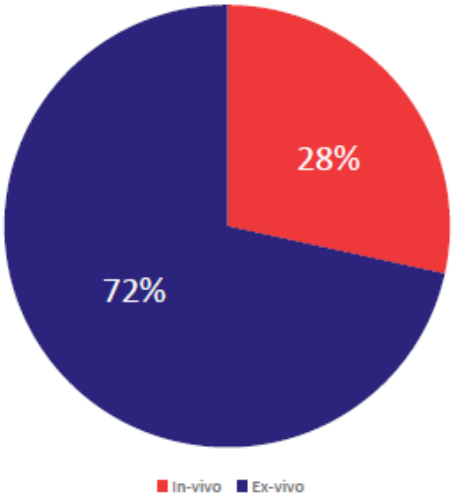
Current landscape

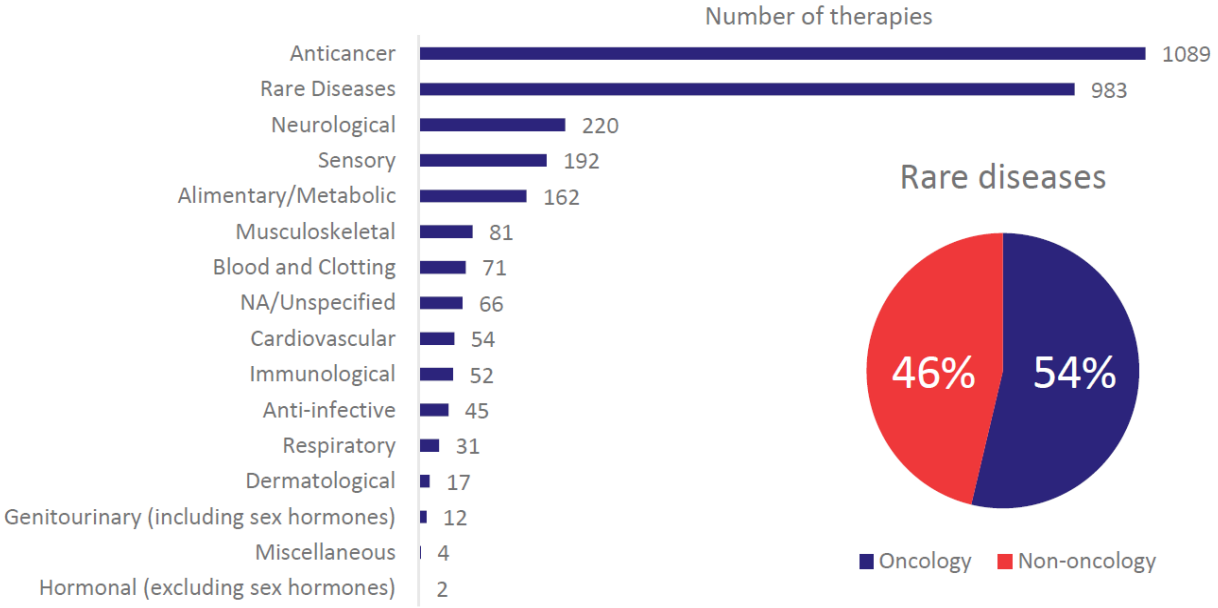
Product	Indication	Market Authorization	Scotland (SMC)	the Netherlands (ZIN)	England (NICE)
ChondroCelect®*	Cartilage defect in the knee	November 2009	-	Negative recommendation	-
Glybera®*	Hyperlipo-proteinemia	November 2012	-	-	-
MACI®*	Cartilage defect in the knee	June 2013	-	-	-
Provenge®*	Prostate cancer	October 2013	-	-	-
Holoclar®	Limbal stem cell deficiency	December 2014	-	-	Restricted recommendation
Imlyglic®	Metastatic melanoma	December 2015	-	-	Restricted recommendation
Strimvelis®	ADA-SCID	June 2016	-	-	Positive recommendation
Zalmoxis®*	Adjuvant to HSCT in hematologic malignancies	September 2016	-	-	-
Spherox®	Cartilage defects in knee	July 2017	-	-	Positive recommendation
Alofisel®	Crohn's disease	March 2018	Negative Recommendation	-	Negative Recommendation
Yescarta®	DLBCL	Augustus 2018	Restricted recommendation	Positive recommendation	Restricted recommendation
Kymriah®	ALL	August 2018	Restricted recommendation	Restricted recommendation	Restricted recommendation
	DLBCL	August 2018	Negative recommendation	Negative recommendation	Restricted recommendation
Luxturna®	Inherited retinal dystrophy	November 2018	Restricted recommendation	Restricted recommendation	-
Zynteglo®	β-thalassaemia	June 2019	-	-	-
Zolgensma®	SMA type 1	March 2020	-	-	-

Current landscape

Products in development, Q1 2023 (preclinical, clinical, pre-registration):

- 2,022 gene therapies

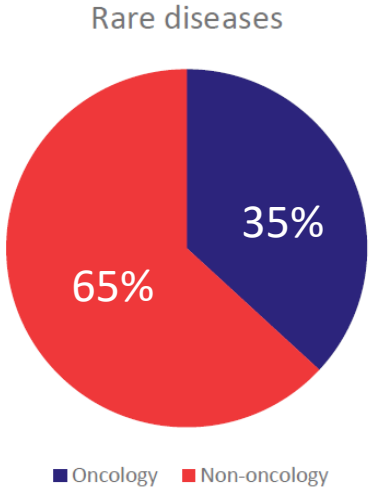


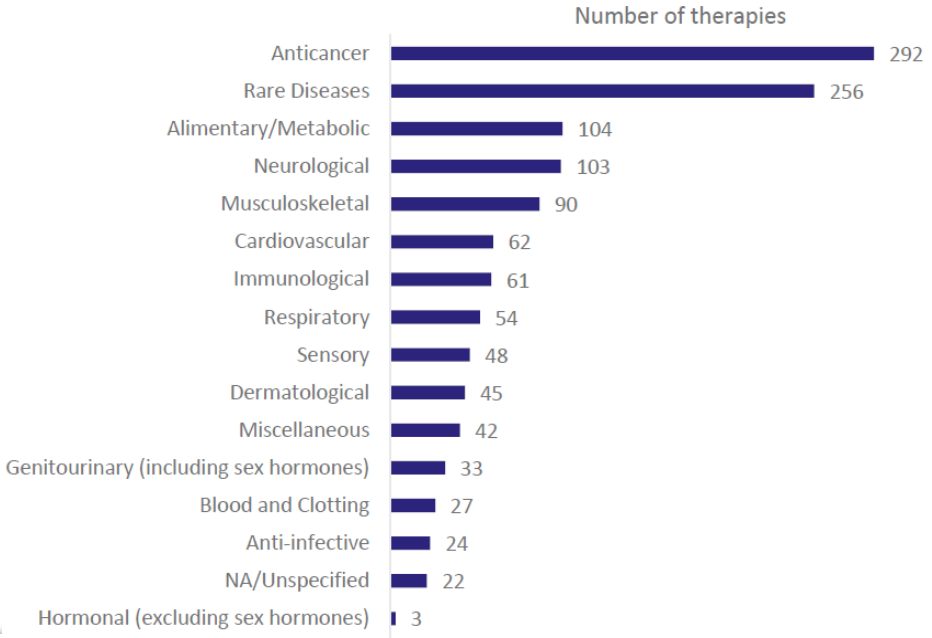


Current landscape

Products in development, Q1 2023 (preclinical, clinical, pre-registration):

- 813 non-genetically modified cell therapies





ASGCT/Citeline, Q1 2023

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Plenary assessment challenges in the ATMP lifecycle

Goals current meeting

- To facilitate and enhance interaction between stakeholders

- To identify and assess current challenges in the ATMP lifecycle
  - Pre-clinical and clinical development, regulatory assessment, reimbursement, and market and patient access
  - Multistakeholder fashion

> Assess the top challenges in more detail in break-out sessions

Next steps

Agenda setting for future RSNN SIG Advanced Therapies meetings

Input used for ZonMw/FAST project (report)

Scientific publication based on this meeting's learnings and other work

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ATMPs and the new Pharmaceutical Legislation

The proposed revision of the pharmaceutical legislation- impact for ATMPs

Marcel Hoefnagel; Senior Assessor Biopharmaceuticals MEB

DISCLAIMER:

Personal views only, these may not necessarily reflect the views/opinions of MEB or EMA

This presentation is a snap shot of the proposed revisions with impact for ATMPs and cannot be considered complete

GOOD MEDICINES USED BETTER

Objectives of the new legislation 1/2

1. Create a **Single Market for medicines** ensuring that all patients across the EU have **timely and equitable access to safe, effective, and affordable** medicines;

2. Continue to offer an attractive and **innovation-friendly framework** for research, development, and production of medicines in Europe;

3. Reduce drastically the **administrative burden** by speeding up procedures significantly reducing authorisation times for medicines, so they reach patients faster;

Q&A: Revision of the Pharmaceutical legislation (europa.eu)

Objectives of the new legislation 2/2

4. Enhance **availability** and ensure medicines can always be supplied to patients, regardless of where they live in the EU;

5. Address **antimicrobial resistance** (AMR) and the presence of pharmaceuticals in the environment through a One Health approach;

6. Make medicines more **environmentally sustainable.**

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

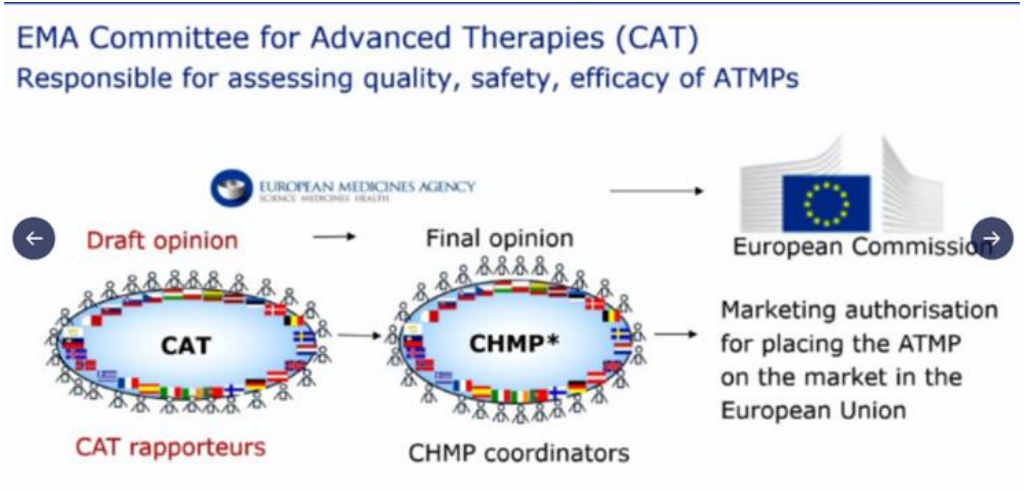
Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

EMA committee structure

Current structure



Draft proposal

- The structure of the Agency's scientific committees is simplified and reduced to two main Committees: the CHMP and PRAC.

- The expertise of the CAT, the COMP, the PDCO and the HMPC is retained through **working groups, working parties** and a pool of experts who are organised based on different domains and who are giving input to the CHMP and PRAC.

EMA committee structure

- The CHMP shall include four members and one alternate members appointed by the Commission, representing **healthcare professionals**; and four members and four alternate members appointed by the Commission, to represent **patient organisations**.

- The Agency's scientific committees should be able to delegate some of their evaluation duties to working parties which should be **open to experts from the scientific world** and appointed for this purpose, whilst retaining complete responsibility for the scientific opinions issued by them.

Regulatory data protection (orphan)

- The standard duration of market exclusivity will be 9 years. A maximum of 13 years may be reached, while today the maximum is 10 years.

- Companies can benefit from additional periods of market exclusivity:
  I. If they address a high unmet medical need (hUMN) (+1 year),
  II. If they launch the medicine in all Member States (+ 1 year),
  III. for new therapeutic indications (up to 2 extra years).

- The various elements of the criterion-based definition of UMN (e.g. “remaining high morbidity or mortality”) will be further specified in implementing acts (of the commission).

Environmental impact (1/2)

- One single application process for the complete clinical trial (ERA submission in CTIS).
- The CHMP is tasked with evaluating the ERA for investigational medicinal products including GMO.

Environmental impact (2/2)

- For first in class or when a novel question is posed, CHMP shall carry out necessary consultations of relevant GMO competent authorities at national level, otherwise optional.

- If the applicant fails to submit a complete or sufficiently substantiated ERA or they do not propose risk mitigation measures to sufficiently address the risks identified in the environmental risk assessment, the application shall be considered as withdrawn.

Hospital exemption

Current: variations in how MS interpret HE regulations, proposals in new legislation to harmonize across MS.

Draft Directive, article 2: Role for EMA in oversight of HE

- MS must notify the EMA of approved HE.
- Where a MS revokes a HE approval as a result of safety or efficacy concerns, it must inform the EMA and the NCAs of the other Member States.
- The NCAs must report the data related to the use, safety and efficacy of ATMPs prepared under the hospital exemption to the EMA annually (publication in data repository) > examine whether an adapted framework should be established for certain less complex ATMPs that have been developed and used under the hospital exemption.
- EC will adopt implementing legislation for type and format of the data to be collected.
- EMA is required to report to EC on experiences gained with HE approvals.

Decentralised manufacturing

- A registration in the Union database, which will be created by the EMA, is then necessary to enable manufacturing activities to commence in the decentralised site.

- The Commission is expected to further detail GMP principles for decentralised manufacturing of medicinal products.

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Wrap-up

Next steps

- Agenda setting for future RSNN SIG ATMP meetings
- Inputs used for FAST/ZonMW project (output report)
- We aspire to translate discussions into (scientific) publication

Thank you

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