Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

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From research to market approved medicines – the regulatory perspective

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Martina Schuessler-Lenz, M.D.

Department Haematology, Cell and Gene therapy (HZG)
Paul-Ehrlich-Institut

The views expressed in this presentation are those of the speaker, and may not be understood or quoted as being the official opinion of the Paul-Ehrlich-Institut.

No conflict of interest declared.

- Do you want to answer a research question?
- Do you intend to develop your research candidate to the clinic?
- Do you want to develop a medicine to EU approval?

I intend to develop my research candidate to the clinic

Strategic planning

- Medicine development follows certain rules
  - Legal European frame to ensure safe and efficacious medicines of high quality
  - EU regulations, directives, guidelines, national legislations
- What is your product?
  - Define your product
    - Chemical
    - Biological, e.g. (bi-specific) monoclonal antibody; CART cell, TCR-T cell, gene edited cells -> advanced therapy medicinal product (ATMP)

I intend to develop my research candidate to the clinic

Strategic planning (2)

- Do you want to translate your development candidate towards a first-in-human clinical trial -> scientific and procedural aspects of clinical trials -> authorisation by member states

- Do you want to develop your product towards marketing authorisation -> EU market (commercialization) -> authorisation by member state delegated experts in EU committees at EMA -> prizing and reimbursement discussions in member states

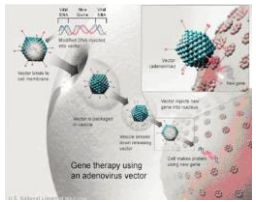
Define your product/development candidate

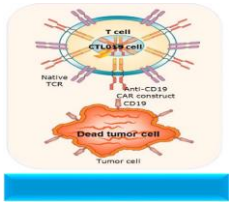
- Classification of medicines in national responsibility
  - Chemical, small molecule
  - Biological
    - Recombinant proteins, eg. Epoetin alpha
    - Vaccines
    - Monoclonal antibodies
    - Gene and cell therapies (advanced therapies, ATMP)
  - Relevant in terms of regulatory oversight, authorisation, surveillance
    - Differential responsibilities in Germany.
    - Federal Institute for drugs and medical devices (BfArM)
    - Paul-Ehrlich-Institute
    - Competent authorities Laender
  - Relevant in terms of applicable legal frames, guidelines

EU Regulation for Advanced Therapy Medicinal Products (ATMPs)
(EC) No1394/2007

- Stipulates EU authorization via the centralized procedure, coordinated by European Medicines Agency (EMA)
- Principles of existing legislation apply: quality, safety, efficacy, pharmacovigilance, post-authorisation patient follow-up, GMP, GCP
- Classification advice from EMA Committee for Advanced Therapies

Gene therapy



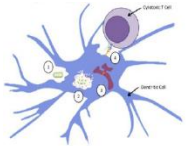


➔ **Recombinant nucleic acid**

Rek. AAV vectors

Genetically modified cells

Somatic cell therapy



➔ **Pharmaco-immunological…**

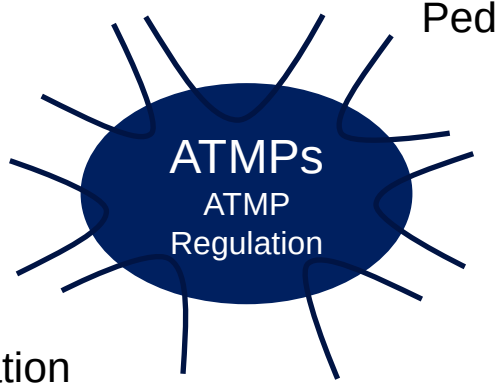
Expanded allogeneic MSC, complex anal fistula

Tissue engineered product

➔ **Regeneration, repair**

Cultured chondrocytes, Regeneration knee cartilage

The EU legal frame for gene and cell therapies (ATMPs)
Interfacing legislation



Medicines legislation

Pediatric legislation

Physicians legislation

Orphan legislation

Pharmacovigilance legislation

Hospital legislation

Genetically modified organisms (GMO) legislation

Clinical Trials Regulation

Blood, tissues and cells (BTC) legislation

Medical device legislation

Medical Device Regulation

In vitro diagnostic Regulation

The medicine life cycle

ATMP DEVELOPMENT

MARKETING AUTHORISATION

POST-APPROVAL LIFE CYCLE MANAGEMENT, PHARMACOVIGILANCE

Discovery
Pre-clinical

Clinical Evaluation

Clinical trial authorisation

CAT*

PRAC*

CHMP*

Benefit-risk assessment / opinion

(Conditional) Approval

Post-authorisation data generation,
Real World Data,
Clinical trials, indication extension

HTAs, Reimbursement

Patient access

RWD

National Scientific Advice

Simultaneous NSA

EMA

National HTA advice

EMA/HTA parallel advice

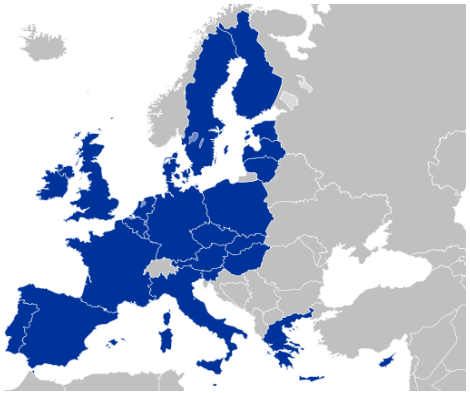
Scientific assessments and authorisations by experts from NCAs throughout life cycle

*Committee for Advanced Therapies
•Committee for Medicinal Products for Human Use
•Pharmacovigilance Risk Assessment Committee

Translation of development candidate towards first-in-human clinical trial

- Scientific aspects
- Regulatory - methodological aspects
- Operational - procedural aspects
- Funding aspects

The EU Clinical Trials/Clinical Trial Information System CTIS



Clinical Trials Directive (EU 2001/20/EC)

Some harmonisation, but **national systems & processes varied**

Entered into application 1 May 2004

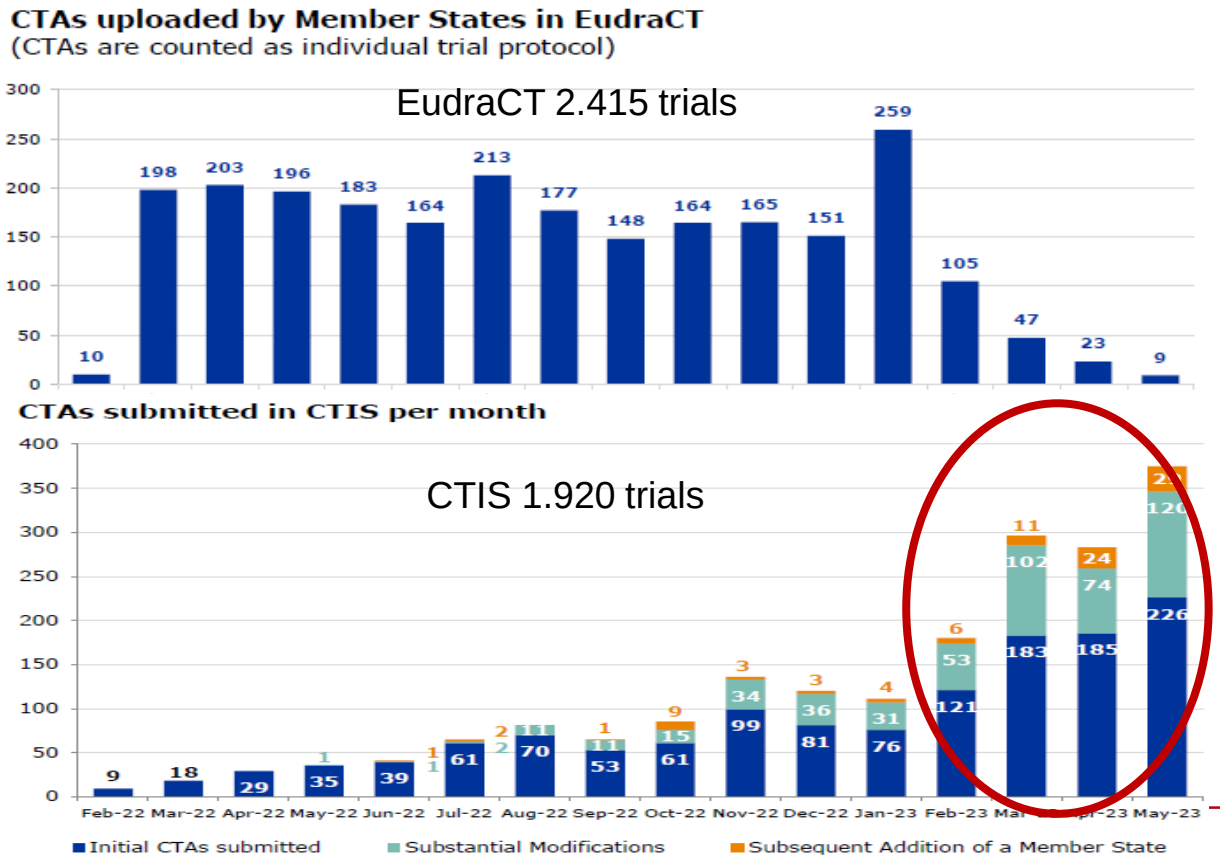
Clinical Trials Regulation (No.536/2014)

Full harmonisation, efficiency through collaborative assessment of multinational trials

Develop EU as competitive center for innovative clinical research

Source European Medicines Agency

The EU clinical research/trial landscape since 2.2022



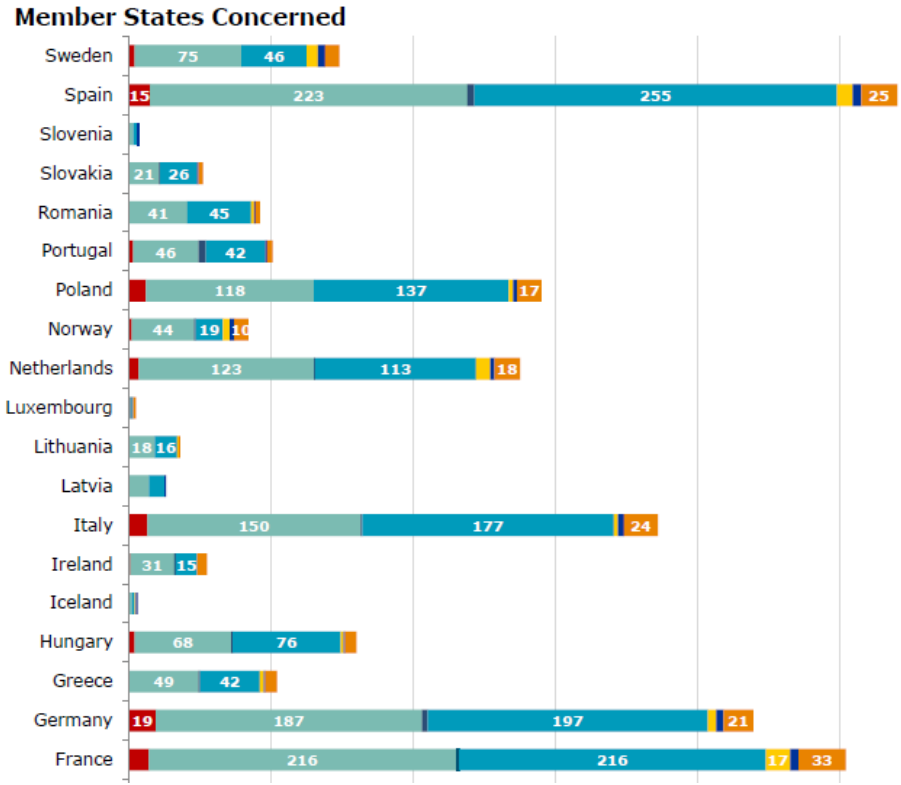
Jan. - June 2023

EU-CTIS n= 791
clintrials.gov: n= 20.030
clinical trials registered

https://www.ema.europa.eu_ACT EU_KPIs

The EU clinical trial landscape

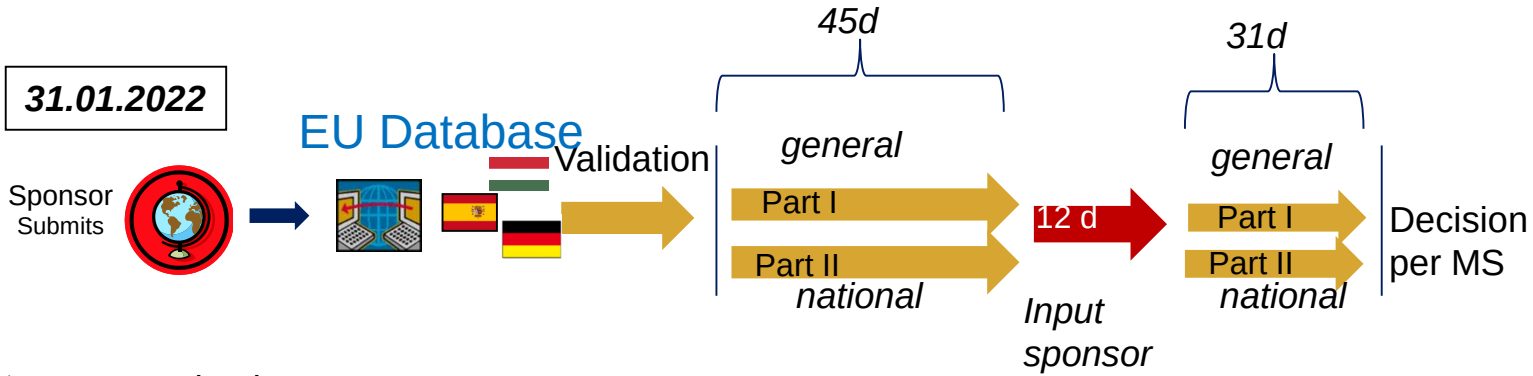
CTIS clinical trial applications 1.2022 – 6.2023 by EU member state



1.930 clinical trial applications in CTIS since 1.2022

Submitted applications
Spain > France > Germany
Includes multinational trials

The EU Clinical Trials/CTIS system - Regulation 536/2014
Procedural aspects

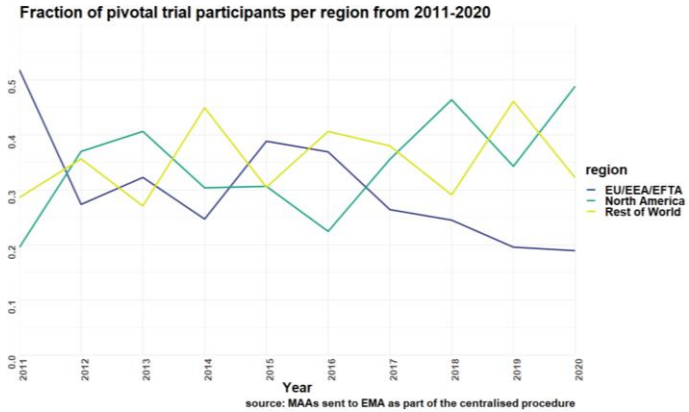


- Harmonized
  - Sponsor submits dossier through CTIS/EU portal
  - Assessment by national competent authorities - co-ordinated multinational assessment, „reporting“ and „concerned“ member states
  - Very short timelines (12d) for sponsors to address questions

- Member states retain authorisation and oversight

https://https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/

EU Clinical Research Landscape
Where do we stand?



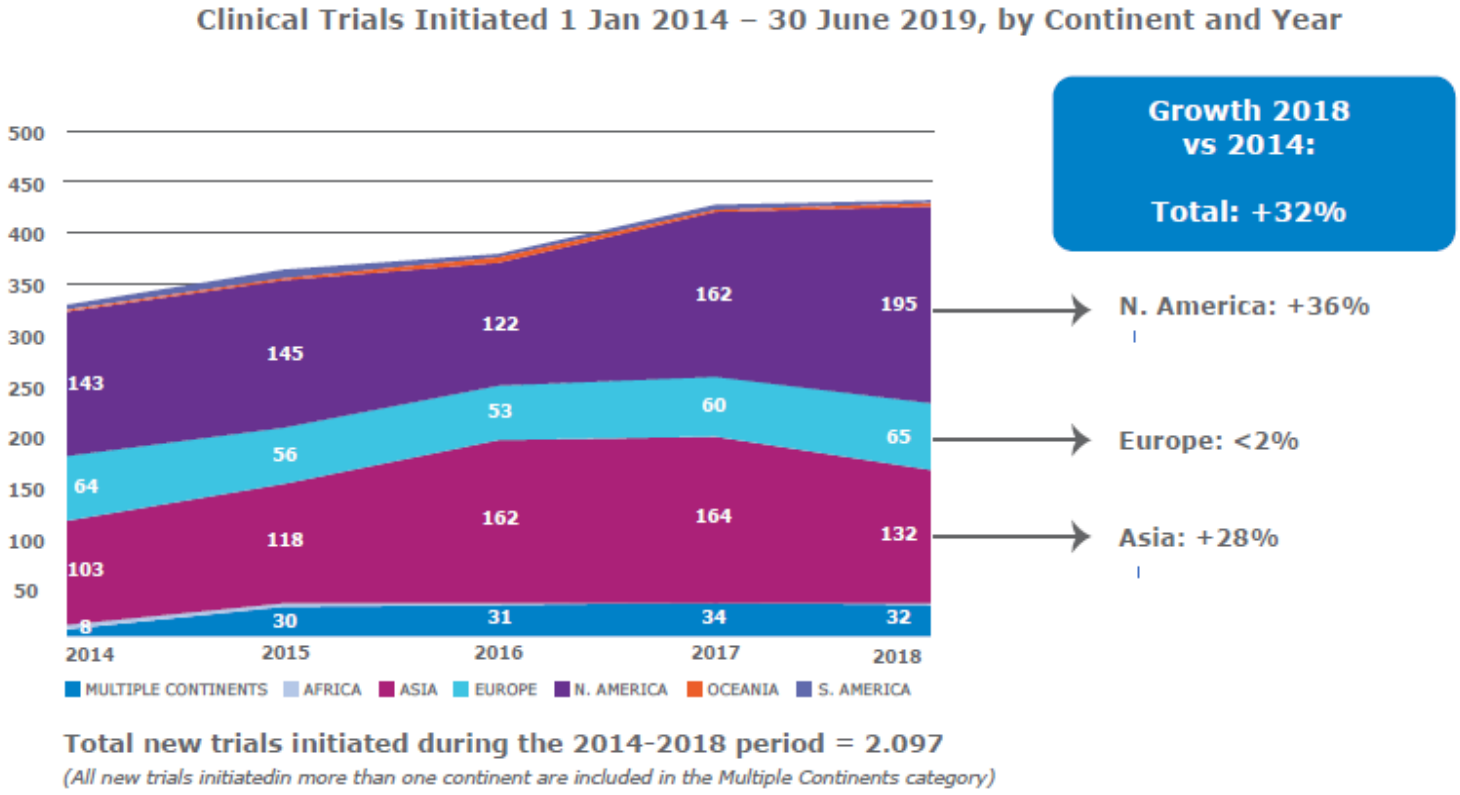
The fraction of EU/EEA trial participants is trending downwards (EMA data)

- < 10% of (ATMP) clinical trials worldwide are conducted in the EU*

  10% of these are non-commercial/investigator-initiated trials*

  CTR/CTIS increases challenges for sponsors and assessment teams (NCAs)
  - 5-10 times higher workload at agency, bad usability
  - Shorter timelines (12 days) for sponsors to address questions
  - Interface problem for gene therapies (GMO issue).
  - The “Accelerating Clinical Trials” EU/EMA initiative does not tackle the translational and clinical trial bottle neck

The Global Clinical Research and Trial Landscape
Gene and cell therapies 2014 - 2019 (Alliance for Regenerative Medicine)



The First-in-human trial application
Scientific – regulatory – methodological aspects

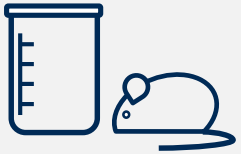
Strategic planning

Key discussion points prior to FIH trial

- Is my investigational ATMP sufficiently characterized (quality characterisation) to generate reproducible trial results?
- Have I planned for the manufacturing licence of the investigational ATMP?
- Is my non-clincial data package suitable for a FIH trial?
  - Pharmacodynamics – in vivo proof of principle – small and large animal models
  - Biodistribution and toxicology studies
    - immunogenicity, genomic stability, tumorigenicity, (starting) dose in humans, administration/surgical procedure
- Have I considered the main design aspects of FIH trial?
  - Patient population, safety and efficacy endpoints (clinical/biomarker), dose (escalation), administration procedure, feasibility
- Am I sufficiently prepared to navigate the Clinical Trials/CTIS system?

Support tool prior to clinical trial application
National Scientific Advice

- Driven by concept to support academia in ATMP development (PEI 2007)
- Low threshold to access regulatory-scientific advice
- Structured and less structured interaction
- Workshops

Pre-Advice	National Scientific Advice			Joint Scientific Advice	Portfolio Meeting
				Paul-Ehrlich-Institut Gemeinsamer Bundesausschuss	
Drug Discovery / Therapy Concept	CMC / Quality	Non-Clinical Study Concepts	Clinical Trial Protocols	Pivotal Study Protocols	Pipeline Presentation

https://www.pei.de/EN/regulation/advice/advice-content.html

Support tool prior to clinical trial application
Simultaneous National Scientific Advice Pilot Phase 2

Multi-National Scientific Advice

CMC / Quality

Non-Clinical Study Concepts

Clinical Trial Protocols

- ….for multinational clinical trials
- ….single entry point @ SNSA@pei.de
- …may help but is not forcing to align national positions.
- …is a pilot project of the EU-Innovation Network.

Applicant determines a coordinating authority for the scientific advice meeting

Additional NCAs dial in per phone/web-conferencing

National scientific advice as support tool to tackle the EU translational/clinical trial gap

- Has become even more important in light of the new CT-Regulation.
- Make use of 2-3 in-depth scientific advices along your product development with overlapping areas.
-
- SNSA could be a useful advice format for multinationl trials.
- When planning pivotal clinical trials (PhII/PhIII), ask for and bring in the positions of the EMA and/or HTA to ensure alignment with marketing authorisation and HTA (e.g. added benefit) requirements.

The medicine life cycle

ATMP DEVELOPMENT

MARKETING AUTHORISATION

POST-APPROVAL LIFE CYCLE MANAGEMENT, PHARMACOVIGILANCE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical Trials

Clinical trial authorisation

CAT

CHMP

PRAC

Benefit-risk assessment / opinion

(Conditional) Approval

Post-authorisation data generation,
Real World Data,
Safety monitoring

HTAs, Reimbursement

Patient access

Discovery

Non-clinical

National Scientific Advice

Simultaneous NSA

EMA

National HTA advice

EMA/HTA parallel advice

RWD

Scientific assessments and authorisations by experts from NCAs throughout life cycle

Strategic planning

Key discussion points prior to marketing authorisation submission

- Is my manufacturing process consistent, mature, valid for set-up of commercial manufacturing?
- Is the non-clinical data package complete?
- Is the clinical data package comprehensive and robust with compelling evidence of efficacy and safety, even if limited and based on a single arm trial?
- Have I done a feasibility analysis for post-authorisation studies (e.g.registry-based)?
- Do I have orphan designation and an agreed pediatric investigation plan?
- Are the companion diagnostic aspects considered?
- Have I planned for interaction with Health Technology Assessment (HTA) bodies
- Have I considered member state-specific reimbursement rules?

AADC deficiency - Upstaza, eladocagene exuparvovec
Marketing Authorisation in 7.2022

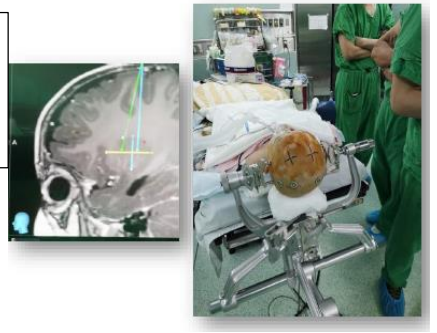
- Disease:
  - Ultra-rare genetic disease, 200 patients known/published, loss of dopamine production, no head control, sit, stand or walk, other symptoms, no approved treatments

- Indication
  - Patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency with a severe phenotype.

- Treatment concept:
  - Gene replacement based on AAV2 vector containing the cDNA of human dopa decarboxylase gene under control of CMV promoter
- Posology and method of administration
  - 1.8 × 10exp11 vg, intraputaminal infusion, two sites per putamen, stereotactic neurosurgical practice

AADC deficiency - Upstaza, eladocagene exuparvovec
Post-authorisation data generation

No EU-based subjects in clinical trials (founder mutation Taiwan)
Marketing authorisation under exceptional circumstances
Annual reassessment



Feasibility of high quality Real World Data collection supports regulatory and HTA decision making

Provide more data on safety and efficacy including patients treated in the EU for annual reassessment

Is a public registry available as secondary data source?
Is it possible for the company to collaborate with the iNTD registry*?
Is the registry able to comply with regulatory requirements, e.g. real time data capture, consistent data collection? Who owns the data and may publish?

*iNTD patient registry: only global registry, set up by team of scientists/clinicians wordwide

Gene therapy on the move

2009 First CAT plenary meeting

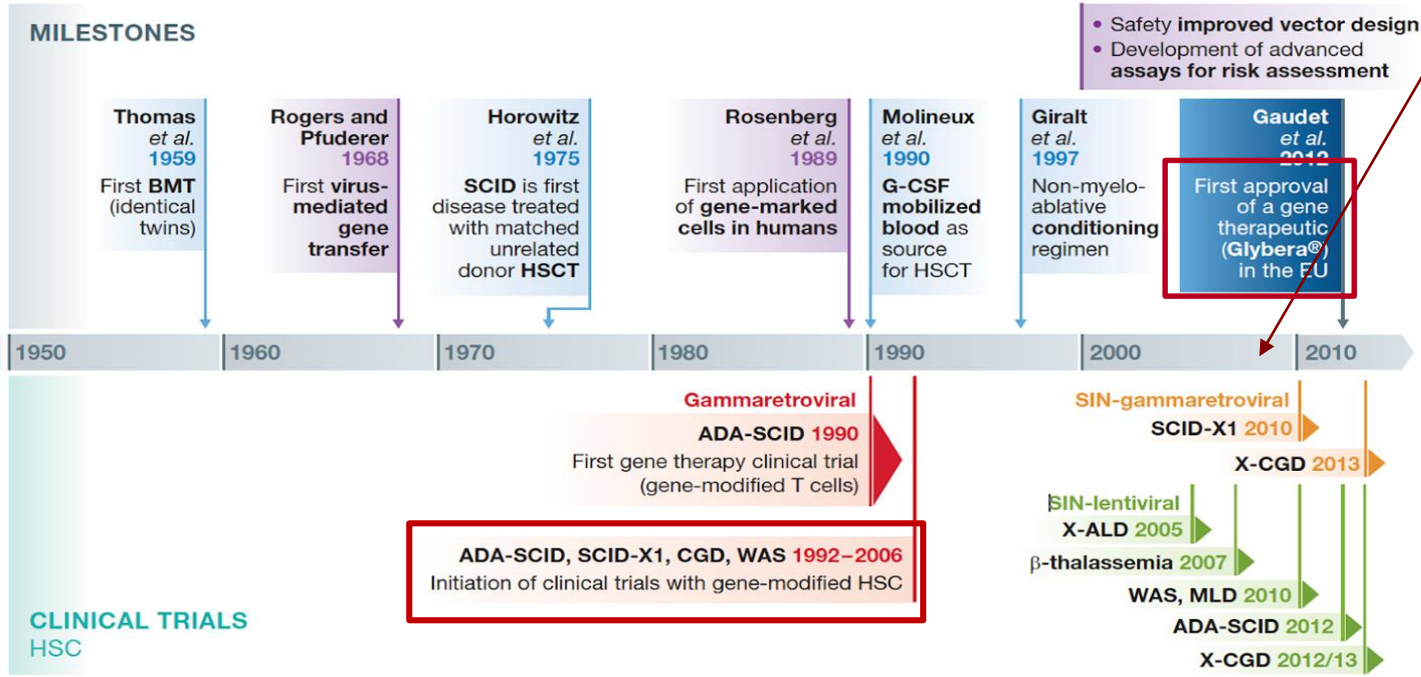
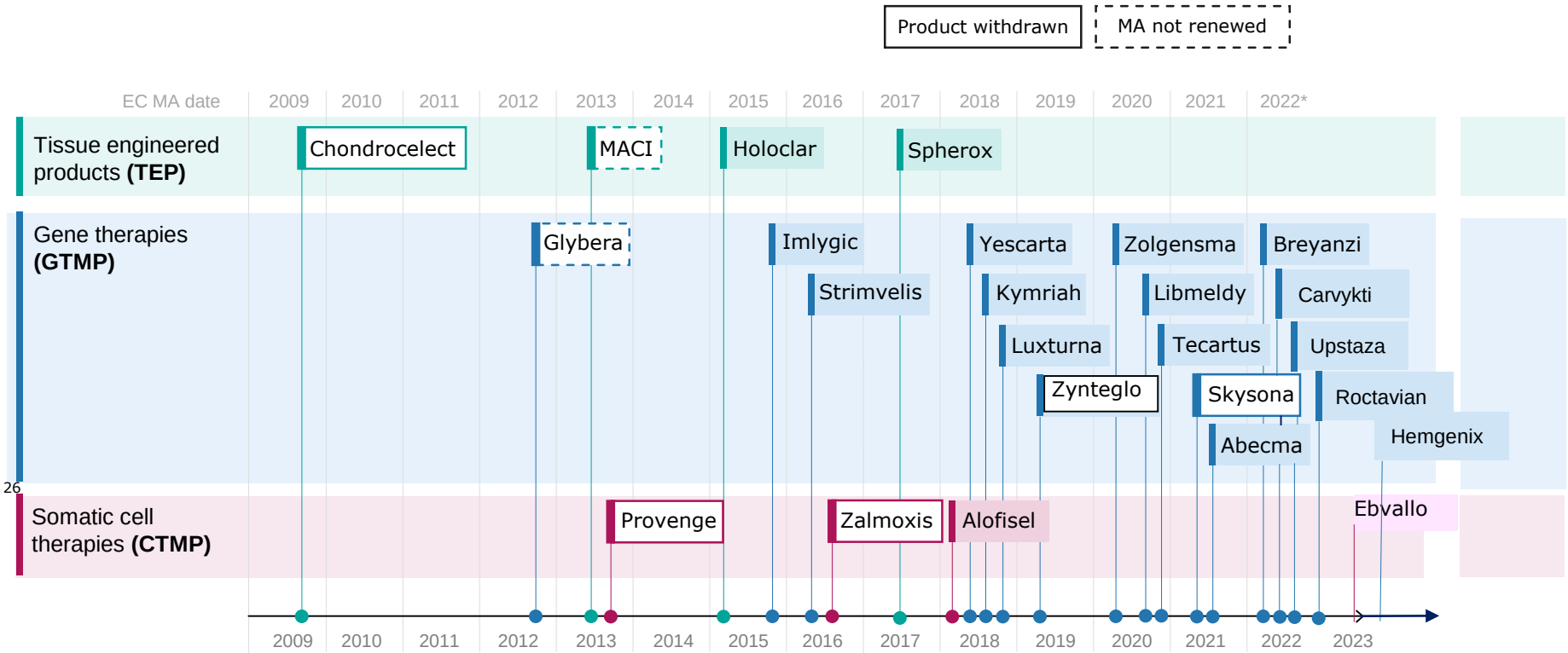


Image: Kaufmann et al. EMBO Mol Med 2013

Approved ATMPs 2023



- EU scientists and researches stand for pioneering achievements in the area of gene and cell therapies.
- We see a steep increase in market approvals in the EU of highly innovative medicines like gene and cell therapies (ATMPs).
- Developing your research candidate to the clinic requires well thought and early strategic planning.
- Improvements on different levels are needed to tackle the downward trend in EU-based innovative medicine developments and close the translational gap.

Paul-Ehrlich-Institut, Langen

Thank you for your attention

Martina.Schuessler-Lenz@pei.de