EMA
EUROPEAN MEDICINES AGENCY

15 years of ATMPs:

EU regulatory framework

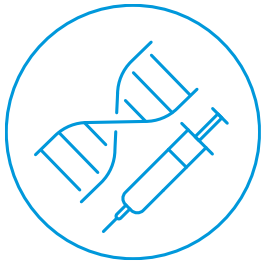
Caroline Pothet
Head of advanced therapies and haemato-oncology

I do not have any conflict of interests.

- Regulatory Framework
- Key Challenges and learnings
- Support tools, including for academic developers

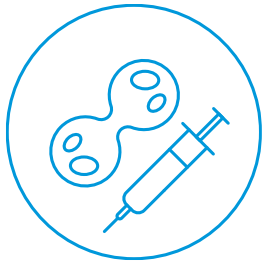
Regulatory framework for ATMPs: Scope and Definitions

Gene therapy medicinal product



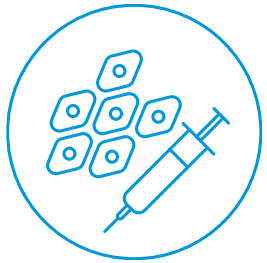
- recombinant nucleic acid
- to regulate, repair, replace, add or delete a genetic sequence

Somatic cell therapy medicinal product



- substantially manipulated cells/tissue
- not intended to be used for the same essential function
- to treat, prevent or diagnose a disease (pharmacological, immunological, metabolic action)

Tissue engineered product

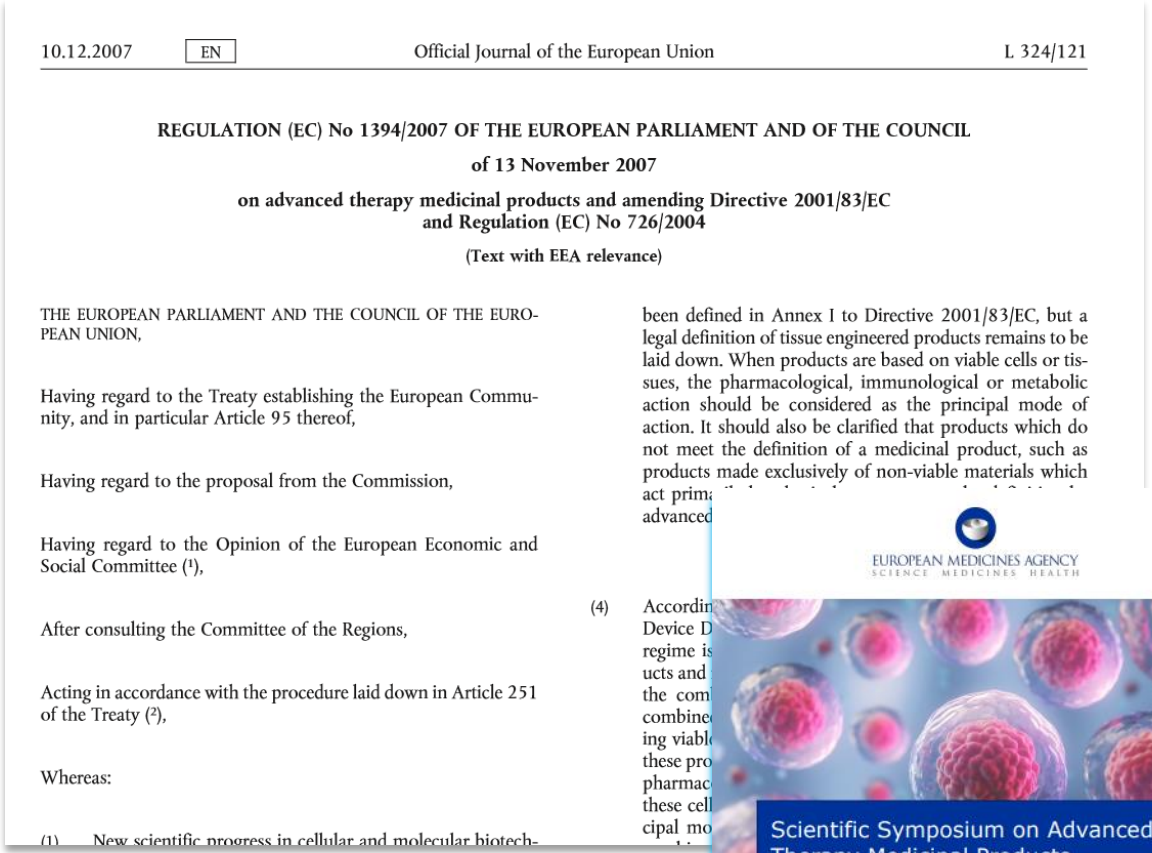


- substantially manipulated cells/tissue (human/animal origin)
- viable/non-viable
- not intended to be used for the same essential function
- to regenerate, repair or replace a human tissue

Combined ATMP

EC proposal: Gene therapy definition updated encompass gene editing and ‘synthetized’ products.

Regulatory framework : 'Lex specialis'



10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

Whereas:

(1) New scientific progress in cellular and molecular biotech-

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act prima
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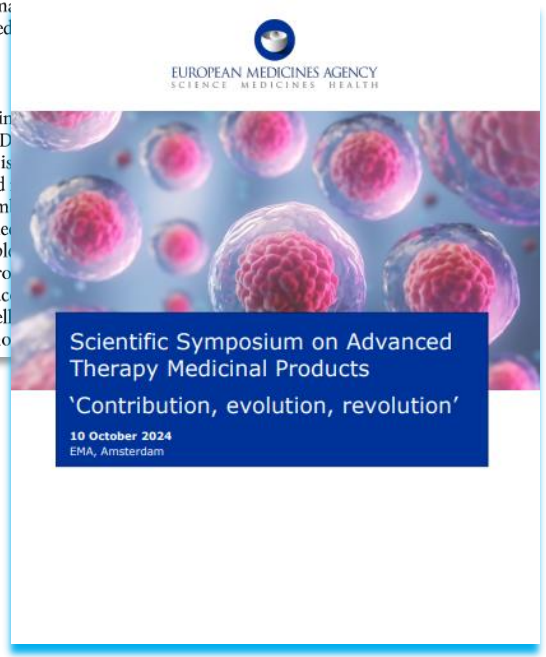


Regulation (EC) No 1394/2007

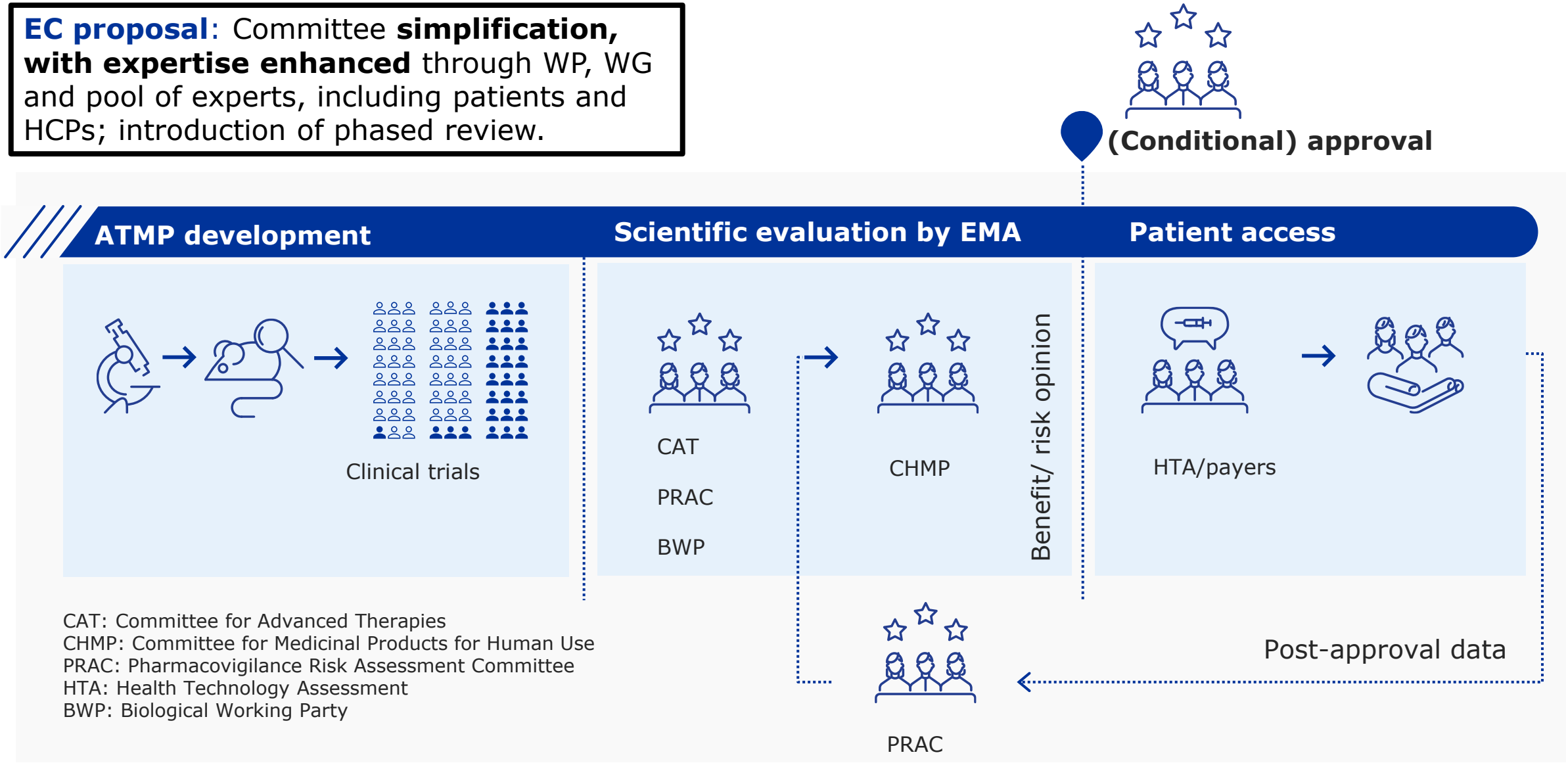
- Definitions of ATMPs (Classification)
- Establishment of the CAT => Jan-09
- Mandated centralised procedure
- Demonstration of Q and positive benefit:risk)
- Post-MA follow-up of efficacy and safety
- Incentives, incl. certification for SMEs

* CAT: Committee for Advanced Therapies

Regulator as Gatekeeper

EUROPEAN MEDICINES AGENCY

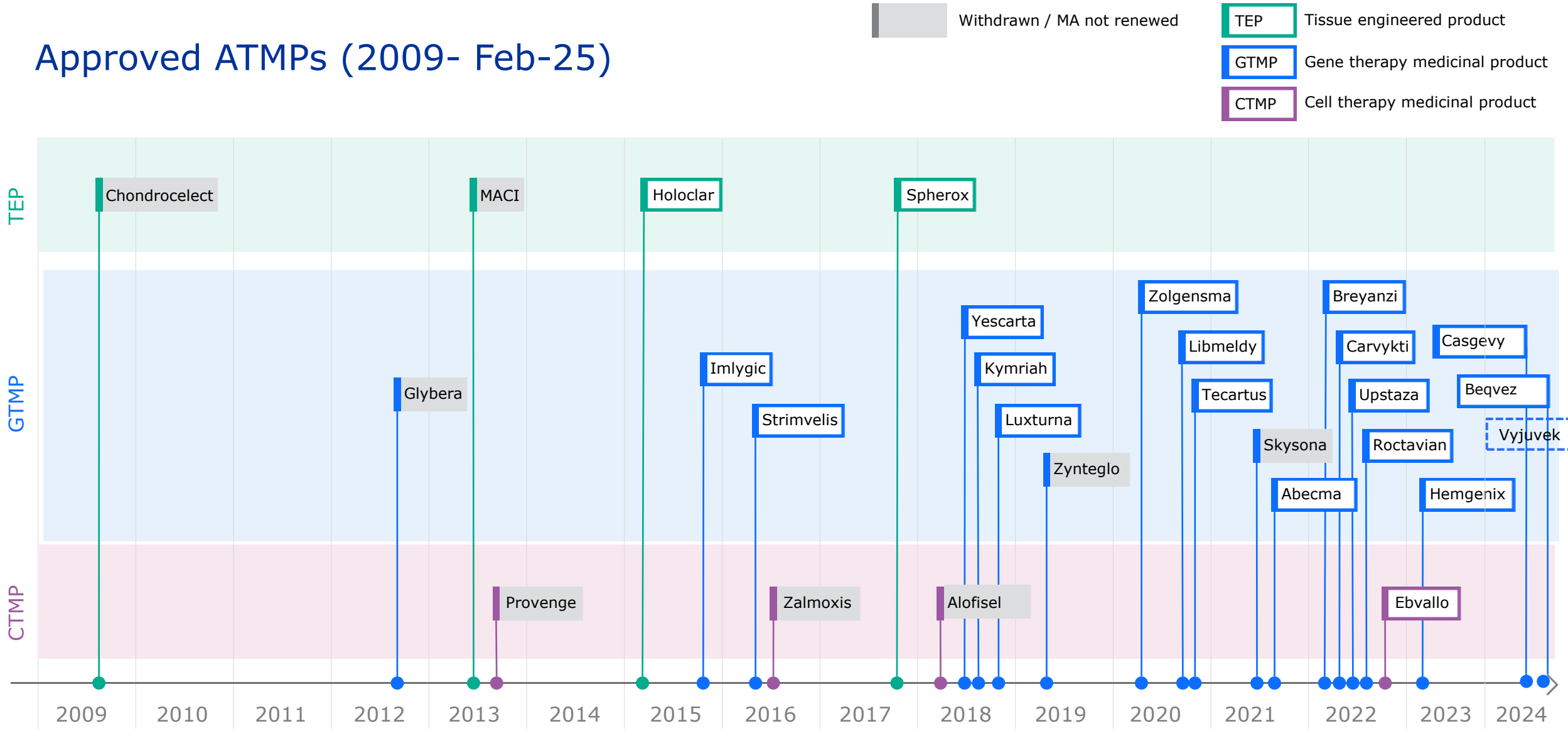
EC proposal: Committee **simplification, with expertise enhanced** through WP, WG and pool of experts, including patients and HCPs; introduction of phased review.



CAT: Committee for Advanced Therapies
CHMP: Committee for Medicinal Products for Human Use
PRAC: Pharmacovigilance Risk Assessment Committee
HTA: Health Technology Assessment
BWP: Biological Working Party

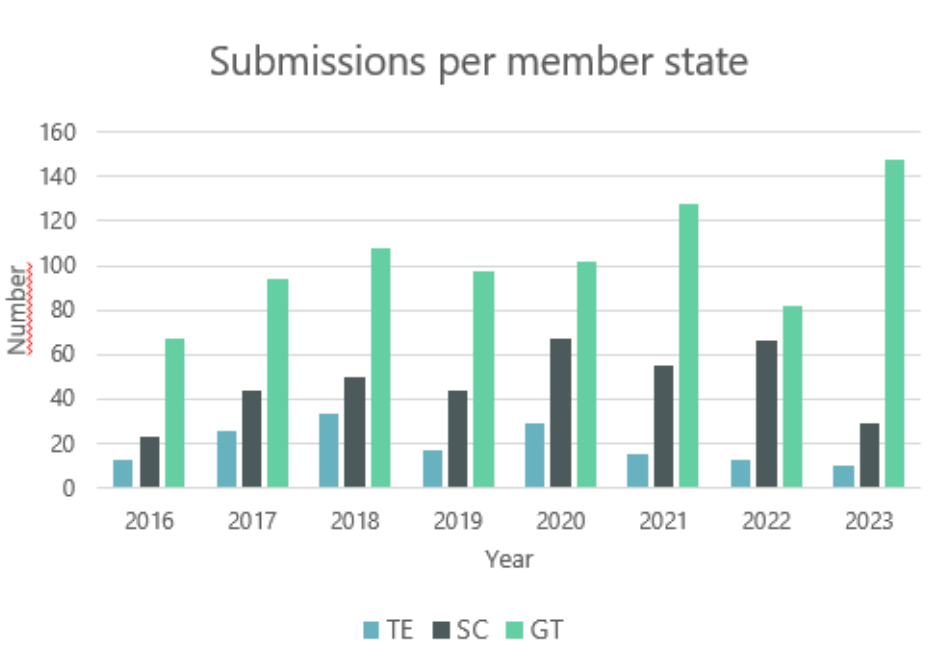
Regulator as Gatekeeper

Approved ATMPs (2009- Feb-25)



From clinical trials to ‘first in class’ highly innovative products

Slide from Ilona Reischl



Ex vivo genetically modified cells

T-cells	(Shortened) Indication	Approval	OD
Kymriah®	B-ALL, NHL subtype	MA	✓
Yescarta®	NHL subtype	MA	✓
Tecartus®	B-ALL, NHL subtype	cMA	✓
Abecma®	NHL multiple myeloma	cMA	✓
Breyanzi®	NHL subtypes	MA	✓
Carvykti®	NHL multiple myeloma	cMA	✓
CD34+ cells			
Zynteglo®	β-thalassaemia	cMA	✓
Skysona®	Adrenoleukodystrophy	MA	✓
Libmeldy®	Metachromatic LD	MA	✓
Casgevy®	Sickle cell disease, β-thalassaemia	cMA	✓

In vivo gene therapies

rAAV vector	(Shortened) Indication	Approval	OD
Luxturna®	Retinal dystrophy	MA	✓
Zolgensma®	Spinal muscular atrophy	cMA	✓
Upstaza®	AADC deficiency	Exceptional	✓
Roctavian®	Haemophilia A	cMA	✓
Hemgenix®	Haemophilia B	cMA	✓
Durveqtix®	Haemophilia B	cMA	✓

Marketing authorisations (MA)	16
Orphan designations	16
Conditional MA (cMA)	9
Full MA	6
Exceptional circumstance	1

Slide from Martina Schuessler-Lenz

BIOBUSINESS BRIEFS

REGULATORY WATCH

European regulatory experience with advanced therapy medicinal products

The developers of advanced therapy medicinal products (ATMPs) such as gene and cell therapies face specific challenges due to the inherent complexity of these products, especially with regards to quality. Although the number of approved ATMPs in Europe so far is low, more marketing authorisation applications (MAAs) can be expected in the next few years given the high number of such products for which classification ($n = 286$) and scientific advice (SA) ($n = 278$) have been sought at the European Medicines Agency (EMA; FIG. 1a). In addition, out of the 34 medicines eligible for PRIME designation as of May 2018, 15 were ATMPs (see Related links).

During the initial evaluation of the first 20 MAAs for ATMPs (listed in Supplementary Table 1), a number of common issues were identified as 'major objections', that is, issues that would prohibit licensing of the product if not resolved. These issues include suitable quality and clinical data demonstrating the efficacy and safe use of the ATMP (FIG. 1b; Supplementary Box 1 and Table 2). To identify 'hot spots' in ATMP development, we analysed the 20 MAAs and all SA given for ATMPs by the EMA so far, which provide the basis for the general points highlighted in this article and the more detailed recommendations provided in Supplementary Box 1. The EMA also has several tools in addition to PRIME designation that can help ATMP developers in building a robust data package for their MAA, such as the opportunity for small and medium-sized enterprises developing ATMPs to receive an opinion from the EMA's Committee for Advanced Therapies on the approvability of their quality and non-clinical data (see Supplementary Box 2).

Overall, for ATMPs, it is particularly important to carefully map the product definition and initial development strategy at the beginning to avoid the need to unexpectedly have to generate new data and/or conduct additional studies at a later stage. Early characterization of the product in terms of identity, purity, stability and strength is necessary to identify the critical parameters that will be used for in-process, release and stability testing. This has particularly been a challenge for cell therapies owing to their complexity and the multitude of parameters from which to choose.

Building evidence for clinical efficacy starts with optimal selection of the active substance and evaluation of the proof-of-concept to provide the foundation for the generation of robust clinical data. A common issue resulting in major objections for both gene therapies and cell therapies has been the chosen potency assay, which should ideally reflect the biological activity of the product. In order to define the potency specification for commercial manufacturing, the assay should be in place early on and validated before the pivotal clinical trials. Ultimately, the assay is expected to reflect the intended clinical efficacy claim.

ATMPs are often being developed for rare diseases, and so combining multiple objectives in a clinical trial, such as proof-of-concept and dose-finding,

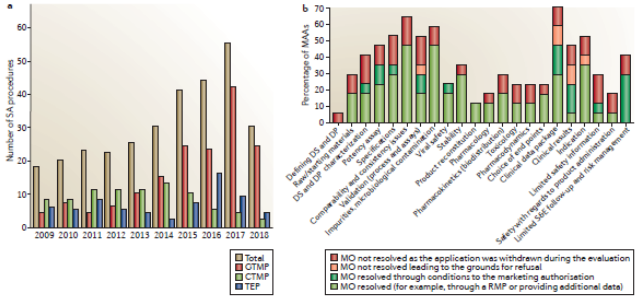
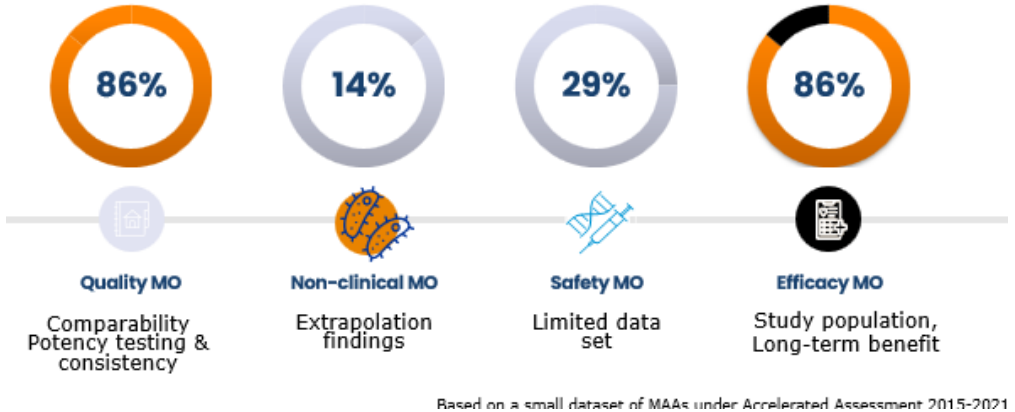


Figure 1 | Experience in the evaluation of advanced therapy medicinal products in Europe. a | The number of scientific advice (SA) procedures for advanced therapy medicinal products (ATMPs) from January 2009 to June 2018 is shown. **b** | The characteristics of the major objections (MOs) raised during the evaluation of the marketing authorisation applications (MAAs) for ATMPs from December 2007 to June 2018 are shown. See Supplementary Table 2 for details. CTMP, cell therapy medicinal product; DS, drug substance; DP, drug product; GTMP, gene therapy medicinal product; RMP, risk management plan; S6E, safety and efficacy; TEP, tissue engineered product.

Barkholt, L., Voltz-Girolt, C., Raine, J. *et al.* European regulatory experience with advanced therapy medicinal products. *Nat Rev Drug Discov* 18, 8–9 (2019). https://doi.org/10.1038/nrd.2018.200



Minimum follow-up requirements for recent ATMP approvals

CAR-T cell-based therapies (Carvykti, Breyanzi, Abecma): 15 years

Zolgensma (AAV9, IV): 15 years

Upstaza (AAV2, intraputaminal infusion by stereotactic neurosurgery): 10 years

Ebvallo (allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy): 3 years

Roctavian, Hemgenic (AAV5): 15 years

Casgevy (CD34+ edited ex vivo by CRISPR/Cas9): 15 years

Key learnings:

A**ddressing quality and nonclinical issues** before entering the pivotal phase of ATMP development ANF

Effective **planning for post-authorisation evidence generation (incl. data sources)**

will clear the path for a smooth and speedy marketing authorisation, and incremental knowledge gain.

Regulator as enabler of innovation

[Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials]

I Pilot: SAWP CTCG

II Pilot: Pre-CTA Advice

Procedural and scientific guidance

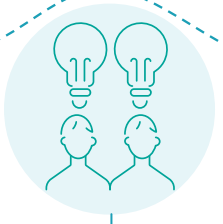
Orphan Drug Designation

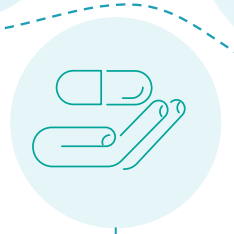
Qualification of **novel methodologies**

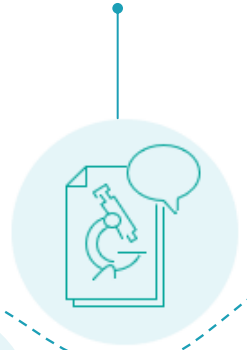
Scientific Advice / Protocol Assistance

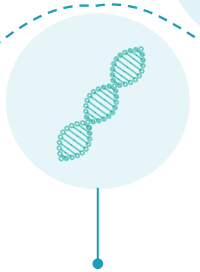
[Consolidated advice on clinical trials - European Union]

MAA PSM Submission of MAA









SME Office
Reg assistance, SME Briefing Meeting, SME incentives

SME@ema.europa.eu

Academia entry point
Academia@ema.europa.eu

Innovation Task Force (ITF) & **EU Innovation Network**

Quality Innovation Group (QIG

PRIority MEdicines (**PRIME**) **Academic support pilot**

ATMP **Classification** & **Certification**

Paediatric Investigation Plan (PIP)

e.g. QIG Listen-and-learn focus group meeting on 7th and 8th April 2025 (personalized medicines)

EMA

Regulator as enabler : Academic support pilot for academic developers

EUROPEAN MEDICINES AGENCY

- ATMP support pilot for **academic** developers **launched Sep-22** with first product/applicant (ARI-0001; Hospital Clinic Barcelona)
  - EMA pilot offers enhanced support to academic and non-profit developers of advanced therapy medicinal products | European Medicines Agency (europa.eu)
- In line with framework of collaboration with academia : payment of fees identified by academia as a key hurdle.
- 2 new products selected in 2024
  - **TregTacRes**, modified (tacrolimus resistant) T regulatory cells, developed by Berlin Center for Advanced Therapies (BeCAT) as adjunctive therapy after living donor kidney/solid organ transplantation.
  - **Telethon003**, autologous CD34+ cells transfected with a lentiviral vector (containing the human WAS cDNA), developed by Fondazione Telethon (Italy) for Wiskott Aldrich Syndrome.

→ *In kind* regulatory support and fee incentives

To be cont'ed…

Committee for Advanced Therapies (CAT): Work Plan 2025

Adopted by the Committee on 22 January 2025

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Affordable, accessible, and innovative medicines

EMA

Key messages

- Robust and adapted framework
- Support tools to overcome **challenges in navigating and complying with regulatory requirements**
- **=> ITF, guidelines, iterative PIP, QIG, CTA**
- Carefully **addressing quality and nonclinical issues** before entering the pivotal phase of ATMP development and **robust plan for post-evidence generation** will clear the path for a **smooth and speedy** MA and future market access
- **=> PRIME, Scientific Advice, ATMP certification (SME only), Joint scientific consultation**

Advanced therapy medicinal products: Overview | European Medicines Agency (EMA) (europa.eu)

Quality Innovation Group | European Medicines Agency (EMA)

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