Supporto all'innovazione in ambito farmaceutico ed allo sviluppo di ATMPs: il ruolo dell'autorità regolatoria e del dialogo precoce

Presentazione del VIII Report Italiano sugli ATMP

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	☐	☐	☐	X
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional
10. Serious reasons of convenience	X	☐	☐	☐ optional

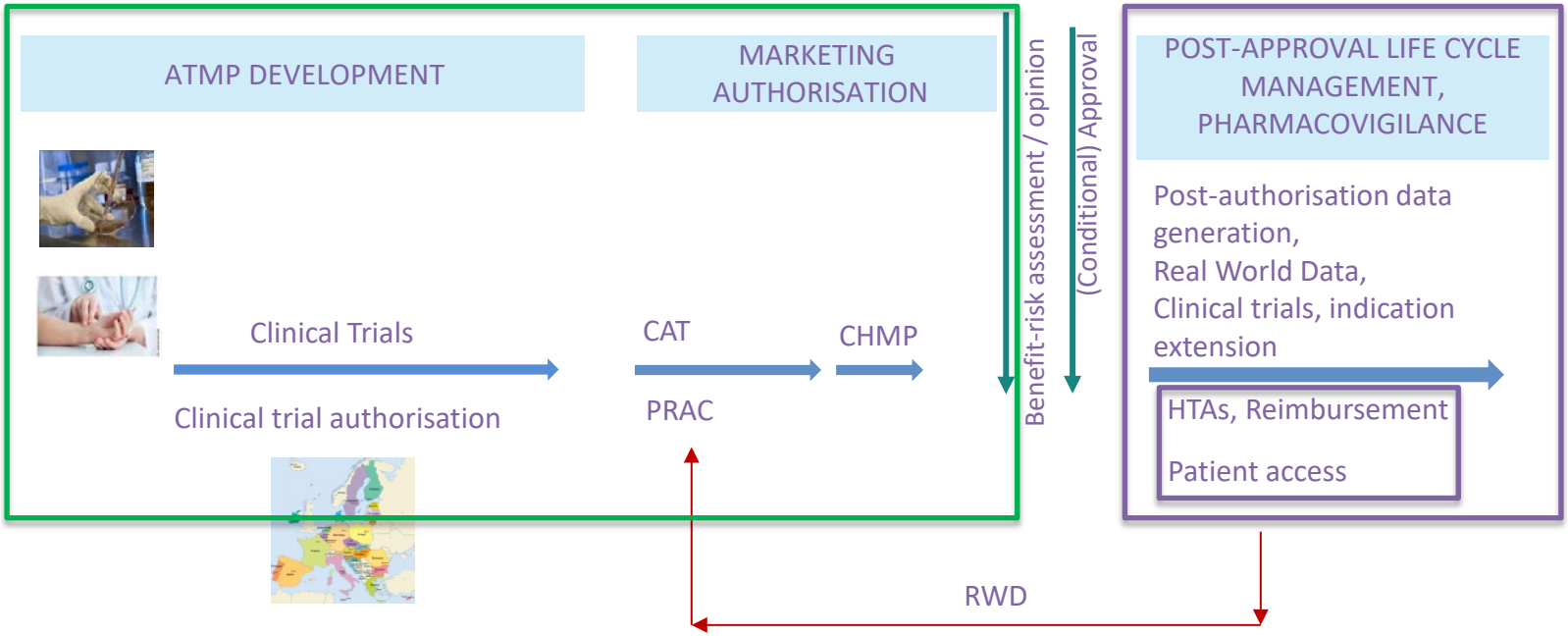
*Barbara Bonamassa, in accordance with the Regulation for the prevention and handling of conflicts of interest of the Italian Medicines Agency, approved by AIFA Board of Directors (Resolution no. 9 - 12 February 2025).

N.B. I am not receiving any compensation

1. Introduction,
2. Regulatory and scientific support tools to medicinal product developers: general aspects,
3. Regulatory and scientific support tools to medicinal product developers: ATMP specific- aspects,
4. Summary and conclusions.

ATMP report: new – Innovation and Pharmaceutical Strategy Department, AIFA

ATMP report: so far



Scientific assessments and authorisations by experts from NCAs throughout life cycle

(The life cycle management of Advanced Therapy Medicinal Products (ATMPs) – a regulatory perspective– Dr. Schuessler-Lenz M. (https://express.converia.de/frontend/index.php?page_id=25930), Scientific and Regulatory Aspects of Innovative Gene Therapy Medicinal Products - Paul-Ehrlich-Institut (PEI) Workshop, September 27th, 2022

From Basic Research to Access to Medicines in the EU - Key Challenges

🔬 Scientific & Translational

- Limited predictability of preclinical models
- Gaps in translation from lab to clinic

💰 Financial

- Scarce funding vs High costs

🔄 Technology Transfer

- Weak academia-industry links
- IP and manufacturing scalability issues

🤝 Stakeholder Coordination

- Fragmented collaboration across EU actors
- Limited data-sharing infrastructure

📋 Regulatory

- Complex, evolving EU/national frameworks
- Need for early and strategic regulatory engagement

🧪 Clinical Trials

- Difficult patient recruitment
- Legal/ethical challenges in multinational trials

🏥 Market Access

- Diverse HTA and reimbursement systems
- Challenges in proving cost-effectiveness

.....AND MORE?

Regulatory support to innovation - Key principles

- **Regulators** must adapt to rapid technological advancements,
- **Developers** should adhere to regulatory standards from the early stage of development,
- **Mutual exchange** to **adapt regulatory standards** to keep pace with innovation, ensuring **proportionate risk-mitigation measures**,
- **Identify** the most **critical interventions** and **prioritize** them accordingly.

WORKING TOGETHER FOR THE COMMON GOOD

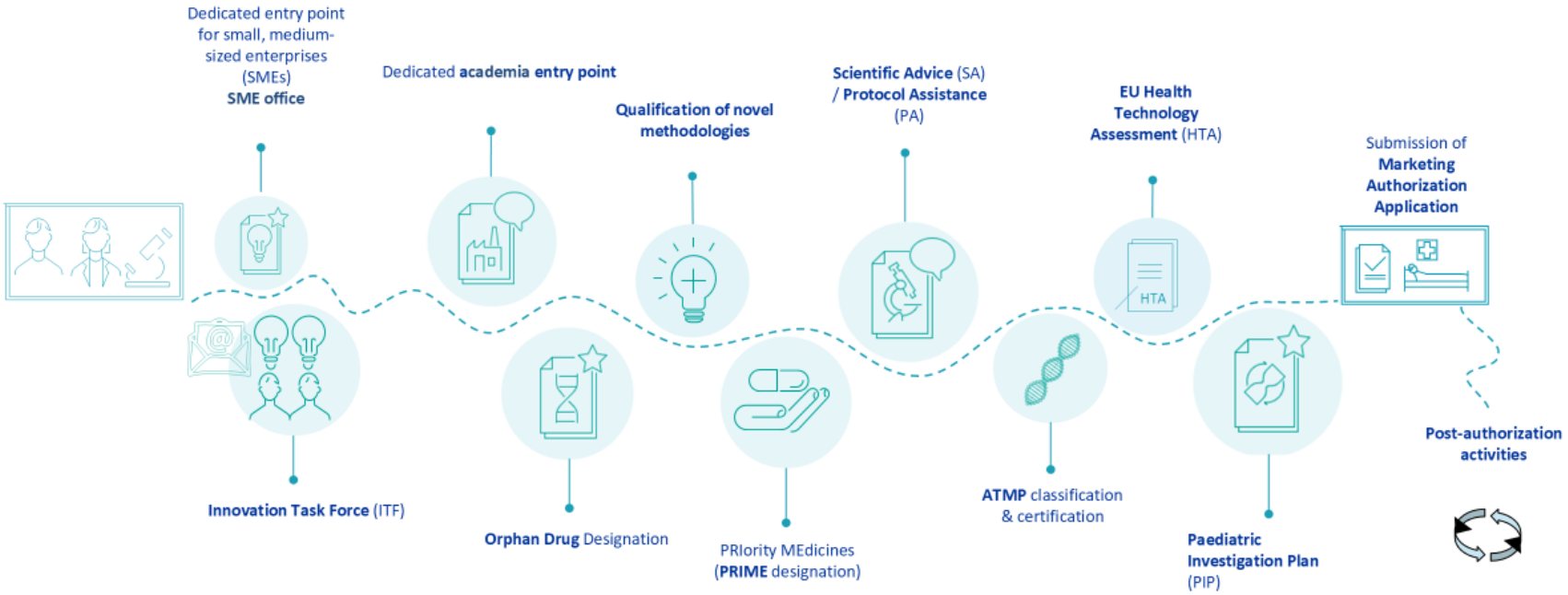
European medicines agencies network strategy to 2028: six strategic focus areas

- **Accessibility** – pathways for access to medicines through NH systems in the EU,
- **Leveraging data, digitalisation and artificial intelligence** – improve decision-making, optimise processes and increase efficiency,
- **Regulatory science, innovation and competitiveness** – accelerate the translation of innovation and improves competitiveness of the EU's healthcare sector,
- **Antimicrobial resistance and other health threats** – to prepare the EU,
- **Availability and supply** - to strengthen the availability of medicines,
- **Sustainability of the network** – to ensure that the network has available resources to support its scientific and regulatory decision-making.

Innovation @AIFA: 4 strategic pillars

- **Support Tools for developers**: Innovation Meetings (IM) and Scientific Advice/Protocol Assistance (SA/PA) to enable early dialogue with regulators. And more…,
- **Training & Capacity Building:** Provide regulatory training for researchers (universities, IRCCS, SMEs) to enhance translational impact. Academia training regulators on emerging innovations,
- **Regulatory Science:** Engage with stakeholders to identify innovations, address regulatory gaps, and adapt standards for safe implementation,
- **International Collaboration:** Participate in EU/global regulatory networks to share knowledge on emerging technologies and harmonize approaches.

EMA interactions across the medicine life cycle



Innovation Meeting (IM) – AIFA & EMA (Innovation Task Force (ITF) meetings)

Multidisciplinary platform
for preparatory dialogue and orientation on
innovative methods, technologies and medicines

NCA -> EU- IN (scale to the European network with the Applicant's agreement)

- Support **innovative** drug development
- **Early informal** dialogue with opinion leaders
- 1,5-hour discussion – *Free of charge*
- Brainstorming "style" on innovation in areas without existing guidance
- First step to engage is submit completed 3-page template

(IM @AIFA info here: https://www.aifa.gov.it/innovazione-e-scientific-advice
ITF @EMA info here: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/innovation-task-force-briefing-meetings)

Scientific Advice (SA) / Protocol Assistance (PA) – AIFA & EMA

Advising developers on product-specific questions during development of medicines *to meet regulatory and scientific requirements:*

1	how to manufacture them
2	how to test them in non-clinical studies
3	how to test them in humans in clinical trials
4	how to study them in specific populations (e.g., rare diseases and children)
5	prospective in nature, it is NOT a pre-assessment

Not legally binding

(https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance, https://www.aifa.gov.it/scientific-advice)

Scientific Advice (SA)/Protocol Assistance (PA) – AIFA & EMA

- **National Scientific Advice (NCA):** feedback from AIFA on GMP aspects, suitability of the proposed development plan (Q, NC, C, post-approval measures) to support a national MAA, suitability of the proposed development plan (Q, NC, C) concerning clinical trials to be conducted only in IT,

- **Simultaneous National Scientific Advice (Coordinating Unit - PEI, AEMPS and FAGG-AFMPS):** feedback from the concerned NCAs on the suitability of the proposed development plan (Q, NC, C) concerning clinical trials to be conducted in multiple EU Member states - Accelerating Clinical Trials in the EU (ACT EU Priority Action 7),
  - Pre-CTA advice pilot: feedback from the Member States concerned on pre-CTA submission topics, i.e., technical and regulatory support and not scientific.

- **EMA Scientific Advice (EMA/SAWP)**: feedback from the EMA on the suitability of the proposed development plan (Q, NC, C, post-approval measures) to support a centralized MAA.
  - Joint Scientific Consultation: feedback on the suitability of the proposed development plan from EMA (MAAs) and HTA bodies to minimize avoidable divergences,
  - SAWP/CTCG pilot on SA: feedback on the suitability of the proposed development plan from SAWP (MAAs) and CTCG (CTAs) to minimize avoidable divergences.

PRIority Medicines (PRIME) scheme

PRIME: in brief

Medicines eligible for PRIME must address an unmet medical need.

Preliminary data must be available showing the potential to address this need and bring a major therapeutic advantage to patients.

EMA will provide early and enhanced support to optimise the development of eligible medicines, speed up their evaluation and contribute to timely patients' access.

- CAT/CHMP enhanced support for the development of medicines that target an unmet medical need and has potential to be a “game-changer”,
- building on existing regulatory tools (SA/PA and accelerated assessment),
- PRIME eligibility based on “proof-of-concept” data,
- early-entry PRIME eligibility, based on “proof-of-principle”/FIH data only, allowed and encouraged for SMEs/Academic developers – to be switched into a full PRIME eligibility,
- early and enhanced dialogue. How?

(https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines, https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years experience_en.pdf, https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines#key-figures-12641)

The PRIME as a journey

Qualification of Novel Methdologies

Procedure to guide the development of novel, more efficient ways to develop medicinal products (development of new endpoint for clinical trials, new imaging methods, new biomarkers, etc)

Voluntary, scientific pathway for innovative methods or drug development tools not yet integrated in the drug development and clinical management paradigm

Qualification advice

- On future protocols and methods for further development towards qualification
- Evaluation of scientific rationale and preliminary data
- Confidential

100 days

Qualification opinion

- On the acceptability of a specific use of the proposed method in an R&D context
- Assessment of submitted data
- Publicly available

130 days + 60 days public consultation

Examples: methods to predict toxicity, strategies to enrich a patient population for a clinical trial, surrogate clinical endpoints, patient/caregiver reported outcomes, patient registries…

(https://www.ema.europa.eu/en/qualification-novel-methodologies-medicine-development)

EMA webpage “Supporting Innovation”

- **Advice mechanims**
  - Innovation meeting, Portfolio and Technology Meetings, Regulatory Support for SMEs and for Academia, SA, Qualification of novel methodologies, Quality Innovation Group.
- **Key Innovation Topics**
  - **ATMPs**, Genome editing, Artificial Intelligence, etc.
- **Innovation initiatives**
  - **EU-IN**, ACT-EU, Regulatory Science Research Needs, EU4Health,
- **Fundings**
  - EC Funding Programmes, European Partnerships (IHI, EU4ERA, Personalised Medicines and Rare Diseases Partnership fund).

(https://www.ema.europa.eu/en/human-regulatory-overview/research-development/supporting-innovation)

The Committee for Advanced Therapies (CAT)

(a) five members or co-opted members of the CHMP coming from five Member States, with alternates;

(b) one member and one alternate appointed by each EU Member State whose national competent authority is not represented among the members and alternates appointed by CHMP;

(c) one member and one alternate appointed by their respective Member States from the EEA/EFTA (Iceland, Liechtenstein, Norway);

(d) two members and two alternates to represent clinicians;

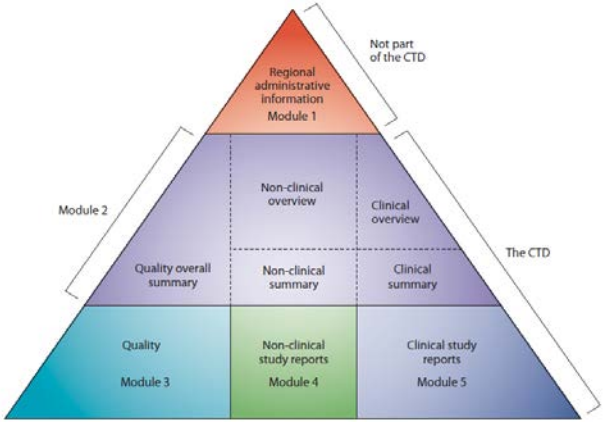
(e) two members and two alternates appointed to represent patients' associations.

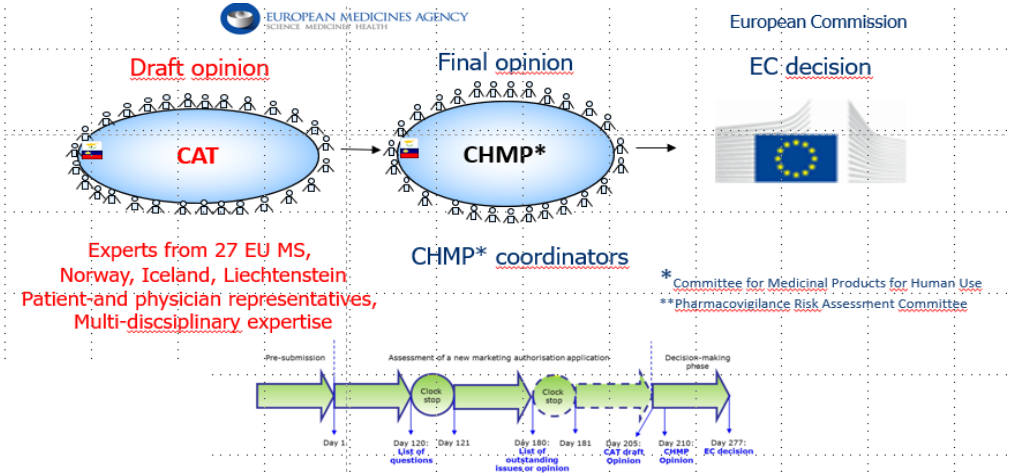
CAT framework under revision (Revision of the EU general pharmaceuticals legislation - EU pharmaceuticals strategy (https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en)).

(https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat)

- **Primary CAT responsibility**: assessment MAAs, i.e., quality (M3), non-clinical (M4), clinical (M5) & post-authorization measures, via a centralised procedure:

- one license valid in entire EU/EEA (Regulation (EC) 1394/2007/EC & 726/2004),
- 210-day procedure (or 150 days, as applicable),
- CAT assessment & draft opinion -- Committee for Medicinal Products for Human - Use (CHMP) final opinion -- EC decision -- granting of the MA.





Is the benefit / risk ratio positive?

(Guidelines relevant for advanced therapy medicinal products:
https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products)

- CAT statistics

TABELLA 3.1 • Domande di autorizzazione all'immissione in commercio relative a medicinali per terapie avanzate valutate dal CAT

	2009-2021	2022	2023	2024	2025*	TOTAL
Submitted MAAS	35	1	4	7	2	49
Positive draft opinions	20*	6	1	1	2	30#
Negative draft opinions	4**,#	0	0	0	0	4
Withdrawals	8**,¶	1#	1†	0	0	10
Ongoing MAAS						9

Elaborazione grafica da *CAT quarterly highlights and approved ATMPs May 2025*
#Corrispondenti a 29 ATMP (vedi lista ATMP autorizzati). *Una *negative draft opinion* e due *positive draft opinion* per *Glybera*. **Negative draft opinion* e ritiro per Cerepro. #Due *negative draft opinion* per Heparesc. ¶Luxceptar, Roctavian, Artobend. ‡Sitoiganap. †Lumevoq.

TABELLA 3.4 • Richiesta di ammissibilità allo schema PRIME discusse per medicinali per terapie avanzate dal CAT

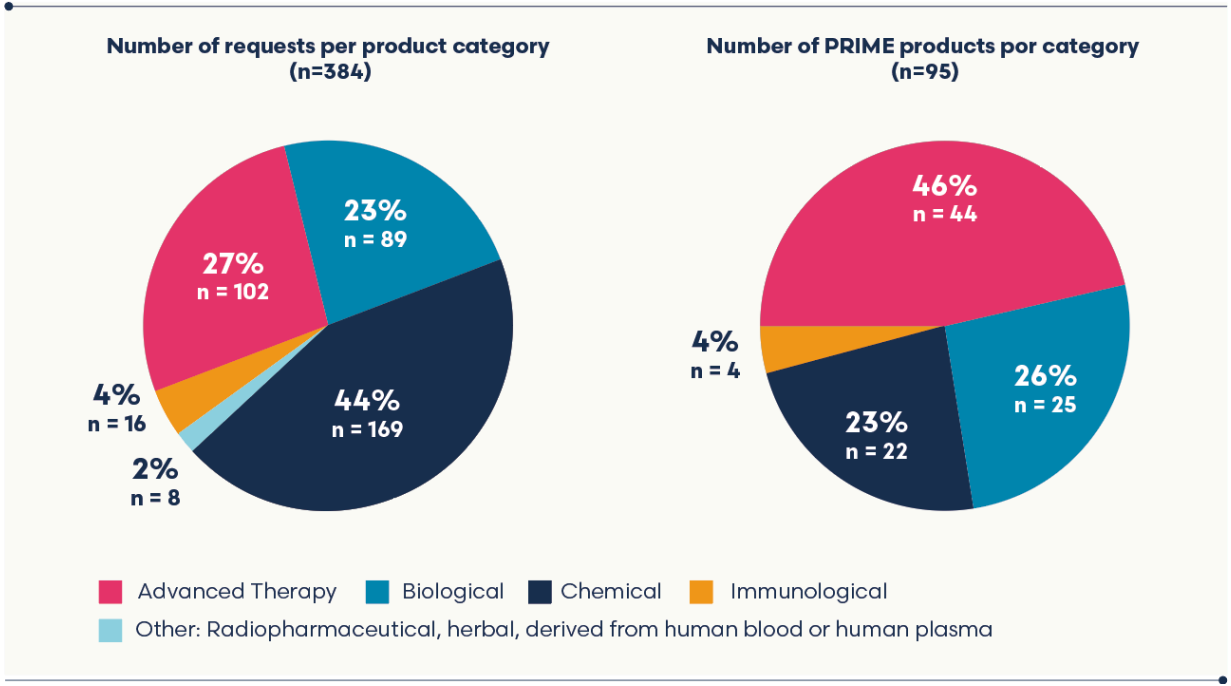
	2016-2021	2022	2023	2024	2025*	TOTAL
Discussed	105	10	13	17	9	154
Granted	46	4	9	6	2	67

Elaborazione grafica da *CAT quarterly highlights and approved ATMPs May 2025*
*Period: January-may 2025

(https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-approved-atmps-may-2025_en.pdf)

- CAT & PRIME

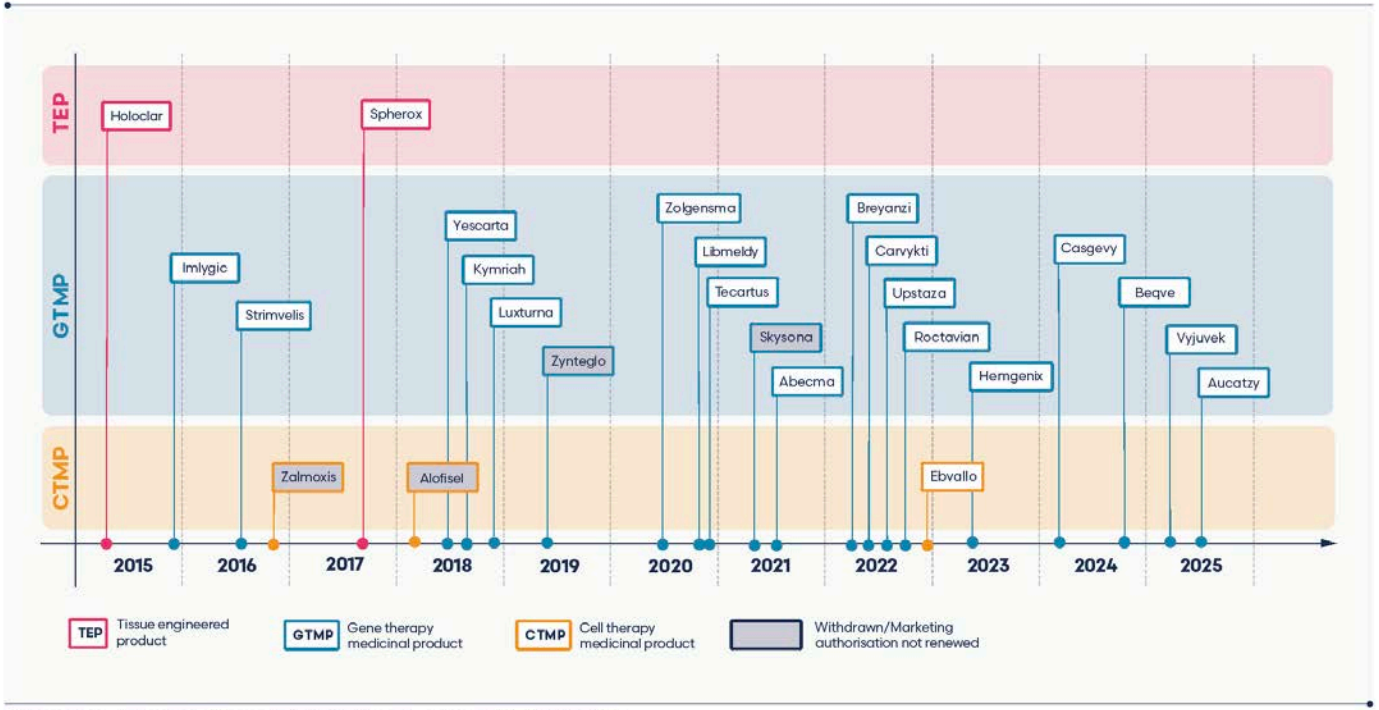
FIGURA 3.1 • Categorie di prodotti medicinali per i quali viene richiesta e concessa l'eleggibilità allo schema PRIME



(https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines, https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years experience_en.pdf, https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines#key-figures-12641)

- The last 10 years of ATMPs

FIGURA 3.2 • Prodotti medicinali per terapie avanzate in commercio



Elaborazione grafica da *CAT quarterly highlights and approved ATMPs May 2025*

(https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-approved-atmps-may-2025_en.pdf)

- **Classification procedure:**
  - for anybody (SMEs, pharmas, no-profit),
  - 60 days procedure,
  - confirmation of compliance with ATMP definitions,
  - classification outcomes are published.

TABELLA 3.2 • Raccomandazioni scientifiche sulla classificazione di ATMP valutate dal CAT

	2009-2021	2022	2023	2024	2025*	TOTAL
Submitted	555	51	43	40	16	705
Adopted	544	46	52	39	17	698

Elaborazione grafica da *CAT quarterly highlights and approved ATMPs May 2025*
**Period: January-may 2025*

- **Certification procedure:**
  - for SMEs only,
  - 90 days procedure,
  - pre-evaluation of Q and NC data, any stage of the ATMP development,
  - product development on track for a future MA application,
  - positive evaluation: certificate.

(https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-approved-atmps-may-2025_en.pdf)

- **Scientific advice (SA) / protocol assistance (PA):**
  - questions on Q, NC and C development + post-marketing issues,
  - written scientific & regulatory guidance to ATMP developers,
  - 90% fee reduction for SMEs, 65% for others,
  - Protocol assistance free-of-charge to SMEs & academic developers. SA free-of-charge to academic-owned PRIME and ATMP PILOT products. Starting Jan-25, SA free-of-charge to no-profit developers.

TABELLA 3.3 • Procedure di SA/PA relative a medicinali per terapie avanzate con contributo del CAT

	2009-2021	2022	2023	2024	2025*	TOTAL
Numbers of procedures	506	53	57	61	27	704

Elaborazione grafica da *CAT quarterly highlights and approved ATMPs May 2025*
**Period: January-may 2025*

- Involvement in **any scientific or regulatory matter / context** requiring expertise in ATMPs including early dialogue platforms fostering innovation (*e.g.*, innovation task force (ITF) meetings).

(https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-approved-atmps-may-2025_en.pdf)

EMA pilot “Enhanced support to academic developers of ATMPs”

EMA will provide enhanced regulatory support for up to five selected ATMPs that address unmet clinical needs and are developed solely by academic and non-profit developers in Europe.

- Academic developers are a key source of ideas and basic research,
- Aim is to increase the level of translation of basic research into medicines / products,
- Learn how to interact, support and adapt to academic developers,
- Focused regulatory support within the existing regulatory frame,
- Up to *5 academic products*, so far three products selected:

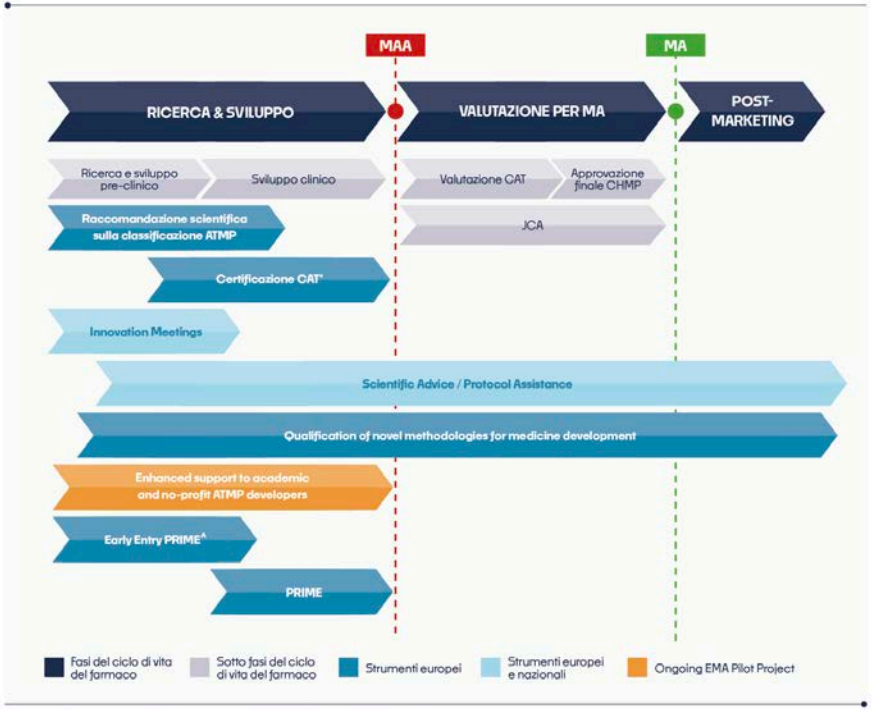
✓ ARI-0001; Hospital Clinic Barcelona,

✓ 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.

(https://www.ema.europa.eu/en/news/ema-pilot-offers-enhanced-support-academic-and-non-profit-developers-advanced-therapy-medicinal-products)

FIGURA 3.3 • *Run chart* degli strumenti regolatori a supporto dello sviluppo di un ATMP lungo il ciclo di vita del farmaco



*Solo per Piccole e Medie Imprese (SMEs). ^Per SMEs e sviluppatori accademici.

Acronimi: CAT: *Committee of Advanced Therapies;* **CHMP:** *Committee for Medicinal Products for Human Use;* **JCA:** *Joint Clinical Assessment;* **EMA:** *European Medicines Agency;* **MAA:** *Marketing Authorization Application;* **MA:** *Marketing Authorization;* **PRIME:** *PRIority MEdicine.*

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