



Development and marketing authorization for ATMPs in the EU

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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 previous years
<i>DIRECT INTERESTS:</i>				
1.1 Employment with a company: pharmaceutical company in an executive role	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> mandatory
1.3 Employment with a company: other activities	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
2. Consultancy for a company	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X
3. Strategic advisory role for a company	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
4. Financial interests	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
5. Ownership of a patent	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
<i>INDIRECT INTERESTS:</i>				
6. Principal investigator	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
7. Investigator	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
8. Grant or other funding	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
9. Family members interests	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
10. Serious reasons of convenience	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 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

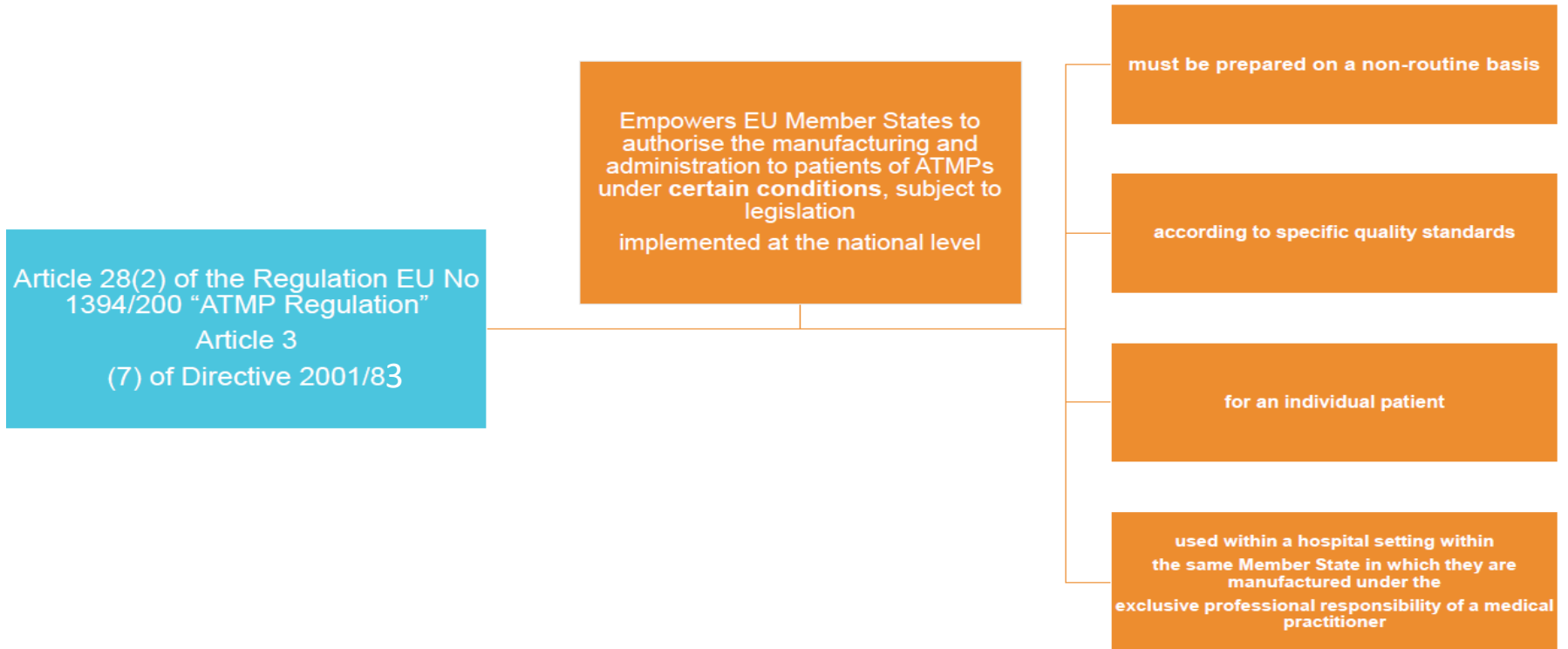
The views expressed in this presentation are those of the speaker, and may not be understood or quoted as being the official opinion of AIFA, EMA or any of its Committees.

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1. ATMPs evaluation pathways:

- the hospital exemption (HE) framework,
- the clinical trial framework,
- the Marketing Authorization (MA) framework & the Committee for Advanced Therapies (CAT),

2. Other regulatory tools.



Italian regulatory framework: *D.M. 16 gennaio 2015 Disposizioni in materia di medicinali per terapie avanzate preparati su base non ripetitiva:*

- Lack of suitable therapeutic alternative,
- Clinical case of urgency and emergency,
- AIFA authorization for manufacture,
- AIFA authorization for clinical use,
- Quality & clinical monitoring provisions.

- Regulatory framework for ATMPs: parallel systems with no regulatory overlap,

Centrally authorised ATMPs

Clinical trials with investigational ATMPs

Hospital exemption

- Advantages & limitations of the HE scheme,



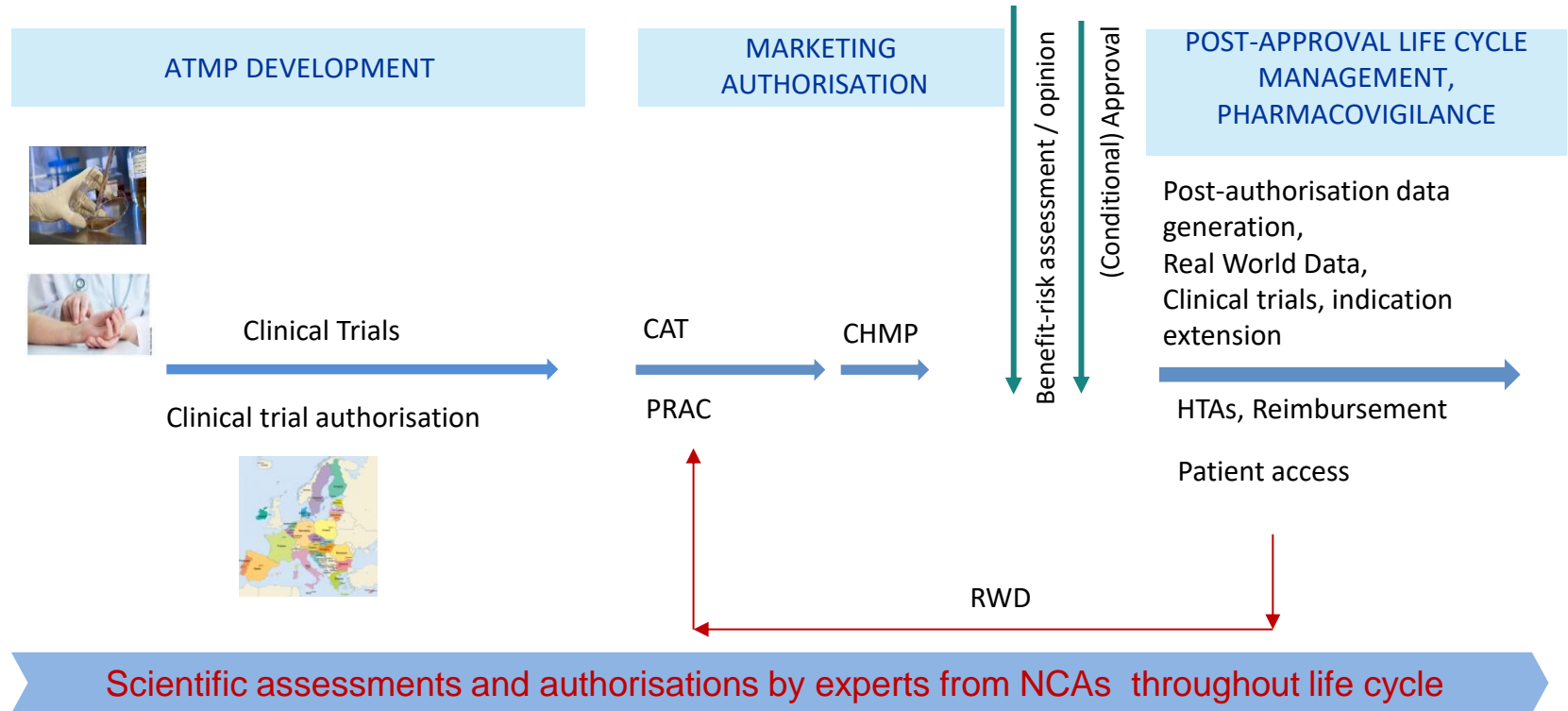
Provide access to patients with innovative, potentially life-saving treatments

- Success stories confirm the therapeutic effect and quality of HE ATMPs: the case CAR-T ARI 0001 of the Hospital Clinic of Barcelona
- The number of patients that have been treated by hospital ATMP preparations

The recognition and interpretation of the provision in MS differs substantially:

- Definition of "non-routine basis"
- Manufacturing
- Clinical data requirements
- Lack of reporting & transparency of use

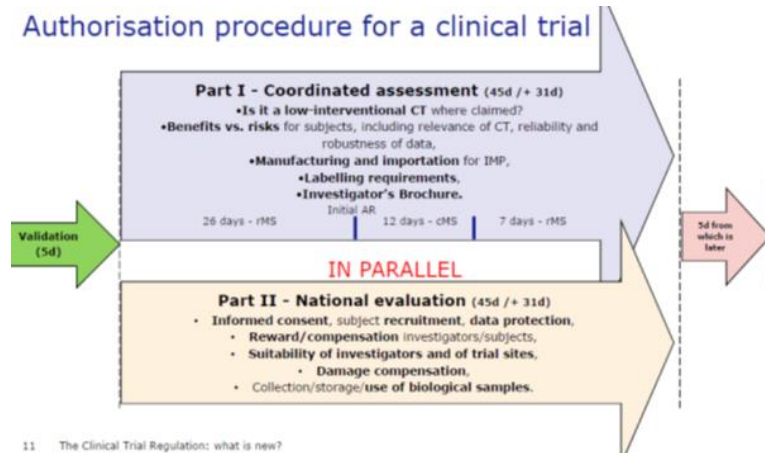
- Criticalities: divergence in the national rules for HE, clinical evidence for HE authorization, limitations in use in terms of number of patients, continuation of supply of ATMPs developed in hospitals when commercial ATMPs are authorised (central MA), etc.
- HE framework under revision (Revision of the EU general pharmaceuticals legislation - EU pharmaceuticals strategy).



- Clinical Trial Regulation (CTR) 536/2014: From 31 January 2023, clinical trial sponsors will need to use EU database (CTIS) for all initial CTA in the EU/EEA.



Authorisation procedure for a clinical trial



- Harmonized:
 - facilitate conduct of large clinical trials in multiple EU member states,
 - single application and procedure,
 - assessment by national competent authorities - co-ordinated multinational assessment.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 January 2025
EMA/CAT/22473/2025
Committee for Advanced Therapies (CAT)

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

- Harmonized:

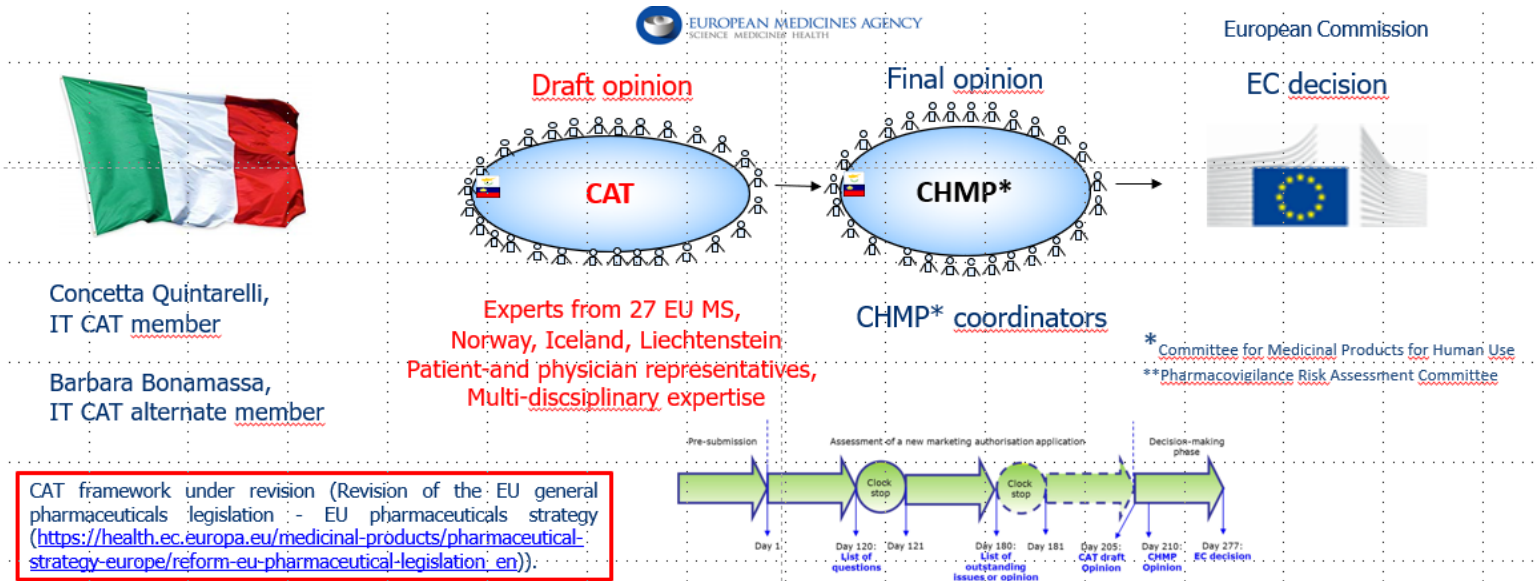
Ethics Committee specific for ATMPs established in Italy (HE and compassionate use assessment excluded):

Decreto del Ministro della salute 3 marzo e 4 aprile 2025 di nomina dei componenti del Comitato etico per le sperimentazioni cliniche relative alle terapie avanzate presso l'AIFA

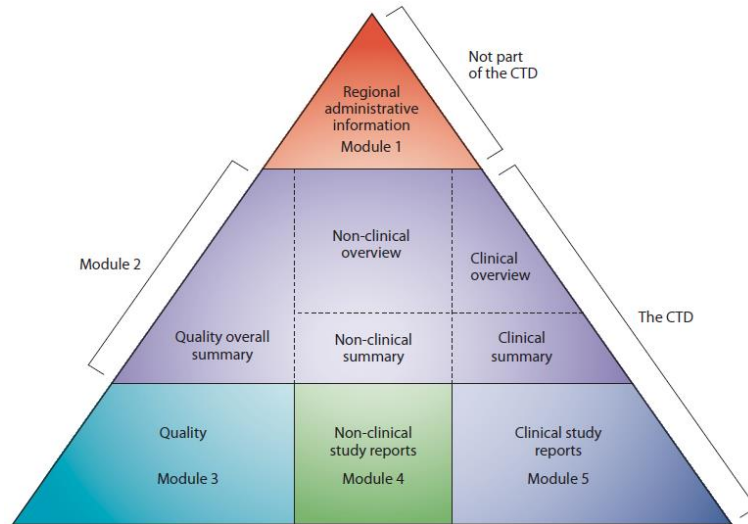
- **Not** harmonized:

- CTs with genetically modified organism (GMO) - approval by national GMO authorities required (Directive 2001/18/EC and/or Directive 2009/41/EC),
- no harmonization of GMO authorisation procedure,
- GMO evaluation not adjusted in the CTR (Article 91 of CTR),
- not possible to submit any GMO documentation via CTIS,
- a step toward harmonization....good practice document on the GMO-related aspects assessment & common application form to be used for authorisation under the GMO framework (https://health.ec.europa.eu/medicinal-products/advanced-therapies_en)

- Centralised MA:
 - 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.



- Primary CAT responsibility for ATMPs MAA: assessment for the full dossier, i.e., quality (M3), non-clinical (M4), clinical (M5) & post-authorization measures:



Module 3 (quality)

manufacturing process validation [DS/DP (in case of GMCs, RVV/LVV starting material)],



Module 4 (non clinical)

pharmacology,
pharmacokinetics (biodistribution),
toxicology.



Module 5 (clinical)

clinical efficacy & safety

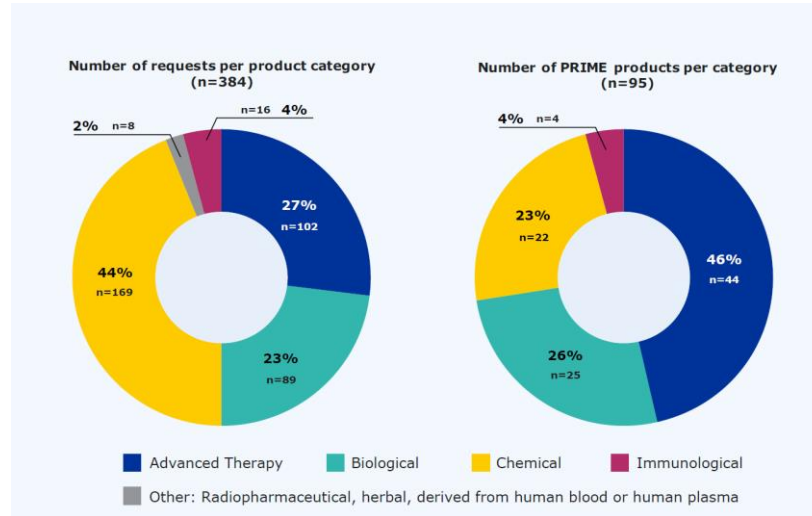


Is the benefit/risk ratio positive?

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>

- The PRiORITY Medicines (**PRIME**) scheme:
 - CAT/CHMP enhanced support for the development of medicines that target an unmet medical need,
 - building on existing regulatory tools (scientific advice and accelerated assessment),
 - ATMPs account for approximately 27% of the requests received for PRIME eligibility, they present the highest success rate corresponding to 46% of all PRIME products (7 March 2016 - 30 June 2021). Such rate is confirmed up to April 2025.



(<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>)

- CAT statistics

Initial Evaluation of Marketing Authorisation Applications (MAA) for ATMP						
	2009-2021	2022	2023	2024	2025*	Total
Submitted MAAs	35	1	4	7	2	49
Positive draft Opinion	20 ⁱ	6	1	1	2	30 [#]
Negative draft opinions	4 ^{i,ii,iii}	0	0	0	0	4
Withdrawals	8 ^{ii,iv}	1 ^v	1 ^{vi}	0	0	10
Ongoing MAAs						9

Corresponding to 29 ATMPs (see List of authorised ATMPs)

ⁱ One negative draft opinion and two positive draft opinions for the Glybera

ⁱⁱ Negative draft opinion and withdrawal for the Cerepro

ⁱⁱⁱ Two negative draft opinions for Heparesc

^{iv} Luxceptar, Roctavian, Artobend

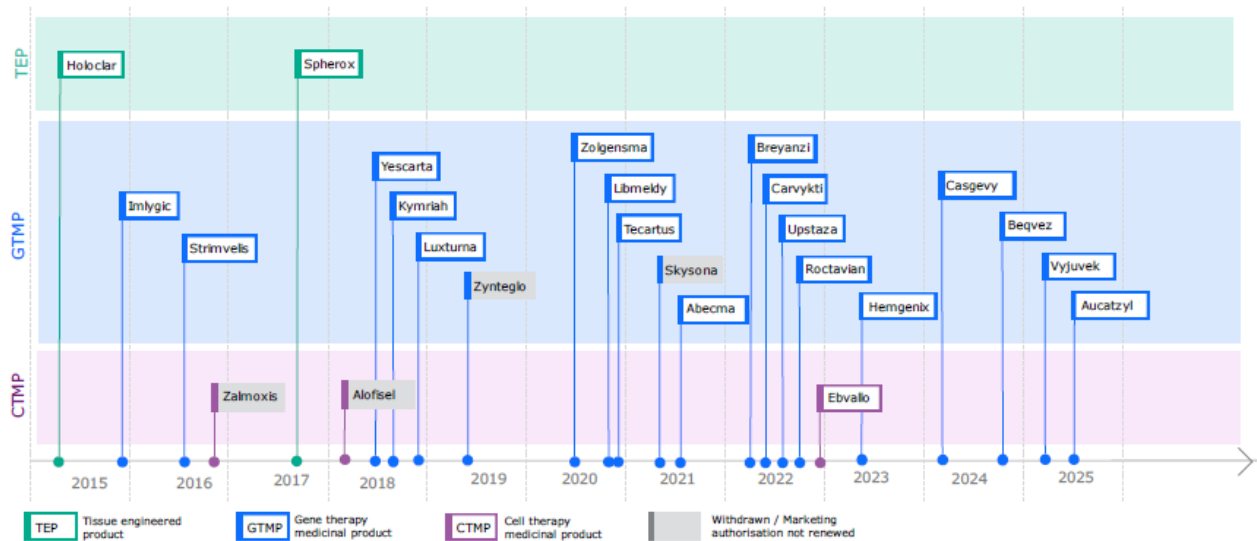
^v Sitoiganap

^{vi} Lumevoq

PRIME ² Eligibility for ATMPs						
	2016-2021	2022	2023	2024	2025*	Total
Discussed	105	10	13	17	9	154
Granted	46	4	9	6	2	67

* Period: January – May 2025

The last 10 years of ATMPs



Advanced therapy medicinal products



Classified as Internal/staff & contractors by the European Medicines Agency

- **Classification procedure:**

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

- **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.

- **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 academic-developed products.

- 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).

Scientific recommendation on advanced therapy classification¹

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

Scientific advice procedure for ATMPs

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

- **CAT cluster activities**
- **ATMP cluster teleconference(s)**
 - Established: 2008,
 - Meeting frequency: every other month,
 - Participants: regulators (EMA/CAT – FDA - Health Canada – PMDA- Swissmedic),
 - The objective of the cluster is to develop a common understanding of each Agency's regulatory approaches for ATMPs.
 - Documents exchanged include scientific advice, ATMP classification reports and assessment reports of marketing-authorisation applications from EMA and Investigational New Drug (IND), pre-IND, and pre-biologics-license-application meeting minutes from the FDA. Both agencies share their (draft) guidelines.
- **Collaboration on gene therapies for (ultra) rare diseases (CoGenT) - the CoGenT pilot EMA-FDA CBER project**
 - International regulatory partners participating in internal regulatory meetings and meetings that include the Sponsors,
 - Exploring the potential for concurrent submissions and collaborative reviews of gene therapy applications with international regulatory partners (under strict confidentiality agreements),
 - Reducing delays, facilitating cross-agency coordination, and expediting reviews,
 - Reduce duplication of efforts across borders,
 - Accelerating the availability of gene therapies to global patient populations.

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.



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