EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overcoming the challenges getting ATMPs approved in the European Union

CASSS – CGTP 2021

Global Regulatory Updates Session

Presented by Patrick Celis, PhD on 10 June 2021
Office of Advanced Therapies, European Medicines Agency

Disclaimer

The presenter does not have any conflicts of interest.

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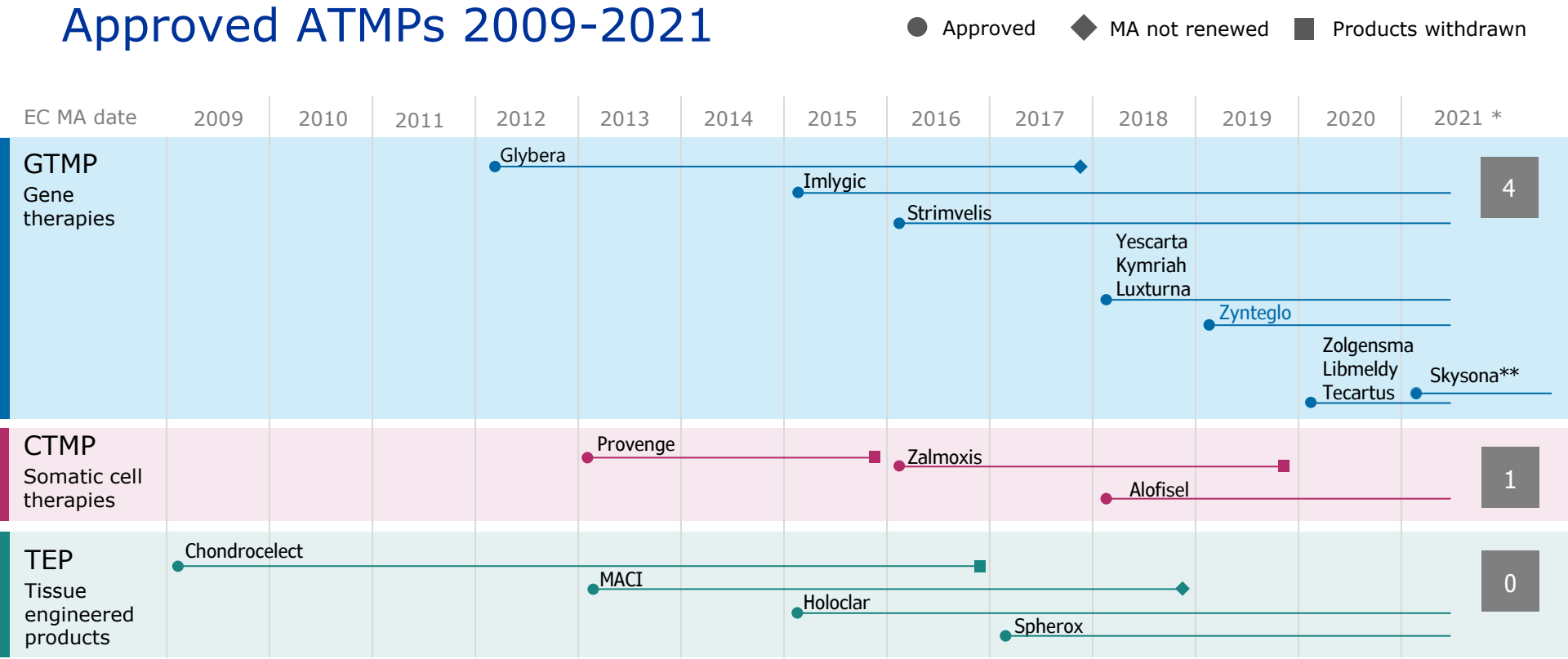
Approved ATMPs 2009-2021



** Skysona: the scientific review has been concluded and the formal Commission decision is pending

* 5 Ongoing MAA (May 2021)

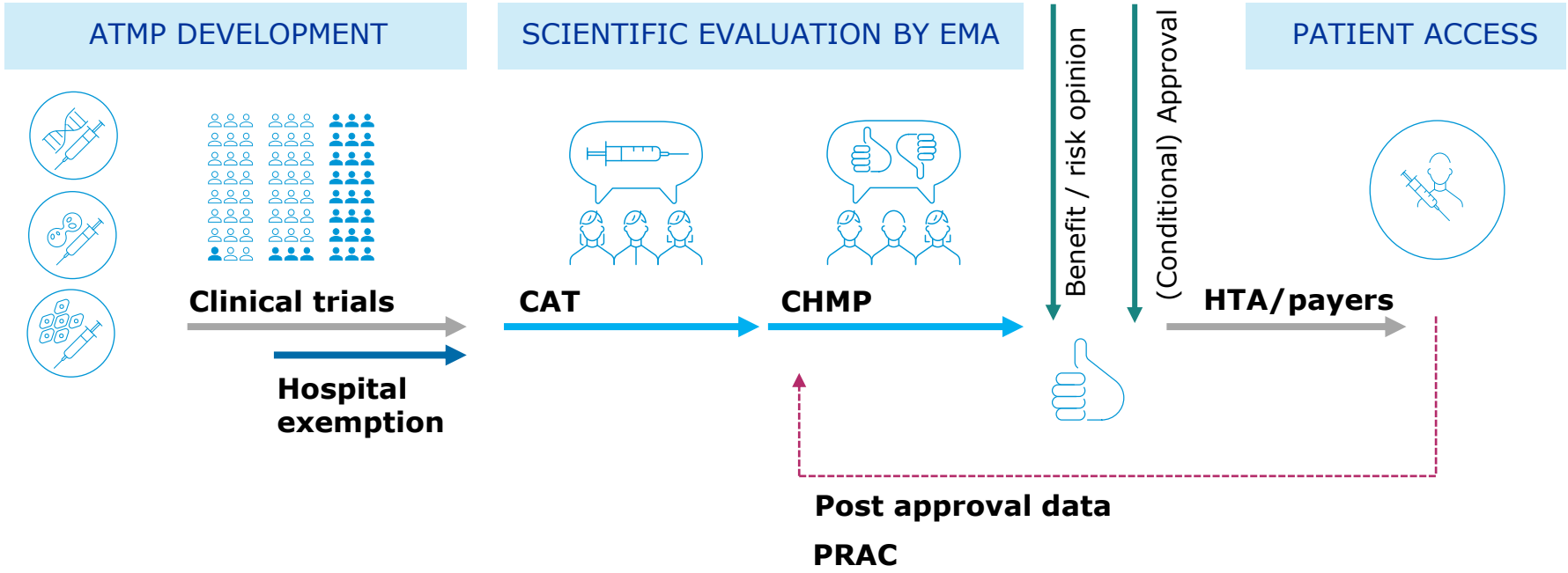
Ongoing ATMP MAA applications

International non-proprietary name (INN) (salt, ester, derivative, etc.) / Common Name	Therapeutic area (ATC level 2)	AA (Art. 14(9) Reg 726/2004)	Orphan Product	Generic or Biosimilar	Start of evaluation
Lenadogene nolparvovec	Ophthalmologicals	N	Y	N	29/10/2020
Autologous glioma tumor cells, inactivated / autologous glioma tumor cell lysates, inactivated / allogeneic glioma tumor cells, inactivated / allogenei	Antineoplastic medicines	N	Y	N	01/10/2020
Elivaldogene autotemcel	Other nervous system medicines	N	Y	N	01/10/2020
Lisocabtagene maraleucel	Antineoplastic medicines	N	Y	N	16/07/2020
Idecabtagene vicleucel	Antineoplastic medicines	N	Y	N	21/05/2020
Eladocagene exuparvovec	Other nervous system medicines	N	Y	N	28/01/2020

→ Skysona

Source: Applications for new human medicines under evaluation by the CHMP (May 2021)
https://www.ema.europa.eu/en/medicines/medicines-under-evaluation#2021-section

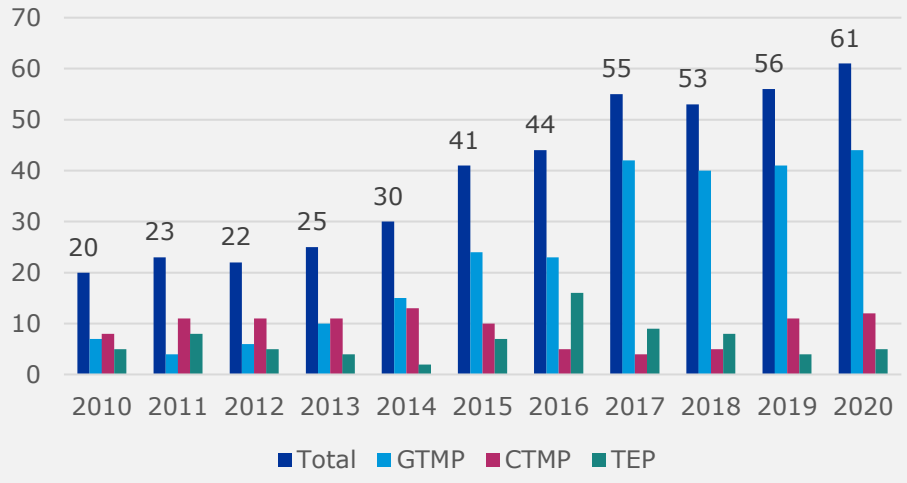
Entry route of ATMPs to the EU market



CAT: Committee for Advanced Therapies
CHMP: Committee for Medicinal Products for Human Use
PRAC: Pharmacovigilance Risk Assessment Committee

ATMP pipeline

SA procedures for ATMPs (2009-2020)



Original predictions, similar to FDA:

10/year approx.

Current predictions, higher – but:

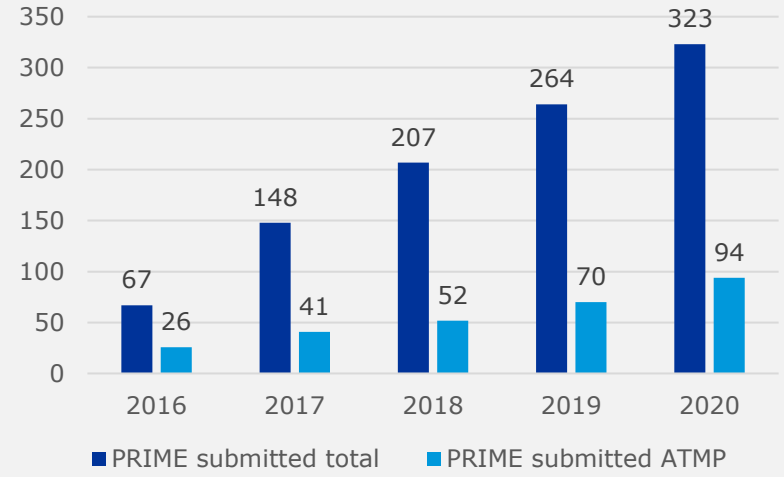
- COVID-19 impact
- Attrition rate high
- Development delays very frequent

- Lots of activity (SA, PRIME, classifications)
- Most gene therapies
- Great mix (academic, SMEs, large pharma…)

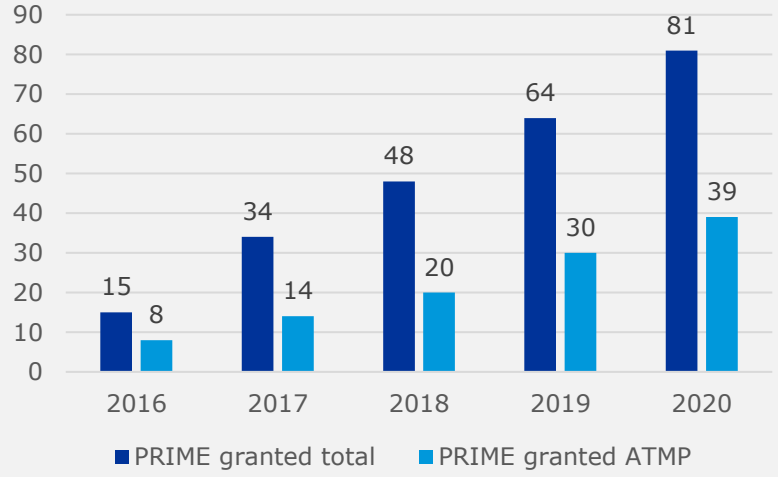
ATMP PRIME: submissions and successes (2016-2020)

https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

PRIME submitted (cumulative)



PRIME granted (cumulative)



ATMPs – challenges in their lifecycle

Innovative therapeutic approaches

High complexity

Specificities in development affect ATMP approvals and patient access

- product consistency
- proof of concept
- small populations
- optimal study designs
- sustained efficacy
- retreatment
- real world data / disease registries

Critical aspects to be addressed during development

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DOI: 10.1111/bcp.14672

ORIGINAL ARTICLE-THEMED ISSUE

Towards a better use of scientific advice for developers of advanced therapies

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Scientific advice (SA) is an important tool offered by regulators to help developers generate robust evidence on a medicine's benefits and risks. Drawing on accumulated experience and looking at the SA provided by the European Medicines Agency in 2018 to advanced therapy medicinal products originally developed by public bodies, we discuss most commonly raised issues and the complexity and timings of the questions posed. Earlier and more frequent SA could help advanced therapy medicinal product developers to pre-empt delays at the marketing authorisation stage. Carefully addressing quality and nonclinical issues before entering the pivotal phase of development will clear the path for a smooth clinical development and successful marketing authorisation.

KEYWORDS
advanced therapy medicinal products, drug development, drug regulation, scientific advice

1 | INTRODUCTION

Public bodies (including academic institutions, research organisations, hospitals), public–private partnerships and small and medium-sized enterprises (SMEs) represent an important source of innovative therapeutics.[1] This holds particularly true for the area of advanced therapy medicinal products (ATMPs), as research on these products and their initial development is conducted to a great extent by public bodies and SMEs.[2] This is confirmed by a recent survey, which concluded that the European ATMP field is still in early phase of maturity with a high representation of SMEs (65%) and 72% of reported therapeutics in early clinical development (phases I–II).[3]

Public bodies and SMEs tend to have limited resources to conduct late-stage clinical trials and the majority of authorised ATMPs in the EU needed collaboration of SMEs or public partners with large pharmaceutical companies (e.g. Strimvelis, Imlygic, MACI, Holoclar, Zolgensma). Moreover, academic institutions and SMEs may encounter more challenges in navigating—and complying with—regulatory requirements on various aspects of development compared with large pharmaceutical companies.[4] These challenges could cause delays at different stages of development and even lead to abandonment of potentially promising projects.

The scientific advice (SA) service is provided by regulators around the globe and is a useful tool to support the timely and sound development of high-quality, effective and safe medicines, for the benefit of patients. At the European Medicines Agency (EMA), this service is provided by the Scientific Advice Working Party supported by the Committee of Advanced Therapies.[5] This is, however, a voluntary procedure in which developers can ask the regulators' opinion on the most appropriate way to generate robust

(Tavridou, Rogers et al, *Br J Clin Pharmacol*, 2020)

1. Comparability and control strategy

2. Toxicity & bridging

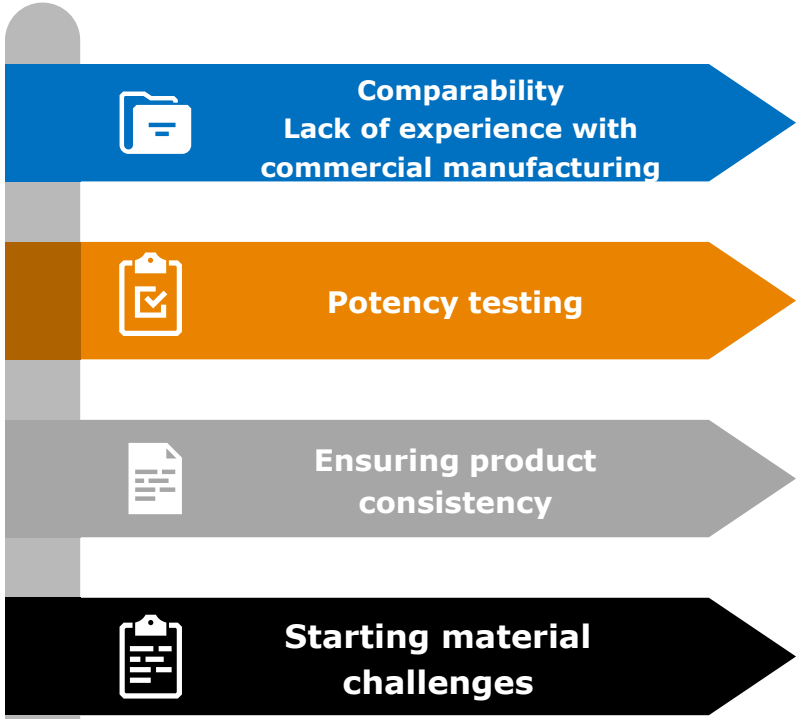
3. Small patient population

4. Study design

5. Data contextualisation

6. Follow-up

Critical Quality questions for ATMP approval



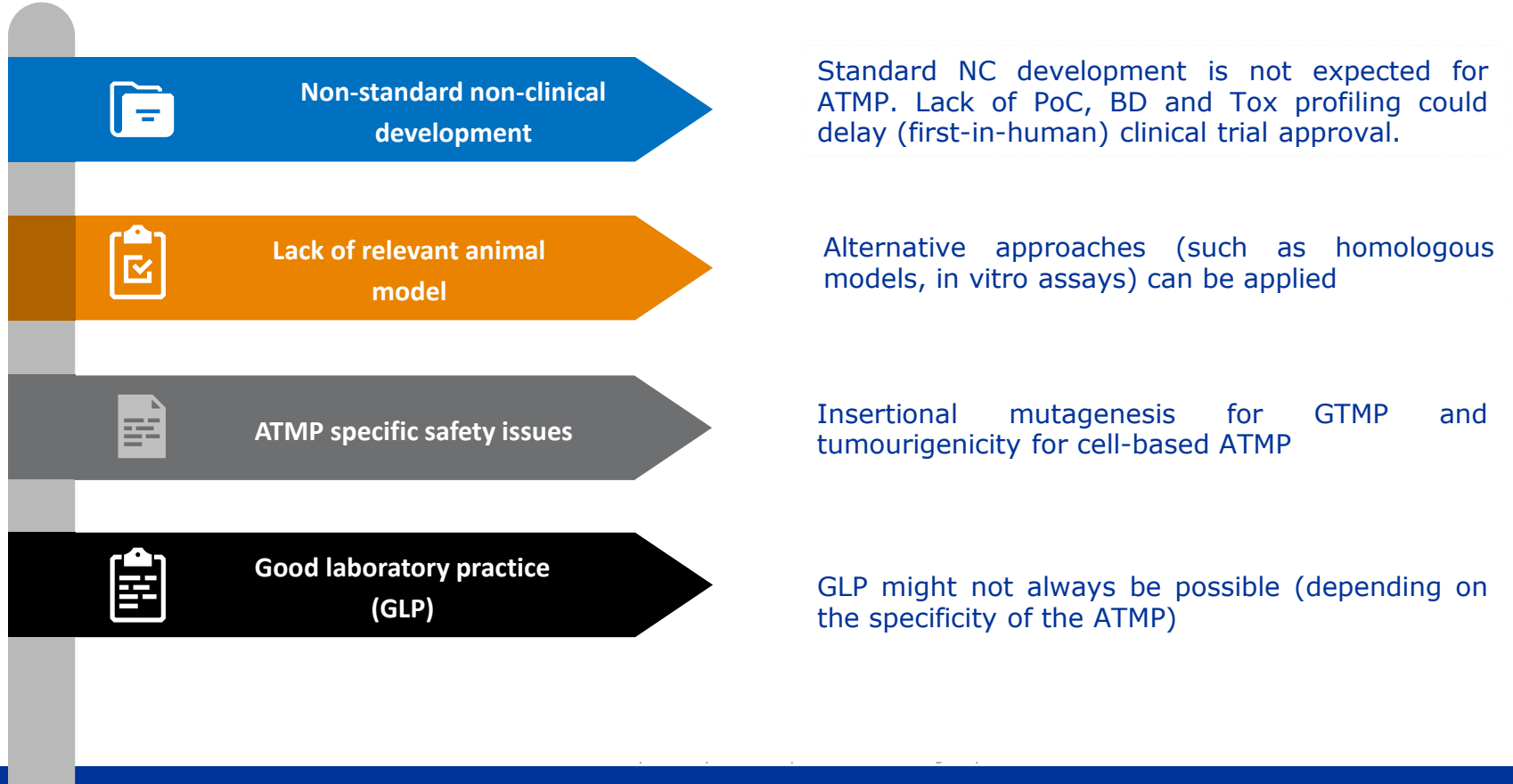
Scalability, improvements in the manufacturing process and site transfer are specially challenging for ATMPs

Linking the result to biological activity in terms of clinical effect, to distinguish between potent/subpotent batches. Essential to demonstrate comparability.

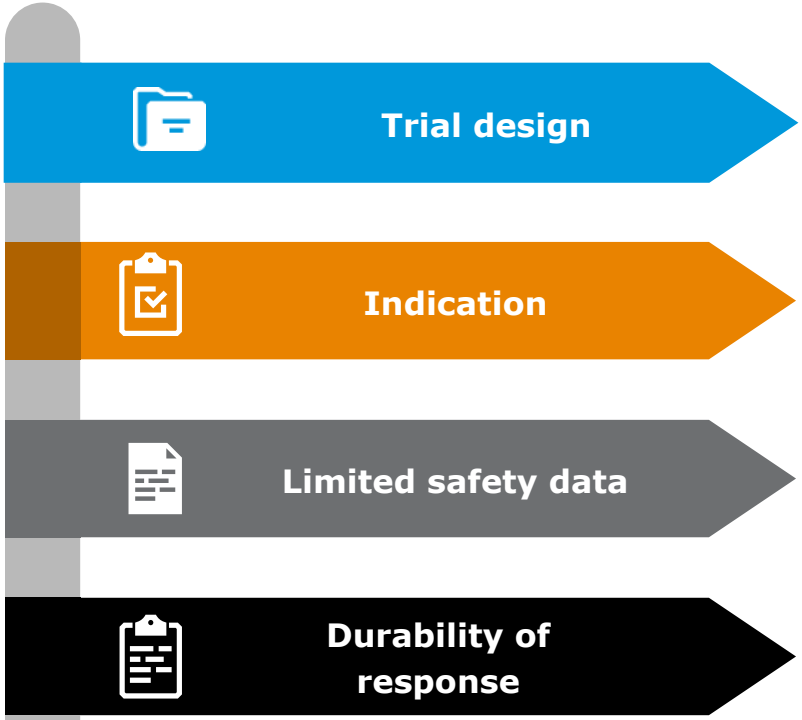
Complex by nature, ATMPs are difficult to manufacture. Variability of the starting/raw materials also adds up to the challenge. Adapted GMP for ATMPs.

Consistent source of starting material is key - SM to be thoroughly characterised and well defined.

Critical Non-clinical questions for ATMP approval



Critical Clinical questions for ATMP approval



Dose finding, lack of randomisation, non comparative trials (single arm trials), external controls, low patient numbers

Not reflecting patient included in clinical trials

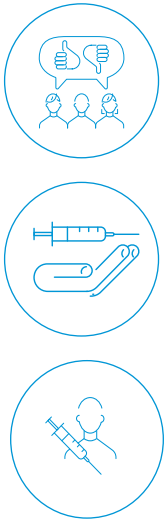
Limited study population, route of administration / surgical procedures, dose, tumorigenicity, biodistribution, integration, concomitant medication

Early planning of registries to bridge the gap on long term efficacy and safety is essential to build confidence for all stakeholders and demonstrate the magnitude of health benefit

Supporting innovation to advance patient access

GENERAL SUPPORT

- Scientific advice
- Innovation Task Force
- Parallel consultation with HTAs
- ATMP Classification procedure
- ATMP Certification procedure
- PRIME (early access)
- Qualification of novel methodologies, e.g. registries
- Paediatric and Orphan framework
- Scientific guidelines
- SME support
- Academia cooperation
- Fee incentives



AUTHORISATION

ACCESS DECISION

POST-LICENSING EVIDENCE

Dedicated scientific guidance

European Commission

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Commission-DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs

The term "advanced therapy medicinal products" ("ATMPs") is used to designate gene therapies, somatic cell therapies and tissue engineered products.

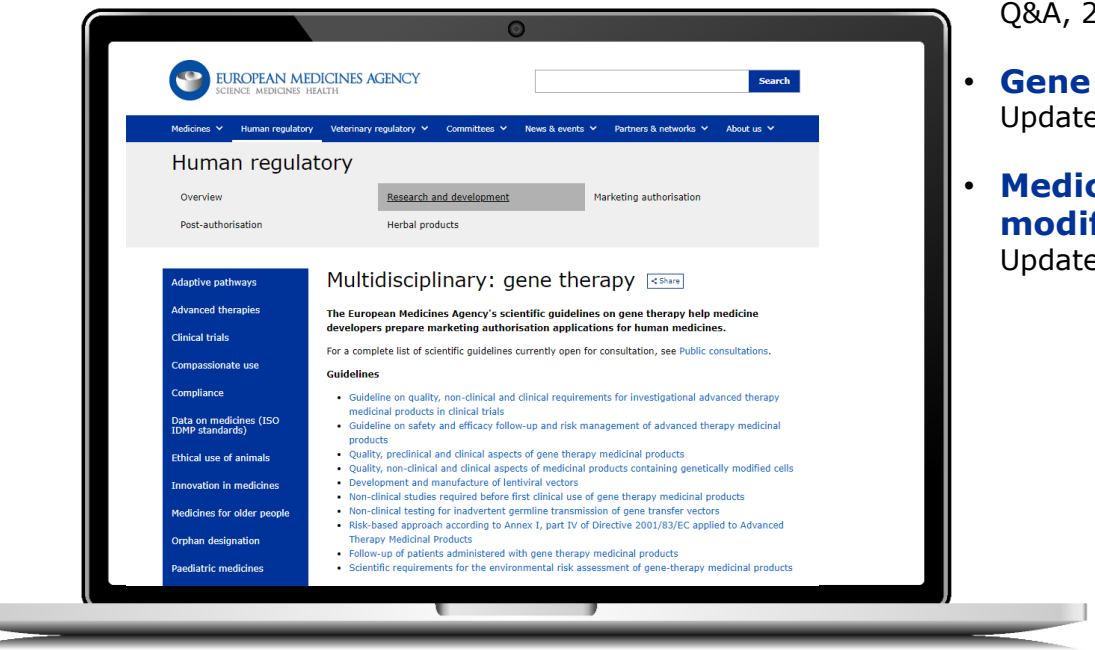
In the EU, these products are governed by Regulation 1394/2007 on advanced therapy medicinal products ("ATMP Regulation"). The cornerstone of the Regulation is that a marketing authorisation must be obtained prior to the marketing of ATMPs. The evaluation of these products is led by a specialised committee within the European Medicines Agency (EMA) i.e. by the Committee for Advanced Therapies ("CAT") who prepares a draft opinion before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion and the authorisation is granted by the Commission. The ATMP Regulation also empowers Member States to permit the use of advanced therapies that have not been authorised by the Commission under certain conditions (so-called "hospital exemption").

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

- **Risk-based approach** applied to ATMPs
  in effect since 2013
- **GMP** specific to ATMPs
  EC Guideline, in effect since 2018
- Safety & Efficacy **follow-up & risk management**
  Updated EMA guideline, 2018
- Streamlining of the **GMO* consultation process**
  July 2018
- **Comparability** for ATMPs
  Q&A, 2019
- **GCP** considerations for ATMPs
  EC guideline
- **GLP** principles in relation to ATMPs
  Q&A

* GMO: Genetically modified Organisms

Dedicated scientific guidance (continued)



- **Non-substantially manipulated cell-based** ATMPs Q&A, 2017
- **Gene therapy medicinal products** Updated 2018
- **Medicinal products containing genetically modified cells** Updated November 2020

Take home messages

- Specific framework but subject to **same high standards** further supported by **tailored guidance and a risk-based approach**
- Efficacy and safety starts with **Quality**
- Relevant and unambiguous **evidence from early stages**, especially transition from non-clinical to clinical development essential
- Importance of early planning and execution of **long-term data collection** for efficacy and safety in the post-authorisation phase
- Tools and incentives available to support ATMP development in the EU

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Thank you for your attention

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