Overcoming the challenges getting ATMPs approved in the European Union

CASSS – CGTP 2021

Global Regulatory Updates Session

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Office of Advanced Therapies, European Medicines Agency
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The presenter does not have any conflicts of interest.
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Approved ATMPs 2009-2021

**GTMP** Gene therapies
- Glybera
- Imlygic
- Strimvelis
- Yescarta
- Kymriah
- Luxturna
- Zysteglo
- Zolgensma
- Libmeldy
- Tecartus
- Skysona**

**CTMP** Somatic cell therapies
- Provenge
- Zalmoxis
- Alofisel

**TEP** Tissue engineered products
- Chondrocellect
- MACI
- Holoclar
- Spherox

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**Approved**
**MA not renewed**
**Products withdrawn**

**EC MA date**
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
- 2020
- 2021 *

**Approved Products**

**Products withdrawn**

**MA not renewed**

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**Notes**
- **Skysona**: the scientific review has been concluded and the formal Commission decision is pending
- **5 Ongoing MAA (May 2021)**
## Ongoing ATMP MAA applications

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<th>International non-proprietary name (INN) (salt, ester, derivative, etc.) / Common Name</th>
<th>Therapeutic area (ATC level 2)</th>
<th>AA (Art. 14(9) Reg 726/2004)</th>
<th>Orphan Product</th>
<th>Generic or Biosimilar</th>
<th>Start of evaluation</th>
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Entry route of ATMPs to the EU market

**ATMP DEVELOPMENT**

**Clinical trials**

**Hospital exemption**

**SCIENTIFIC EVALUATION BY EMA**

**CAT**

**CHMP**

**Benefit / risk opinion**

**(Conditional) Approval**

**HTA/payers**

**PATIENT ACCESS**

**Post approval data**

**PRAC**

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

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...)

SA procedures for ATMPs (2009-2020)
ATMP PRIME: submissions and successes (2016-2020)


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

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

- **Comparability**
  - Lack of experience with commercial manufacturing

- **Potency testing**

- **Ensuring product consistency**

- **Starting material challenges**

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

- **Non-standard non-clinical development**
  
  Standard NC development is not expected for ATMP. Lack of PoC, BD and Tox profiling could delay (first-in-human) clinical trial approval.

- **Lack of relevant animal model**
  
  Alternative approaches (such as homologous models, in vitro assays) can be applied.

- **ATMP specific safety issues**
  
  Insertional mutagenesis for GTMP and tumourigenicity for cell-based ATMP.

- **Good laboratory practice (GLP)**
  
  GLP might not always be possible (depending on the specificity of the ATMP).
Critical Clinical questions for ATMP approval

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

**Indication**
- Not reflecting patient included in clinical trials

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

**Durability of response**
- 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

- **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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