Advanced therapy medicinal products (ATMPs) and ATMP Regulation

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Patrick Celis on 8 March 2018
CAT Secretariat
• Advanced therapy medicinal products (ATMPs): what are they? why are they so different from other medicines?

• Why is there a special legislation for ATMPs? The European regulatory framework

• ATMP classification and certification procedures
The Beauty and the Beast

Genes

Cells

ATMPs:
- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products
Advanced Therapy Medicinal Product (gene-based)

- Treatment of inherited disease
- Cancer therapies
- Tissue regeneration (e.g. loss of sight)

Pinterest.com
Advanced Therapy Medicinal Product (cell-based)

- Treatment of cartilage defects
- Treatment of Parkinson's disease, Alzheimer's, and ALS
- Product for cardiac repair
- Skin replacement
- Cancer Immunotherapy

Products against immune diseases, ...

Pinterest.com
Example of approved Gene therapy medicinal products

In vivo gene therapies

Example: Glybera
• Treatment of lipoprotein lipase deficiency
• Replication-deficient adeno-associated viral vector designed to deliver and express the human LPL gene variant LPLS447X

Ex-vivo gene therapies

Example: Strimvelis
• CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence
• Treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)
Example of an approved somatic cell therapy medicinal product

Example: Provenge

- Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)
- Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer
Example: Holoclar
• Ex vivo expanded autologous human corneal epithelial cells containing stem cells
• Treatment of adult patients with moderate to severe limbal stem cell deficiency unilateral or bilateral, due to physical or chemical ocular burns.
Wrap-up (1): ATMPs are ...

- Medicinal products based on cells or genes
- Very different from medicines based on chemical entities or biological / biotechnological origin
- But same requirement for testing / controlling each batch
  - Impact on cost of manufacture of the ATMPs
  - Very small batch size (autologous CBMP: batch size = 1)
- In EU: GTMPs, CTMPs and TEPs approved
Medical Devices (93/42/EEC)  
Regulation on Advanced Therapies  
Medicinal Products (2001/83/EC)

Legislation

Advanced Therapies

Science

Medical Devices  
Tissue Engineering  
Cell Therapy  
Gene Therapy  
Biotech (e.g. insulin)  
Pharmaceuticals (e.g. hypertension drugs)

Committee for Advanced Therapies (CAT) Specific expertise

CHMP expertise
ATMPs and the EU legal framework – Lex specialis

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)
Some highlights of the ATMP Regulation

- **ATMPs**
  - Gene therapy MP, Cell therapy MP and Tissue engineered products
  - Are medicinal products
  - ATMPs are authorised in the EU via the centralised procedure

- **Principles of existing legislation on medicines apply to advanced therapies:**
  - marketing authorisation
  - demonstration of Quality, Safety & Efficacy
  - GMP, GCP (adapted to ATMPs)
  - post-authorisation vigilance and RMP
Committee for Advanced Therapies

CHMP members or CHMP Co-Opted Members = 5
* their 5 Alternates = 10

1 NO + 1 IC + their Alternates = 4

2 Patient + their alternates = 8

23 Experts from National Competent Authorities + their Alternates = 46
CAT covers the scientific areas relevant to advanced therapies, including:

- medical devices
- tissue engineering,
- gene therapy,
- cell therapy,
- biotechnology,
- surgery,
- pharmacovigilance & risk management
- ethics.
Tasks of the Committee for Advanced Therapies (CAT)

Scientific Advice
Support to PDCO
Support to CHMP / COMP
Interaction with stakeholders
Publications, Guidelines

EVALUATION
CERTIFICATION
CLASSIFICATION
Marketing Authorisation of ATMPs

- Centralised MA: one license valid in entire EU
- 210-day procedure
- Review by CAT
- Final opinion adopted by CHMP
Marketing authorisations (until December 2017)

- 10 ATMPs authorised (3 GTMP, 3 CTMP, 4 TEP)
  - Glybera – GTMP – Comm Dec 25/10/12 / MA ended Oct 2017
  - MACI – TEP, combined ATMP – Comm Dec 27/6/13 / MA suspended Sept. 2014
  - Holoclar – TEP – Comm Dec 17/2/15
  - Imlygic – GTMP – Comm Dec 16/12/15
  - Strimvelis – GTMP – Comm Dec 26/5/16
  - Zalmoxis – CTMP - Comm Dec 18/8/16
  - Chondrosphere – TEP – Comm Dec 10/7/17
Incentives

- **Scientific Advice:**
  - Questions on Quality, Non-clinical and clinical development
  - Aim: provide scientific certainty to ATMP developers
    - 90% fee reduction for SMEs, 65% for others

- **Scientific recommendation on advanced therapy classification**
  - ‘Is the product I am developing an ATMP?’
  - Aim: provide regulatory certainty

- **SMEs: Certification of quality and non-clinical data**
  - ‘Is my product development so far on track for a future Marketing Authorisation Application?’
  - Aim: provide scientific certainty to SME Developers
ATMP classification: what is it?

- Simple procedure, incentive included in the ATMP Regulation
  - 60 day procedure (often shorter), no fee
- To provide regulatory certainty to the ATMP developers:
  - ‘Am I developing an ATMP?’ (what legislation do I have to consult)
  - ‘What guidelines are applicable to my product?’
- For early developments (no expectation that the product is already in non-clinical or clinical development)
Classification procedure for ATMPs – until Dec. 2017

- All classification outcomes are published (summary)

- Up to end Dec 2017:
  - 286 procedures finalised
  - 290 procedures submitted

(Status Dec 2017)
ATMP Certification procedure

- Incentive: early-late
- For SMEs only

- **Scientific certainty**
  - ‘Is my product development so far on track for a future Marketing Authorisation Application?’

- CAT will perform a scientific evaluation of
  - (early) quality / development data
  - (early) non-clinical data
ATMP Certification procedure

- 90 day procedure

- The applicant will always received the evaluation report and List of issue for future consideration
  - If positive evaluation: Certificate by EMA

- 10 Certification procedures finalised
  - 1 withdrawn because ‘too early’ (Q-certification)
  - In recent cases: pre-assessment of Q/NC data, shortly before MAA.
Wrap-up (2) – ATMP Regulation

- Adapted legislation established in EU (in force since 2009)
  - Definitions
  - Specialist Committee (CAT)
  - Authorisation procedure
  - Incentives
  - Hospital exemption
- ‘Lex specialis’: Pharma legislation applies unless specified differently in ATMP regulation
ATMPs in Europe (2009-2017)

~ 500 clinical trials using ATMPs in EU
~ 290 ATMP classifications
~ 270 scientific advice requests

19 MAAs reviewed
10 ATMPs approved

3 withdrawn
1 Suspended

Market
6 licensed ATMPs
Conclusions

- ATMP Regulation provides a clear regulatory framework for ATMP developers
- The approval of products for each of the 3 categories (GTMP, CTMP, TEP) indicates that the system is workable
- Incentives (ATMP specific, other)
- Most activities of the CAT in the pre-submission phase (SA, classification)
- Lot of ATMP clinical trials (review and approval of CTs by national authorities)
- ATMP developers need support from authorised (before, during and after MAA)
Thank you for your attention

Further information

Patrick Celis
Patrick.celis@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone  +44 (0)20 3660 6000  Facsimile  +44 (0)20 3660 5555

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Support for advanced therapies:
from developers to patients

2nd International Awareness Session - The EU medicines regulatory system
and the European Medicines Agency

Presented by Ana Hidalgo-Simon on 8 March 2018
Head of Specialised Scientific Disciplines, European Medicines Agency
Advanced Therapies (ATMPs)

- Development: help and Incentives
- Towards Marketing authorisation: Innovation Task Force, Scientific Advice, PRIority MEdicines
- Post-authorisation: pharmacovigilance, Registries
- Supporting access to patients
Which are the tools to develop & license ATMPs in Europe?

- Medicinal Products Legal framework Directive 2001/83/EC
- EMA support activities (ITF, Scientific Advice, Orphan designation, Paediatric development, CAT classification, Certification)
- Scientific Guidance
- EMA, CAT, EC Stakeholder Interaction and Plans
Incentives for ATMP developers

• **Scientific Advice:**
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EMA support to innovation

- Support to all developers
  - Scientific advice
  - EU Innovation network and ITF meetings
  - SME
- ATMP Specific incentives
  - ATMP classification
  - ATMP certification
- Early access mechanism
  - Conditional MA and Accelerated Assessment
  - PRIME
Early support – ITF (more on this tomorrow)

EMA’s Innovation Task Force
- Discussion platform for early dialogue with applicants (SMEs, academia, researchers)
- ITF Briefing meetings with EMA staff, with involvement of members of Committees/Working Parties
- Discussion of regulatory and scientific issues

EU Innovation Network
- Regulatory support to medicines innovation and early development of new medicines
- Collaborative effort of EMA and EU national competent authorities
20 out of 41 ITF meetings in 2016 were for SME applicants.
Scientific Advice (more to come)

Incentive: early – late / scientific certainty

- Open to all applicants
  - Fee reduction for SMEs
  - Fee reduction for ATMP developers (non-SMEs)
  - Protocol assistance (free) for Orphan medicinal products

- Scientific advice is given from the SAWP of the CHMP in collaboration with the CAT (+ other committees & working parties)

- Simple, fast procedure: 40 or 70 days (if face to face meeting with the Applicant)

- Possibility for parallel SA with FDA / parallel SA with HTA
Scientific Advice for ATMPs

• 279 SA procedures started – CAT involved (routinely) in all SA for ATMPs
• Increase in SA’s for ATMPs over period 2012 – 2017
• Majority of SA nowadays for GTMP (76% in 2017)

Scientific Advice (SA) requests until end of 2017
How we support innovative medicines: PRIME Scheme

PRIME

Addressing patients’ needs

- 20 requests granted (as of 30 May 2022)
  - 12 advanced therapy
  - 7 biological medicines
  - 1 protein/peptide medicine
  - 1 other medicinal product

1 in 3 medicines targets a disease for which no treatment exists

96 requests processed (end of April 2022)

PRIME medicines

- Strategy
- Thromboembolism
- RARE
- Oncology
- Cardiovascular
- Immunology
- Pulmonary
- PRIME medicines
- Transplantation

22% success rate

71 requests denied

20% of patients actually benefit from or with concomitant therapy

PRIME medicines

Why PRIME is needed

Patients want to bring promising innovative medicines to patients better by optimising and supporting medicine development

Benefits of PRIME

- Focused on patients’ needs
- It focuses on innovator’s needs
- It fosters a major therapeutic advance over current treatment options for patients with rare diseases
- It promotes the timely availability of innovative medicines
- It brings medicines to patients faster

PRIME in brief

PRIME helps develop promising medicines faster, cheaper, and better.

PRIME in brief

Medicines eligible for PRIME must address an unmet medical need.

PRIME selection process is based on scientific grounds.

How we support innovative medicines: PRIME Scheme

PRIME - PRIORITY MEDICINES

Paving the way for promising medicines for patients

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PRIME in brief

Medicines eligible for PRIME must address an unmet medical need.

PRIME selection process is based on scientific grounds.
Out of the 34 PRIME granted, 14 were for ATMPs (41%):
- 13 are GTMPs, 1 CTMP
- 8 Oncology, 4 Haematology, 1 Transplantation, 1 Neurology
MAA for ATMPs: guidance

- The EMA provides procedural and guidance documents to help companies applying for a marketing authorisation for ATMPs

Questions relating specifically to the authorisation of ATMPs may be submitted to: advancedtherapies@ema.europa.eu


Guideline on cell-based medicinal products (2008)

Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)

Reflection paper on Chondrocyte containing MPs for cartilage repair (2009)

Guideline on Xenogeneic CBMPs (2009)

Reflection paper on stem-cell based MPs (2010)

Guideline on MPS containing genetically modified cells (under revision)

Guideline on Safety & Efficacy Follow-up – Risk Management of ATMPs (under revision)

Question & Answer on requirements for minimally manipulated ATMPs (2017)

Guideline on the quality, non-clinical and clinical requirements for investigational ATMPs in preparation

Guidelines on cell therapy products
EMA Guidelines on gene therapy products

Scientific Requirements for the ERA of GTMPs 2008

Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors 2007

Quality, preclinical and clinical aspects of gene therapy medicinal products 2017 (in revision)

Follow-up of patients administered with gene therapy medicinal products 2010

Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells in revision

Scientific and Regulatory considerations on gene editing technologies In preparation

Design modifications of gene therapy medicinal products during development 2012

Management of clinical risks deriving from insertional mutagenesis 2013

Non-clinical studies required before first clinical use of gene therapy medicinal products 2008

Development and Manufacture of Lentiviral Vectors 2005

Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors 2010
European Public Assessment Reports (EPAR)
Advanced therapy medicinal products

Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes or cells. They offer groundbreaking new opportunities for the treatment of disease and injury.

ATMPs can be classified into four main groups:

- **Gene therapy medicines**: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting ‘recombinant’ genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources;
- **Somatic cell therapy medicines**: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;
- **Tissue-engineered medicines**: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue;
- **Combined ATMPs**: these contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

For detailed definitions of the different groups of advanced therapy medicinal products, refer to Regulation (EC) No 1394/2007 and Directive 2001/83/EC.

### Advanced therapies in the product lifecycle

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Role of the European Medicines Agency

All advanced therapy medicines are authorised centrally via the European Medicines Agency (EMA). They benefit from a single evaluation and authorisation procedure.

As with all medicines, the Agency continues to monitor the safety and efficacy of advanced therapy medicines after they are approved and marketed. The Agency also gives scientific support to developers to help them design pharmacovigilance and risk management systems used to monitor the safety of these medicines.

Committee for Advanced Therapies

The Agency’s Committee for Advanced Therapies (CAT) plays a central role in the scientific assessment of advanced therapy medicines. It provides the expertise that is needed to evaluate advanced therapy medicines.

During the assessment procedure, the CAT prepares a draft opinion on the quality, safety and efficacy of the advanced therapy medicine. It sends this to the Committee for Medicinal Products for Human Use (CHMP). Based on the CAT opinion, the CHMP adopts an opinion recommending or not the authorisation of the medicine by the European Commission. The European Commission makes its final decision on the basis of the CHMP opinion.

The CAT also:

- Provides recommendations on the classification of advanced therapy medicines;
- Evaluates applications for certification of quality and non-clinical data for SMEs, following which the Agency issues a certificate;
- Contributes towards giving scientific advice on advanced therapy medicines;
- Is involved in any procedure regarding the provision of advice for undertakings on the conduct of efficacy follow-up, pharmacovigilance and risk management systems of ATMPs;
- Advises, at the request of the CHMP, on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in ATMPs;
- Assists scientifically in the elaboration of any documents related to the fulfilment of the objectives of Regulation (EC) No 1394/2007;
- Contributes towards an environment that encourages the development of advanced therapy medicines;
- Provides, at the request of the European Commission, scientific expertise and advice for any initiatives related to the development of innovative medicines and therapies.

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Patient Registries

Patient registries are organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time.

• Key roles: monitoring the safety of medicines, long-term efficacy/lack of efficacy

• Challenges to overcome: coordination between ongoing initiatives at national and international levels; harmonised protocols, scientific methods and data structures; data sharing and transparency; sustainability.

• EMA initiative for patient registries (launched 2015 - to make better use of existing registries and facilitate the establishment of high-quality new registries)

• CAR-T Cell Therapy registries workshop, EMA 9th February 2018.
ATMP Landscape in Europe

271 EU developers
38% Response rate

In 2016
65% of developers are SMEs, 35% are large developers.

ATMP Type

- Gene Therapy: 59%
- Cell Based Therapy: 46%
- Comb ATMP: 3%

Developer Development Stage

- Early Clinical Stage (phase I-II): 41
- Late Clinical Stage (phase III): 10
- Regulatory Approval Appl: 6
- Product Com: 7

By Renske ten Ham, MSc - Division of Pharmacoepidemiology and Clinical Pharmacology - Utrecht University
EU regulation vs National Challenges

European Level

- Orphan Designation ➔
- Priority Medicine (PRIME) Scheme ➔
- Good Manufacturing Practice (GMP)
- Scientific Advice ➔
- Marketing Authorisation Application ➔
- Committee for Advanced Therapies (CAT) ➔
- SME office ➔
- Post Authorisation Commitment (PAC) ➔

National Level

- Product Discovery ➔
- Clinical Research ➔
- Regulatory Approval ➔
- Commercialisation ➔

Legend

- Driver
- Barrier

- ATMP Classification ➔
- Clinical Trial Application (CTA) ➔
- Genetically Modified Organisms (GMO) Legislation ➔
- Hospital Exemption (HE) ➔
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

Action plan on ATMPs - background

- Multi-stakeholder workshop at EMA on 27 May 2016 to explore solutions to identified challenges to ATMP development and patient access

- **Stakeholders** from Academia, Industry (SME and Big Pharma), Pharmacists, treating physicians, patient representatives, consortia, incubators, investors, Health technology assessment (HTA) bodies, EU Regulators and EC

- **Action plan** is a direct response to the identified solutions

- proposal for actions by **EMA** in close collaboration with **National Competent Authorities** and the **European Commission**

- **Priority**: actions according to feedback received from stakeholders and actions that can be started in 2017

- Actions that would require changes in the **legal framework of ATMPs** are **not included**

- Additional suggestions and proposals can be re-visited in the future, and included to the plan, as required
Action plan on ATMPs – some of the objectives:

- European Commission services to initiate a reflection process with the Member States on the hospital exemption with a view to discuss with Member States the current situation and address possible options. Explore increase of transparency.

- Provide enhanced scientific support for the development of ATMPs through increased opportunities for early dialogue with multidisciplinary or multi-stakeholder expert teams; streamlined EMA procedures for scientific advice, incl. strengthened interaction between EMA committees.

- EMA Scientific Guidelines on ATMPs.

- GCP for ATMPs to address as appropriate any specific needs to ATMP developers.

- Specific action plan for SMEs published.

- Foster increased interaction between EMA and EUnetHTA on ATMPs to increase understanding of health technology assessment, regulatory processes and clinical added value of ATMPs.

- To reduce discrepancies across the EU regarding the application of GMO rules (Directives on deliberate release or contained use) to ATMPs containing or consisting of GMOs.

- EMA Guideline on Investigational ATMPs - To avoid discrepancies across the EU regarding the requirements for ATMPs in the clinical trial phase.

- Reduce administrative burden in the post-marketing phase through the revision of the EMA Guideline on Safety and Efficacy and Risk Management Plans for ATMPs.
Take home messages

- **EMA’s key principles**: based on a regulatory network, collective decision making, transparency, supporting innovation.

- **The centralised procedure**: one application leading to one marketing authorisation valid in all EU member states and the EEA, one invented name & one common product information (available in all languages). Compulsory for ATMPs.

- **Early access tools and strong support for ATMPs**: scientific advice, PRIME, ATMP certification/classification, accelerated assessment, conditional marketing authorisation, marketing authorisation under exceptional circumstances.

- **Engaging with EMA**: pipeline meetings, innovation task force, SME office, pre-submission meetings, academia framework of collaboration. Early engagement encouraged for ATMPs.
Thank you for your attention

Further information

Ana Hidalgo-Simon
Head of Department
Specialised Scientific Disciplines

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone  +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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