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

Credit: Christoph Bock/Max Planck Institute for Informatics
Advanced Therapy Medicinal Product (gene-based)

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

DNA
Advanced Therapy Medicinal Product (cell-based)

Products against immune diseases, ...

Treatment of Parkinson’s disease, Alzheimers, ALS

Treatment of cartilage defects

Product for cardiac repair

Skin replacement

Cancer Immunotherapy
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 of an approved Tissue engineered product

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
Legislation

Medical Devices 93/42/EEC

Regulation on Advanced Therapies

Medicinal Products 2001/83/EC

Science

Advanced Therapies

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 and 2 Clinicians + 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 receive 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)

- Approximately 500 clinical trials using ATMPs in EU
- Approximately 290 ATMP classifications
- Approximately 270 scientific advice requests
- 19 MAAs reviewed
- 10 ATMPs approved
- 3 withdrawn
- 1 Suspended
- 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

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