EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

An agency of the European Union

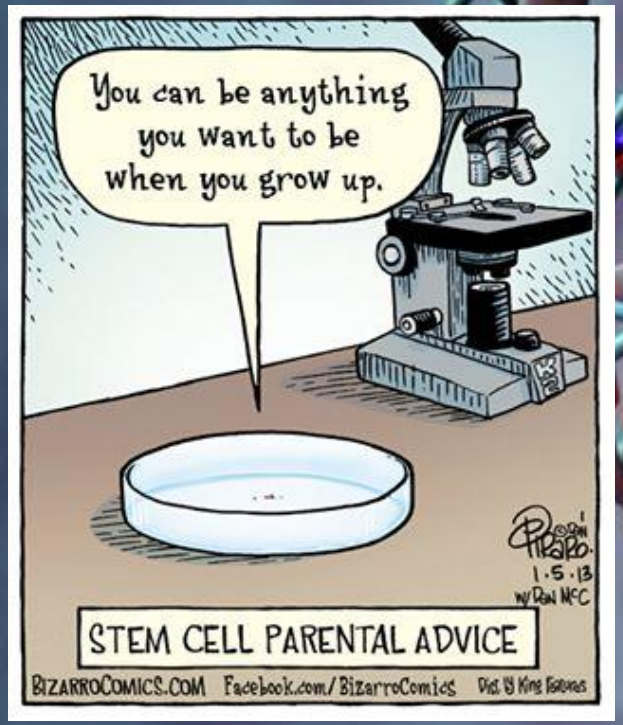
- Advanced therapy medicinal products (ATMPs): what are they? why are they so different from other medicines?

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

- ATMP classification and certification procedures

The ~~Beauty~~ and the ~~Beast~~

Genes **Cells**



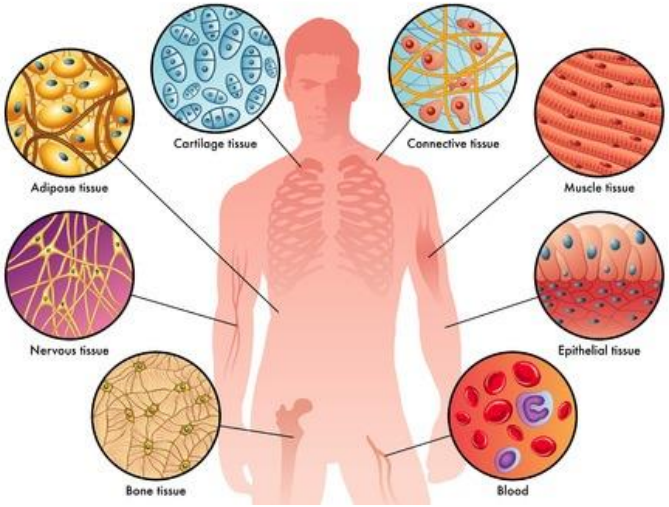
ATMPs:

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products

Credit: Christoph Bock/Max Planck Institute for Informatics

Pinterest.com

Advanced Therapy Medicinal Product (gene-based)



Pinterest.com

DNA

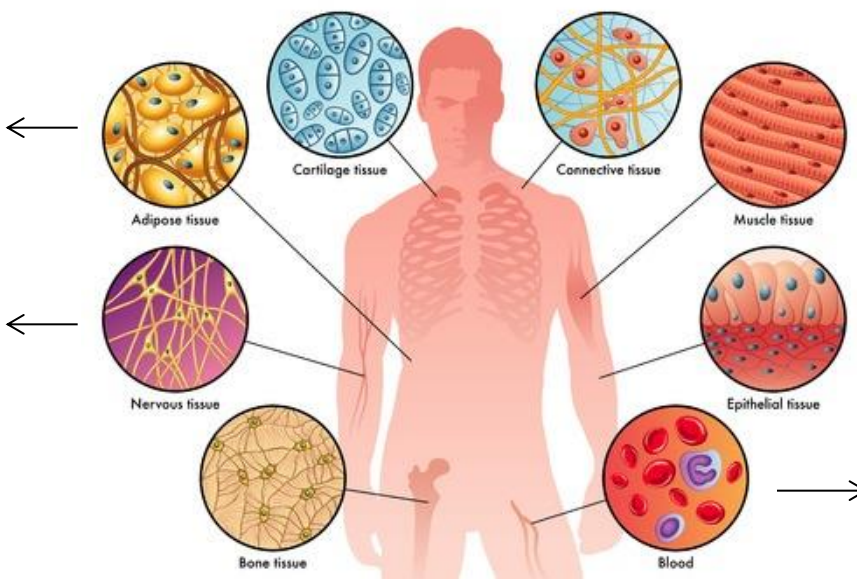
- Treatment of inherited disease
- Cancer therapies
- Tissue regeneration (e.g. loss of sight)

Advanced Therapy Medicinal Product (cell-based)

Treatment of cartilage defects

Products against immune diseases, …

Treatment of Parkinson's disease, Alzheimers, ALS



Product for cardiac repair

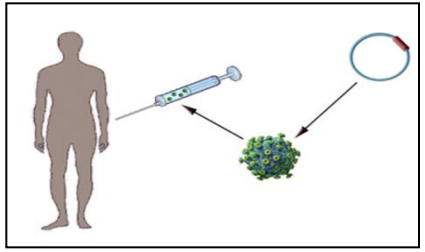
Skin replacement

Cancer Immunotherapy

Pinterest.com

Example of approved Gene therapy medicinal products

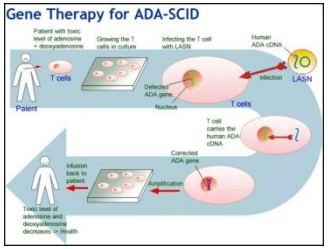
In vivo gene therapies



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

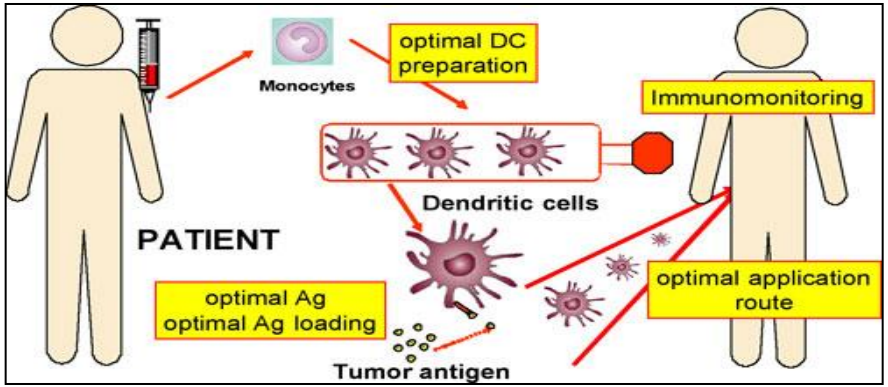
•CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence

•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

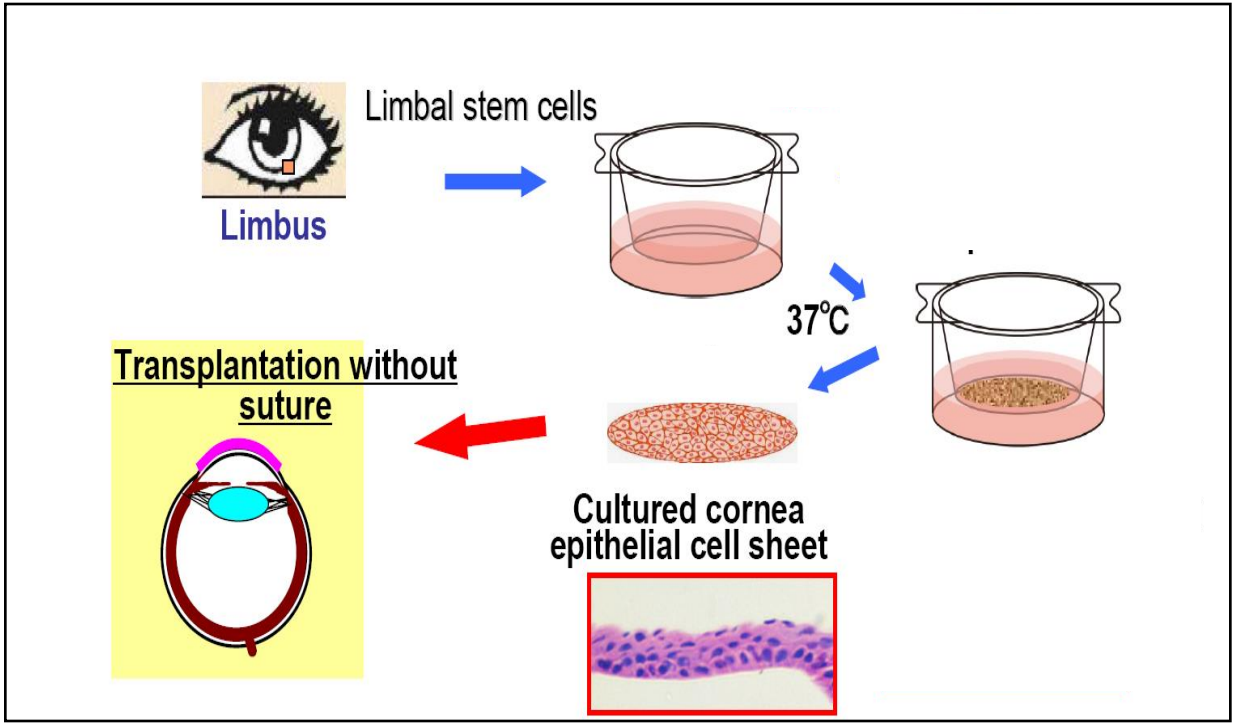
- Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)
- Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer



Example of an approved Tissue engineered product

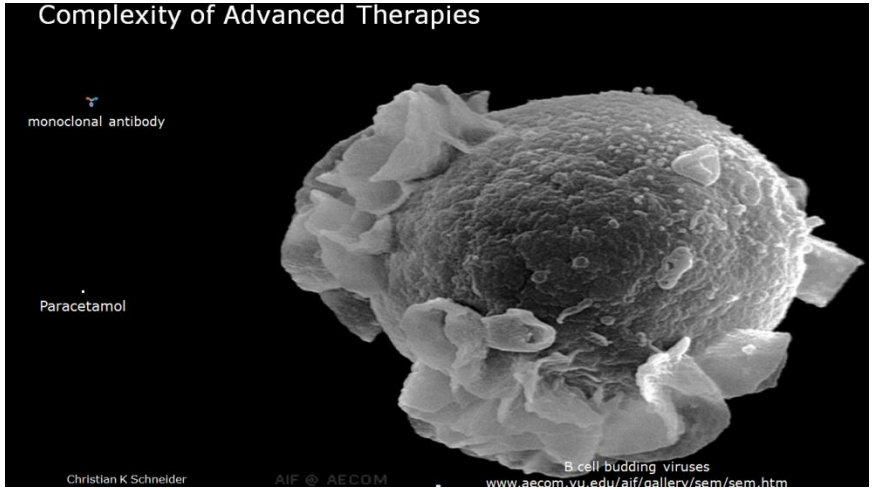
Example: Holoclar

- 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

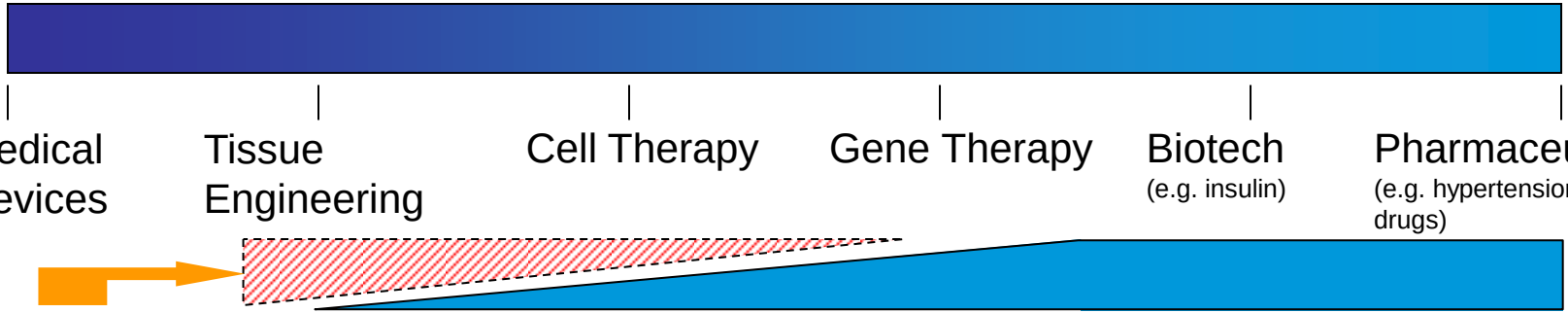


- But same requirement for testing / controlling each batch
  - Impact on cost of manufacture of the ATMPs
  - Very small batch size (autologous CBMP: batch size = 1)
- In EU: GTMPs, CTMPs and TEPs approved

Legislation

Science

Advanced Therapies



Committee for Advanced Therapies (CAT) Specific expertise

CHMP expertise

ATMPs and the EU legal framework – Lex specialis

10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

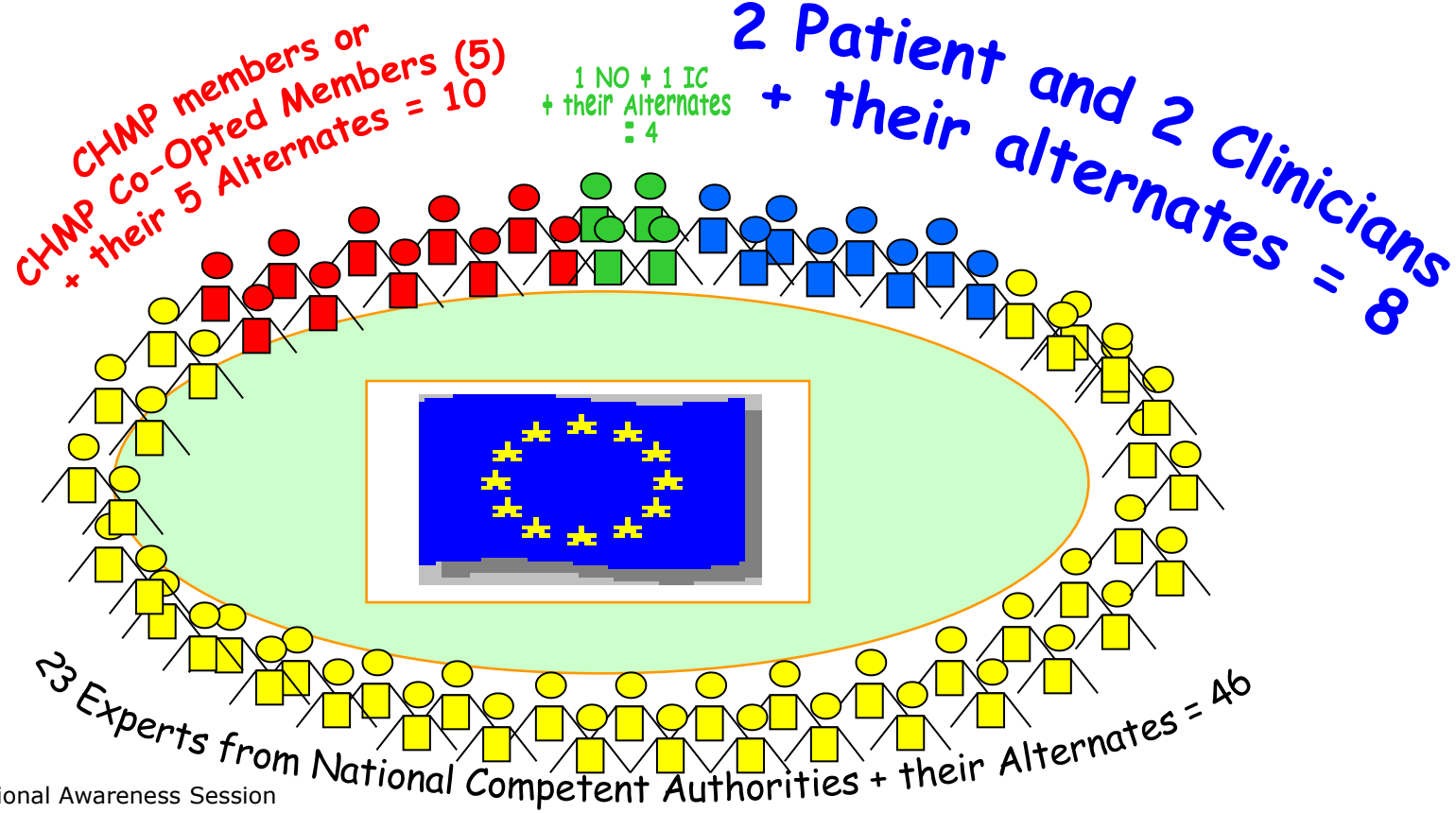
(Text with EEA relevance)

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

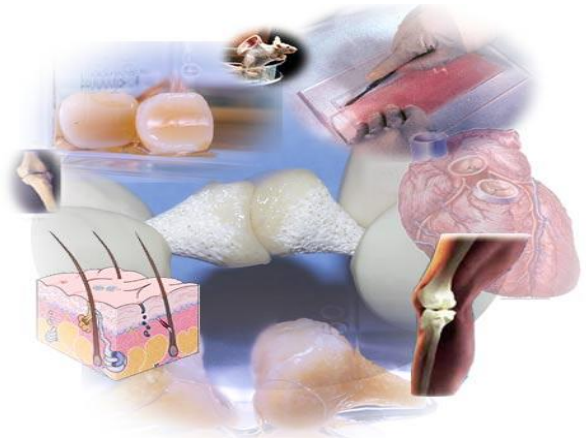


Expertise

CAT covers the scientific areas relevant to advanced therapies, including:

- medical devices
- tissue engineering,
- gene therapy,
- cell therapy,
- biotechnology,
- surgery,
- pharmacovigilance & risk management
- ethics.

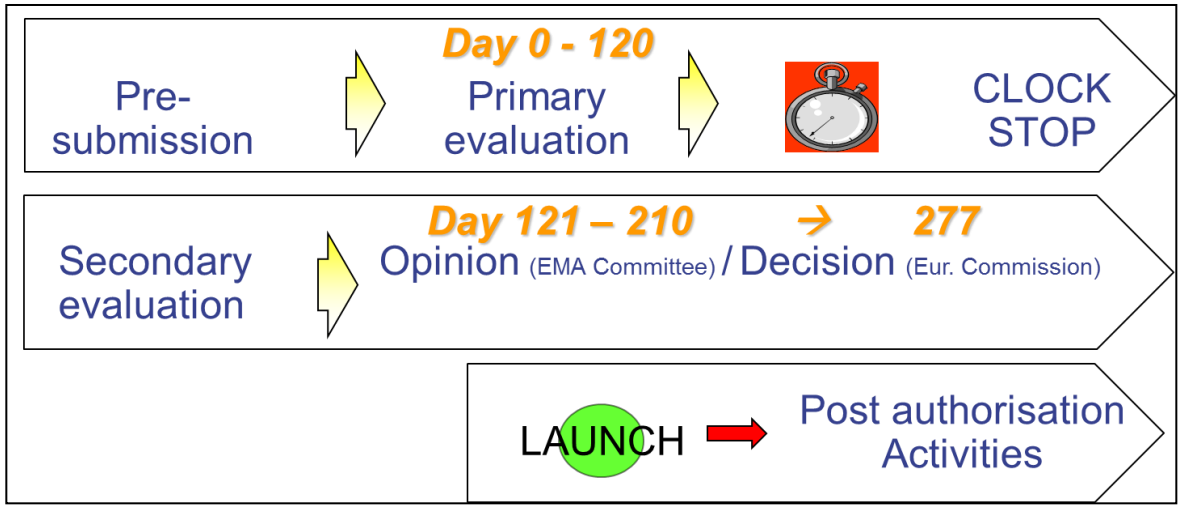
Tasks of the Committee for Advanced Therapies (CAT)



- EVALUATION
- CERTIFICATION
- CLASSIFICATION
- Scientific Advice
- Support to PDCO
- Support to CHMP / COMP
- Interaction with stakeholders
- Publications, Guidelines

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)
  - Chondrocelect – TEP – Comm Dec 5/10/09 / MA withdrawn July 2016
  - Glybera – GTMP – Comm Dec 25/10/12 / MA ended Oct 2017
  - MACI – TEP, combined ATMP – Comm Dec 27/6/13 / MA suspended Sept. 2014
  - Provenge – sCTMP - Comm Dec 6/9/13 / MA withdrawn May 2015
  - 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
  - Alofisel – CTMP – Opinion 12/17 (Comm Dec. Pending)

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)

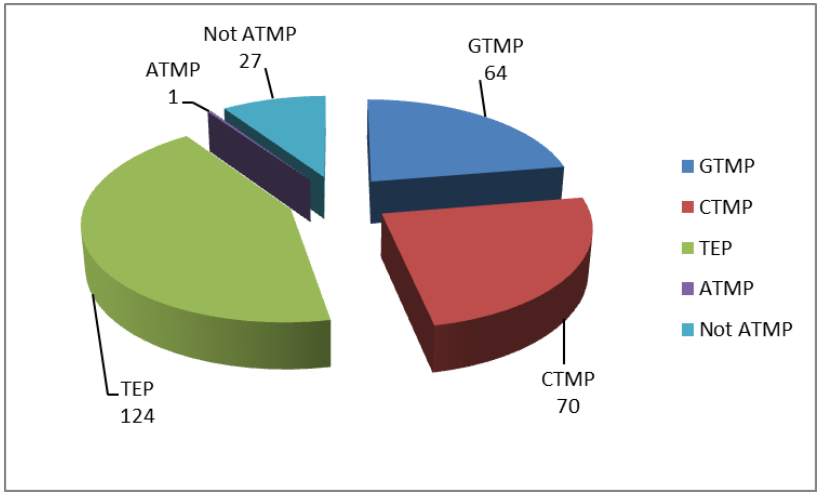
Classification procedure for ATMPs – until Dec. 2017

- All classification outcomes are published (summary)

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500126681.pdf

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

Finalised classifications



(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)

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~ 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
Send a question via our website www.ema.europa.eu/contact

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