



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Advanced therapy medicinal products (ATMPs) and support to developers

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SME Info day

Presented by Patrick Celis on 26 October 2018  
CAT Secretariat

An agency of the European Union

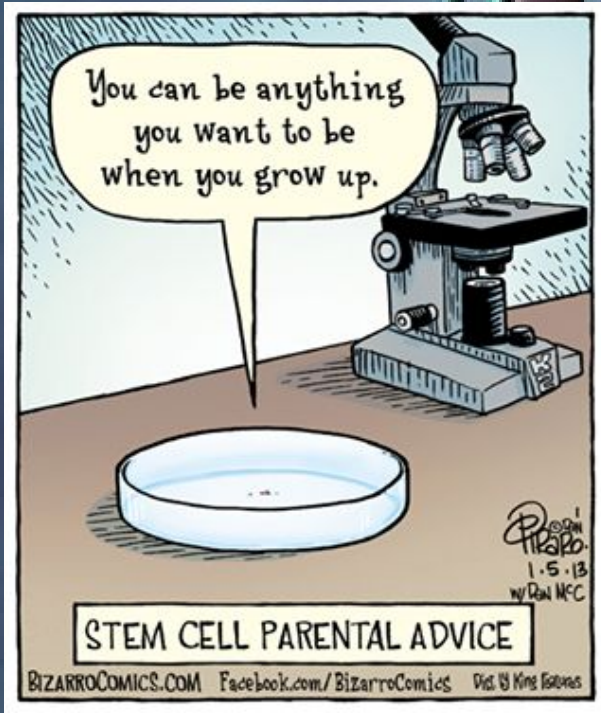




- Advanced therapy medicinal products (ATMPs): what are they? why are they so different from other medicines?
- Incentives in the ATMP Regulation: experience with classification, certification and scientific advice for ATMPs
- Support to ATMP developers

# ~~The Beauty and the Beast~~

## Genes Cells



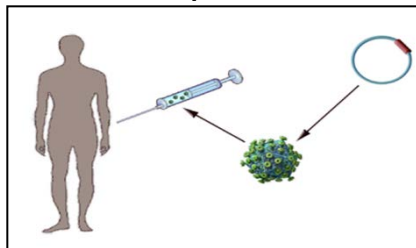
### ATMPs:

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



# Example of approved Gene therapy medicinal products

## In vivo gene therapies

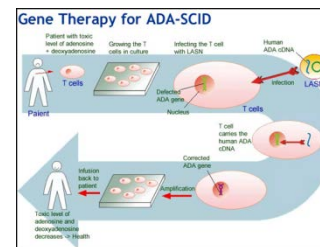


### Example: Glybera

- 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



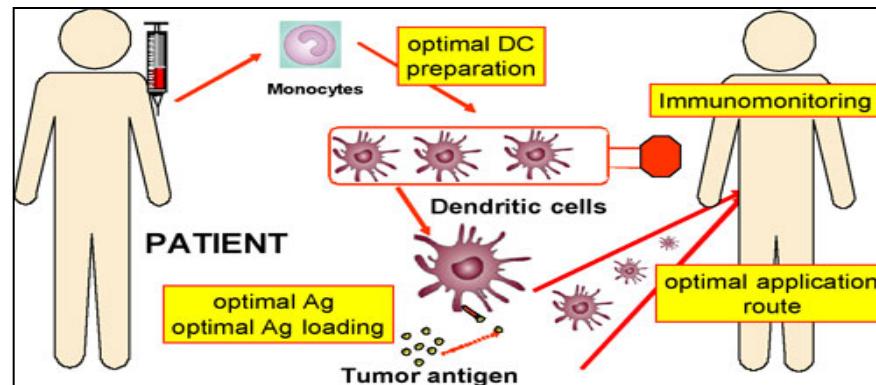
### Example: Strimvelis

- 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

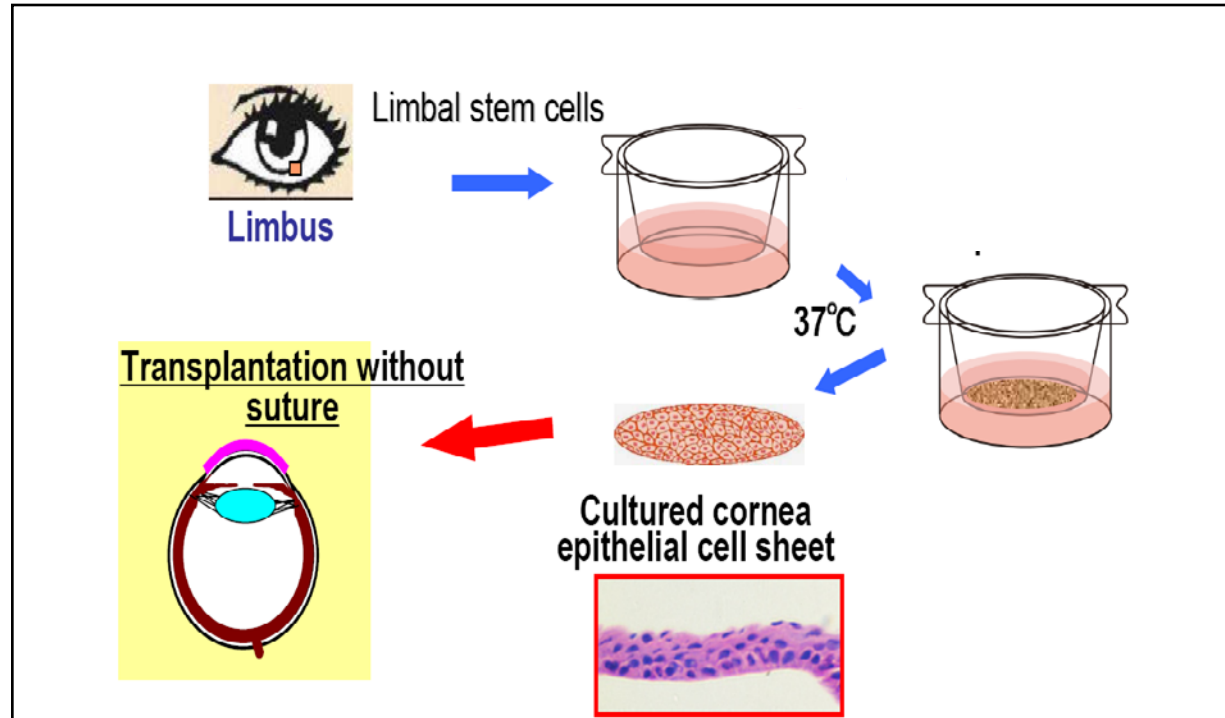
- Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)
- Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer



# Example of an approved Tissue engineered product

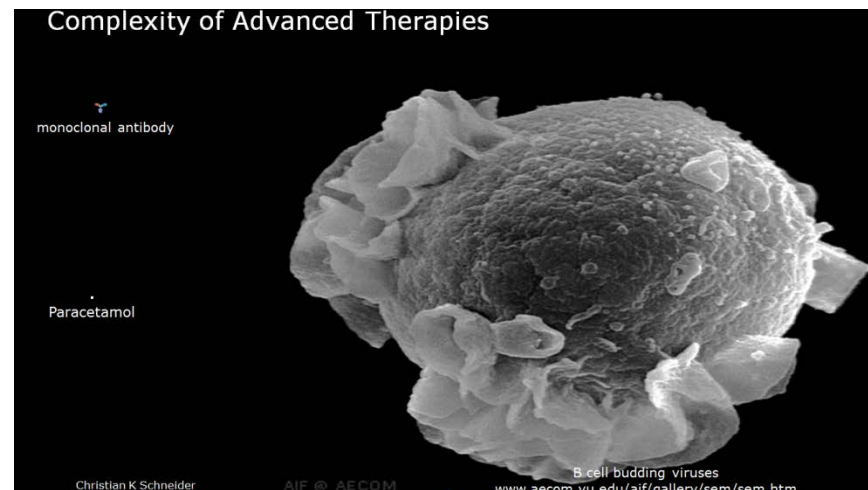
## Example: Holoclar

- 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.



## ATMPs are ...

- Medicinal products based on cells or genes
- Very different from medicines based on chemical entities or biological / biotechnological origin
- But same general requirement as for other medicines
  - Testing & control / GMP
  - Clinical trials / GCP, Marketing authorisation, PhVig and RMP
- In EU: GTMPs, CTMPs and TEPs approved





# 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)

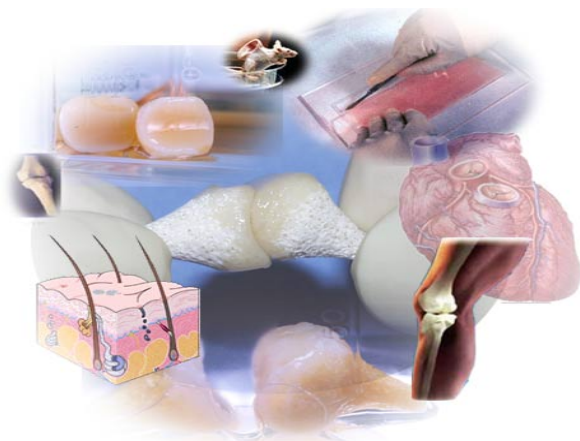


## Some highlights of the ATMP Regulation (1397/2007)

- ATMPs
  - Definitions
  - ATMPs are medicinal products, 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
- Sets up a specialist Committee, the Committee for Advanced Therapies (CAT)
- Incentives for ATMP developers



# Tasks of the Committee for Advanced Therapies (CAT)



**Evaluation**

**Support to PDCO**

**Classification**

**Support to CHMP  
/ COMP**

**Certification**

**Interaction with  
stakeholders**

**Scientific Advice**

**Publications,  
Guidelines**



# Incentives in ATMP Regulation

- 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)

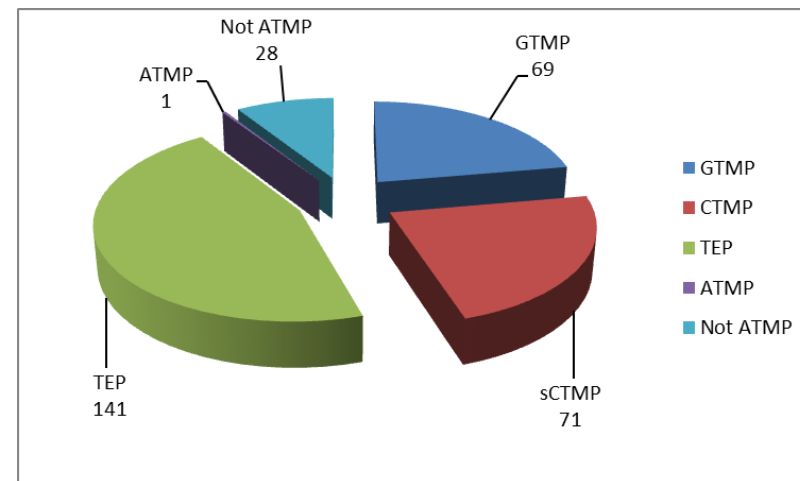
## Classification procedure for ATMPs

- All classification outcomes are published (summary)

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2012/04/WC500126681.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500126681.pdf)

- Up to October 2018:
  - 316 procedures finalised
  - 324 procedures submitted


### Finalised classifications



(Status July 2018)

## Borderline sCTMP/TEP versus tissue or cell preparations (1)

- Criteria: (1) substantial manipulation **or** (2) different essential function
- Substantial manipulation:
  - cell culture, cell activation, enzymatic digestion (most of the time)
- Non-substantial manipulation:
  - list in Annex I to Regulation 1394/2007
  - Cell sorting / selection; radiolabelling of cells
- Different essential function ('non-homologous use'): more tricky
  - Same function = cell maintain original function + in same anatomical/histopathological environment
  - E.g. bone marrow cells or PBMC for any other use than for immune reconstitution = ATMP

- 
- cutting
  - grinding
  - shaping
  - centrifugation
  - soaking in antibiotic or antimicrobial solutions
  - sterilization
  - irradiation
  - cell separation, concentration or purification
  - Filtering
  - lyophilization
  - freezing
  - cryopreservation
  - vitrification

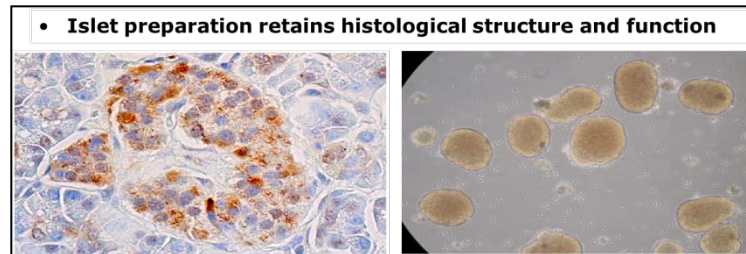
## Borderline sCTMP/TEP versus tissue or cell preparations (2)

### Classified as ATMP

- CD34+ cells (not expanded) for cardiac repair: TEP
- Bone marrow cells for bone or joint healing: TEP
- Umbilical cord derived stem cells for neurological indications (e.g. ALS, stroke, spinal cord injury): TEP/CTMP

### Not ATMP

- CD1c (BDCA)+ myeloid dendritic cells in oncology indication
- Pancreatic islets



## Borderline GTMP vs medicinal product (1)

- GTMP or Vaccines against infectious disease?
    - Live recombinant lentiviral vectors for treatment of HIV infected patients: non-ATMP (vaccine)
    - DNA plasmid encoding an inactive human telomerase reverse transcriptase protein fused to ubiquitin for treatment of malignancies: GTMP
    - Plasmid DNA encoding a mutation-inactivated E7-E6 fusion protein from human Papillomavirus for vaccination of HPV and prevention and treatment of HPV induced pre-malignancies and malignancies: GTMP
- If a product is intended to treat/prevent a viral infection, it is classified as a vaccine
- If a product is intended to treat pathologies caused by the infection (e.g. malignancies), it is classified as a GTMP



## Borderline GTMP vs medicinal product (2)

- Other borderline classification
  - Genetically modified bacteria excreting human protein: GTMP
    - Live recombinant *S typhi* secreting fusion protein of PSA-cholera toxin, treatment prostate cancer
  - mRNA encoding immunostimulatory proteins for the treatment of melanoma: GTMP
  - Nuclease resistant synthetic double-stranded siRNA, treatment of hepatic fibrosis: non-ATMP



## 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
- 11 Certification procedures finalised
- ‘pre-assessment’ tool

## Scientific Advice

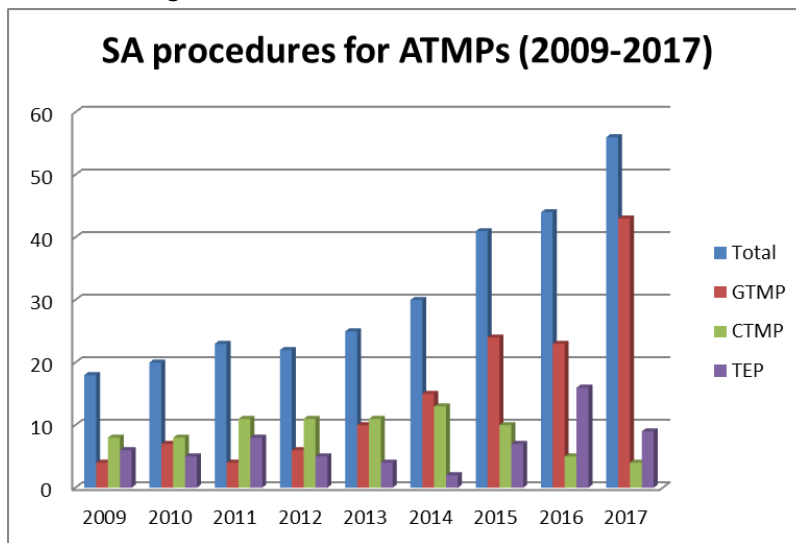
Incentive: early – late / scientific certainty

- Open to all applicants
  - Fee reduction for SMEs
  - Fee reduction for ATMP developers (non-SMEs)
  - Protocol assistance (reduced fee) 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

- 313 SA procedures started (Oct 2018) – CAT routinely involved in all SA for ATMPs
- Increase in SA's for ATMPs over period 2012 – 2017
- Majority of SA nowadays for GTMP (76% in 2017, 80% in 2018)



Scientific Advice (SA)  
requests until  
end of 2017

## Early support for innovative medicines

### ➤ 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

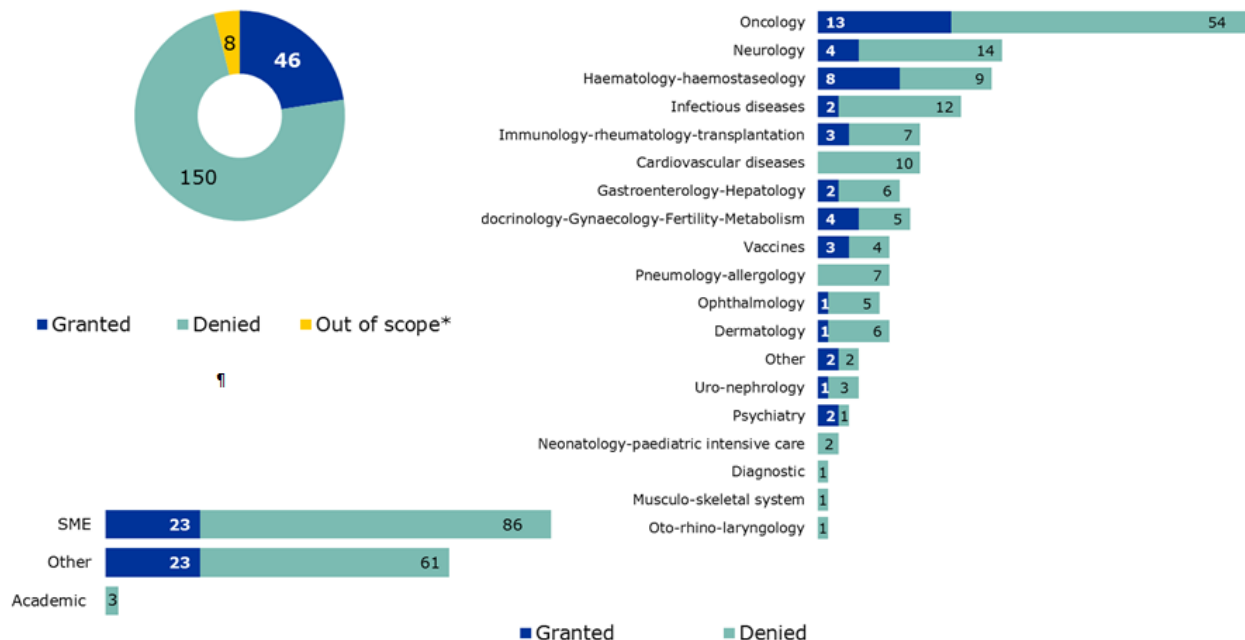


# PRIME

- New procedure since April 2016
  - Aim: to enhance support for the development of **medicines that target an unmet medical need**
  - Early and proactive support to medicine developers to optimise the generation of robust data on a benefits and risks and enable accelerated assessment of medicines applications
- CAT involved in eligibility discussion for ATMPs
  - 52 ATMP PRIME eligibility request submitted
    - = 25 % of all valid eligibility requests
  - 20 ATMP PRIME eligibilities granted



## Cumulative overview of recommendations on PRIME eligibility requests adopted by 18 October 2018¶



\*This indicates eligibility requests received but not started by EMA as they were deemed outside the scope of the scheme or with a format and content inadequate to support their review. These are not included in the breakdown by type of applicant or by therapeutic area.¶

Out of the 46 PRIME granted, 20 were for ATMPs (43%):

- 18 are GTMPs, 2 CTMP
- 9 Oncology
- 5 Haematology
- 2 Immunology – rheumatology – Transplantation
- 1 Ophthalmology
- 2 Neurology
- 1 Other (X-linked myotubular myopathy)



## **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
- proposals for actions by **EMA** in close collaboration with **National Competent Authorities** and the **European Commission**
- **Priority:** actions according to feed-back 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	Objectives	Status
1	EC Guideline on GMP for ATMPs.	To reduce administrative burden and adapt the manufacturing requirements to the specific characteristics of ATMPs. Subsequently to the adoption of the Guideline, EMA will organise specific training to inspectors with a view to achieve more harmonisation.	GL published
2	Exchange of information on GMP inspections within the network.	IWG meetings are being used as a platform for exchange of information and experience on the application of GMP to ATMPs.	Ongoing
3	The European Commission services will initiate a dialogue with national competent authorities to address the interplay between the GMO and the medicines legislation.	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. Issues relevant for both clinical trials and marketing authorisation will be addressed. The aim is to help create coherent approaches for the assessment of these novel products without changing the basic legislation.	Repository of national requirements Q&A Simplified ERA for GM cells
4	Revision of EMA procedures regarding the assessment of ATMPs.	To reduce administrative burden, avoid overlaps between the tasks of the various committees involved, and address the specific needs of ATMP developers (e.g. longer clock stops).	Procedure on interaction of Committees revised and published
5	Provide enhanced scientific support for the development of ATMPs.	Increased opportunities for early dialogue with multidisciplinary or multi-stakeholder expert teams. Streamlined EMA procedures for scientific advice, incl. strengthened interaction between EMA committees.	Ongoing



6	EMA Guideline on Investigational ATMPs.	<p>To avoid discrepancies across the EU regarding the requirements for ATMPs in the clinical trial phase.</p> <p>The Guideline will not change the competence of Member States to approve clinical trials but it will help create common standards for the assessment of these novel products.</p>	GL under development
7	EMA Scientific Guidelines on ATMPs.	<p>The adoption of the guideline on gene therapy and the review of the guideline on genetically modified cells will support developers of these novel therapies by clarifying regulatory expectations.</p> <p>The development of guidance on comparability will also address the questions commonly confronted by ATMP developers.</p>	<p>GL on GTMP published</p> <p>GL on GM cells revised (consultation)</p> <p>Not yet initiated</p>
8	GLP for ATMPs: development of adapted guidance.	To facilitate the approval of clinical trials/granting of marketing authorisation in cases where GLP compliant preclinical studies are not feasible.	Published
9	Revision of the EMA Guideline on Safety and Efficacy and Risk Management Plans for ATMPs.	To reduce administrative burden in the post-marketing phase.	Revision published for consultation
10	The European Commission services to initiate a reflection process with the Member States on the hospital exemption.	To discuss with Member States the current situation and address possible options.	Ongoing
11	EMA Q&A on the application of the risk-based approach for ATMPs that have not been subject to substantial manipulation.	To explain to developers the possibilities afforded by the risk-based approach (flexibility, reduction of certain requirements for the submission of a marketing authorisation application depending on specific risks).	Q&A published



12	GCP for ATMPs. Led by the European Commission.	To address as appropriate any specific needs to ATMP developers.	Draft GL published for consultation
13	Scientific considerations on gene editing technologies.	To reflect on emerging techniques on gene editing.	Ongoing / partly addressed in GL for GM cells
14	Awareness and training of the network.	Awareness sessions for the EU network on ATMP-related topics (e.g. AAV Vectors, genome editing); expert meetings organized by CAT	Outcomes of expert meetings published
15	Increased stakeholder support - SMEs	Publication of a specific action plan for SMEs.	Action plan for SMEs published
16	Increased stakeholder support - Academia	Publication of an action plan specifically designed on the framework of collaboration with academia.	Action plan for collaboration with academia published
17	Increased stakeholder support - ATMP topic-specific	Update the ATMP dedicated webpage on EMA's website to act as a central resource of relevant information.	Webpage updated
18	Increase awareness of stakeholders on EU regulatory processes and framework.	Development of targeted communication/training material in particular for small developers, academia and stakeholders supporting ATMP development; participation at workshops and relevant fora.	EMA and CAT participation at European & international conferences
19	Interaction with <del>EU</del> UnethTA	Foster increased interaction between EMA and <del>EU</del> UnethTA on ATMPs to increase understanding of health technology assessment, regulatory processes and clinical added value of ATMPs.	Collaboration in the frame of the EMA- <del>EU</del> UnethTA 2017-2020 Work Plan started.





# GMO assessment for ATMPs in clinical trials



[https://ec.europa.eu/health/human-use/advanced-therapies\\_en](https://ec.europa.eu/health/human-use/advanced-therapies_en)

## ❖ GMO requirements for investigational products

- [Questions & Answers document](#)  

### Human cells genetically modified

A [Good Practice document](#)   on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified has been developed by the national competent authorities and the Commission services. This document, which builds on possibilities under the existing legislation to facilitate the conduct of clinical trials with this type of medicinal products, has been endorsed by Austria, Belgium, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Luxembourg, Malta, Portugal, Romania, Spain, Sweden and Norway. Developers that intend to conduct a clinical trial in these countries can follow the approach laid down in this document.

Moreover, a [common application form](#)   has been endorsed by the competent authorities in Austria, Belgium, Cyprus, Denmark, France, Germany, Greece, Hungary, Italy, Luxembourg, Malta, Portugal, Romania, Spain and Norway.

### Repository of national regulatory requirements

Clinical trials with medicinal products that contain or consist of GMOs (Genetically modified organisms) are subject to both clinical trials and GMO legislations.

Dissemination of information about national regulatory requirements in respect of GMO aspects is expected to facilitate the development of gene therapy medicinal products in the EU.

- A [repository of national regulatory requirements](#) has been created to this effect

## GMO assessment for ATMPs in clinical trials

- **Repository** of national regulatory requirements
- **Questions and Answers** (Q&A) addresses questions related to:
  - Authorisation of clinical trials with GMOs
    - e.g. *Is it possible to submit a single application to seek authorisation of GMO aspects for more than one clinical trial (corresponding to different phases of the same clinical development)?*
  - Scope of the GMO environment
    - e.g. *Are medicinal products that contain or consist of genetically modified human cells subject to the GMO framework?*
    - e.g. *Are medicinal products that consist of plasmids subject to the GMO framework?*

## GMO assessment for ATMPs in clinical trials

**Good practice document** on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vectors

- Builds on existing legal framework
- Provides the environmental risk assessment and data requirement
- Addressed manufacturing requirements and containment levels
- Annex: Simplified ERA for these products

**Common application form** for clinical research with human cells genetically modified by means of retro/lentiviral vectors

- This will streamline the submission of clinical trial applications with these GMOs to the environmental and pharmaceutical authorities

# Guideline on requirements for investigational ATMPs

## Content:

- Multidisciplinary guideline for all investigational ATMPs (SC, TE, GT)
- Quality, non-clinical and clinical guidance
- Considering device aspects

Focus on requirements for first-in-human and exploratory studies, but guidance for later development will also be included



# Guideline on requirements for investigational ATMPs

## Quality section

- Common text where applicable and split into cell therapy / gene therapy where needed
- Extensive guidance (stand-alone) – headings as per CTD to facilitate the development of the clinical trial application
- Specific considerations for genetically modified cells and integral medical devices are included

# Guideline on requirements for investigational ATMPs

## Non-clinical section

- Specificities in the non-clinical development pathway for ATMPs
- Defining data requirements for FIH studies and for later development phases
- Aim to introduce flexibility into the nonclinical development to foster clinical development
  - Focus on the areas where risks related to the clinical use of the product are foreseen.
  - The extent of the non-clinical data needed to support initiation of clinical development and further clinical development are dependent on the perceived risks related to the product itself, previous scientific knowledge and clinical experience with similar type of products.
  - Flexibility in GLP requirements for ATMPs

# Guideline on requirements for investigational ATMPs

## Clinical section

- Specific challenges to design & conduct of clinical trials involving ATMPs
- Early Exploratory Phase
  - Population
  - First dose in Human clinical trials
  - Dose finding & dose escalation, PK, PD, Safety Objectives
- Confirmatory Phase
  - Trial design, study population, protocol content
  - Assessment of efficacy & safety; Long-term follow-up



## Conclusions

- ATMP Regulation provides a clear regulatory framework for ATMP developers
  - GTMP, CTMP and TEP have been approved
- GMP and GCP specific for ATMP
- 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)
  - Substantial ATMP pipeline (PRIME, SA)
- ATMP developers need support from authorities (before, during and after MAA)



## Some recommendations to SME developers (of ATMPs)

- Seek scientific support from authorities
  - Make strategic use of all EMA tools at key stages of product development: ITF, SA, Certification, PRIME
- Parallel EMA-HTA SA
  - Initial evidence generation for MAA/reimbursement, and post licensing evidence generation (PA studies, Registries), or broad advice
  - ATMPs, likely to be high impact (either cost or complexity), may have small populations and/or complex development plan → parallel advice is even more highly recommended.



# Thank you for your attention

## Further information

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