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CURE THROUGH INNOVATION

# Clinical development challenges and regulatory requirements in gene therapy - Genethon experience and challenges in Europe harmonization

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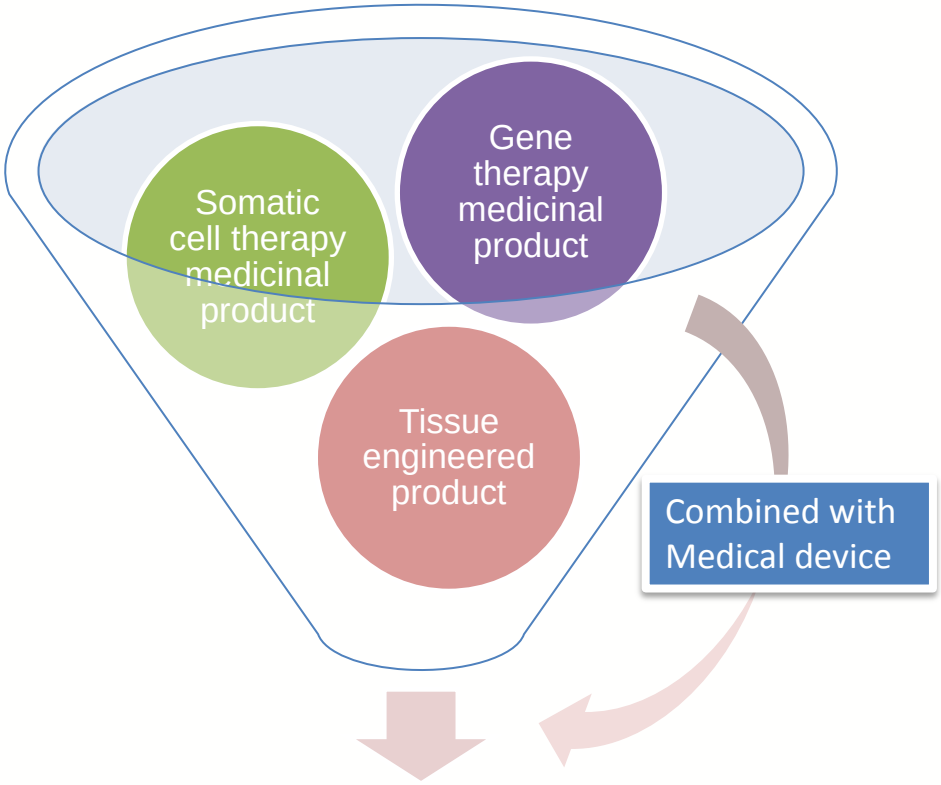
# Advanced Therapy Medicinal Product (ATMP)

## Medicinal Product

**EU Directive 2001/83**: Medicinal Products for human use (ATMP: part IV of annex I)

## Biological Medicinal Product




## ATMP

**EU Regulation 1394/2007**: Advanced Therapy Medicinal Products

# Gene Therapy Medicinal Product (GTMP)

*Directive 2001/83 – part IV- amdt 2011*

Gene therapy medicinal product means a **biological medicinal product** which has the following characteristics:

(a) it contains an active substance which contains or consists of a **recombinant nucleic acid** used in or administered to human beings with a view to **regulating, repairing, replacing, adding or deleting a genetic sequence**;

**AND**

(b) its **therapeutic, prophylactic or diagnostic effect** relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

**Gene therapy medicinal products shall not include vaccines against infectious diseases**.

# Somatic Cell Therapy Medicinal Product

*Directive 2001/83 – part IV- amdt 2011*

Somatic cell therapy medicinal product means a **biological medicinal product** which has the following characteristics:

(a) contains or consists of cells or tissues that have been **subject to substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are **not intended to be used for the same essential function(s) in the recipient and the donor**;

**AND**

(b) is presented as having properties for, or is used in or administered to human beings with a view to **treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues**.

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# Tissue Engineered Product

***Regulation 1394/2007 – art.1 b)c)***

‘Tissue engineered product’ means a product that:
(a) have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved.
(b) are not intended to be used for the same essential function or functions in the recipient as in the donor
(c) is presented as having properties for, or is used in or administered to human beings with a **view to regenerating, repairing or replacing a human tissue**.

# Additional Regulation in ATMPs development

## GMO

- EU 2001/18 related requirements
- Autorisation for dissemination (R&D, Manufacturing, clinical trial, MAA)

## Biological Material

- Material for process validation
- Autorisation for importation, storage, manipulation of biological samples

# 7 EU approved ATMPs (1)

ATMPs are authorised under the centralised procedure

| Product | Description | indication | Class | Autorisation |
|---|---|---|---|---|
| Chondroselect (Tigenix) | characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins | Cartilage Diseases | TEP | 2009 Withdrawn |
| Glybera (UniQure) | alipogene tiparvovec (AAV1) | Hyperlipoproteinemia Type I | GTMP | 2012, O, E |
| MACI (Genzyme) | autologous cultured chondrocytes | Fractures, Cartilage | TEP combined | 2013 Suspended |
| Holoclar (Chiesi) | ex vivo expanded autologous human corneal epithelial cells containing stem cells | Corneal Diseases | TEP | 2015, O, C |
| Provenge (Dendreon) | autologous peripheral-blood mononuclear cells including a minimum of 50 million autologous CD54+ cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor | Prostatic Neoplasms | SCTMP | 2015 Withdrawn |
| Imlygic (Amgen) | oncolytic virus derived from HSV-1 | treatment of melanoma | GTMP | 2015 |

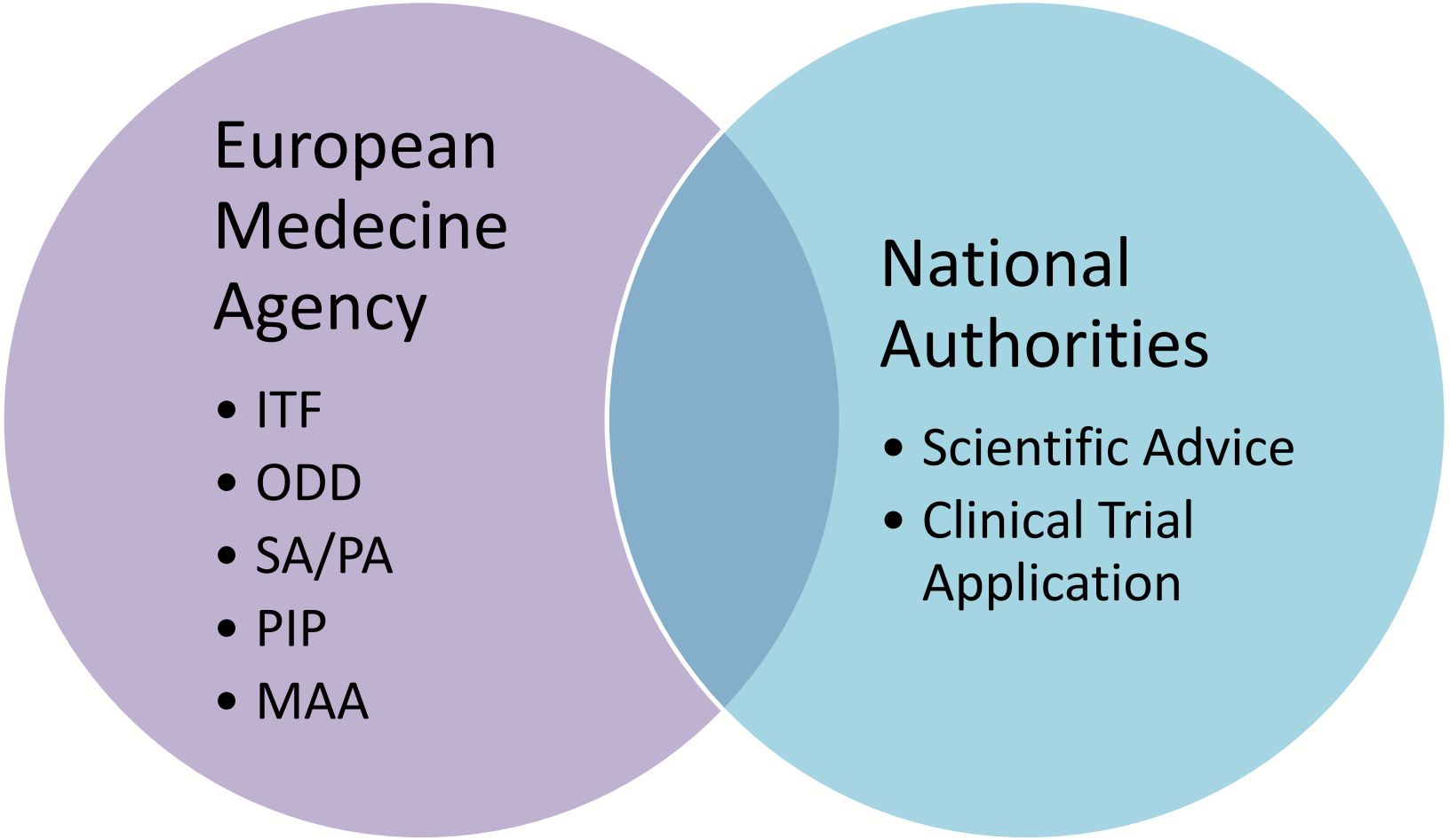
O: Orphan, E: exceptional circumstances, C: conditional approval

# 7 EU approved ATMPs (2)

| Product | Description | indication | Class | Autorisation |
|---|---|---|---|---|
| Strimvelis (GSK) | autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells | Severe Combined Immunodeficiency | GTMP | 2016, O |

O: Orphan, E: exceptional circumstances, C: conditional approval

# Interaction with Agencies in EU (1)




ITF: Innovative Task Force
ODD: Orphan Drug Designation
SA: Scientific Advice

PA: Protocole Assistance
PIP: Paediatric Investigation Plan
MAA: Marketing Autorisation Application

# EMA Innovation Task Force (ITF)

Objective:

- multidisciplinary group (scientific, regulatory and legal competences)
- **early dialogue** with applicants, informal exchange of information
- free of charge

Criteria: **voluntary** procedure

Timing: early in the development process (Proof of Concept phase)

Procedure : 60 days from start of procedure

# Classification of ATMPs

Objective: confirmation that the product is an ATMP

Criteria:

- **voluntary** procedure
- product based on genes, cells or tissues

Timing: early for borderline classification (e.g. with medical devices)

NB: EMA **publishes the outcome** of the assessment of the classification of ATMPs as summary reports

Procedure: 30 - 60 days from start of procedure

# EMA Oprphan Drug Designation (ODD)

Objectives:

- acknowledgement of medical plausibility
- market exclusivity (10 years after MAA)
- fees reduction for Protocol assistance (75%), MAA, inspection

NB: fee reduction for SA in case of ATMP (65%) and for paediatric product (100%)

Criteria : **voluntary** procedure

- life-threatening or chronically debilitating;
- prevalence of the condition in the EU ≤ 5 in 10,000
- no current satisfactory medicine

Timing: no earlier than POC establishment to just before MAA at the latest

TBD depending on ressources, confidentiality matter, etc.

Procedure : 90 days from start of procedure

# Scientific Advice: Scope of Questions

## Quality

- Manufacturing site
- Process Validation strategy
- Product testing impurity profile

## Non Clinical

- Global non-clinical program
- Design of studies, animal model

## Clinical

- study endpoints for efficacy and tolerance
- Number of patients, statistical analysis

# Paediatric Investigation Plan (PIP)

Objective:

**PIP**: Clinical development program to support authorisation of a medicinal product in children

**Waiver:** indication not applicable for children

**Deferral:** studies in children are performed after MAA for safety reasons

**-> program to be agreed by the Paediatric Committee (PDCO)**

Criteria: **mandatory** procedure (Regulation (EC) No 1901/2006 ), applicable to all the drugs for which a MAA in Europe is planned.

Timing: phase II/phase III, before pivotal study

Compliance check before MAA

Procedure: 60 or 120 days from start of procedure, modifications 30 days

# Certification Procedure

Objective: scientific evaluation of **quality and non-clinical** data

Certification is recommended by the Committee for Advanced Therapies (CAT) and issued by EMA to confirm that the **available data comply with the standards for MAA**.

Criteria: **voluntary** procedure for SME

Timing: any stage of ATMPs development

Procedure : 90 days from start of procedure