Infarmed 30 Anos
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.
A PROTEGER A SUA SAÚDE

Com o Alto Patrocínio de Sua Excelência
Under the High Patronage of the President of the Portuguese Republic

O Presidente da República

EVENTO PRESENCIAL

Medicamentos de terapia avançada

10 de novembro de 2023 | 09:00 - 13:30
Auditório do INFARMED, I.P., Lisboa, Portugal

PAINEL – TRANSPOSIÇÃO DA INOVAÇÃO PARA O VALOR CLÍNICO
MODERADOR: Miguel Forte | Sociedade Internacional de Terapia Celular e Genética (ISCT)

Bruce Levine | Universidade de Pensilvânia
Luís Pereira de Almeida | Faculdade de Farmácia da Universidade de Coimbra
Isabel Vieira | INFARMED, I.P
Margarida Menezes Ferreira | Consultora independente para ATMPs

Margarida Menezes Ferreira

margaridamenezesferreira@gmail.com

2007 - 2010

Cell-Center
at the Institute for Regenerative Medicine

Português
Dansk
Deutsch
English

Início | Sobre nós | Tratamentos | Pedido de informaç

Síntese | Doenças tratadas | Resultados | Glossário | FAQ

Related topics
ELA
Alzheimer
Autismo
Doenças cardiovasculares
Paralisia cerebral
Diabetes
Erectile dysfunction
Síndroma d
Degeneraç
Esclerose m
Osteoartrit
Parkinson
Lesões da
Paralisia ce

Tratamento com células estaminais da esclerose l
amiotrófica

Introdução

Se você ou um familiar seu sofrem de ELA, sabe provavelmente que
cura. A esperança média de vida a partir do seu diagnóstico é 2 - 5 ano

A Esclerose lateral amiotrófica (ELA), também chamada de doença de L
uma doença neurodegenerativa que afecta as células nervosas no c
espinal medula. Os neurónios motores vão do cérebro para a espinal

Regenecell®
Bringing bioscience to life™

हिन्दी
USA/Canada Toll Free: 1-800-655-5844
Intl Tel: +27 21 712 1824
Follow us on facebook

Home | About Us | Stem Cells | Treatments | Location | Evaluation | Contact | Links

Monday 17 May 2010 | World News feed

Log in | Register now

Cerebral Palsy - Stem Cells Treatment in China
Tiantan Puhua Hospital - Stem Cells Treatment Center for Neurological Disorders
click for more information
www.StemCellsPuhua.com/_Contact_Us

ough Knowledge
expectations, we are inspired to

Telegraph.co.uk

Home | News | Sport | Finance | Lifestyle | Comment | Travel | Culture | Tec

UK | World | Politics | Celebrities | Obituaries | Weird | Earth | Science | Health News

USA | Barack Obama | Asia | China | Europe | Australasia | Middle East | Africa

HOME > NEWS > WORLD NEWS

Delhi stem cell jabs 'help woman walk aga

By Peter Foster in New Delhi and Nic Fleming
Published: 12:01AM BST 14 Apr 2007

Sonya Smith learns to walk again at the Indian clinic

An Australian woman who was told she would never walk again after a car accident has claimed to be on her way to recovery after embryonic stem cell treatment from an Indian doctor.

Share
Digg submit
0 tweet
Email
Text Size

World News
News

Ads by Google
Stem Cell Treatment
New Delhi Girl
Fortis Delhi

VISÃO
13-05-2010
SOCIEDADE SAÚDE

with
the
and

Pioneira, mas duvidosa

Uma clínica, em Cascais, já está a fazer transplantes com células estaminais – usando uma técnica cientificamente controversa. As autoridades desconheciam tal actividade

POR POR SARA SÁ

transplante do género. Através de uma injecção no espaço epidural (na coluna), recebeu uma das três doses de células incluídas no pacote que comprou.

Christa Lancastre, a mulher do cirurgião Jaime Freitas, e directora de *marketing* da clínica, foi a responsável por trazer para Portugal a técnica desenvolvida pela empresa alemã Ticeba, que

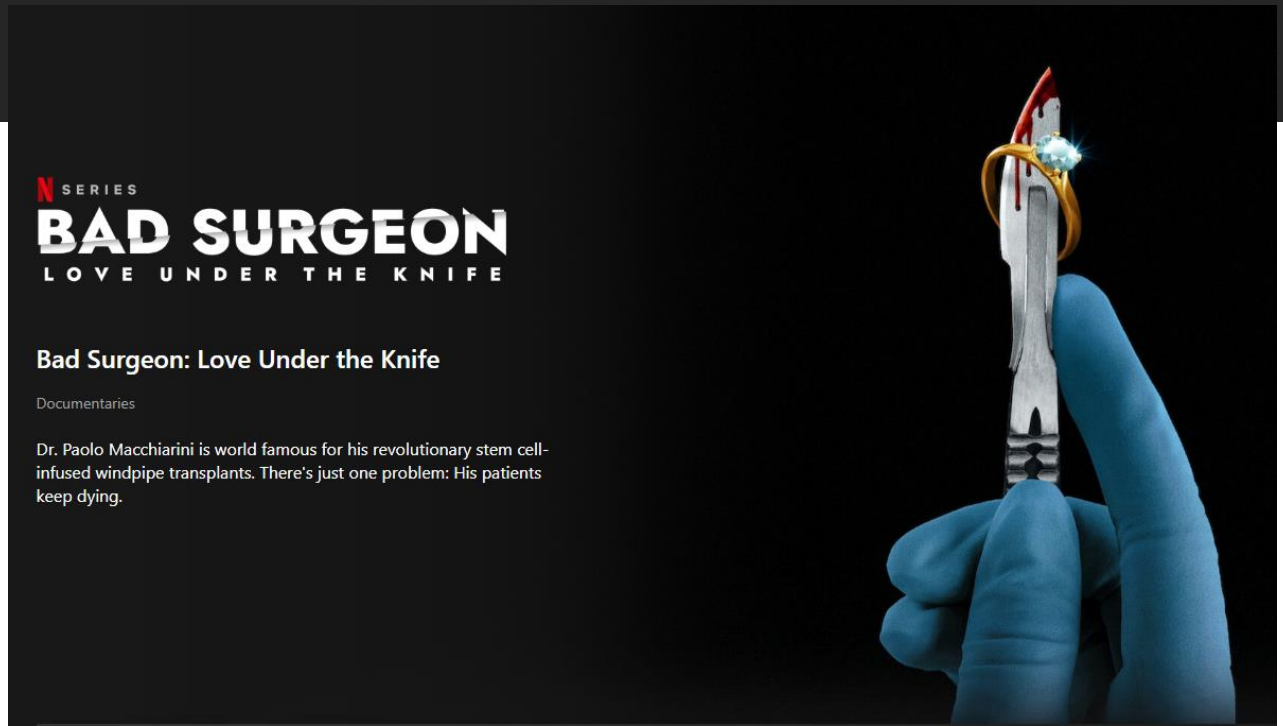
– free for four weeks.

SCIENCEINSIDER | PEOPLE & EVENTS

Transplant surgeon sentenced to prison for failed stem cell treatments

Paolo Macchiarini found guilty of gross assault against three patients on whom he tested synthetic tracheae

21 JUN 2023 • 8:20 AM ET • BY GRETCHEN VOGEL



Cardiac repair – non manipulated cells
Can conclusions be drawn from experience?

European Journal of Heart Failure (2016) **18**, 133–141
doi:10.1002/ejhf.422

REVIEW

Cell-based therapies for cardiac repair: a meeting report on scientific observations and European regulatory viewpoints

Martina Schüssler-Lenz[1,2†*], Claire Beuneu[1,3†], Margarida Menezes-Ferreira[1,4†], Veronika Jekerle[5†], Jozef Bartunek[6], Steven Chamuleau[7], Patrick Celis[1,5], Pieter Doevendans[1,8], Maura O'Donovan[1,9], Jonathan Hill[10], Marit Hystad[1,11], Stefan Jovinge[12], Ján Kyselovič[1,13], Metoda Lipnik-Stangelj[1,14], Romaldas Maciulaitis[1,15], Krishna Prasad[16,17], Anthony Samuel[1,18], Olli Tenhunen[1,19], Torsten Tonn[20], Giuseppe Rosano[17,21], Andreas Zeiher[22], and Paula Salmikangas[1,19†]

- **non-substantially manipulated cell-based ATMPs** : flexibility via risk-based approach **– EMA published in 3 July 2017**
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/07/WC500230417.pdf

Autologous cells not substantially manipulated = no risk of tumoourigenicity = do not trigger immune response = do not pose risk of disease transmission to the recipient .

Safety concerns with impurities, microbial contamination and altered cell environment

- GMP Guide and RBA - non substantially manipulated - premises and equipment validated / authorised to process cells/tissues for transplantation no need to revalidate

LEGIS - ADVANCED THERAPY MEDICINAL PRODUCTS – ATMP
Pharma legislation under revision

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

Centralised marketing authorisations (MA) from 1/2009

CAT
Non-substantial manipulation
Long term efficacy follow up
Hospital exemption
...

COMMISSION DIRECTIVE 2009/120/EC
of 14 September 2009
amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

ATMP specific Dossier requirements for MA

Directive 2001/83/EC revised

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

- **Definitions suporting regenerative medicine TEP / Combined - medical devices**
- **Clarfying fronteers - Non-substantial manipulation to separate from transplantation**
- **Centralised MA from Jan 2009 / new Committee CAT**
- **Traceability – flow between cell donation vigilance - pharmacoviglance**
- **national system for hospital exemption for named patient and non routine**
- **Specific GMP requirements**
- **Long term efficacy follow up**
- **hESC - national prohibitions apply**
- **Incentives for SME**
- **Revise Annex 1 of Directive 2001/83/EC to establish new dossier requirements**

Directive 2009/120/EC – specific requirements for MA of ATMP's

07/03/2016
Launch

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRIME – PRIORITY MEDICINES

PRIME: in brief

Medicines eligible for PRIME must address an unmet medical need.

Preliminary data must be available showing the potential to address this need and bring a major therapeutic advantage to patients.

EMA will provide early and enhanced support to optimise the development of eligible medicines, speed up their evaluation and contribute to timely patients' access.

Special support for SMEs and academia

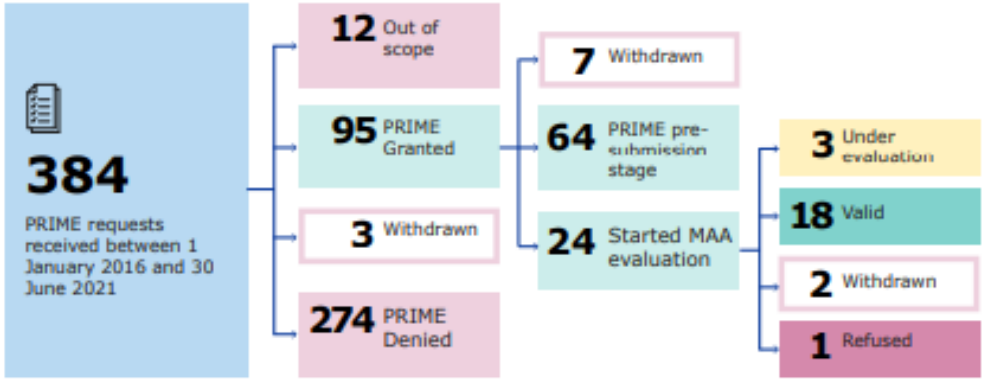
Micro-, small- and medium-sized enterprises (SMEs) and applicants from the academic sector can apply for PRIME at an earlier stage of development when they have compelling non-clinical data and tolerability data from initial clinical trials. They may also request a fee waiver for scientific advice.

SMEs and academia can particularly benefit from earlier scientific and regulatory support since they often lack experience with the regulatory framework.

	Name* **MARCH 2019**	Substance type	Therapeutic area	Therapeutic indication	Type of data supporting request	Type of applicant	Date of granting PRIME eligibility
AAV	Adeno-associated viral vector containing factor IX gene variant (PF-06838435/SPK-9001)	Advanced therapy	Haematology - Hemostaseology	Treatment of haemophilia B	Nonclinical + Clinical exploratory	Other	23/02/2017
AAV	Adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene (BMN 270)	Advanced therapy	Haematology - Hemostaseology	Treatment of haemophilia A	Nonclinical + Clinical exploratory	Other	26/01/2017
AAV	Adeno-associated viral vector serotype 5 containing human factor IX gene or variant (AMT-060, AMT-061)	Advanced therapy	Haematology - Hemostaseology	Treatment of severe haemophilia B	Nonclinical + Clinical exploratory	SME	21/04/2017
AAV	Adeno-associated viral vector serotype 8 containing the human MTM1 gene (AT132)	Advanced therapy	Other	Treatment of X-linked Myotubular Myopathy	Nonclinical + Clinical exploratory	SME	31/05/2018
AAV	Adenovirus associated viral vector serotype 8 containing the human CNGB3 gene (AAV2/8-hCARp.hCNGB3)	Advanced therapy	Ophthalmology	Treatment of achromatopsia associated with defects in CNGB3	Nonclinical + Tolerability first in man	SME	22/02/2018
LENTI/RETRO	**Autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene (OTL-300)**	Advanced therapy	Haematology-haemostaseology	Treatment of transfusion-dependent β-thalassemia	Nonclinical + Clinical exploratory	SME	20/09/2018
LENTI/RETRO	Autologous CD4 and CD8 T cells transduced with lentiviral vector containing an affinity-enhanced T cell receptor to target the cancer-testis tumour antigen NY-ESO-1 (NY-ESO-1c259T)	Advanced Therapy	Oncology	Treatment of HLA-A*0201, HLA-A*0205, or HLA-A*0206 allele positive patients with inoperable or metastatic synovial sarcoma who have received prior chemotherapy and whose tumour expresses the NY-ESO-1 tumour antigen	Nonclinical + Clinical exploratory	Other	21/07/2016
LENTI/RETRO	Autologous CD4+ and CD8+ T cells Expressing a CD19-Specific Chimeric Antigen Receptor (JCAR017)	Advanced therapy	Oncology	Treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL)	Nonclinical + Clinical exploratory	Other	15/12/2016
LENTI/RETRO	Autologous haematopoeitic stem cells transduced with lentiviral vector Lenti-D encoding the human ATP-binding cassette, sub-family D (ALD), member 1 (ABCD1) from cDNA	Advanced therapy	Neurology	Treatment of cerebral adrenoleukodystrophy	Nonclinical + Clinical exploratory	Other	26/07/2018
LENTI/RETRO	Autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor (CAR) for B-cell maturation antigen (BCMA) (JNJ-68284529)	Advanced therapy	Oncology	Treatment of adult patients with relapsed or refractory multiple myeloma, whose prior regimens included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on the last regimen	Nonclinical + Clinical exploratory	Other	28/03/2019
LENTI/RETRO	**Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (KTE-X19)**	Advanced therapy	Oncology	Treatment of adult patients with relapsed or refractory mantle cell lymphoma	Nonclinical + Clinical exploratory	Other	31/05/2018
LENTI/RETRO	Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains (bb2121)	Advanced Therapy	Oncology	Treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody	Nonclinical + Clinical exploratory	Other	09/11/2017
HSV	Genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII (KB103)	Advanced therapy	Dermatology	Treatment of Dystrophic Epidermolysis Bullosa	Nonclinical + Clinical exploratory	SME	28/03/2019

PRIME start 4/16 to 6/21

Figure 1. PRIME eligibility requests received



2023 –granted 124
47% ATMP

Figure 2. Outcome of PRIME eligibility request

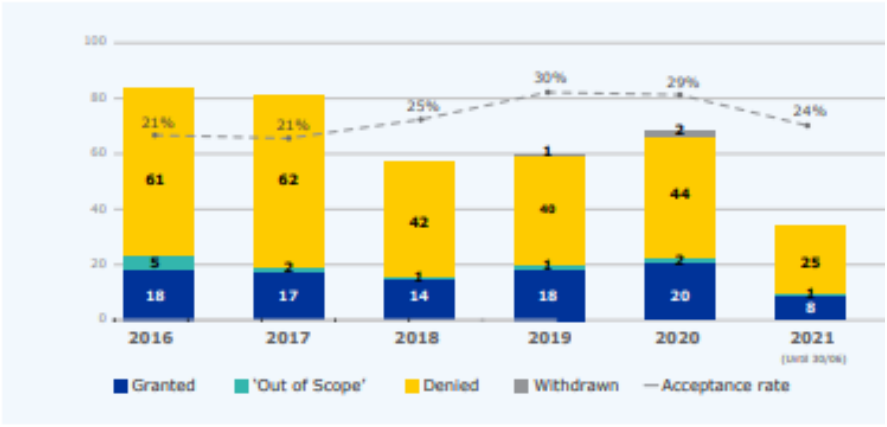
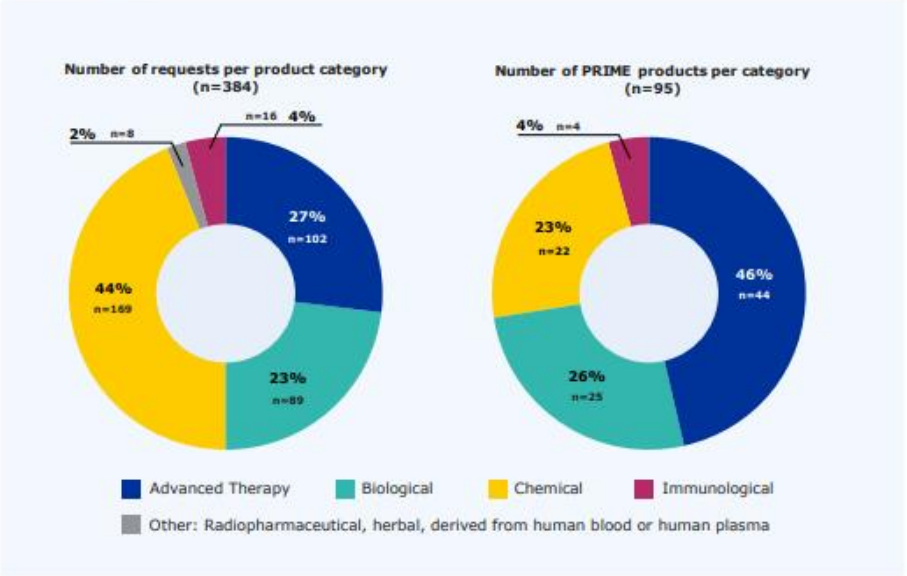


Figure 4. Product category



https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

Market Authorisation Applications
Approved - CAT 2009 - 1T 2023

PRIME

	Holoclar - limbal stem cell deficiency, 2015
	Imlygic - advanced melanoma, 2015
ORPHAN	**Strimvelis** - ADA-SCID, 2016
	Spherox - for cartilage repair < 10 cm^2, 2017
	Alofisel - complex anal fistulas in Crohn's disease, 2018
	Kymriah - children + adult <25yo ALL and adult DLBCL, 08/2018
	Yescarta - adult DLBCL and PMBCL, 08/2018
ORPHAN	**Luxturna** - children and adult retinal dystrophy biallelic RPE65 mutations, 09/2018
ORPHAN	**Zolgensma** – Spinal muscular atrophy 5/2020
ORPHAN	**Libmeldy** - children with metachromatic leukodystrophy (ARSA gene MLD), 12/2020
ORPHAN	**Tecartus** – Adult Mantle Cell Lymphoma, 12/2020
ORPHAN	**Abecma** – Multiple myeloma, 8/2021
ORPHAN	**Carvykti** – relapsed /refractory Multiple Myeloma 3/2022
ORPHAN	**Breyanzi** – DLBCL, PMBCL, FL3B 4/2022
ORPHAN	**Upstaza** – severe aromatic L-aminoacid decarboxylase (AADC) deficiency 7/2022
ORPHAN	**Roctavian** – severe Hemophilia A 8/2022
	Ebvallo – EBV lymphoproliferative disease after transplantation 12/2022
ORPHAN	**Hemgenix** – Hemophilia B 2/2023

Market Authorisation Applications

WITHDRAWN

CAT 2009 - 1T 2023

APPROVED AND LATER WITHDRAWN:

ChondroCelect - for cartilage repair, 2009 *(withdrawn 06/2016)

MACI - for cartilage repair, 2012 *(closure of EU manufacturing site 09/2014)

Provenge - advanced prostate cancer, 2013 *(withdrawn 05/2015)

RARA **Glybera** - LPL deficiency, 2013 ..... withdrawn 10/2017

Zalmoxis - high-risk haematological malignancies (adjunctive to HSCT), 2016 (withdrawn 6/2020)

RARA **Skysona** – Cerebral adrenoleukodystrophy 9/2021 (withdrawn 11/2021)

RARA **Zynteglo** – β Thalassemia - >12yo, non β0/β0, 03/2019 (withdrawn 11/2022)

PRIME **Market Authorisation Applications under assessment (2023)**

PF-06838435/SPK-9001 (Fidanacogene elaparvovec)
Haemophilia B (PRIME start 23 February 2017)

CTX001 (Autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the BCL11A gene) – EXA-CEL
Sickle cell disease (PRIME start 17 September 2020)
transfusion-dependent β-thalassemia (PRIME start 22 April 2021)

Gene Editing

- DNA is inserted, deleted, or replaced in the genome of an organism using site-specific nucleases
- Nucleases create site-specific double strand breaks (DSBs) at desired locations in the genome
- Induced DSBs are repaired through non-homologous end-joining (NHEJ) or homology directed repair (HDR)
- Resulting in targeted mutations (edits)

Base editing - NEW
direct conversion of A, C, G, or T into another, without making double-strand breaks

use of base editors that combine a catalytically impaired Cas9 protein with a cytidine or adenosine deaminase enzyme.

Prime editing - NEW
addition, deletion, or substitution of genetic material, without making double-strand breaks.

This technique uses a prime editor that is a fusion of a catalytically impaired Cas9 protein with a reverse transcriptase enzyme.

ATMP – Major Developments

https://ec.europa.eu/health/human-use/advanced-therapies_en

EU Framework for Advanced Therapies

The EU's Regulation on advanced therapies, is designed to ensure the free movement of advanced therapy products within Europe, to facilitate access to the EU market, and to foster the competitiveness of European companies in the field, while guaranteeing the highest level of health protection for patients.

GMP for ATMPs

The European Commission adopted Guidelines on Good Manufacturing Practice (GMP) specific for Advanced Therapy Medicinal Products (ATMP) in November 2017. The Guidelines provide a specific GMP framework that is adapted to the specific characteristics of ATMP.

•Guidelines on Good Manufacturing Practices (GMP)

GMO requirements for investigational products

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

Action Plan on ATMPs

The Commission services and the European Medical Agency (EMA) have launched a joint action plan to foster the development of advanced therapy medicinal products (ATMPs), with the aim of streamlining procedures and better addressing the specific requirements of ATMP manufacturers.

The concept of similarity in an ATMP setting

This Q&A document

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

To foster ATMP development in the EU - changes introduced :

- **GMP for ATMP – EC published in 22 November 2017**
- **Non-substantially Manipulated Cell-based ATMPs** : flexibility via risk-based approach **– EMA published in 3 July 2017**
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/07/WC500230417.pdf
- **Revised overarching Gene Therapy Guideline - adopted Feb 2018**
- **Application of GLP through development – EMA published in Jan 2017**
  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/07/WC500231181.pdf
- **Revise definition for Orphan Designation – EC published 28 May 2018**
- **Q&A on Comparability –published end 2019**
- **Revision 1 GM Cell Guideline – effective June 2021**
- **Revision 1 of Safety and Efficacy Follow-up and Risk Management Guideline - consultation ended Q2/18 – under revision**
- **ATIMP Guideline - consultation ended Q4/18 – extensive revision awaited**

European Commission

Public Health

26 April 2023

Reform of the EU pharmaceutical legislation

https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

- Proposal for a Regulation EN ••• of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

- Proposal for a Directive EN ••• of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

Proposal 1st reading at the European Parliament

Revision of **Pharma Regulation** and ATMPs: CONCERNS

Disappearance of CAT – will CHMP follow adaptations needed for these particularly complex MP?

CAT was instrumental :

- to set GMP for ATMPs (specificities such as administration of OOS, decentralised manufacturing, more agile provisions as for testing on importation etc),
- ATMP classification and respective guidance minimizing possible impact with SoHO Authorities
- guidance on minimally manipulated cell for use in different function,
- requirements for GLP studies,
- orphan designation principles required for gene and cell based therapy products,
- definition of new active substance,
- post market surveillance and specificities of risk management plan

BWP not fully representative of EU MS:

- Quality assessment not fully discussed and endorsed by all MS, implications for limiting OMCL and inspection exposure both acting at national level

Revision of **Pharma Regulation** - **SUPPORT**

Classification as MP and ATMP - Article 61 gives the mandate to the Agency to recommend classification - MS disagreement is possible.

GMO in CT - Article 177 revises Clinical Trial Regulation 534/2014:

- ERA filed via EU portal CTIS
- centralised assessment of GMO according to Directive 2001/18 on deliberate release by CHMP.
- Consultation of Environment authorities only for 1st in class
- Guidance by the Commission through delegated act:

> The delegated act by the Commission shall specify the content of the ERA taking into account the common application forms and Good Practice Documents for genetically modified human cells and for adeno-associated viral vectors that were published by the Agency.

Revision of **Pharma Directive** and ATMPs:

Article 2 – reintroduces authorisation under **HOSPITAL EXEMPTION** for ATMPs – competition between national vs centralized products remain – **CONCERN**

Article 26 – **additional master files** for substances not chemical and participating in the process possible – certification by Agency with inspection – **WELCOME**

Article 81 . Regulatory data protection – reduced to 6 + 2 years – INDUSTRY CONCERN

Article 153 . QP role – **testing on importation** required but relieved if "appropriate arrangements have been made by the Union with the exporting country to ensure that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union" – MEANING?

> *GMP for ATMPs 11.17. accepts that it may be justified to rely on testing performed in the third country in cases where the limited amount of material available (e.g. autologous products) or the short shelf-life impedes double release testing. In such cases, the testing in the third country should be conducted in GMP-certified facilities (in the case of authorised ATMPs) or under GMP conditions equivalent to those applicable in the EU (in the case of investigational ATMPs).*

New SoHO REGULATION

EUROPEAN
COMMISSION

Brussels, 14.7.2022
COM(2022) 338 final

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

Classification as MP and ATMP - The delineating criteria are set by definitions in the pharmaceutical framework and are not altered by this proposal. **OK**

Import / export as staring materials for ATMP - (Article 2.3.) the activities of SoHO release, distribution, import and export relate to SoHOs prior to their distribution to an operator regulated by the other Union legislation referred to in this subparagraph, the provisions of this Regulation shall also apply. **NOT OK -**

BEYOND what is provided in ATMP Regulation 1394/2007 recital and article 3 :
Where an advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are covered by this Regulation.

This is should be under the sole responsibility of manufacturer to qualify starting materials – GMP issue and inclusion criteria confidentiality for IMP


Thank You !
Questions?