



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Advanced Therapy Medicinal Products: Regulatory Framework

28 November 2011

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EMA, CAT Secretariat

An agency of the European Union

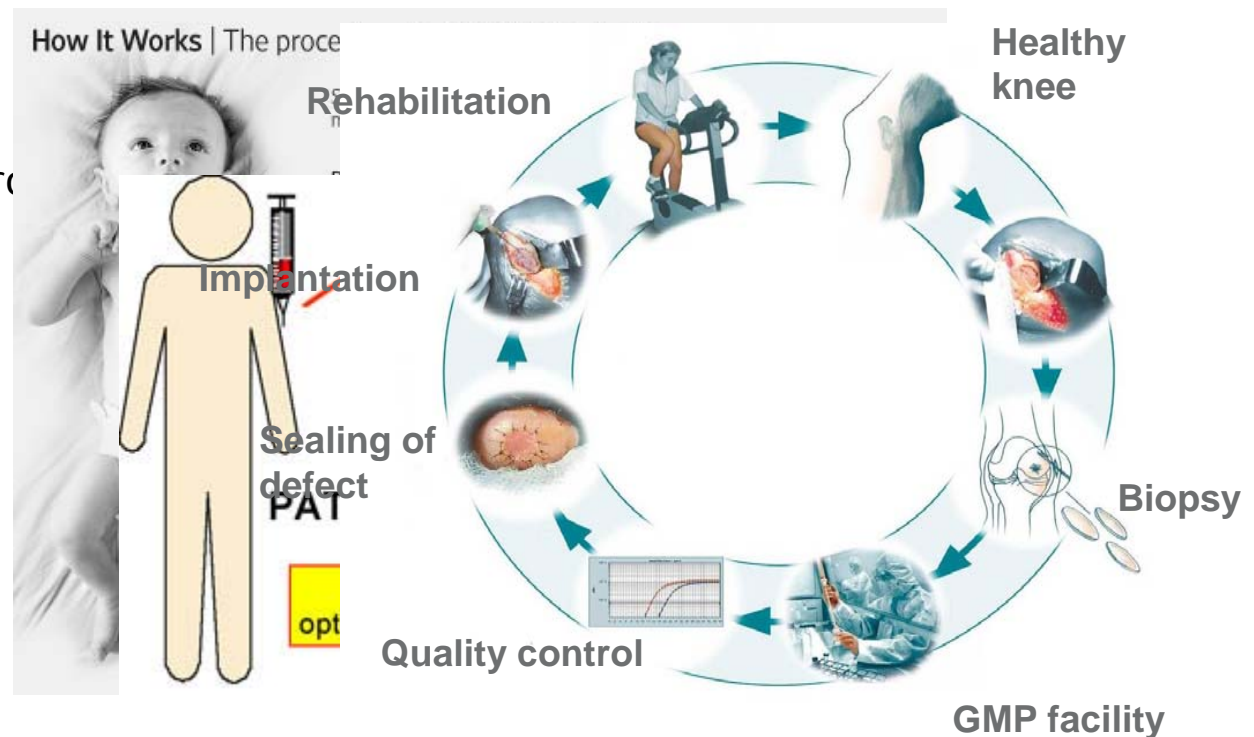




- Advanced Therapy Medicinal Products (ATMPs)
- Regulatory Framework for ATMPs
- Challenges for companies developing ATMP

What are ATMPs?

- Gene Therapy MP
- Cell Therapy MP
- Tissue Engineered Products
 - Chondrocelect



ATMPs vs Cell/Tissue preparations

- 2 Legal frameworks:
 - Non-substantially manipulated cells/tissues: Tissue and Cell Directive (2004/23/EC and implementing directives)
 - E.g. bone marrow transplants, cornea, bone
 - Engineered or substantially manipulated cells/tissues: ATMP Regulation (Reg. 1394/2007)
 - Cell therapy medicinal products
 - Tissue engineered products
 - ATMP Regulation and T&C Directive are interlinked:
 - ATMPs will have to follow T&C Directive for donation, procurement and testing.

ATMPs vs Cell/Tissue preparations

- What is 'engineered'?
 - Substantial manipulation; or
 - Not intended to have the same function in donor & recipient
 - Same concept in definitions of CTMP and TEP
- Examples
 - Mesenchymal Stem cells, extracted from bone marrow and cultured (expanded) for treatment of GvHD = substantial manipulation → ATMP
 - Bone marrow for immune reconstitution (in cancer therapy after chemotherapy) = homologous use → Tissue/Cell
 - Bone marrow for cardiac repair = not substantial manipulation, but non-homologous use → ATMP

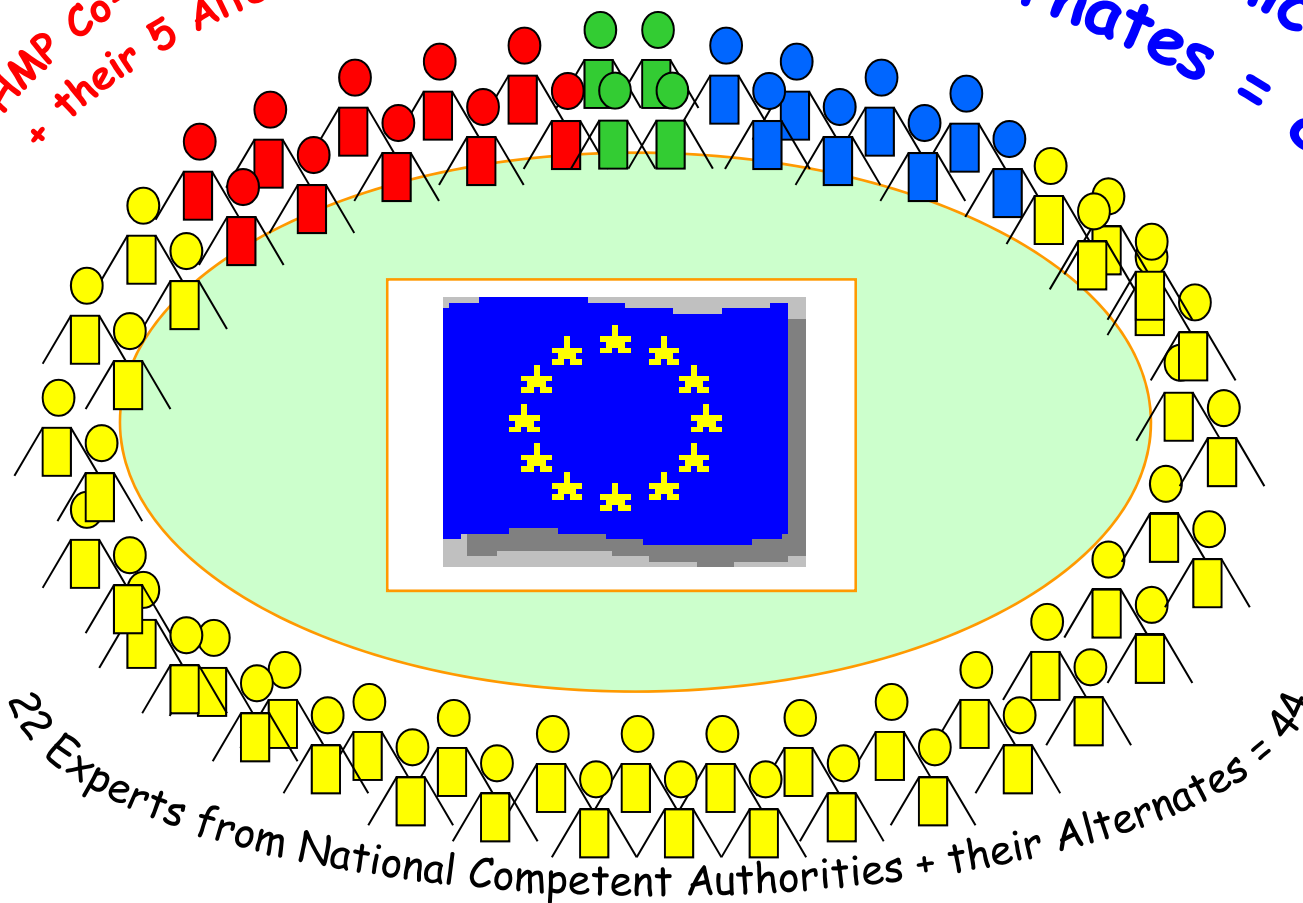
- Advanced Therapy Medicinal Products (ATMPs)
- **Regulatory Framework for ATMPs**
 - **Committee for Advanced Therapies**
 - **Marketing authorisation (licencing) procedure**
 - **ATMP classification and ATMP certification**
 - **Hospital exemption**
- Challenges for companies developing ATMP

CAT composition

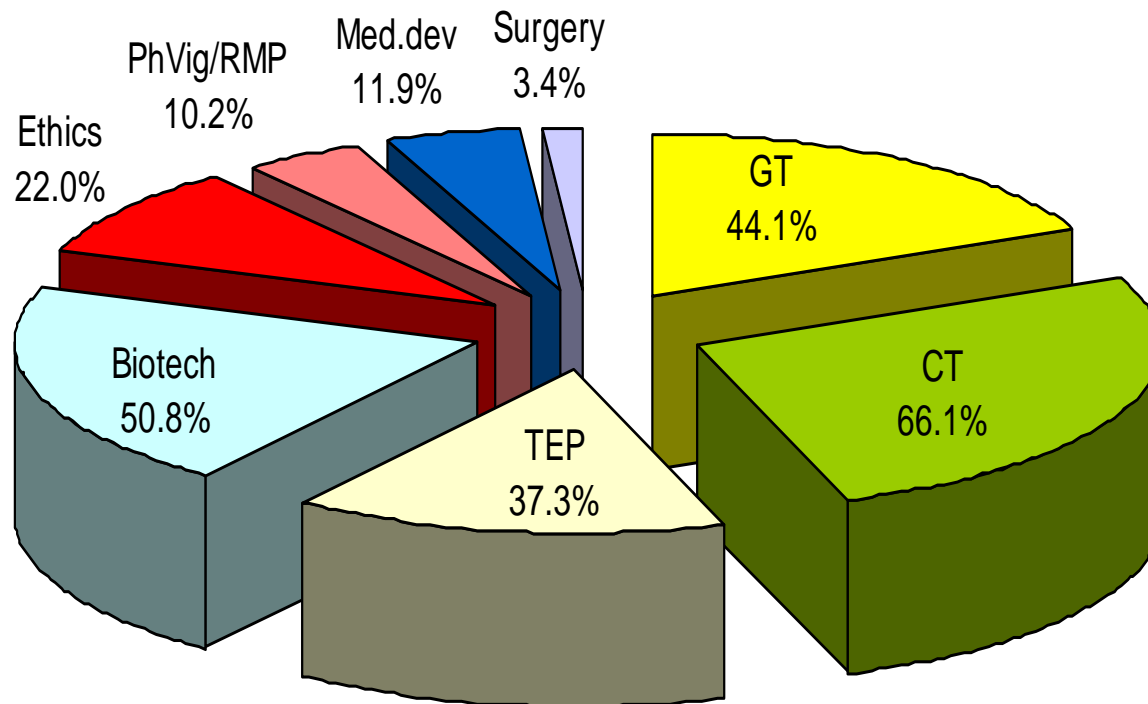
CHMP members or
CHMP Co-Opted Members (5)
+ their 5 Alternates = 10

1 NW + 1 IC
+ their Alternates
= 4

2 Patient and 2 Clinicians
+ their alternates = 8



Percentage of CAT members with a given expertise



■ GT ■ CT □ TEP □ Biotech ■ Ethics ■ PhVig/RMP ■ Med.dev □ Surgery

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**

ATMP Evaluation procedure

ATMPs will follow the Centralised procedure (mandatory scope) → single MA (marketing authorisation = license) for entire EU:

- 210 Day procedure
 - Scientific opinion from CAT → to CHMP* (for adoption) → to Commission
- Evaluation by two independent teams
 - Rapporteur and CoRapporteur team (from CAT)
- All scientific discussions and adoption of key documents at CAT

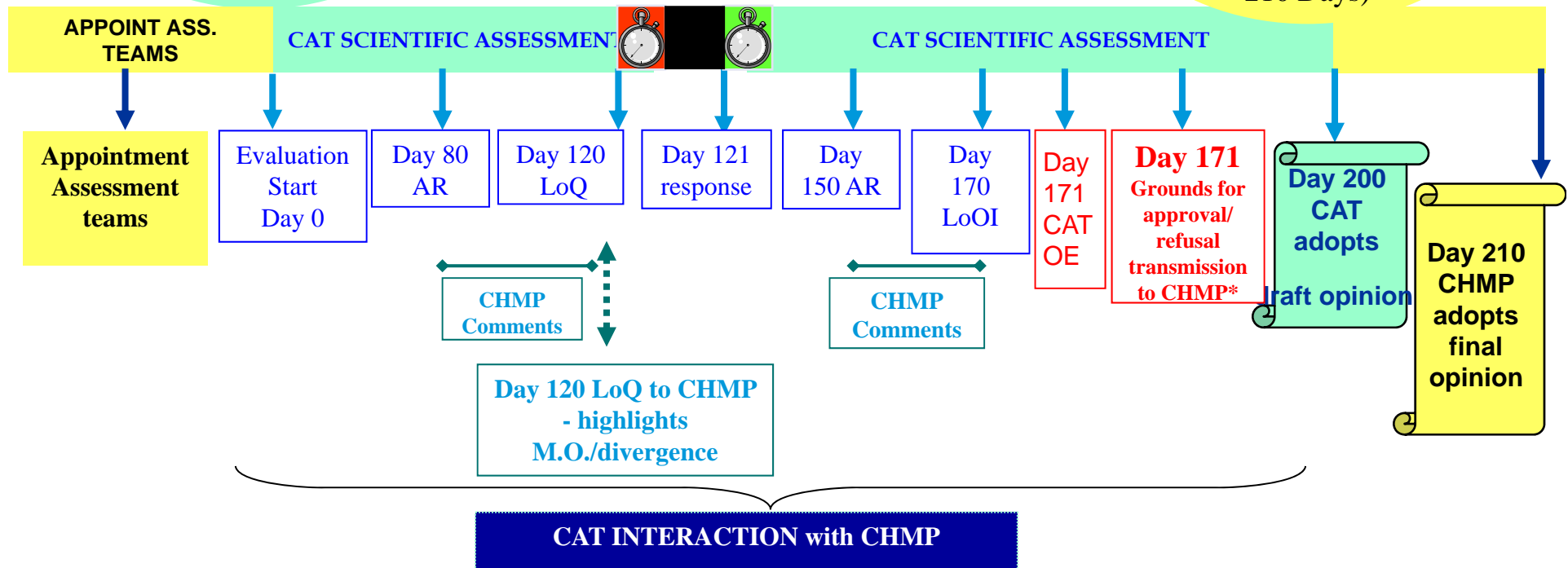
ATMP evaluation procedure builds on full transparency between CAT and CHMP to avoid divergent views.

ATMP EVALUATION

CAT
 * **Scientific Assessment**
 (incl. Day 80/150 AR, Adoption LoQ, LoOI)
 * **Adopt draft opinion**
 (Day 200)

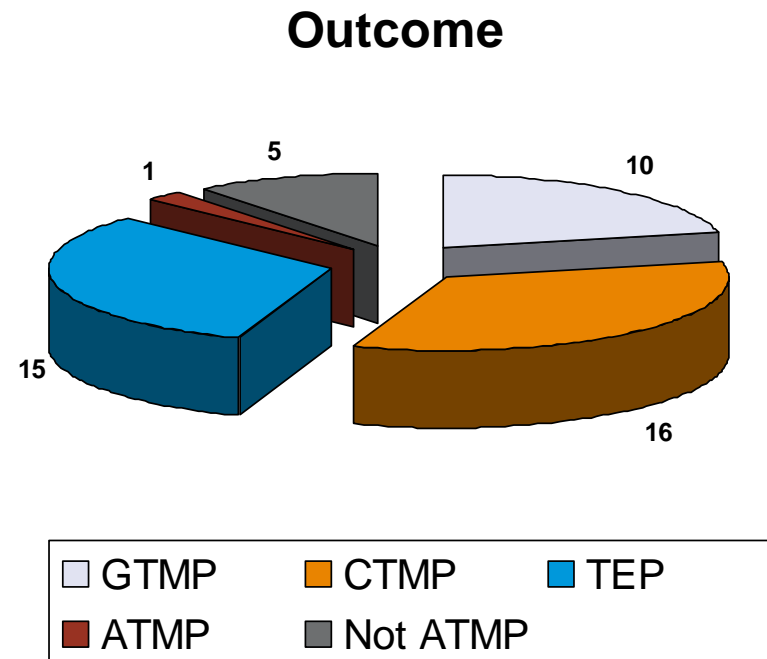
CHMP
 * **Appoint Rapporteur**
 [Art. 62(1) Reg. 726/2004]

 * **Adopt FINAL CHMP opinion** (by 210 Days)






Classification procedure for ATMPs

- Incentive
- Open to all applicants
- Scientific Recommendation from CAT on the Regulatory Classification of their ATMP
- 60-day procedure (often shorter)
- Publication of summary information on classification
- 47 procedures finalised



(Status Sept 2011)

Classification procedures: publication of summaries on EMA website

Product description	Therapeutic area	Classification	Date
 Autologous mesenchymal stem cells (MSC)	Intended for the treatment of chronic heart failure symptoms by improvement in exercise capacity of NYHA class II and III chronic heart failure patients receiving standard therapy	Tissue-engineered product - not combined	29/07/2011
 Human islets of Langerhans	Intended for: Autologous: Post pancreatectomy for benign pancreatic pathologies Allogeneic: Treatment of severe forms of type 1 diabetes	Not an advanced therapy medicinal product	29/07/2011
 Allogeneic bone-marrow derived osteoblastic cells	Intended for the treatment of non-union, delayed union or other bone fractures	Tissue-engineered product - not combined	01/07/2011
Live recombinant lentiviral vectors encoding HIV epitopes to be used for therapeutic HIV vaccination of HIV-1 infected patients	Infectious disease: HIV-1	Not an advanced therapy medicinal product	27/05/2011
Heterologous human adult liver-derived progenitor cells	Intended for the treatment of inborn errors of liver metabolism	Somatic cell therapy medicinal product - not combined	05/05/2011
Allogeneic human fibroblasts cultured onto a biodegradable matrix	Dermatology	Tissue engineered product - combined	04/04/2011



17 August 2011
EMA/681354/2011
Patient Health Protection

Scientific recommendation on classification of advanced therapy medicinal products

Article 17 – Regulation (EC) No 1394/2007

Disclaimer: This document is a summary for public release of a scientific recommendation on classification of advanced therapy medicinal products. The original text adopted by the Committee for Advanced Therapies (CAT) has been redacted to delete commercially confidential information.

The present scientific recommendation refers exclusively to the case as presented to the European Medicines Agency (EMA) without prejudice to future evaluations by the Agency.

This scientific recommendation is not binding and is without prejudice to any decision taken by Member State competent authorities on matters falling within their own remits.

Short descriptor (or name when available) of the proposed active substance

Autologous mesenchymal stem cells (MSC) committed to cardiovascular lineage.

Brief description of the proposed finished product.

Autologous MSC committed to cardiovascular lineage suspended in cryopreservation medium.

Proposed indication

Treatment of chronic heart failure symptoms by improvement in exercise capacity of NYHA class II and III chronic heart failure patients receiving standard therapy.

EMA/CAT comment

Consideration of Article 1(2) of Directive 2001/83/EC (definition of medicinal product – see Annex A)

- The product consists of autologous mesenchymal stem cells which can be considered a 'substance' in the meaning of the pharmaceutical legislation (in accordance with article 1(3) of Directive 2001/83/EC), administered to humans with a view of regenerating tissues.
- The product is presented as having properties for treating disease in human being.
- According to Article 1(2), the restoration, correction or modification of the physiological function is to be mediated by the substances that exert "a pharmacological, immunological or metabolic action". As the product consists of autologous mesenchymal stem cells, it can be agreed that the product acts via metabolic means.

Fulfilment of Article 2(1) of Regulation (EC) No 1394/2007 (definition of advanced therapy medicinal product – see Annex A)

- The product is intended to be placed on the market in the Member States. It will be manufactured under GMP methodologies at an external facility and is therefore regarded as manufacturing by a method involving an industrial process.
- The product can be considered as a not combined ATMP and a tissue engineered product according to the definition in Article 2(1)(b) of Regulation (EC) No 1394/2007 as:
 - it contains engineered cells according to the definition of Article 2(1)(c) second paragraph of Regulation (EC) No 1394/2007, and;
 - it is administered to human beings with a view of regenerating a human tissue;
 - it does not contain medical devices as an integral part of the product and its cellular part contains viable cells.

Based on the above considerations, it is considered that the product falls within the definition of a tissue engineered product as provided in Article 2(1)(a) of Regulation (EC) No 1394/2007.

EMA/CAT conclusion

On the basis that:

- The product contains engineered cells according to the definition of Article 2(1)(c) second paragraph of Regulation (EC) No 1394/2007, and
 - The product is administered to human beings with a view to regenerating a human tissue,
 - The product does not contain medical devices as an integral part of the product and its cellular part contains viable cells.

The EMA/CAT considers that the product falls within the definition of a **tissue engineered product** as provided in Article 2(1)(a) of Regulation (EC) No 1394/2007.

Certification procedure

- Only for SMEs
- Scientific evaluation by CAT of
 - (early) quality / development data (Module 3)
 - (early) non-clinical data (Module 4)
- 90 day procedure
- Evaluation to the scientific standards of a marketing authorisation application
 - The SME applicant will always received the evaluation report (and List of issue for future consideration)
 - If positive evaluation: Certificate by EMA
- 1 Certification procedure finalised (May 2010)
 - Bone marrow derived progenitor cells for cardiac repair

Hospital Exemption

- **ATMP Regulation (art 28.2) foresees the possibility for exemption from licensing for ATMPs that are:**
 - Manufactured on a non-routine basis
 - Under the responsibility of medical practitioner
 - Individual medical prescription for a custom-made product
 - For an individual patient
 - ➔ **Authorisation by the National Competent Authority**
 - ➔ No cross-border use
 - ➔ Note: National implementation (risk of non-uniform interpretation)

- Advanced Therapy Medicinal Products (ATMPs)
- Regulatory Framework for ATMPs
- **Challenges for companies developing ATMP**
 - **How EMA and CAT can assist companies developing ATMPs**

PERSPECTIVES

OPINION

Challenges with advanced therapy medicinal products and how to meet them

The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat

Abstract | Advanced therapy medicinal products (ATMPs), which include gene therapy medicinal products, somatic cell therapy medicinal products and tissue-engineered products, are at the cutting edge of innovation for various diseases for which there are limited or no options. They have therefore been subject to considerable interest. Under the European regulation on ATMPs, a consolidated regulatory framework for innovative medicines has recently been established. Centrally

and the European Free Trade Association (Iceland and Norway are currently represented in the CAT), as well as representatives from patient and medical associations (EMA 2). This independent committee, with a high degree of expertise in both the scientific and regulatory aspects of ATMPs, started its work in January 2009. The CAT gathers dedicated European experts to review the quality, safety and efficacy of ATMPs according to standards established by regulatory authorities, and to debate scientific developments in the field. Information on the declared scientific expertise of the

Nature Reviews Drug
Discovery, vol 9,
March 2010, 185-201

Focus – Advanced therapies

Current challenges in the development of novel cell-based medicinal products

Authors

Paula Salmikangas, Finnish Medicines Agency, Helsinki, Finland; Patrick Collis, European Medicines Agency, London, UK.

Keywords

Introduction

During the past decades, advances in biotechnology, cell biology and biomaterial technology have fostered the development of new potential therapies for diseases and tissue/organ defects for which no satisfactory treatment has been available. Since the mid 20th century, minimally manipulated human cells have been used in transplantation, especially in cancer therapies. Later on, new complex manipulated cell

Regulatory Rapporteur,
vol 8, July-August
2011, 4-7

Challenges with ATMPs

- Scientific challenges
 - Manufacturing constraints & quality issues
 - Non-clinical challenges
 - Clinical challenges

Disclaimer: ATMPs are a very diverse group of products, so the challenges listed in the next slides are only examples!

Challenges with ATMPs

Quality/manufacturing issues

- Control of all starting and raw materials
 - Human cells/tissues + any human/animal reagents (e.g serum)
 - Recombinant growth factors
 - History of cell-lines / vector constructs
- Appropriate characterisation and product testing (including potency assay*)
 - Poor definition and control of a product may directly effect safety & efficacy
 - Good control of the product is essential for manufacturing changes (e.g. product upscale)
- Manufacture in GMP environment

* Potency assay: product specific, at least semi-quantitative, linking product testing with clinical effect
/biological activity

Challenges with ATMPs

Non-clinical challenges

- What animal models to be used to test a human cell-based therapy or gene therapy product?
 - Use of a homologous model? / Disease models?/ Other relevant animal models?
 - Proof of concept studies / toxicity studies
- Dose finding studies?
- Bio-distribution studies?
 - Germ line transmission for GTMP
 - Environmental risk / Shedding studies for GTMP

Challenges with ATMPs

Clinical challenges

- Dose finding studies
 - How to find the most effective dose, e.g. for a TEP?
- Design of clinical trial
 - What is a suitable comparator?
 - Blinding might be very difficult
 - Endpoints for TEP (how to measure structure repair?)
 - Effect of concomitant treatment / surgery on Efficacy & Safety?
- Long term efficacy and safety follow-up studies

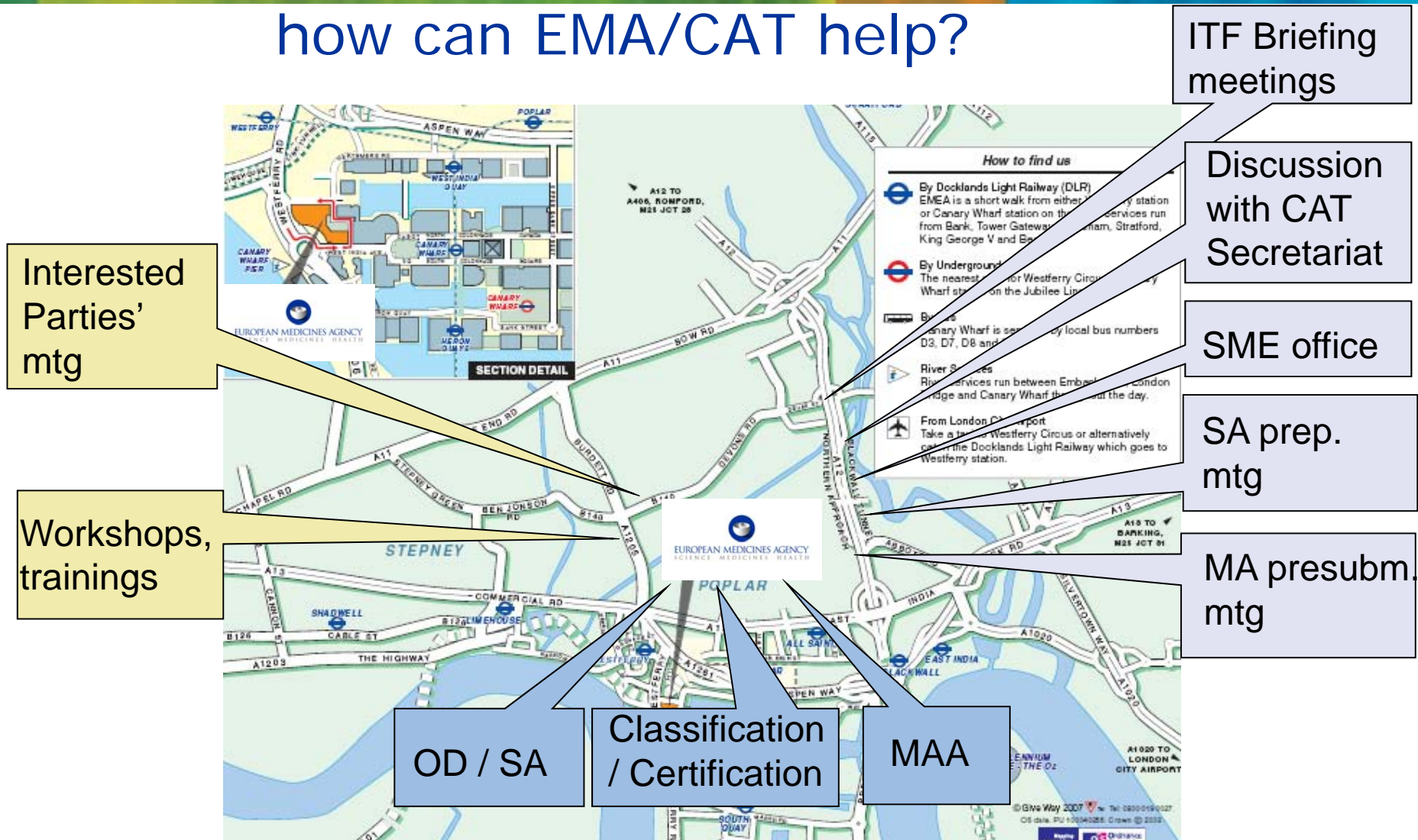
Challenges with ATMPs

- Scientific challenges
 - Yes!
- But not all challenges are scientific!
 - Regulatory issues
 - Lack of regulatory expertise
 - Resources
 - Reimbursement issues
 - Competition with 'hospital exempted ATMPs'

Challenges with ATMPs and how to meet them

- Developers of ATMPs are often not big pharma
 - SMEs
 - Academia, hospitals
 - How to reach these developers?
 - They are unaware of EMA & will not visit our website
 - They are unaware of authorisation procedures
- Publication in scientific journals
- Informal (& formal) meetings
- Presentations at scientific/regulatory conferences

Challenges with ATMPs: how can EMA/CAT help?



Interactions with CAT Secretariat

- CAT secretariat is the entry door for all ATMP classifications requests
- We can help you to sort out practicalities
- Liaison with ITF secretariat for briefing meetings
- Liaison with CAT

AdvancedTherapies@ema.europa.eu

- Use this mail for any queries on ATMP

Briefing meetings: Innovation Task Force

- Aimed at **early contacts** with companies developing innovative medicines & ATMPs
- Information on next steps
 - SME, OD, SA
 - ATMP classification / certification
- Initial discussion of scientific issues
 - Involvement of CAT or WP members
 - Not binding / high level input
 - Not to replace the Scientific Advice procedure
- Contact ITFSecretariat@ema.europa.eu



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Committee for Advanced Therapies adopts five-year work programme to foster development of advanced therapies



Press release

Committee for Advanced Therapies adopts five-year work programme to foster development of advanced therapies

Work programme 2010-2015 aims to help bring more advanced-therapy medicines to the market

The European Medicines Agency's Committee for Advanced Therapies (CAT) has unveiled a Work Programme to 2015, intended to help increase the number of advanced-therapy medicinal products (ATMPs) that make it from the early research stage to the market.

CAT workprogramme

Why a work programme?

- CAT is a key player in the successful implementation of the ATMP Regulation
- Point of reference for guidance on scientific/technical requirements for ATMPs
- Foster innovation and research
- Contribute to promotion and protection of public health

CAT Workprogramme

- A shared vision to address challenges of ATMPs
- Being empowered to take decisions also means taking responsibilities and learn to balance
- Understand the environment
 - Identify issues and hurdles
- Provide adequate actions / tools to overcome barriers to translation
- Guidelines in line with scientific progress
 - Is it the product that has to stretch to the guideline, or is it the guideline that has to be realistic for the product?

CAT Workprogramme Objectives

- ▶ **1.** To successfully respond to implementation of the provisions of Article 29 of Regulation (EC)1394/2007: assessment of products legally on the EU market

- ▶ **2.** To facilitate development of ATMP and access to registration procedure
 - **Strengthen dialogue with Stakeholders**

- ▶ **3.** Promote the use of available regulatory procedures and introduce potential improvements

CAT Workprogramme Objectives

- ▶ **4.** To explore possibilities offered by the regulatory procedures to the ATMP field (by improving existing procedures and reflecting on alternative procedures)
- ▶ **5.** Foster innovation
- ▶ **6.** Promote access and availability to ATMP for EU patients



Thank you for your attention

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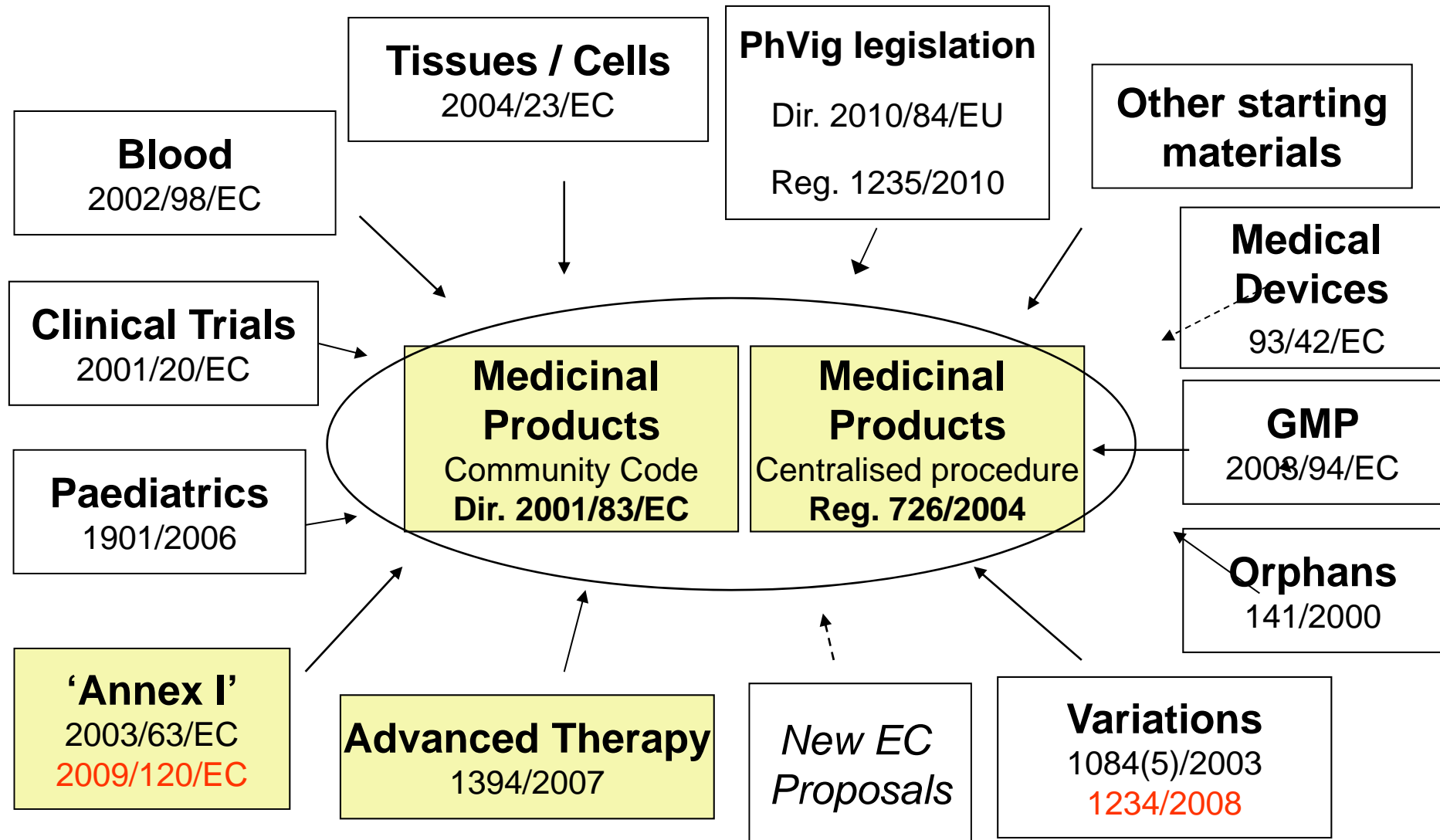
Queries: AdvancedTherapies@ema.europa.eu



Backup Slides

- EU Legal/Regulatory framework for medicinal products
- Definitions of Gene therapy medicinal product, cell therapy medicinal product and tissue engineered product
- CAT Workprogramme objectives

The EU legal/regulatory framework





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

L 102/48

EN

Official Journal of the European Union

7.4.2004

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 31 March 2004
on setting standards of quality and safety for the donation, procurement, testing, processing,
preservation, storage and distribution of human tissues and cells

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4)(a) thereof,

Having regard to the proposal from the Commission ⁽¹⁾,

Having regard to the opinion of the European Economic and Social Committee ⁽²⁾,

Following consultation of the Committee of the Regions,

- (4) There is an urgent need for a unified framework in order to ensure high standards of quality and safety with respect to the procurement, testing, processing, storage and distribution of tissues and cells across the Community and to facilitate exchanges thereof for patients receiving this type of therapy each year. It is essential, therefore, that Community provisions ensure that human tissues and cells, whatever their intended use, are of comparable quality and safety. The establishment of such standards, therefore, will help to reassure the public that human tissues and cells that are procured in another Member State, nonetheless carry the same guarantees as those in their own country.

GENE THERAPY MEDICINAL PRODUCT

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;
- (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.

- Definition in Annex I to Directive 2001/83/EC

CELL THERAPY MEDICINAL PRODUCTS

- 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;
- 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.

Definition in Annex I to Dir 2001/83/EC

Tissue Engineered product

- Contains or consist of **engineered cells or tissues**
- Presented as having properties for, or is used in or administered to humans with a view of **regenerating, repair or replacing a human tissue**

Definition of engineered cells/tissue

- Substantial manipulation; or
- Not intended to have the same function in donor / recipient

Definition in Regulation (EC) No 1394/2007 (ATMP Regulation)

CAT Work Programme Objective 1

- ▶ **To successfully respond to implementation of the provisions of Article 29 of Regulation (EC) 1394/2007: assessment of products legally on the EU market**

Know the number and kind of products legally on EU market

Reflect on the criteria for MAA assessment

Proactive dialogue with potential applicants and MSs

Report on the experience to EC and MSs in 2010-2011

CAT Work Programme Objective 2

- ▶ To facilitate development of ATMP and access to registration procedure

B) Strengthen dialogue with stakeholders:

- Draft a structured work programme tailor-made for the **specific needs of different parties** (industry, SMEs, Academia, research groups, patients' groups).
- Increase the list of **CAT Interested Parties**
- Engage in dialogue with **charity foundations and trusts** concerning products they are developing .
- Organise a **joint conference** on ATMPs involving EMA/CAT, EFPIA, EBE, EUROPABIO, Learned Societies to share clinical, scientific and regulatory expertise in the field for the benefit of all stakeholders

CAT Work Programme Objective 3

- ▶ **Promote the use of available regulatory procedures and introduce potential improvements**

Provide regular tutorial training/workshop for all stakeholders (including assessors, inspectors)

Developing an European training and education platform for SMEs and Academia

Dedicated assistance for ATMP certification submissions

CAT Work Programme Objective 4

- ▶ To explore possibilities offered by the regulatory procedures to the ATMP field (by improving existing procedures and reflecting on alternative procedures)

Fast track evaluation?

Extend incentives for SMEs to academia, hospitals, trusts and small research groups?

Because the science is evolving fast, on regular basis to screen system to identify potential changes required (and then engage in dialogue with the European Commission)

Appropriate use of follow-up efficacy system

CAT Work Programme Objective 5

► Foster innovation



Dialogue with EC DG Research

**Promote allocation of funds
for ATMP research**

**Reinforce contact with
leaders of EU projects on
ATMP**

CAT Work Programme Objective 6

- ▶ **Promote access and availability to ATMP for EU patients**

Cooperation with CTFG

Dialogue with NCA on 'hospital exemption'

Encourage development of ATMPs for unmet medical needs without alternative treatments.