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 - Role of EMA and National Competent Authorities
- Approval of ATMPs
 - What are ATMPs?
 - Centralised procedure
- Support to ATMP developers



Introductory statements

- This talk is on marketing authorisation (license) applications, not on requirements or approval of clinical trials
- I will not address the use of ATMP under national schemes such as Hospital exemption and Compassioned use schemes / Specials in UK



Role of EMA and National Competent Authorities

- Role of European Medicines Agency (EMA):
 - Authorisation of centrally authorised products (CHMP, CAT) + post marketing surveillance of MP in EU (PRAC)
 - Orphan designation (COMP)
 - Approval of Paediatric investigation plans (PDCO)
 - Scientific advice: both by EMA (SAWP) and national authorities
 - Support to developers (e.g. SMEs): both by EMA and national authorities
 - Scientific guidelines for EU prepared by EMA scientific committees

CAT = Committee for Advanced Therapies; **CHMP** = Committee for Medical Products for Human use;
PRAC = Pharmacovigilance & Risk management Committee; **COMP** = Committee for Orphan Medicinal
product; **PDCO** = Committee for Paediatric medicinal products; **SAWP** = Scientific Advice Working Party

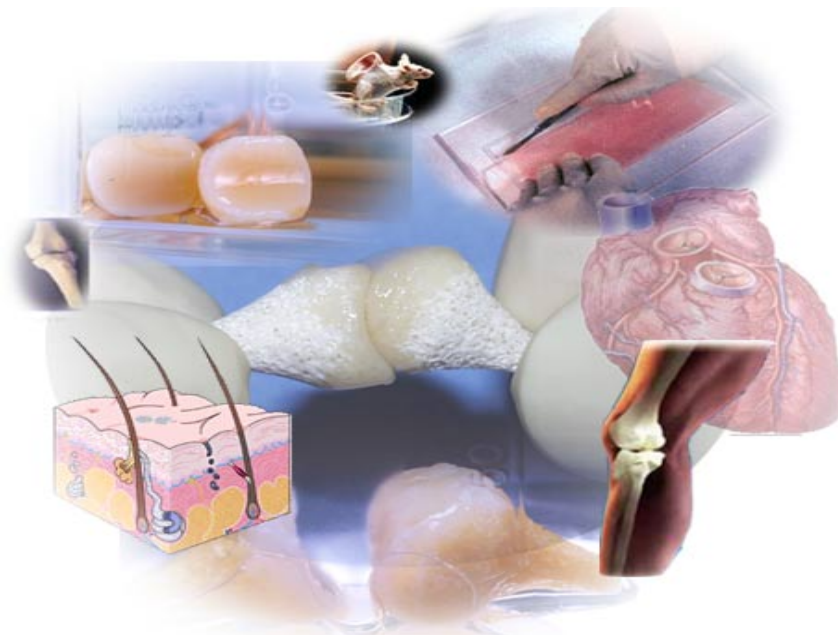


Role of EMA and National Competent Authorities

- Role of member states (eg MHRA)
 - Approval of non-centrally authorised MP
 - Approval of clinical trials
 - Manufacturing licenses (GMP)
 - Inspections (GLP, GCP, GMP)
 - Pricing and reimbursement

Advanced therapy Medicinal Products

Regulation (EC)
No 1394/2007



**Cell Therapy
Medicinal Products
(CTMP)**

**Gene Therapy
Medicinal products
(GTMP)**

**Tissue Engineered
Products (TEP)**

Effective
30 December 2008

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf



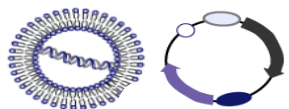
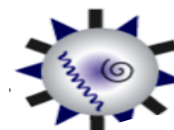

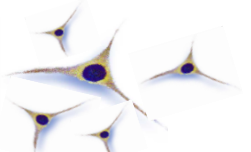
GENE THERAPY MEDICINAL PRODUCT

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.

Gene Therapy Medicinal Products

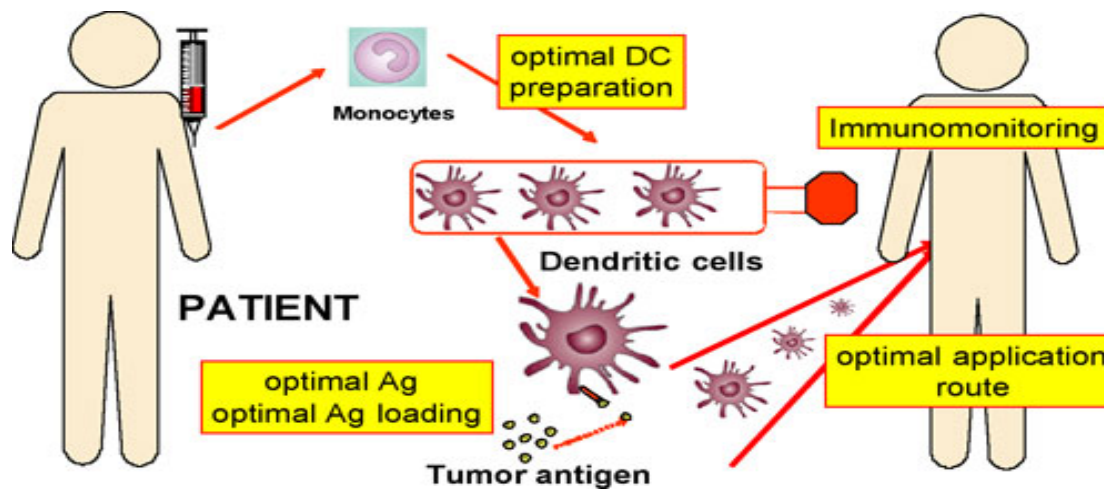
Type of drug substances in GTMPs (recombinant)		Examples
(a) recombinant nucleic acid sequence(s)		<ul style="list-style-type: none">- oligonucleotides (of biological origin)- plasmid DNA <p>→ naked or formulated with synthetic delivery systems such as lipids, polymers and/or peptide ligands</p>
(b) genetically modified virus(es)		<ul style="list-style-type: none">- replication-deficient- replication-competent- conditionally replication-competent <p>→ e.g. retrovirus, adenovirus, adeno-associated virus, herpes simplex, vaccinia virus</p>
(c) genetically modified microorganism(s)		<ul style="list-style-type: none">- <i>Mycobacterium bovis</i> (BCG), <i>Shigella</i>, <i>Clostridia</i> <p>→ genetically modified e.g. by plasmids</p>
(d) genetically modified cells		<ul style="list-style-type: none">- autologous, allogeneic, xenogeneic- primary cells or stable cell lines <p>→ genetically modified by one of the products described above</p>



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.

Example: Cancer Cell therapy





Tissue Engineered product

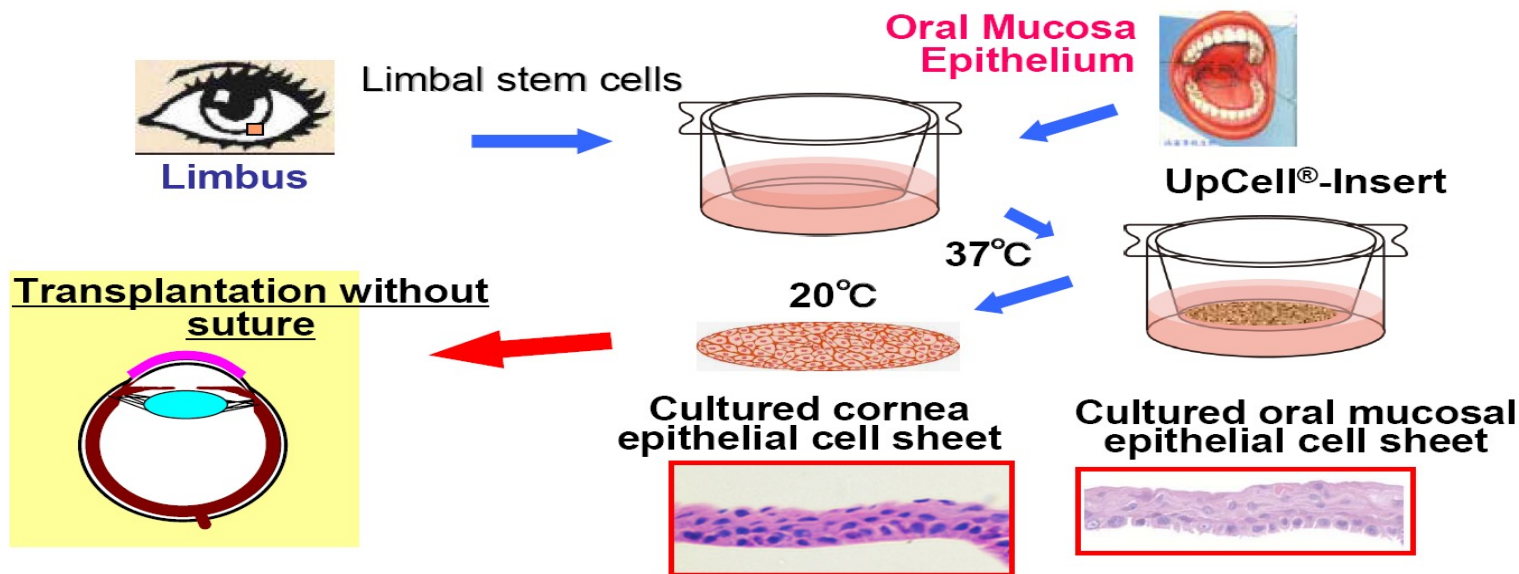
- Contains or consist of **engineered cells or tissues**
- Presented as having properties for, or is used in or administered to humans with a view of **regenerating, repair or replacing a human tissue**

Definition of engineered cells/tissue

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

Tissue engineered product

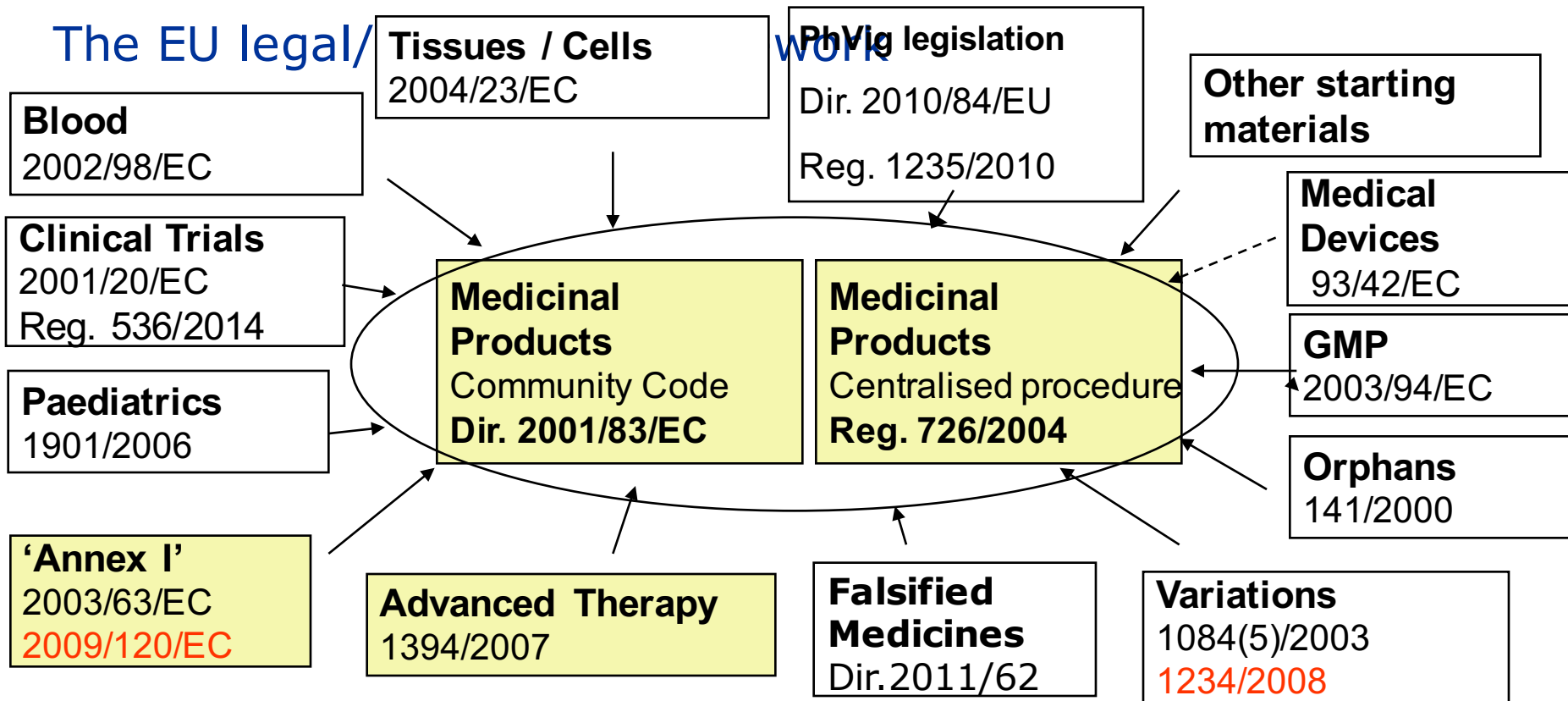
Corneal reconstruction in patients with limbal stem-cell deficiency – OraNera (withdrawn) / Holoclar (authorised)





The EU legal/

work



How are ATMPs authorised in the EU?

ATMPs will follow the **Centralised procedure** → **Single MA for entire EU**

National Authorisation system → **1 MS**

EU Authorisation system → ***some or all MSs***

- 3 EU procedures: Mutual Recognition Procedure (MRP) / Decentralised Procedure (DCP) / Centralised Procedure (CP)
- Route? Choice?
 - Depending on type of product and authorisation history



Eligibility to the CP: “Mandatory Scope”

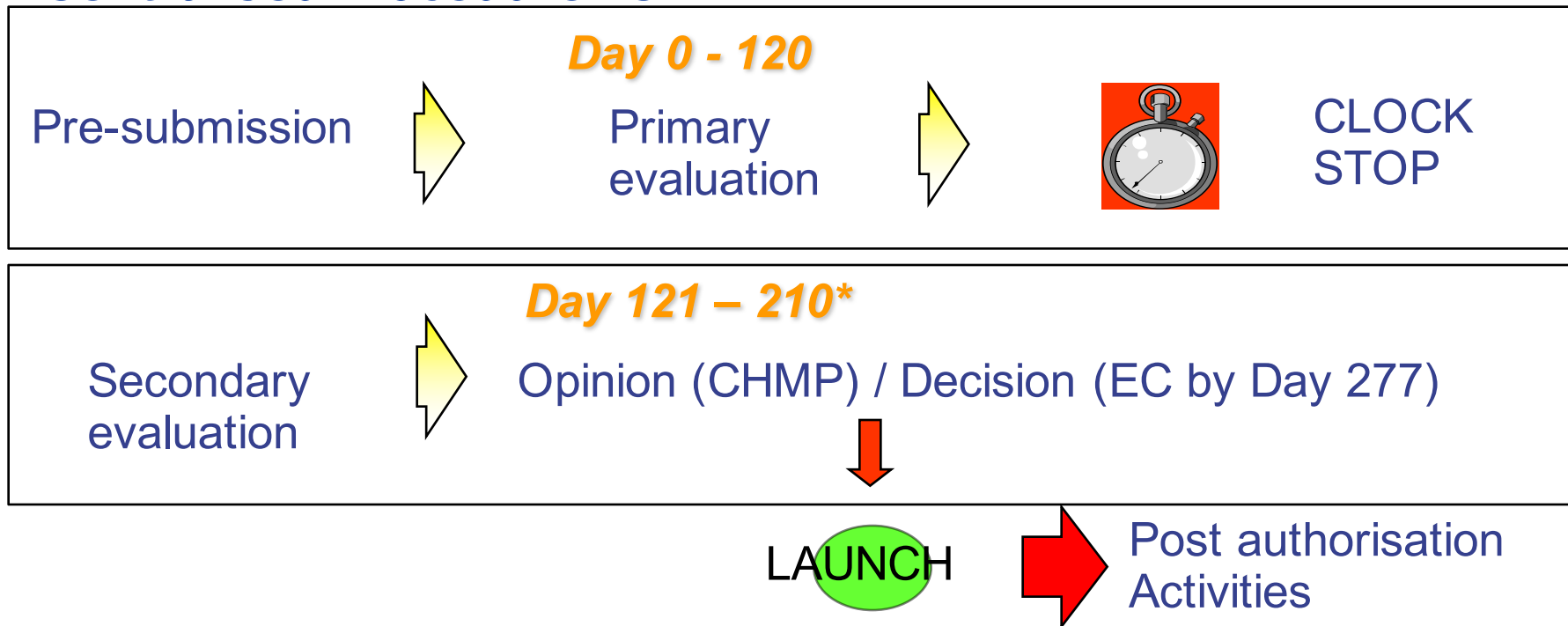
Art. 3(1) of Regulation (EC) No 726/2004 & its Annex

Indent 1	Indent 3	Indent 4
<p>“Biotech” products</p> <ul style="list-style-type: none">• Recombinant DNA technology• Controlled gene expression• Monoclonal AB	<p>“Mandatory therapeutic Classes”</p> <p>New active substance for:</p> <ul style="list-style-type: none">• AIDs• Cancer• Neurodeg. disorders• Diabetes• Viral diseases• Auto-immune diseases	<p>Orphan Designated Medicinal Products</p>

+ **Advanced Therapy Medicinal products** (Regulation 1394/2007)



Centralised Procedure: CHMP



*: additional clock stops for responding to outstanding issues as required.



Marketing authorisations for ATMPs?

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

- What is the same as for non-ATMPs?
 - 210 Day procedure
 - First phase 1 – 120: Initial assessment report (AR), List of questions (LoQ)
 - Second phase 121 – 210: Response AR, List of outstanding issues (LoOI), Oral explanation (OE)
 - Scientific opinion by Day 210 → to Commission for Decision
 - Review by 2 independent assessment teams ('Rapporteur' and 'CoRapporteur')
 - Same internal (EMA) and external (member state) peer review system



Marketing authorisations for ATMPs

What is different?

- 3 Committees involved: CAT + CHMP + PRAC (for review of the Risk management plan = RMP)
- The Rapporteur and CoRapporteur are from CAT
- All scientific discussions (except review of RMP) and adoption of key documents at CAT
- By D200: Draft opinion from CAT → CHMP for adoption of opinion

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



Marketing Authorisations for ATMPs: overview

- 6 ATMPs authorised (centralised procedure)
 - ChondroCelect (TEP), Glybera (GTMP), MACI (TEP, combined)*, Provenge (CTMP)**, Holoclar (TEP), Imlygic (GTMP)
- 3 currently under active review
 - 1 TEP, 1 CTMP, 1 GTMP
- 4 applications withdrawn (before or after negative opinion), 1 negative opinion

*: suspended; **: withdrawn (for commercial reasons)



Support to ATMP developers - Interactions with EMA/CAT

- Briefing meeting with the EMA Innovation Task Force
 - Platform for early dialogue on scientific, regulatory and legal requirements
 - Informal, not binding
 - EMA staff + members for Committees and working parties
 - Since 2009: 66 meetings with ATMP developers; 47 with participation of CAT or WP members.



Support to ATMP developers - Interactions with EMA/CAT

- SME office
 - Facilitate communications with dedicated EMA staff to respond on practical / procedural issues
 - Organise workshops and training
 - sme@sme.europa.eu
- Pre-submission meetings for ATMP certification, Scientific Advice, Orphan Designation and Marketing Authorisation



Support to ATMP developers - procedures

- ATMP classification
 - incentive: early / regulatory certainty
 - open to all applicants – free-of-charge
 - scientific recommendation from CAT on the regulatory classification of their ATMP
- ATMP certification
 - incentive: (early)-late / scientific certainty
 - only for SMEs – reduced fee
 - Scientific evaluation by CAT of quality / development data (Module 3) and non-clinical data (Module 4)
 - 'pre-assessment' of data already generated

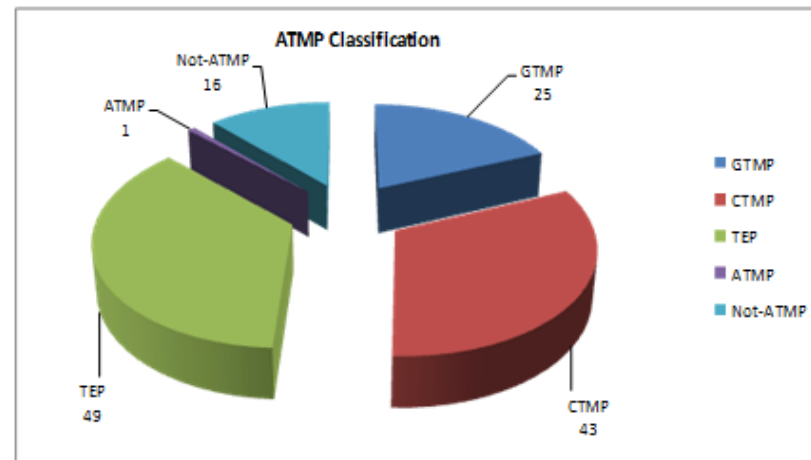
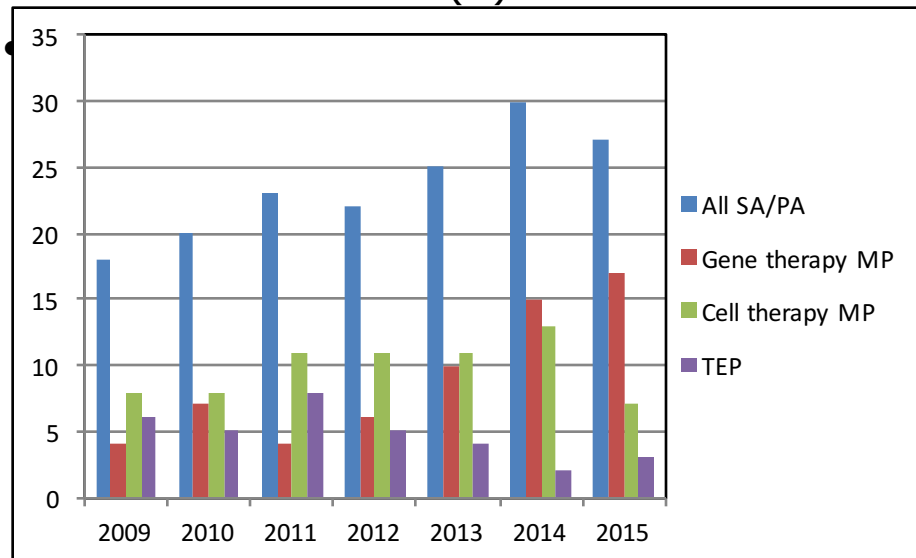


Support to ATMP developers - procedures

- Scientific advice
 - Incentive: Early-late, scientific certainty
 - Advice on future development steps (Q/NC/C), no assessment of data
 - Open to all applicants – reduced fee for ATMPs
 - Possibility for a joint SAWP/HTA advice
 - Scientific advice is given from the scientific advice working party of the CHMP in collaboration with the CAT

CAT Experience in the pre-authorisation phase (Jan 2009 – July 2015)

- ATMP classifications (134)
- ATMP certification (6)





ATMP pipeline

- Majority of the CAT activities is on ATMPs in the development phase.
 - Substantial number of Briefing meetings with developers
 - Number of ATMP classification is increasing over the years
 - Number of Scientific advice requests is increasing over the years (with a clear increase of the number of SA for gene therapy MP)
- An analysis of the Clinical trials in the EU (2004-2010) confirms the pipeline
 - 250 different ATMPs
 - 22% GTMP / 78 % CTMP and TEP, 81% in Phase I and II or I/II
 - CAT will repeat the analysis for 2011-2014 to investigate trends.



Take home messages

- CAT is experienced in review / advice on ATMP applications.
- As a lot of the ATMPs are still in the (clinical) development phase → CAT's activities are more prominent in the pre-authorisation phase
- ATMPs are very diverse, and therefore guidelines are not / will not be available for all types → Developers should interact and consult the regulatory authorities **early and often!**
 - Scientific advice / protocol assistance = key!
- Flexibilities in the system should be used to their full extent.

The role of EMA (CAT) and of the Member States?

	EMA (CAT)	NCA (member states)
Clinical trial approval	No	Yes
Inspections (GMP/GCP/GLP)	No*	Yes
Marketing authorisations (ATMPs)	Yes	No
Hospital exemption / compassionate use ('Specials')	No	Yes
Advice (scientific / regulatory)	Yes	Yes
Support to developers	Yes (SME office, ITF)	Yes (Innovation offices, others)



Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use

During the past decade, a large number of cell-based medicinal products have been tested in clinical trials for the treatment of various diseases and tissue defects. However, licensed products and those approaching marketing authorization are still few. One major area of challenge is the manufacturing and quality development of these complex products, for which significant manipulation of cells might be required. While the paradigms of quality, safety and efficacy must apply also to these innovative products, their demonstration may be demanding. Demonstration of comparability between production processes and batches may be difficult for cell-based medicinal products. Thus, the development should be built around a well-controlled manufacturing process and a qualified product to guarantee reproducible data from nonclinical and clinical studies.

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Margarida Menezes-Ferreira^{4,5}, Ilona Reischl^{1,4,5},
Asterios Tsiftoglou⁵, Jan Kyselovic¹, John Joseph Borg⁵, Sol Ruiz¹, Egbert Flory⁵, Jean-Hugues Trouvin⁵,
Patrick Celis⁵, Janis Ancans⁵,
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Metoda Lipnik-Stangelj¹
& Christian K Schneider¹

CELL & GENE THERAPY INSIGHTS

NAVIGATING THE GLOBAL ATMP REGULATORY LANDSCAPE



SPOTLIGHT

REGULATORY REVIEW

Regulatory viewpoints on the development of advanced stem cell-based medicinal products in light of the first EU-approved stem cell product

Egbert Flory, Paolo Gasparini, Veronika Jekerle, Tiina Palomäki, Patrick Celis, Tomáš Boráň, James W McBlane, John Joseph Borg, Jan Kyselovic, Metoda Lipnik-Stangelj, Toivo Maimets, Margarida Menezes-Ferreira, Guido Pante, Stefanie Prilla, Una Riekstina, Christian K Schneider, Asterios Tsiftoglou and Paula Salmikangas



Thank you for your attention

Further information

See EMA website / Human Regulatory

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