EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European perspective on ATMPs

International Regulatory Forum of Human Cell and Gene Therapy Products

Osaka, Japan 16.3.2016

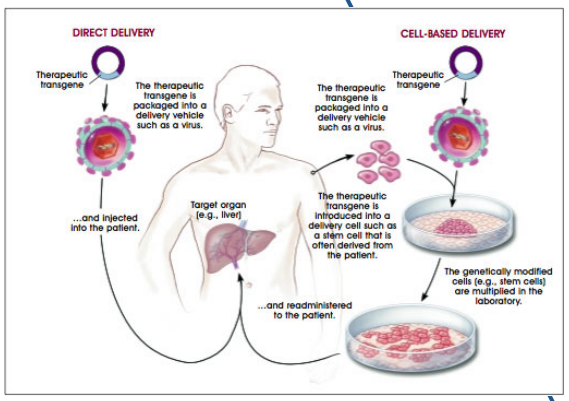
Paula Salmikangas
CAT Chair

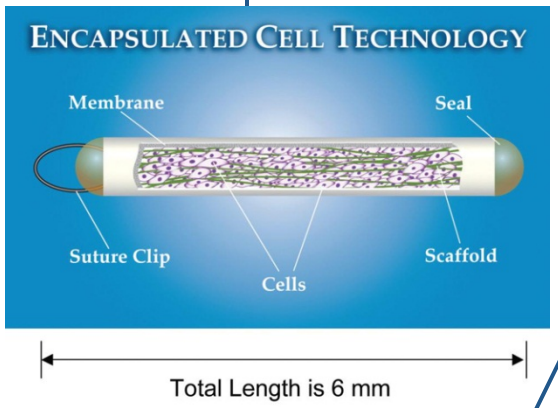
Gene Therapy Medicinal Products

Somatic Cell Therapy Medicinal Products

Tissue Engineering Products

Genetically modified cells

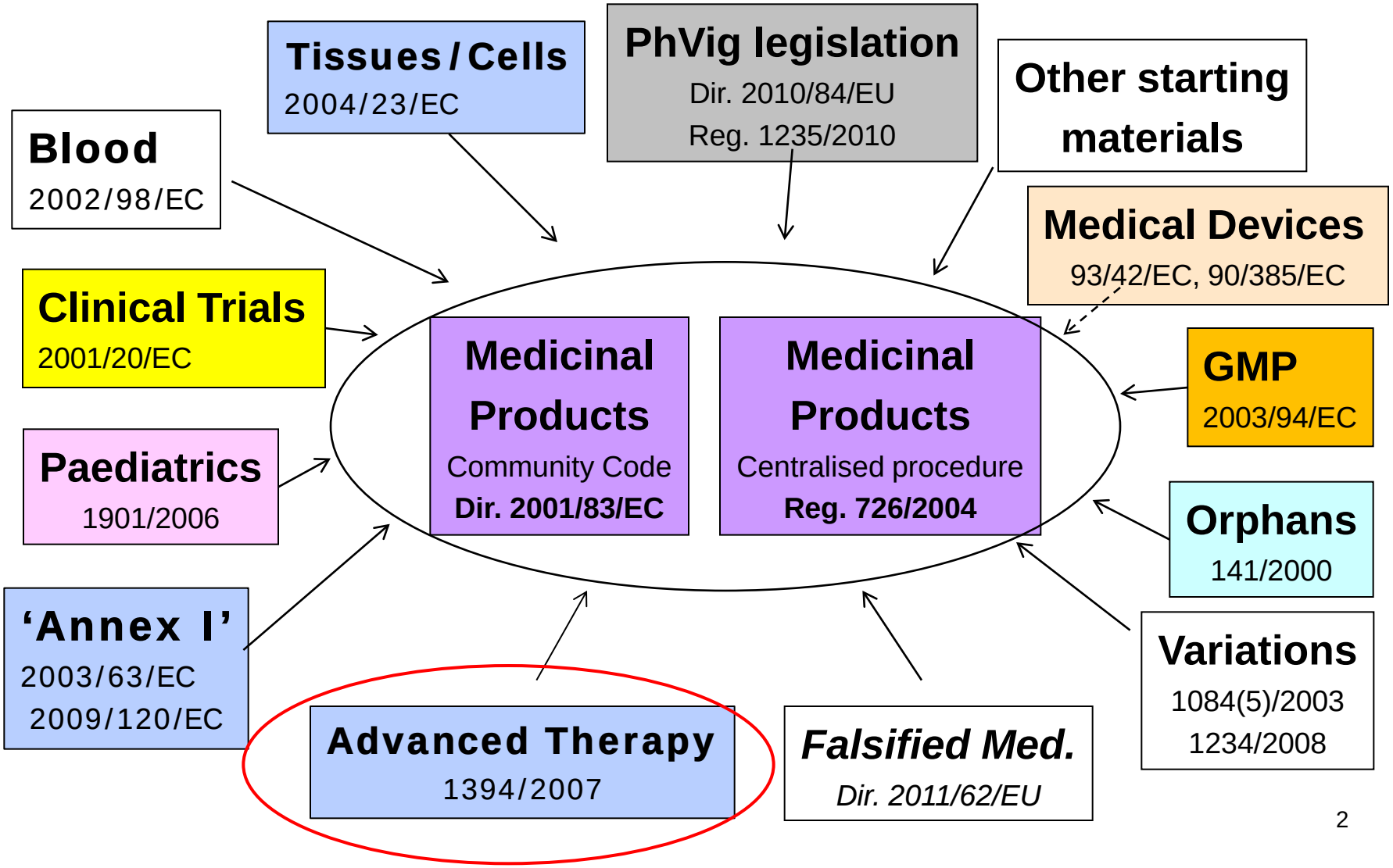





Severe burn victim before and 6 months after treatment with Dermagraft.

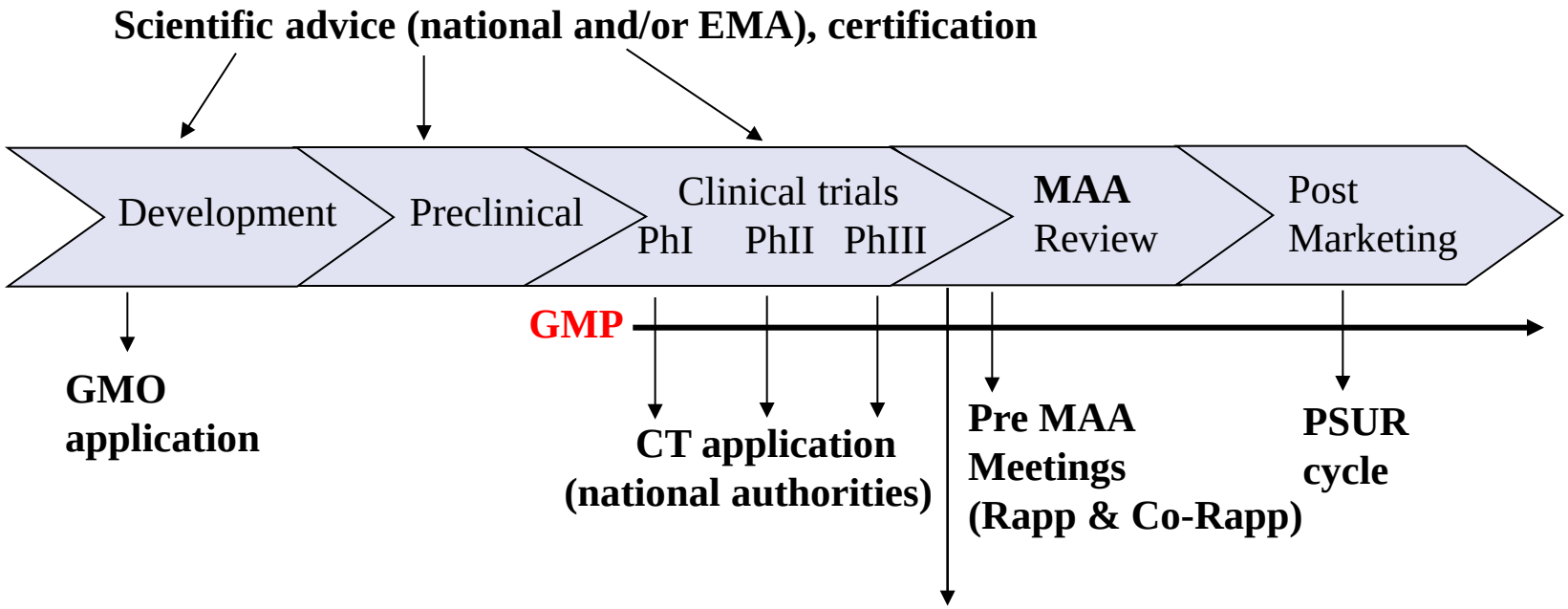
medical device + ATMP → combined ATMP

The EU legal / regulatory framework



→ A new class of medicinal products with a dedicated regulation

Centralized Marketing Authorisation obligatory for ATMPs



Quality & Manufacturing
Safety
Efficacy
Risk Management Plan

Supervision and authorisation of medicinal products

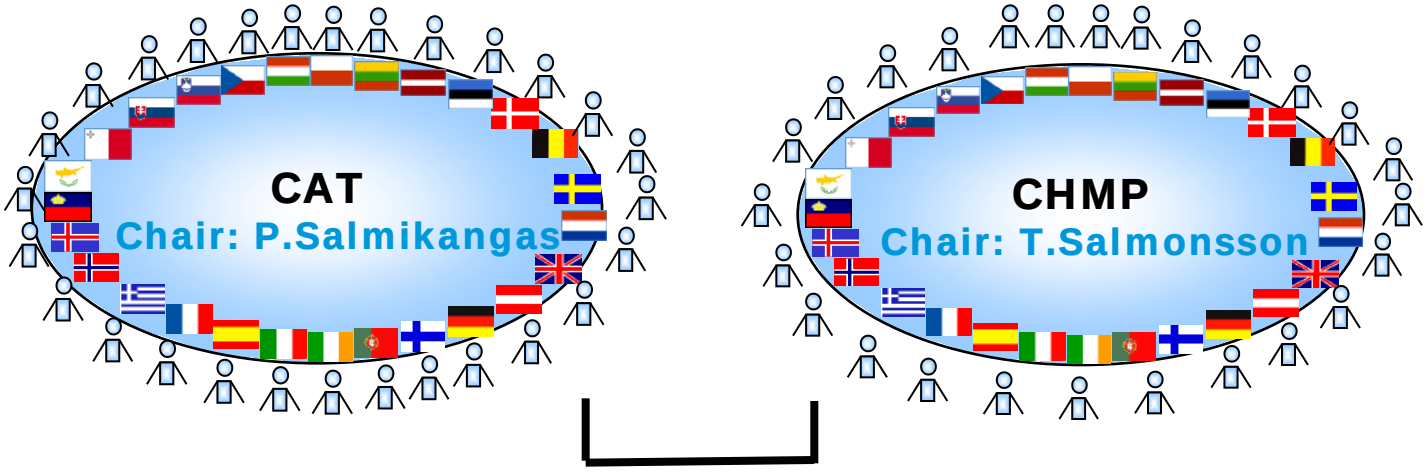
- National Medicines Agencies, European Medicines Agency (EMA), European Commission

- **For Marketing Authorisation** data on Quality, Safety and Efficacy of the **Product** in the intended indication is required, as well as information on the manufacturing process, risk management, GMP production..., Full evaluation by CAT/EMA

- Final opinion always depending on **Benefit / Risk balance**, level/ quality of information, effect size, safety and remaining risks and their mitigation

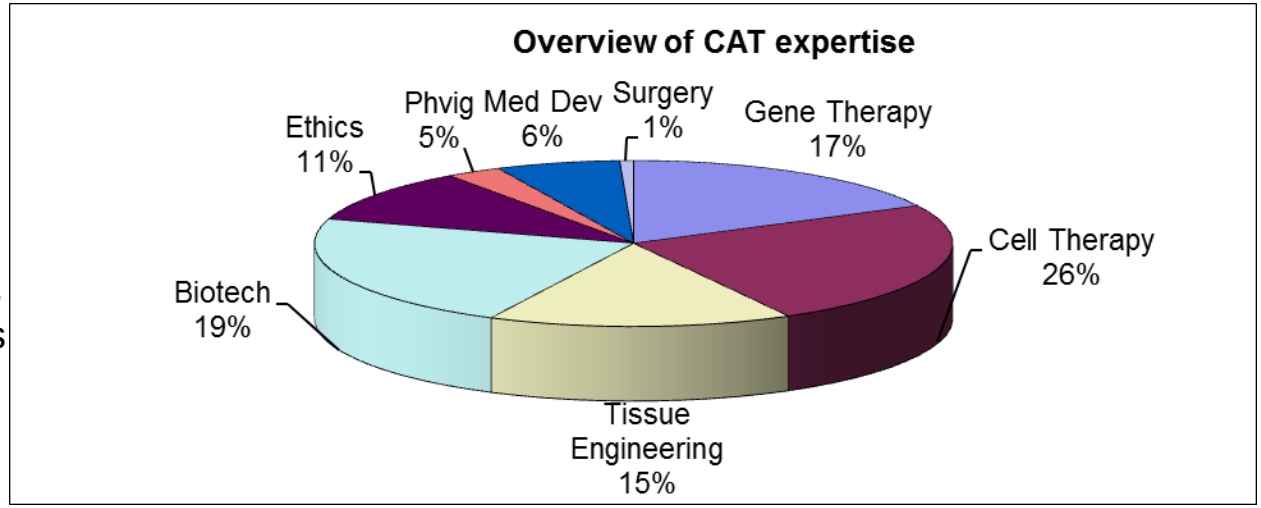
- **For clinical trials** (exploratory and pivotal), authority´s main focus in patient safety; evaluation of quality and manufacturing aspects, pre-clinical safety studies and feasibility of the study design, inspection of the GMP premises before lisence is given, Evaluation by NCA

EMA Committees for ATMPs

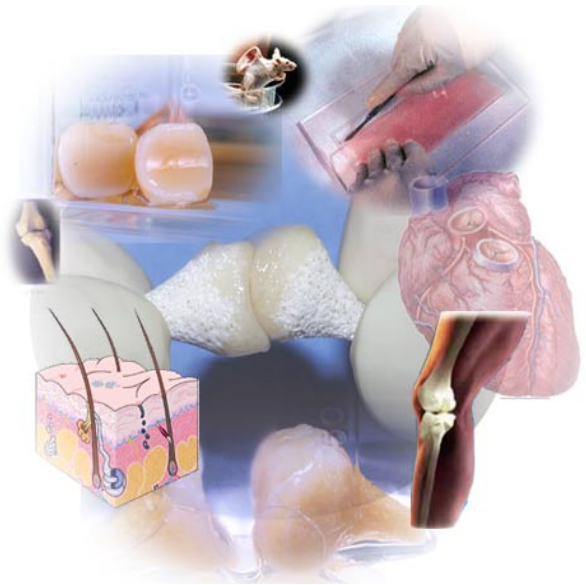


- 18 quality experts
- 12 non-clinical experts
- 21 clinical experts (including 4 members representing physicians)
- 1 inspector
- 4 patient representatives
- 8 other (scientists, heads of departments etc.)

Total **68** experts



Tasks of the CAT



- Scientific Advice
- EVALUATION
- Support to PDCO
- CERTIFICATION
- Support to CHMP / COMP
- CLASSIFICATION
- Interaction with stakeholders
- Publications, Guidelines

TASKS DEFINED PER LEGISLATION

Marketing authorization applications / CAT 2009-2016 (January)

	2009	2010	2011	2012	2013	2014	2015	2016	Total	Approved
Submitted	3	1	2	3	2	2	1		**14**	**6**
GTMP	2	1				2	1		6	2
SCTMP				1					1	1
TEP	1		2	2	1	1			7	3
Variations	0	0	1	1	9	4	3	3	21	

Approved: **ChondroCelect** for cartilage repair, 2009

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

Glybera for treatment of LPL deficiency, 2013

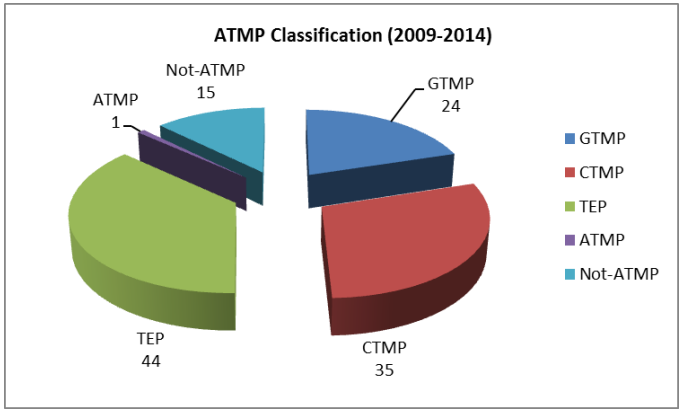
Provenge for treatment of advanced prostate cancer, 2013 *(withdrawn 05/2015)

Holoclar for treatment of limbal stem cell deficiency, 2015

Imlygic for treatment of advanced melanoma, 2015

✓ 3 ATMPs under evaluation, 1 GTMP, 1 CTMP, 1 TEP

Other CAT procedures (Feb 2016)



Scientific recommendation on advanced therapy classification									
	2009	2010	2011	2012	2013	2014	2015	2016	Total
Submitted	22	19	12	22	20	28	61	15	199
Adopted	12	27	12	16	23	29	31	33	183

- **185** scientific advice procedures for ATMPs
- **44** PIPs
- Over **300** ATMPs have been studied in clinical trials during 2011-2015 (~200 CTs during 2004-2010)
- first classification of gene edited cells, CAR-Ts in clinical studies in EU (6)

Introduced changes during the revision EMA/CAT/600280/2010

Reflection paper on classification of advanced therapy medicinal products

Draft Agreed by CAT	June 2014
Adoption by CAT for release for consultation	20 June 2014
Start of public consultation	30 June 2014
End of consultation (deadline for comments)	31 October 2014
Draft Agreed by CAT	
Adoption by CAT	

- Substantial manipulation
  - Enzymatic digestion
- Same essental function(s) in the recipient and the donor
  - Homologous vs non-homologous use
- Additional changes to clarify the existing concepts
  - e.g. the boundary between vaccines against infectious diseases and gene therapy medicinal products and criteria for combined ATMPs

Sound scientific rationale + good product

= successful outcome

Why do products fail?

Due to

- Quality issues?

  hardly, but if product is poorly standardised and controlled, it may have impact on product safety and efficacy, difficulties to get into clinical trials

- Non-clinical issues?

  perhaps not, but without proper safety data it will be difficult to get into the clinical trials

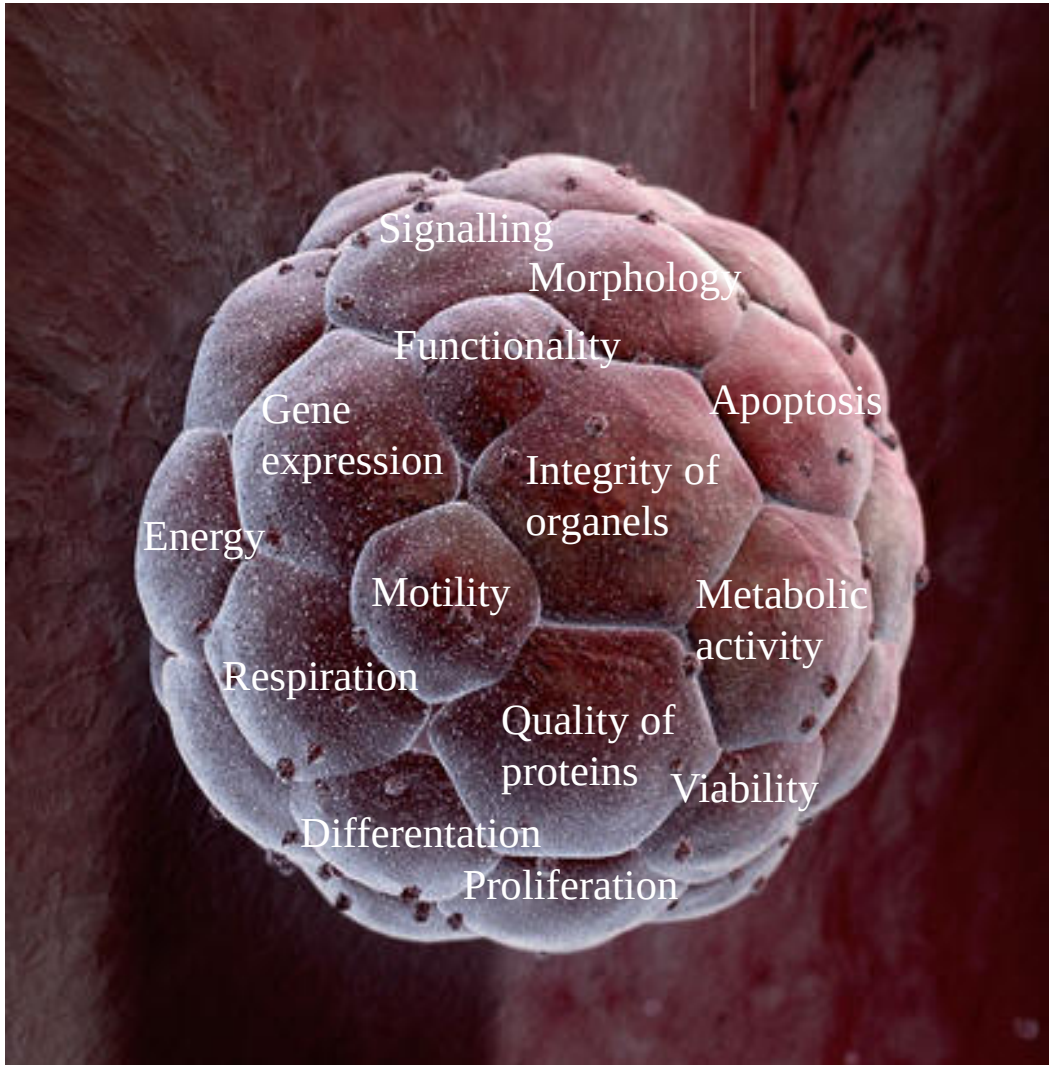
- Clinical issues?

  YES, **efficacy, efficacy, efficacy**, and sometimes safety

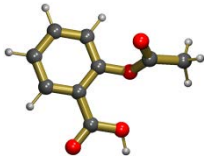
- Risk-management issues?

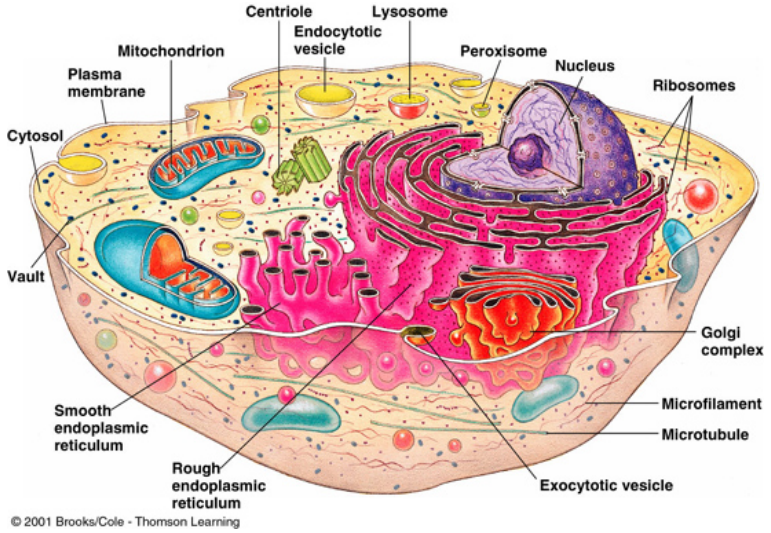
  will not block the licensing, but needs to be handled properly

Cells/Genes as pharmaceuticals?



Aspirin





Eucaryotic cell

Special issues for ATMPs

ATMPs are complex pharmaceuticals

- gene therapy: transgene, type of vector, genetically modified cells
- cell therapy: autologous, allogeneic, complex process, combination products
- development requires expertise from several areas e.g. cell and molecular biology, biotechnology, surgery, risk management, medical devices, ethics…

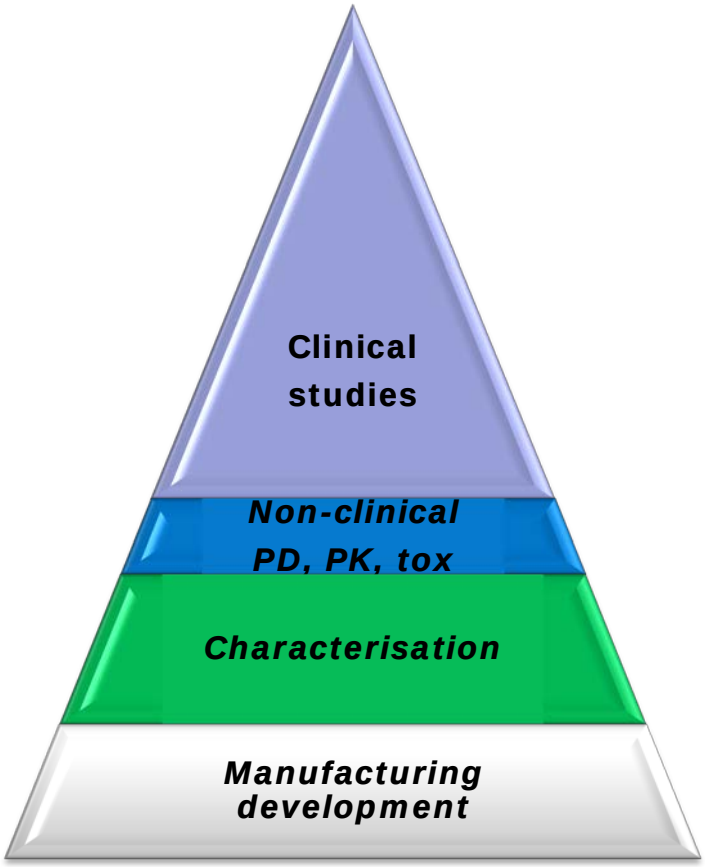
and on REGULATORY REQUIREMENTS

- ATMPs are in the frontline of fast evolving science → a product maybe already ”old”, when reaching the markets
- Manipulation of cells and use of recombinant nucleic acids may bear unknown risks, which may not be solvable through standardisation or quality control
- The product and its´ safety and efficacy profile need to be carefully prospectively planned and the key data should be based on findings that are robust and reliable

Further specificities to consider

- material supply, manufacturing constraints/upscale → comparability issues
- mode of action: treatment of disease or repair/regeneration, multiple MoAs?
- availability of relevant animal models
- dose finding and biodistribution
- specific safety issues (e.g. integrational mutagenesis of GTMPs, biodistribution/ectopic tissue formation of cell-based MPs)
- nature of disease: monogenetic vs multifactorial
- possibilities for blinding, availability of compators
- specific administration of certain ATMPs (catheters, surgery etc.), concomitant medication

Building the evidence



ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Module 1: Administrative Information and Prescribing Information
- 1.1 Table of Contents of the Submission Including Module 1
- 1.2 Documents Specific to Each Region (for example, application forms, prescribing information)

Module 2: Common Technical Document Summaries
- 2.1 Common Technical Document Table of Contents (Modules 2-5)
- 2.2 CTD Introduction
- 2.3 Quality Overall Summary
- 2.4 Nonclinical Overview
- 2.5 Clinical Overview
- 2.6 Nonclinical Written and Tabulated Summaries
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- 2.7 Clinical Summary
  - Biopharmaceutic Studies and Associated Analytical Methods
  - Clinical Pharmacology Studies
  - Clinical Efficacy
  - Clinical Safety
  - Literature References
  - Synopses of Individual Studies

Module 3: Quality
- 3.1 Table of Contents of Module 3
- 3.2 Body of Data
- 3.3 Literature References

Module 4: Nonclinical Study Reports
- 4.1 Table of Contents of Module 4
- 4.2 Study Reports
- 4.3 Literature References

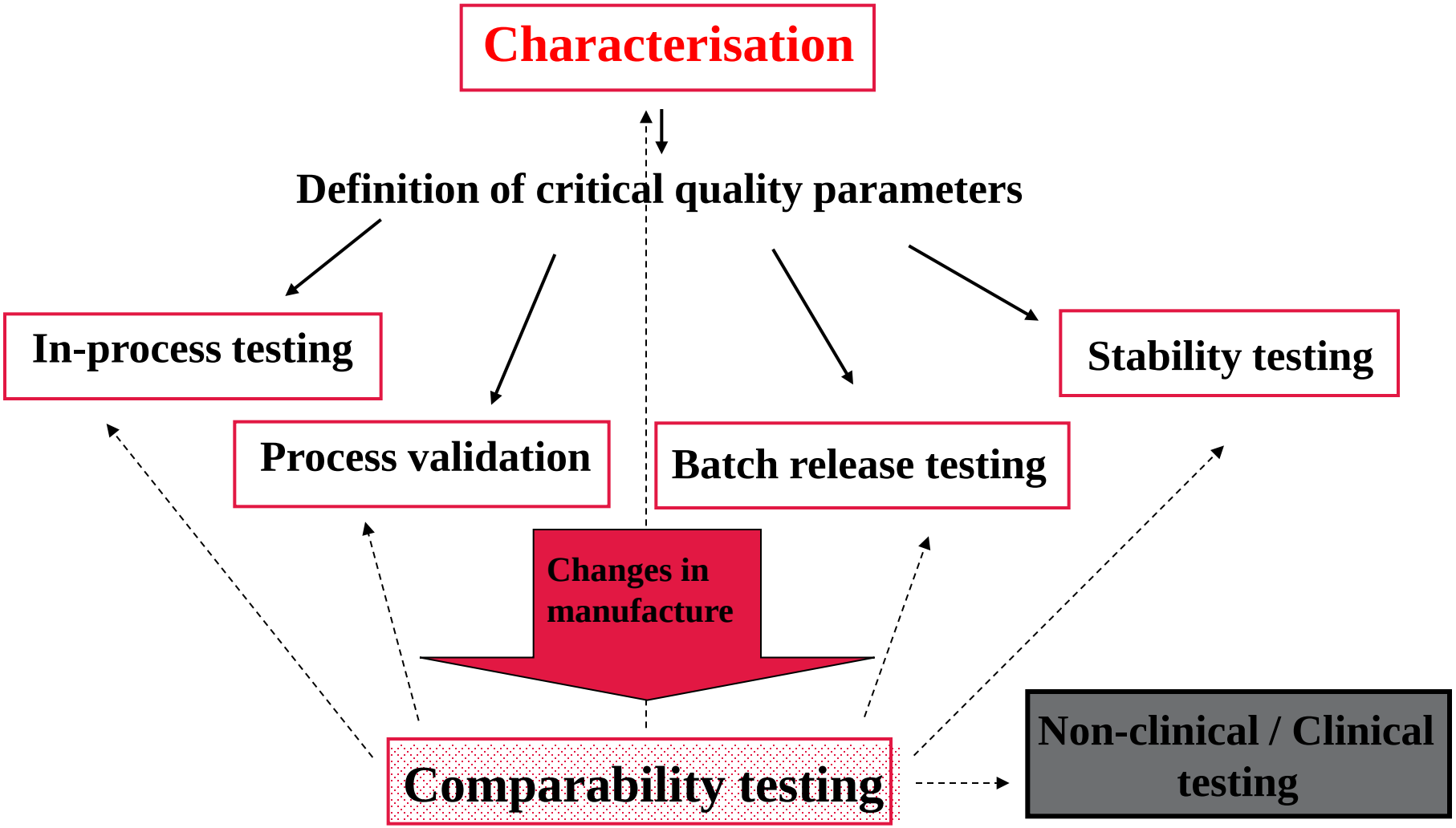
Module 5: Clinical Study Reports
- 5.1 Table of Contents of Module 5
- 5.2 Tabular Listing of All Clinical Studies
- 5.3 Clinical Study Reports
- 5.4 Literature References

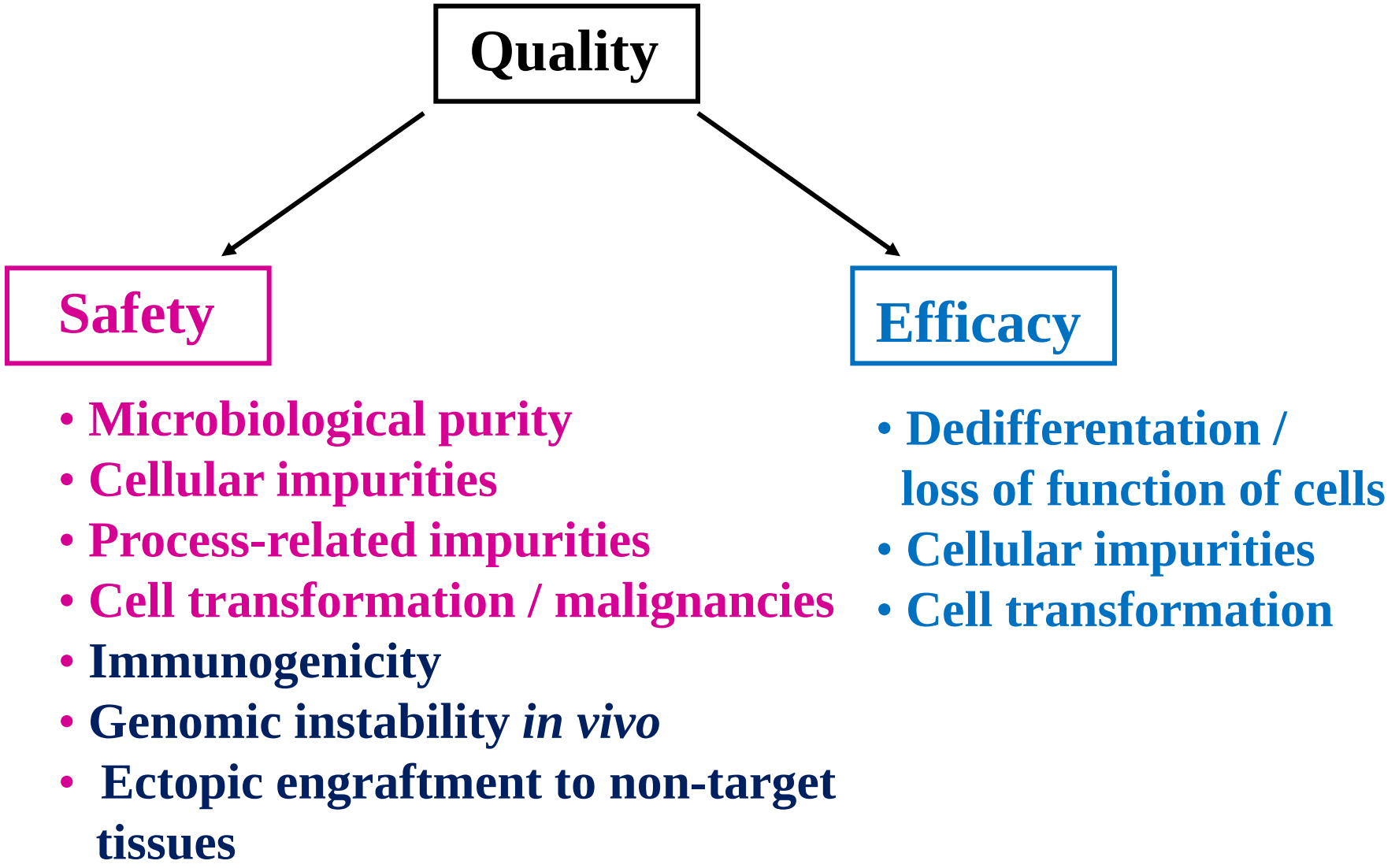
Directive 2001/83/EC
For general MA requirements

Regulation 1394/2007
For specific ATMP provisions

Directive 2009/120/EC
For technical ATMP requirements

Quality development




Quality
Safety
Efficacy
• Microbiological purity
• Cellular impurities
• Process-related impurities
• Cell transformation / malignancies
• Immunogenicity
• Genomic instability *in vivo*
• Ectopic engraftment to non-target tissues
• Dedifferentation / loss of function of cells
• Cellular impurities
• Cell transformation

Pivotal factors for successful outcome

- Standardised and properly controlled product
- Justified dose and posology
- Correct target group
- Well-established safety profile
- Robust design of clinical studies
- Control of concomitant diseases and medications
- Proper Risk Management Plan
- **Long-term follow-up of patients**

- Early contacts with regulatory authorities ITF, Scientific advice (both national and EMA)

Adaptive pathways, PRIME, conditional approval?

- **AP**: Prospectively planned approach for MA with conditions, based on existing procedures (conditional MA, MA with exceptional circumstances, joint EMA/HTA SA…), Pilot phase with multiple ATMPs ongoing
- **PRIME**: early, proactive and enhanced support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicine applications, launched 7.3.2016 (EMA website)
- Guidance for conditional approval and for accelerated assessment updated (no major changes for ATMPs)
  - **Important to understand the impact of conditional MA**

    → post-marketing obligations

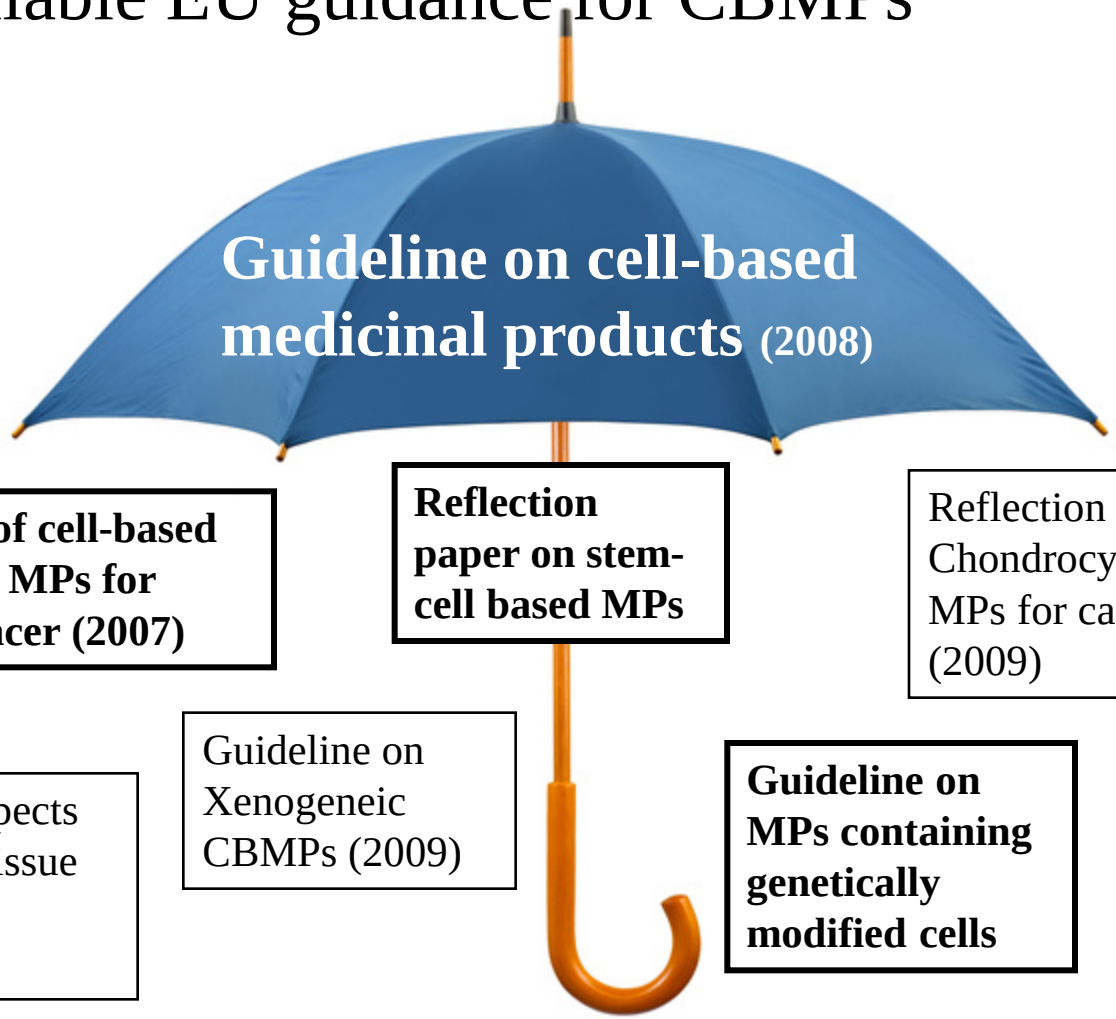
    → impact on reimbursement / HTA expectations

Risk-based approach

- Propectively planned strategy to justify the need for data in the MAA, **proportionate requirements based on risks**
- Does not provide a rigid classification system of different risks of a product as whole (e.g. high-risk product vs. low-risk product)
- Is intended to provide flexibility to regulation of ATMPs
- Should help developers to overcome challenges due to the specific nature of the ATMPs
- How to do the risk/risk factor profiling?

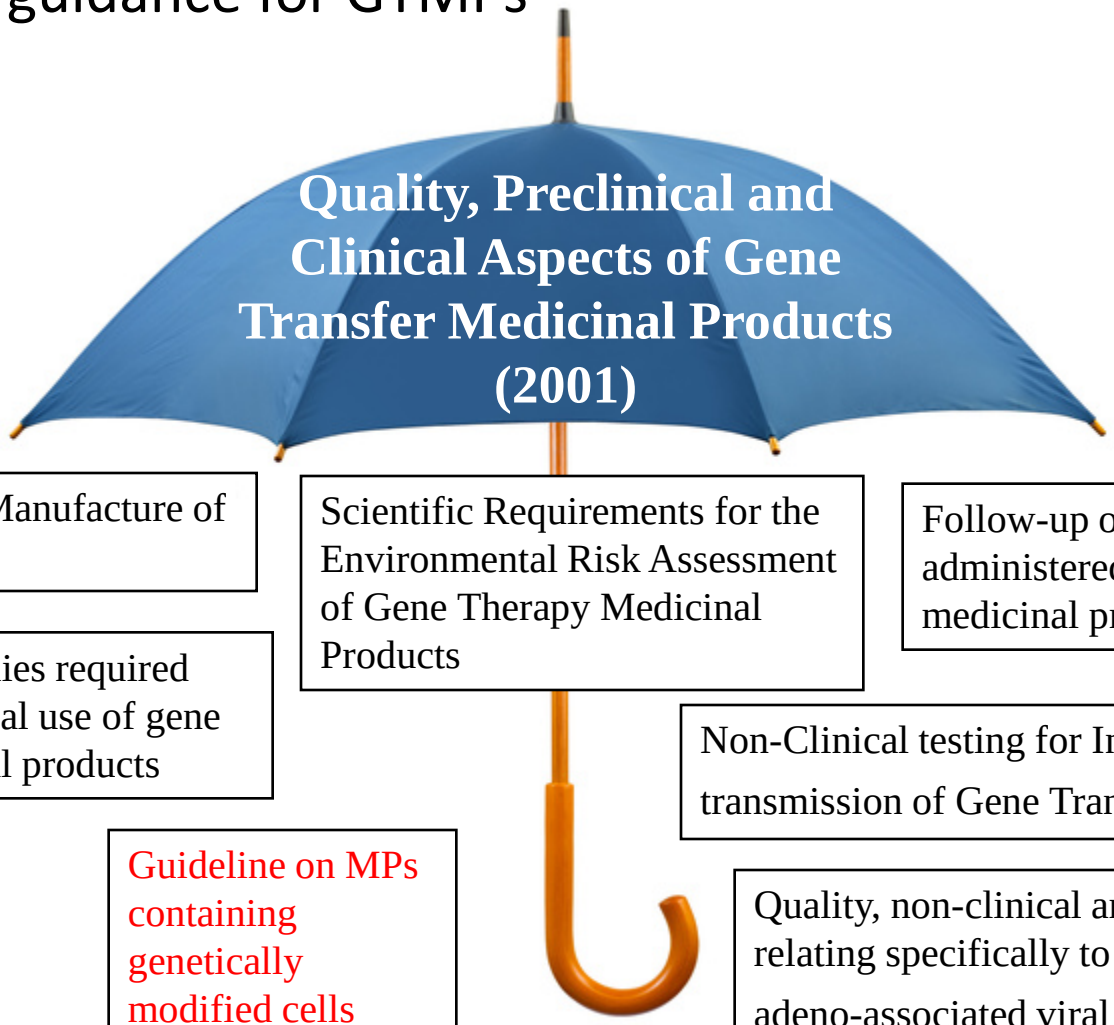
  → GL on risk-based approach (EMA/CAT/CPWP/686637/2011)
  → Q/A document on RBA under preparation
  → scientific advice

Available EU guidance for CBMPs



http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000405.jsp&mid=WC0b01ac058002958a

Available guidance for GTMPs



Other applicable EU guidance

GMP Guideline

Guideline on Safety and Efficacy Follow-up – Risk Management of ATMPs

Available disease specific guidance

Ph.Eur. monographs

EMA / ICH guidelines Q, S, E

traceability guidance

GCP guidance

http://www.ema.europa.eu/htms/human/humanguidelines/biologicals.htm

CAT work plan

2015-2016 – adopted by the Committee on 14 November 2014

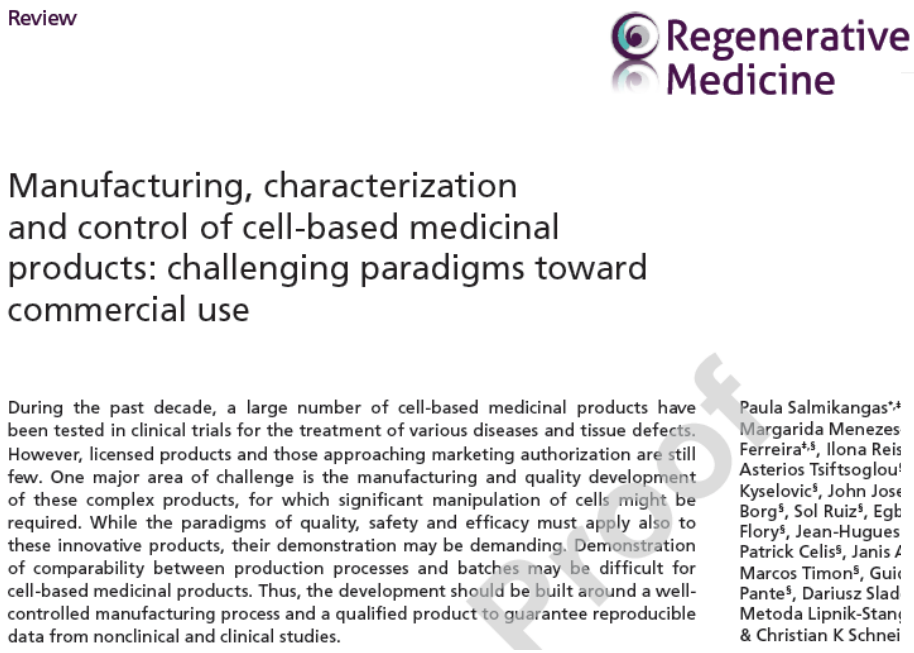
In addition to normal Committee work (MAA evaluation, classifications, scientific advice etc.)

CAT participates to joint cross-committee objectives

- adaptive pathways (3 ATMPs in the pilot), PRIME
- benefit/risk project
- patient registries, ….

CAT specific objectives

- finalise the GL on GTMPs
- **draft a guideline for investigational ATMPs (EC task);** - CAT/IP meeting in relation to the GL on investigational ATMPs
- **support EC in developing GMP guideline for ATMPs**
- **support EC in developing ATMP specific guideline on GCP**
- **CAT workshop with experts on cancer immunotherapy (October 2016)**
- **new survey of clinical trials and developers (2010-2015), publication**

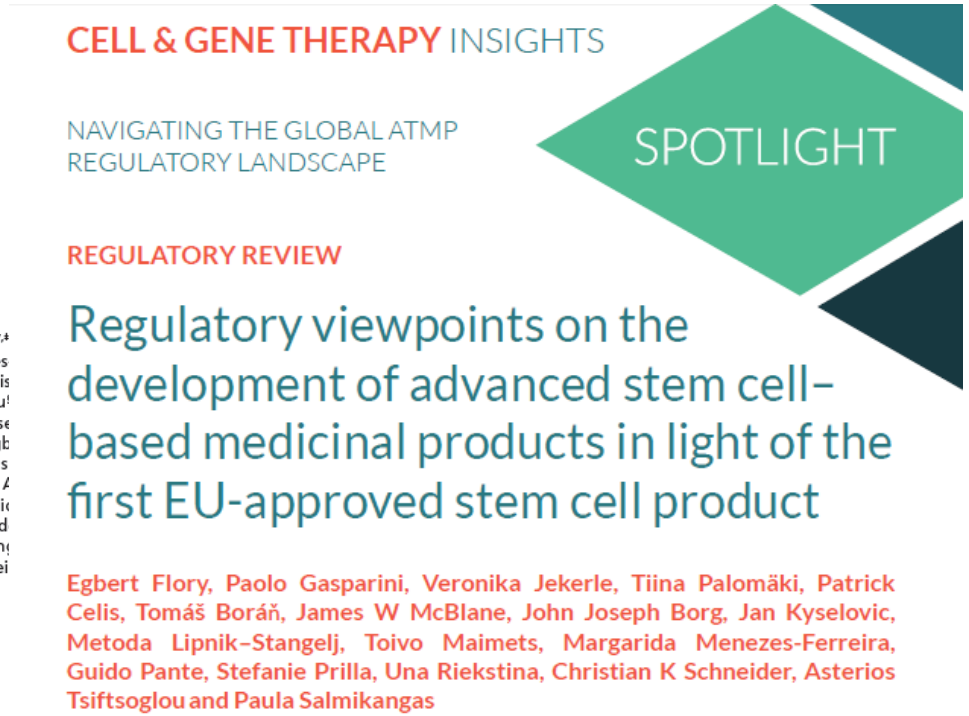

Review

Regenerative Medicine

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.

Paula Salmikangas*,‡ Margarida Menezes Ferreira‡,§, Ilona Reis Asterios Tsiftsoglou Kyselovic§, John Jose Borg§, Sol Ruiz§, Egb Flory§, Jean-Hugues Patrick Celis§, Janis A Marcos Timon§, Guic Pante§, Dariusz Slad Metoda Lipnik-Stan & Christian K Schnei


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 Tsiftsoglou and Paula Salmikangas

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Thank you for your attention!