EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Challenges during the development of ATMPs

CAT-DGTI Workshop

Dresden 11.9.2014

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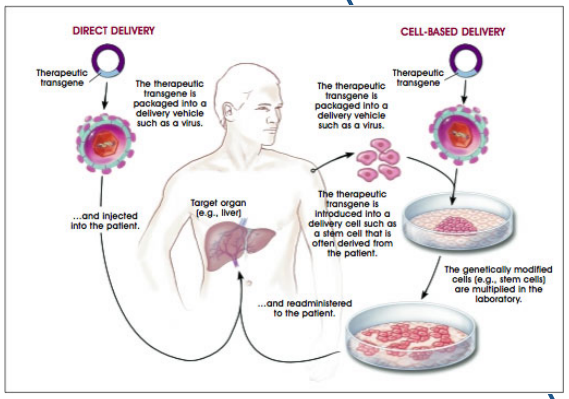
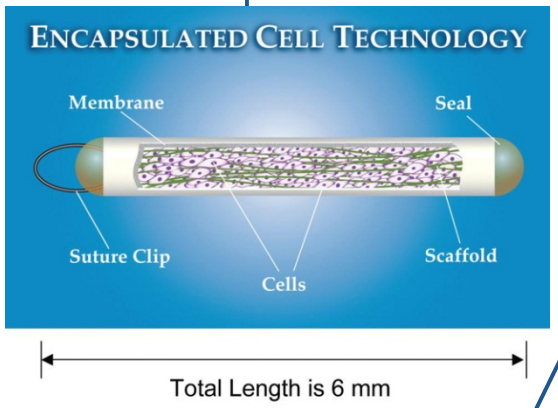
Gene Therapy Medicinal Products

Somatic Cell Therapy Medicinal Products

Tissue Engineering Products

Genetically modified cells



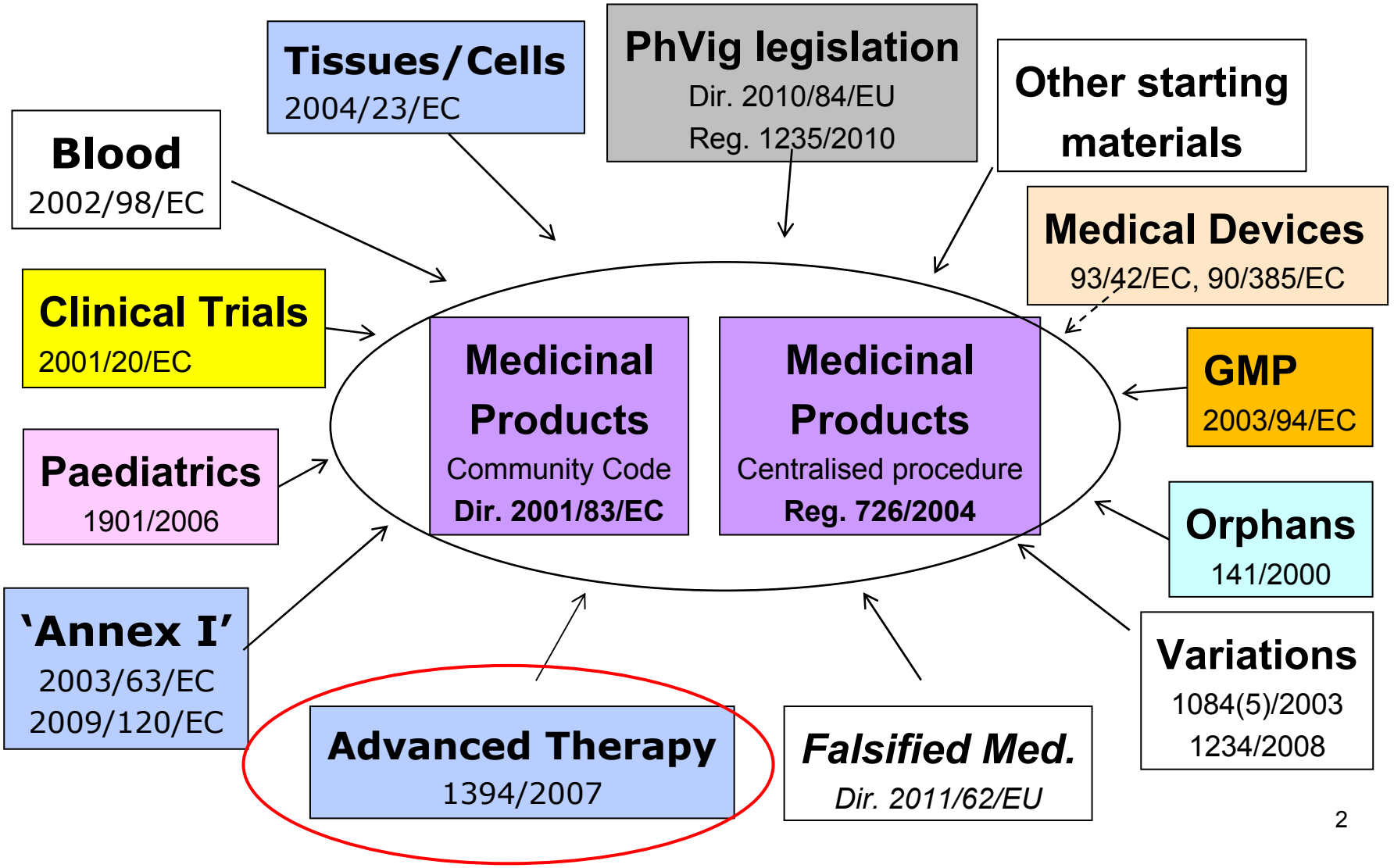





Severe burn victim before and 6 months after treatment with Dermagraft.

medical device + ATMP → combined ATMP

# The EU legal / regulatory framework






→ A new class of medicinal products with a dedicated regulation

# Regulation 1394/2007/EC

- somatic cell therapy products, gene therapy products and tissue engineered products classified as medicinal products (ATMPs)

  → cells either manipulated or intended for non-homologous use

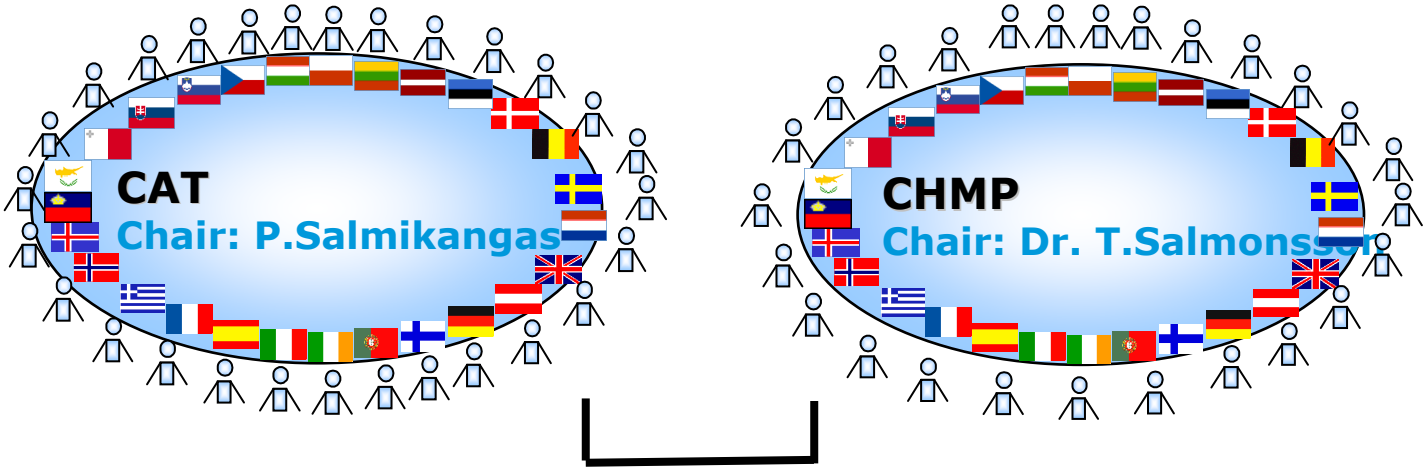
- a centralised marketing authorisation route for all ATMPs

- establishment of Committee for Advanced Therapies, CAT, for
  - classification
  - certification
  - evaluation of ATMPs
  - scientific advice and guidelines

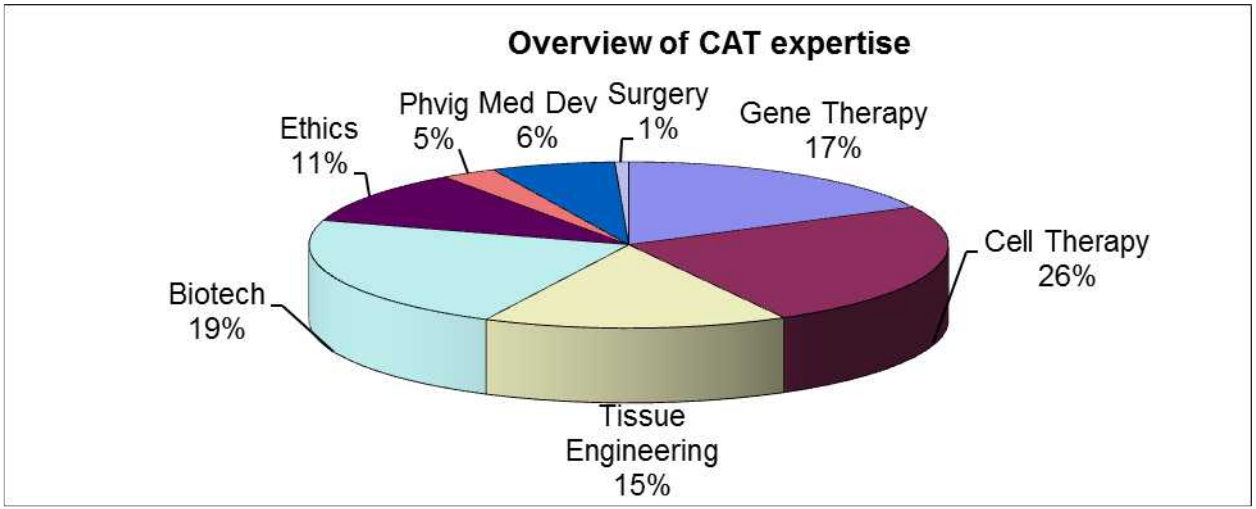
- when marketing authorization granted, it is valid in whole EU

- possible to have post-authorization efficacy and safety studies

# EMA Committees for ATMPs




**5 „double members"**



# Marketing authorization applications / CAT 2009-2014 (May)

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | Total | Approved |
|---|---|---|---|---|---|---|---|---|
| Submitted | 3 | 1 | 2 | 3 | 2 | 1 | **12** | **4** |
| GTMP | 2 | 1 | | | | 1 | 3 | 1 |
| SCTMP | | | | 1 | | | 1 | 1 |
| TEP | 1 | | 2 | 2 | 1 | | 6 | 2 |
| Variations | 0 | 0 | 1 | 1 | 9 | 2 | 13 | |

Approved: **ChondroCelect** for cartilage repair

**MACI** for cartilage repair

**Glybera** for treatment of LPL deficiency

**Provenge** for treatment of advanced prostate cancer

Currently

✓4 ATMPs under evaluation

✓2 new starting Q3-4/2014

# ATMP Classifications 2009-2014 (1Q)

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | Total |
|---|---|---|---|---|---|---|---|
| Gene therapy | 3 | 7 | 1 | 4 | 1 | 4 | 20 |
| Gene therapy, combined ATMP | 0 | 0 | 0 | 1 | | | 1 |
| Cell therapy | 6 | 7 | 3 | 2 | 8 | 2 | 28 |
| Cell therapy, combined ATMP | 0 | 1 | 0 | 0 | | | 1 |
| TEP | 1 | 8 | 5 | 4 | 5 | 6 | 29 |
| TEP, combined ATMP | 0 | 2 | 1 | 1 | 1 | | 5 |
| ATMP (not subclassified) | 0 | 1 | 0 | 0 | | | 1 |
| not ATMP | 2 | 1 | 2 | 4 | 5 | | 14 |
| Total | 12 | 27 | 12 | 16 | 20 | 7 | **99** |

- **> 250** ATMPs in clinical trials during **2004-2010** (EudraCT)
- **176** ATMPs discussed in scientific advice (may2014)
- **35** PIPs for ATMPs

# Special issues for ATMP assessment

- ✓ ATMPs are complex pharmaceuticals

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

- ✓ Specific administration of certain ATMPs (catheters, surgery etc.)
- ✓ Specific safety issues (e.g. integrational mutagenesis of GTMPs, biodistribution/ectopic tissue formation of cell-based MPs)
- ✓ Nature of disease: monogenetic vs multifactorial
- ✓ Mode of action: treatment of disease to repair/regeneration
- ✓ Special challenges concerning manufacturing/quality, safety and efficacy studies

# Regulatory Challenges

- Scientific (quality/manufacturing, non-clinical, clinical)
- Developer-related
- Socio-economic
- Legal / Regulatory / Political

# Scientific challenges

- manufacturing constraints
  - GMP requirements for production
  - starting and raw materials; continuity of material supply
  - immature production technologies, comparability
  - variability and process validation
- characterisation, potency testing (related to clinical outcome)
- non-clinical challenges
  - availability of relevant animal models
  - proof of concept, satefy aspects (species specificities)
- clinical aspects
  - possibilities for blinding, availability of compators
  - feasibility of dose finding and biodistribution studies in humans, concomitant medication/surgical procedures, **efficacy!**
- Product-related challenges:
  - safety: dose, tumourigenicity, biodistribution, integration
  - efficacy: inter-individual variability, administration

# Risks vs. limitations of ATMPs

- infections (microbial contamination of starting materials or during processing)
- tumourigenicity (cell transformation, integration to genome)
- dedifferentation / loss of function of the cells
- immunogenicity, rejection
- ectopic engraftment of cells to non-target tissues
- shedding (genet. modif. CBMPs; germ line, environment)
- small sample sizes, short shelf-lives, availability of proper animal models, applicability of analytical methods etc.

→ **Risk-based approach for all ATMPs**

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf

# Developer-related challenges

- A lot of new products in the pipeline; most still in phase II and **mainly developed by academia / hospitals /SMEs**

→ Limited knowledge and experience on regulatory requirements

→ No other products to be sold when the first MAA is under preparation = poor resources, huge workload

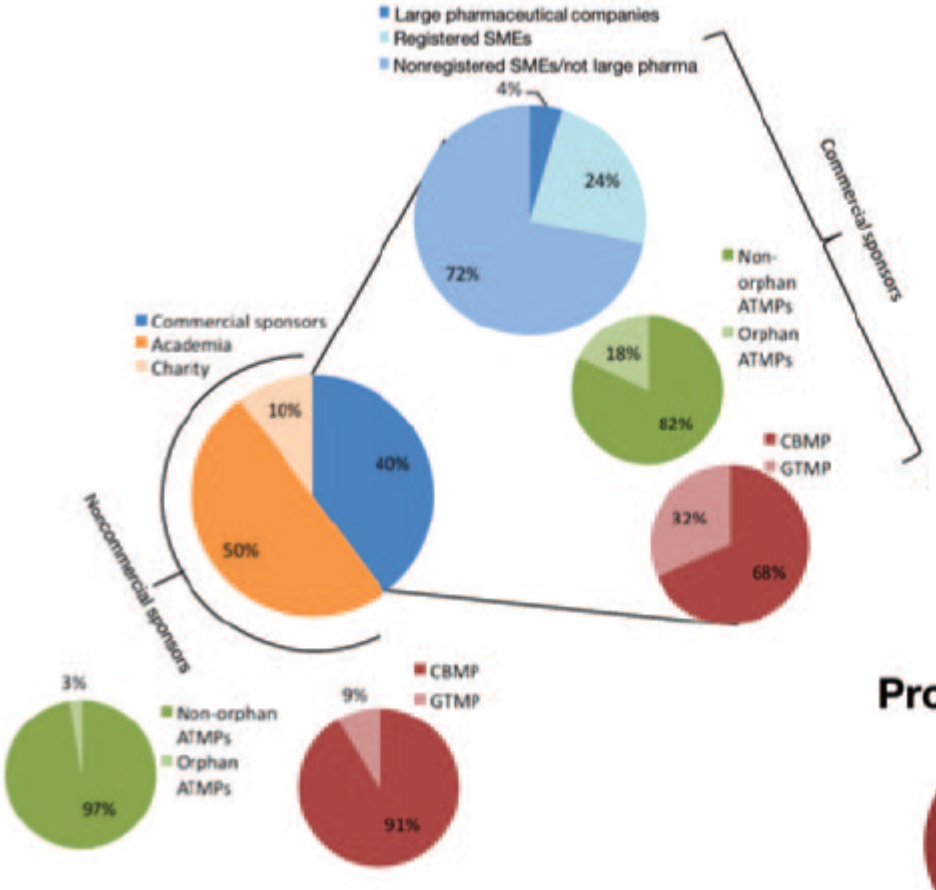
- In some member states, a lot of products have been used under national authorisation before entry of Regulation 1394/2007/EC

→ Difficulties to accept the new standards and requirements, difficulties in gathering all data needed for a centralized lisense

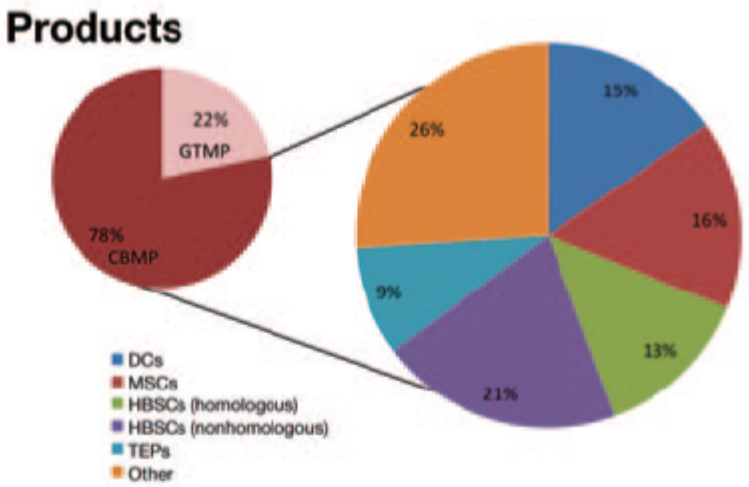
- In hospitals and research centers strong wish to maintain cell-based products as transplantation/transfusion products

→ Conflict with ATMP industry

# ATMP clinical trials in EU (EudraCT Database)




Maciulaitis, R. et al. (2012)
Molecular Therapy 20: 479-482



# Socio-economic challenges

- Different ethical views e.g. on use of cell-based products manufactured from human embryonic stem cell lines
- Development still in hands of small research entities → limited resources and difficult to get funding for clinical trials
  = valley of death?
- Small batches to be manufactured (autologous products, one batch for one patient), short shelf-lives

→ high production and testing costs per batch

→ ATMPs more expensive than traditional drugs

- Difficulties to get novel ATMPs reimbursed; laborous negotiations with HTA bodies, value of ATMPs in various indications not yet established

# Legal / regulatory / political challenges

- Different national requirements for clinical trials (especially multi-center Phase III studies)
- Diverse interpretation of hospital exemption in different member states, development of ”second standard” products for national use

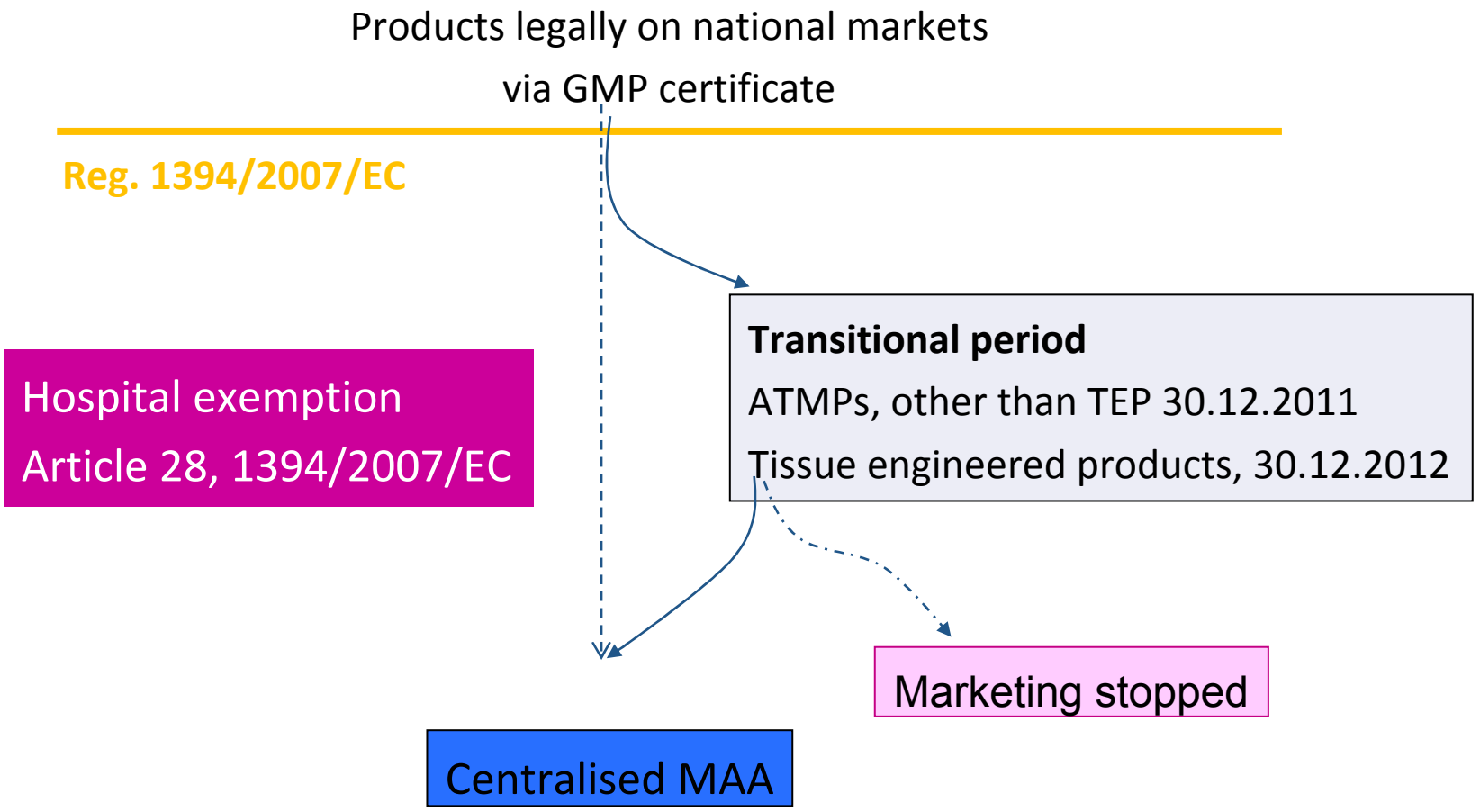
→ conflict with industry

→ ”ATMP tourism”

- Classification of ATMPs on national level; where are the boarders between transplantation/transfusion and ATMPs?

→ Clear definitions for classifications into legislation

# Framework for ATMPs in EU



# Article 28, 1394/2007/EC (Hospital Exemption):

- Any ATMP, …, which is prepared
  - on a non-routine basis
  - according to specific quality standards, and
  - used within the same Member State
  - in a hospital
  - under the exclusive professional responsibility of a medical practitioner

- in order to comply with an individual medical prescription for a custom-made product for an individual patient

→Manufacturing to be authorised by the MS competent authorities

→National traceability and pharmacovigilance requirements

→Specific quality standards … as on the community level

- **1.4.2014 Report from the EU Commission after public consultation**

# Conclusions – HE Report

→ Balance between access to patients and requirements

→ Clarification and harmonisation of conditions

→ Patients should not be exposed to unsafe/ineffective treatments

→ Use of data generated under HE to be used as part of MAA?

→ Clarification of all derogations (art. 5, Dir. 2001/83, art.28, Reg.1394/2007)

# In conclusion

- ✓ A lot of new ATMPs in the pipeline; most still in phase II and developed by academia / hospitals /SMEs for unmet medical need

→ involvement of the big pharma?

- ✓ Challenges in manufacture and quality control, NC and clinical challenges

→ Better manufacturing technologies & analytical techniques; multi-user GMP premises or contract manufacturers for ATMPs?

→ Careful product and study designs; **early scientific and regulatory advice**

- ✓ Phycisians against the ATMP legislation?; different interpretation of the hospital exemption; diversity of the clinical trial decisions

→ The ATMP legislation should be strengthened and **national decisions to be streamlined** (CT, HE, classifications), **clear borders for ATMP classifications**

- ✓ Small developers, limited understanding of regulatory requirements, huge workload, difficult to get funding before and after the MAA

→ **More funding options, improved coherence of the MAA and HTA assessment**

- ✓ **Prospective, thoroughly planned development pathways for ATMPs!**

B.Mellor, Nature 2008

*Thank you for your attention!*

## Colton And Abbygail Ainslie, Siblings With SCID, Among First Cured Of 'Bubble Boy Disease'

(Photo: Facebook/Jessica Ainslie)

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