Challenges during the development of ATMPs

CAT-DGTI Workshop
Dresden 11.9.2014

Paula Salmikangas
CAT Chair
Gene Therapy Medicinal Products

Somatic Cell Therapy Medicinal Products

Tissue Engineering Products

Genetically modified cells

Encapsulated Cell Technology

Medical device + ATMP → combined ATMP
The EU legal / regulatory framework

Blood
2002/98/EC

Clinical Trials
2001/20/EC

Paediatrics
1901/2006

‘Annex I’
2003/63/EC
2009/120/EC

Tissues/Cells
2004/23/EC

PhVig legislation
Dir. 2010/84/EU
Reg. 1235/2010

Other starting materials

Medical Devices
93/42/EC, 90/385/EC

GMP
2003/94/EC

Orphans
141/2000

Variations
1084(5)/2003
1234/2008

Advanced Therapy
1394/2007

Falsified Med.
Dir. 2011/62/EU

→ 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

CAT
Chair: P. Salmikangas

CHMP
Chair: Dr. T. Salmonsson

5 “double members”

Overview of CAT expertise

- Biotech 19%
- Tissue Engineering 15%
- Cell Therapy 26%
- Gene Therapy 17%
- Surgery 1%
- Phvig Med Dev 6%
- Ethics 11%
Marketing authorization applications / CAT 2009-2014 (May)

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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)

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- > **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, safety aspects (species specificities)

- **clinical aspects**
  - possibilities for blinding, availability of comparators
  - 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)
- Dedifferentiation / 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
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 license

- 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

Products legally on national markets via GMP certificate

Reg. 1394/2007/EC

Hospital exemption Article 28, 1394/2007/EC

Transitional period
ATMPs, other than TEP 30.12.2011

Marketing stopped

Centralised MAA
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

✓ Physicisians 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!
Thank you for your attention!