European perspective on ATMPs

International Regulatory Forum of Human Cell and Gene Therapy Products

Osaka, Japan 16.3.2016

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CAT Chair
Gene Therapy Medicinal Products

Somatic Cell Therapy Medicinal Products

Tissue Engineering Products

Genetically modified cells

medical device + ATMP → combined ATMP

Severe burn victim before and 6 months after treatment with Dermagraft.
The EU legal / regulatory framework

Blood
- 2002/98/EC

Clinical Trials
- 2001/20/EC

Paediatrics
- 1901/2006

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

‘Annex I’
- 2003/63/EC
- 2009/120/EC

Advanced Therapy
- 1394/2007

Medicinal Products
Community Code
- Dir. 2001/83/EC

Centralised procedure
- Reg. 726/2004

A new class of medicinal products with a dedicated regulation
Centralized Marketing Authorisation obligatory for ATMPs

Scientific advice (national and/or EMA), certification

Development
Preclinical
Clinical trials
PhI PhII PhIII
MAA Review
Post Marketing

GMO application
GMP
CT application (national authorities)
Pre MAA Meetings (Rapp & Co-Rapp)
PSUR cycle

Quality & Manufacturing
Safety
Efficacy
Risk Management Plan

CE marking/
Evaluation of structural
Component(s) by
Notified Body
Supervision and authorisation of medicinal products

- National Medicines Agencies, European Medicines Agency 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 licence is given, **Evaluation by NCA**
EMA Committees for ATMPs

**CAT**
Chair: P. Salmikangas

- 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.)

**CHMP**
Chair: T. Salmonsson

5 "double members"

Total 68 experts
Tasks of the CAT

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

EVALUATION
CERTIFICATION
CLASSIFICATION

Tasks defined per legislation
### Marketing authorization applications / CAT 2009-2016 (January)

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**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)

- **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

- Substantial manipulation
  - Enzymatic digestion

- Same essential 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

Signalling
Morphology
Functionality
Gene expression
Energy
Motility
Respiration
Quality of proteins
Differentiation
Proliferation
Apoptosis
Integrity of organelles
Viability
Metabolic activity
Respiration
Energy
Morphology
Functionality
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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 comparators
- specific administration of certain ATMPs (catheters, surgery etc.), concomitant medication
Building the evidence
<table>
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<tr>
<th>Directive 2001/83/EC</th>
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Quality development

**Characterisation**

Definition of critical quality parameters

- In-process testing
- Process validation
- Batch release testing
- Stability testing

- Changes in manufacture

Comparability testing

- Non-clinical / Clinical testing
Quality

- Microbiological purity
- Cellular impurities
- Process-related impurities
- Cell transformation / malignancies
- Immunogenicity
- Genomic instability \textit{in vivo}
- Ectopic engraftment to non-target tissues

Safety

Efficacy

- Dedifferentiation / 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

Guideline on cell-based medicinal products (2008)

Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)

Reflection paper on stem-cell based MPs

Guideline on Xenogeneic CBMPs (2009)

Reflection paper on Chondrocyte containing MPs for cartilage repair (2009)

Guideline on MPs containing genetically modified cells

Clinical aspects related to tissue engineered products

Guideline on the Risk-based approach (2013)

Available guidance for GTMPs


- Development and Manufacture of Lentiviral Vectors
  - Non-clinical studies required before first clinical use of gene therapy medicinal products
- Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products
- Follow-up of patients administered with gene therapy medicinal products
- Guideline on MPs containing genetically modified cells
- Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors
- Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors
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

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
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.

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


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Thank you for your attention!