EU Regulatory Network

Challenges and Opportunities for Croatia

5th ALMP Anniversary

13-14 November 2008, Rijeka - Croatia

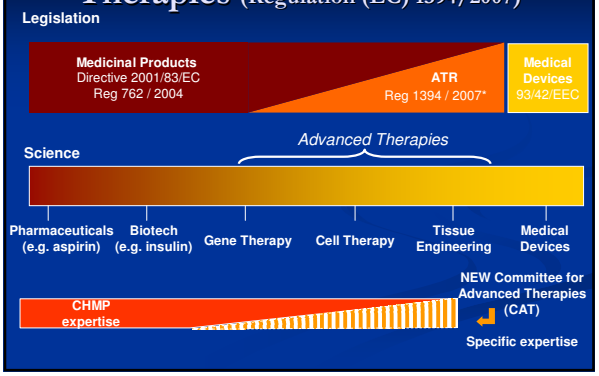
Implementation of Advanced Therapies

Tony Humphreys
EMEA
Head of Sector
Regulatory Affairs and Organisational Support (RAOS)

Content

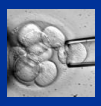
- "Medicinal Product" type
- Access to European Expertise
- Provision Regulatory Framework for Industry
- Centralised Review Process

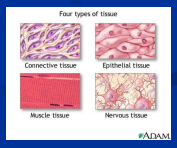
Regulation on Advanced Therapies (Regulation (EC) 1394/2007)



Regulation on Advanced Therapies Key elements

- Advanced Therapy medicinal products (ATMP)
  - Gene therapy products
  - Somatic Cell therapy products
  - Tissue engineered products

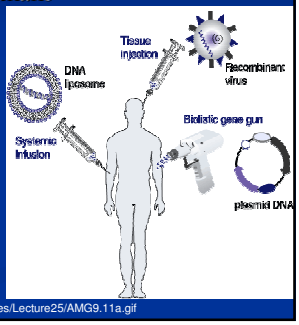




What is a gene therapy product?

- Medicinal product aiming at the transfer of a functional gene into humans

- **Type of gene therapy**
  - non-specific placement
  - swap/repair a gene
  - transcription regulation
- **Vectors**
  - viral/non-viral/hybrid
- **Transduction**
  - ex vivo / in vivo
  - target cells



http://www.biochem.arizona.edu/classes/bioc471/pages/Lecture25/AMG9.11a.gif

Main Indications of Gene Therapy in Clinical Trials

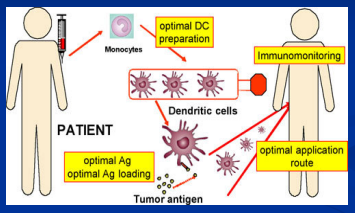
- AAT (a-1-Anti-trypsin deficiency)
- Eye diseases (AMD, inherited retinal degenerations)
- Cystic fibrosis
- Muscular dystrophies
- Severe combined immunodeficiencies
- Chronic granulomatous disease
- Coronary artery disease
- Peripheral vascular diseases
- Skin diseases (*ichtyosis, xeroderma pigmentosum, epidermolysis bullosa*)
- Lysosomal storage disorders
- Neurology (Parkinson's, Huntington's, Alzheimer's diseases)
- HIV/AIDS
- Ornithine transcarbamylase deficiency
- Blood diseases (Hemophilia, Thalasemia, Sicle cells…)
- Cancer
  - Immunotherapy
  - Oncolytic viruses
  - Suicide gene therapy

Ref: E Alton et al: Gene therapy and clinical trials. Gene Therapy (2007) 14, 1439-1447 and 1555-1563

What is a cell therapy product?

- Medicinal product based on the administration of manipulated cells into humans
  - Cells / tissues from patient itself, from another human or from animals
  - Manipulated (engineered) cells / tissues
  - Treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues

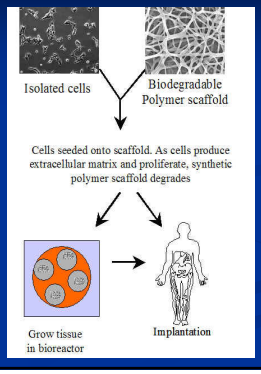
Example: Cancer Cell therapy



What is a Tissue Engineered product?

- Tissue Engineered products (TEP)
  - Contain/consist of engineered cells/tissues
  - Administered to human to regenerate, repair or replace a human tissue
- Examples:
  - Artificial skin (burn wounds)
  - Cartilage repair
  - Neo-organs

Tissue engineered products



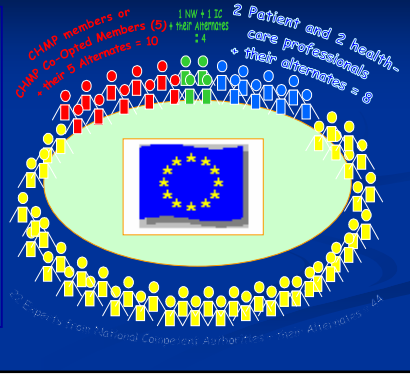
Evaluation procedure for ATMP

- Centralised procedure mandatory:
  - pooling of Community expertise
  - harmonised requirements & evaluation
  - ensure uniform and direct access to market
- Single evaluation and authorisation for the entire EU

CAT Composition

CAT should covers the scientific areas relevant to advanced therapies, including:
- Medical devices
- Tissue engineering,
- Gene therapy,
- Cell therapy,
- Biotechnology,
- Surgery,
-
Pharmacovigilance,
- Risk management and
- Ethics.

[Recital 9 & Art.21]



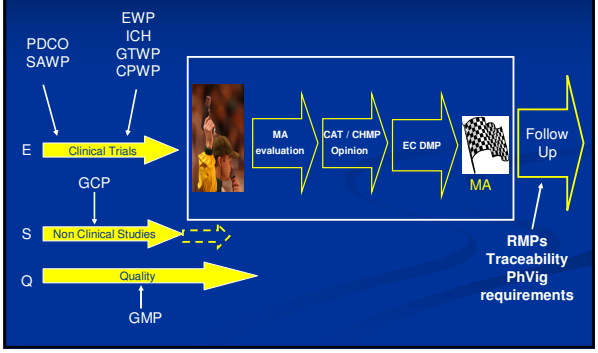
Development of new procedures

- Tasks of CAT: procedures/procedural guideline
  - Evaluation of MAA for ATMP
    - Preparation of draft Opinion for adoption by CHMP within 210 days
    - Interactions with Notified Bodies (combined ATMP)
  - Re-examination procedure
  - Scientific classification of ATMP
  - Scientific advice (contribution to SAWP)

Regulation on Advanced Therapies Key elements

- Principles of existing legislation on medicines apply to advanced therapies:
  - Quality, Safety & Efficacy
  - Marketing authorisation
  - Post-authorisation vigilance

Development Life Cycle ATPs



GMP and GCP for ATMP

- Guidelines to reflect specificities of ATMP: discussions ongoing

- But: No change to Dir 2003/94/EC (GMP) / 2001/20/EC (GCP) / Dir 2001/83/EC (Title IV – Manufacture and importation)

Gene Therapy Products

Development of Guidelines

- Multidisciplinary GL on gene transfer MP
- Lentiviral vector, quality & manufacture
- Inadvertent Germline transmission
- medicinal products containing genetically modified cells
- non-clinical studies required before first clinical use of gene therapy medicinal products
- on clinical monitoring and follow-up of patients exposed to gene therapy/gene transfer medicinal products
- Environmental risk assessment of gene therapy medicinal products

Cell-based Medicinal Products

Development of Guidelines

Guideline on cell-based medicinal product

- *Somatic cell therapy products*
- *Tissue engineered products*
  - *Multidisciplinary GL (Quality, Non-clinical, Clinical)*

- Revision of the PtC on Xenogeneic cell therapy medicinal product
- GL on clinical follow-up of patients exposed to cell-based medicinal products
- Multidisciplinary GL on Xenogeneic Cell Therapy MP

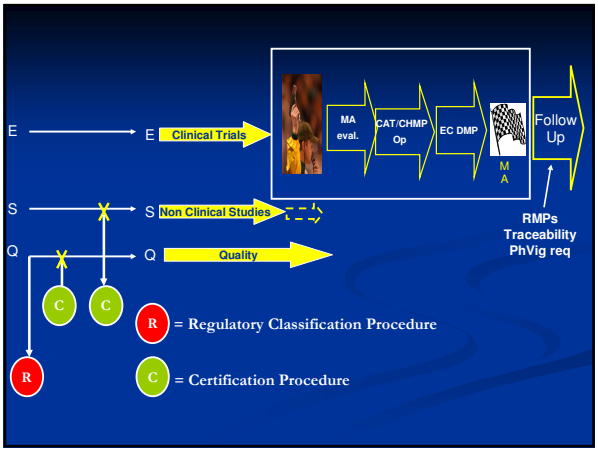
Dossier requirements

- GTMP (revision), somatic CTMP (revision) and TEP (new)
  - Will become part of Annex I of Directive 2001/83/EC
  - Draft published by the EC for external consultation
- Annex I will address:
  - Requirements specific for ATMP
    - E.g. Interactions between cells and structural components
  - Additional flexibility where needed for ATMP

Traceability

Input in GL development by EC

- 3 levels of traceability to work together:
  - From donor to tissue establishment *(DG Sanco Directive*
  - From receipt of cells/tissue in pharmaceutical facility to the delivery of cell-based product at the hospital
  - From receipt in hospital to adminstration to patients & patient follow-up if required
- MAH responsible for the system for traceability
- Sourcing to delivery



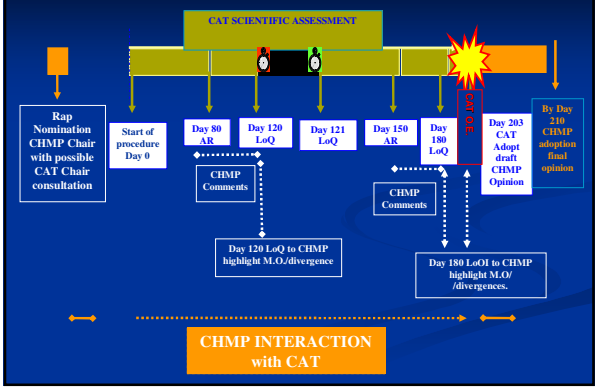
CAT-CHMP interactions

Assessment Team 1

Assessment Team 2

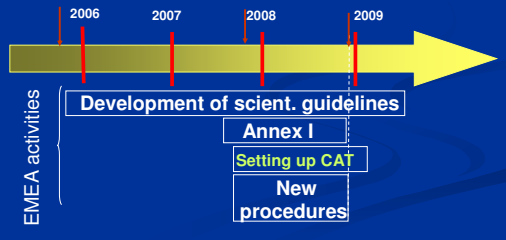
CHMP Rapporteur	CHMP Co-Rapporteur
CAT Rapporteur	CAT Co-Rapporteur
Q / S / E (ATP) experts	Q / S / E (ATP) experts

CAT-CHMP Interactions



Implementation of the Advanced Therapies Regulation

Nov 2005	December 2007	End Dec. 2008
ATMP Regulation Proposal	Publication ATMP Reg. 1394/2007	Application of Reg. 1394/2007



Products legally on market