European Perspectives on Advanced Therapy Medicinal Products (ATMP)

PMDA 2nd International Symposium on Biologics
Tokyo, 17th January, 2008

P. ZORZI
Department for Evaluation of Biologics
OVERVIEW

- Products defined as ATMP
- European Bodies and Procedures
- EC Regulation on ATMP (1394/2007/EC - 13 Nov 2007)
- Cell/Tissues at National level: ex of France
  - National authorizations
  - Clinical trials
  - Biovigilance
Products Defined as ATMP

- Cell therapy Medicinal Products
- Gene Therapy Medicinal Products
- Tissues engineered Medicinal Products

Centralized european procedures mandatory
OVERVIEW

• Products defined as ATMP

• European Bodies and Procedures

• EC Regulation on ATMP (1394/2007/EC - 13 Nov 2007)

• Cell/Tissues at National level: ex of France
  • National authorizations
  • Clinical trials
  • Biovigilance
EU Bodies and Procedures
European Medicines Agency (EMEA)

- 1995: European Agency for the Evaluation of Medicinal Products (EMEA)
- 2004 (EC No 726/2004): European Medicines scientific resources for Agency (EMEA)
  - Coordinates the evaluation, supervision and pharmacovigilance of medicinal products
  - Scientific resources: 27 member states
  - Over 4000 European experts
  - ~440 staff members

http://www.emea.eu.int/
EU Bodies and Procedures
European Medicines Agency (EMEA)

EMEA Scientific Committees

CVMP
Committee for Medicinal Product for Veterinary use

CHMP
Committee for Medicinal Product for Human use

COMP
Committee of Orphan Medicinal Product

HCMP
Committee for Herbal Medicinal Product
EU Bodies and Procedures
European Medicines Agency (EMEA)

**CHMP**
- Responsible for the scientific opinions (Q, S, E)
- 1 representative for each member state
- Chairman (3 years)
- Working groups (permanent, ad’hoc)

CHMP Working Parties

- Efficacy Working Party
- Scientific Advice Working Party
- Pharmacovigilance Working Party
- ‘Biosimilar’ Working Party
- Gene Therapy Working Party
- Biotechnology Working Party
- Blood and Plasma Working Party
- Vaccine Working Party
- Cell Based Working Party
- Quality Working Party
- Inspector Working Party
# EU Bodies and Procedures

## Registration Procedures

<table>
<thead>
<tr>
<th>Dossier Submission</th>
<th>National</th>
<th><strong>Mutual Recognition</strong></th>
<th><strong>Centralized</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>National</td>
<td>Recognition of first country approval</td>
<td>1 EMEA</td>
</tr>
<tr>
<td>Scientific Opinion</td>
<td>National</td>
<td>Each member State Ex: 4 approval, 2 rejection</td>
<td>CHMP/EMEA (London)</td>
</tr>
<tr>
<td>Administrative Decision</td>
<td>National</td>
<td>National Harmonized SPC all EU Ex: commercialized in 4+1 MS</td>
<td>Eur. Com. (Brussels) 1 MA all EU 1 SPC, labelling, package leaflet</td>
</tr>
</tbody>
</table>
European Union adopts legislation in the form of Directives and Regulations

- **Directives** require member states to implement their provisions nationally for the benefit of Europe as a whole.

- **Regulations** directly implement EU policy in member states without the need for member states to enact their own legislation.
OVERVIEW

• Products defined as ATMP

• European Bodies and Procedures

• EC Regulation on ATMP (1394/2007/EC - 13 Nov 2007)

• Cell/Tissues at National level: ex of France
  • National authorizations
  • Clinical trials
  • Biovigilance
# Advanced Therapies Medicinal Products

## Divergent National Systems

<table>
<thead>
<tr>
<th>Framework</th>
<th>Austria</th>
<th>Belgium</th>
<th>Bulgaria</th>
<th>Cyprus</th>
<th>Finland</th>
<th>France</th>
<th>Germany</th>
<th>Ireland</th>
<th>Netherlands</th>
<th>Poland</th>
<th>Slovakia</th>
<th>Spain</th>
<th>Sweden</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>not at all</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as medicinal product (MP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as medical device (MD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as MP or MD, decided on case-by-case basis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>specific national guidance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other regulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>by product authorisation (PA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>by manufacturing authorisation (MA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>by accreditation... of the tissue establishment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>by PA and MA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>from EU MS mandatory through accredited... tissue establishment in your country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>from non-EU country mandatory through accredited... tissue establishment in your country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ref.: Joint Research Centre, European Commission, 2003 (see also impact assessment of the proposal)
Advanced Therapies Medicinal Products
Need for harmonized regulatory framework

• Because of the novelty, complexity and technical specificity, need to have a specially tailored and harmonized rules to ensure free movement of those products within the community

• ATMP
  • Products already covered by European regulations:
    • Gene therapy MP
    • Cell therapy MP
  • Newly included
    • Tissue engineered MP
    • Combination product containing human viable cells/tissues and med devices: regulated under this new regulation
• **Somatic Cell Therapy MP** (from Dir 2001/83/EC) *under revision*
  Autologous, allogeneic or xenogeneic *living* cells,
  biological characteristics substantially modified, altered
  to obtain a therapeutic, diagnostic or preventive effect through
  metabolic, pharmacologic and immunological means

• **Gene Therapy MP** (from Dir 2001/83/EC) *under revision*
  Transfer, to be performed in vivo or ex vivo of a prophylactic, diagnostic
  or therapeutic gene to human or animal cells.
  Gene transfer involves an expression system contained in a delivery
  system known as a vector, which can be of viral as well as non viral
  origin
**Tissue Engineered Product** (Newly covered by the Regulation)
contains cell or tissues of human or animal origin

*cells may be viable or non viable*

may also contain additional substances: cellular products, biomolecules, biomaterials, chemical substances, scaffold, matrices

• TEP means a product that:
contains or consists of engineered cells or tissues
is presented as having properties for, or is used in, or administer to human being with a view to regenerating, repairing or replacing a human tissue

• Combination product containing viable cells and medical devices:
regulated under this new regulation (not any more under med device directives)
Excluded from the definition TEP

Product containing or consisting of non viable cells/tissues, which do not act principally by pharmacological, immunologically or metabolic actions

Excluded from the scope of the regulation

ATMP prepared in a non-routine basis,
Used within the same member state, in a hospital, for an individual patient
In that case: manufacturing is authorized by the MS. Traceability, pharmacovigilance requirements, specific quality standards at national level should be equivalent to the regulation

Case of Embryonic stem cells and animal cells
The use (or not) of medicinal products containing such cells remains a national decision (ex. for ethical reasons...)
Advanced Therapies Medicinal Products

Key principles of the proposal

• No marketing without prior authorization
• Centralized procedure mandatory
• Evaluation by EMEA
• Demonstration of Quality, Safety & Efficacy
• Dossier: same as medicinal product (CTD applicable, with technical adaptations)
• Post-authorization vigilance
Pre-authorization requirements
  • When Medical Device present: Compliance with ‘Essential Requirements’ as defined in the EU Directives on Medical Devices
  • Specific guidelines currently under discussion
    • GMP (Good Manufacturing Practice)
    • GCP (Good Clinical Practice)
  • Specific rules for labeling/packaging

Post-authorization requirements
  • Follow-up of efficacy, adverse reactions and risk management
  • Traceability
General provisions

- **Scientific Advice:**
  - 90% fee reduction for SMEs, 65% for others
  - No limit in time
- **Scientific recommendation on advanced therapy classification:** 60 days
Specific provisions (SMEs, hospitals)

- SMEs: EARLY STAGE OF DEV / Certification by EMEA of quality and non-clinical data
  - Not a marketing authorization
  - Not ‘legally binding’ for the Agency
  - Mostly quality and, where available, non-clinical data

- Additional Fee reduction if applicant is SME or hospital and can prove there is a particular public health interest in the Community
  - 50% fee reduction on MA fee
  - 50% post-authorization activities during one year
  - Applies only during transitional period
• **Transitional period:** products already on the market <30 Dec 2008 (national or Europe)
  - For cell and Gene Therapy MP: shall comply < 30 Dec 2011
  - For Tissue Engineered MP: shall comply <30 Dec 2012

• **During transitional period, no MA fee for upgrade of ‘national products’**

*European Commission*

http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm
Advanced Therapies Medicinal Products
EMEA Technical Guidances


- Human Cell Based MP CPMP/BWP/410869/06 (en consultation)
- Points to Consider on Xenogeneic Cell Therapy MP CPMP/1199/02 (Nov 2000)
- Gene Therapy Product Quality Aspects in the Production of Vectors and Genetically Modified Somatic Cells
- Environmental Risk Assessments for Medicinal Products containing, or consisting of, Genetically Modified Organisms (GMOs) (EMEA/CHMP/473191/06)
- .....
OVERVIEW

• Products defined as ATMP

• European Bodies and Procedures

• EC Regulation on ATMP (1394/2007/EC - 13 Nov 2007)

• Cell/Tissues at National level: ex of France
  • National authorizations
  • Clinical trials
  • Biovigilance
French organization
Afssaps

Agence française de sécurité sanitaire des produits de santé
(French Health Products Safety Agency)

- National Agency
- ~900 employees
- ~2000 experts

http://afssaps.sante.fr/
Main Laws

- GMO (92) - Bioethical (94, revised each 5 years) - DMOSS (96) - "Afssaps"(98)
- Decree 1st Oct 2001

Afssaps: Authority Responsible

- Cellular Therapy / Gene Therapy products
- « Ancillary » products
- Tissues, Organs
Afssaps Authorizations

- **Establishments**
  - Private Cies: pharmaceutical establishments
  - Public organisms
- **Products**
  - Proprietary medicinal products
  - Non proprietary med products
- **Clinical trials**

Afssaps Responsabilities

- **Inspection**
- **Biovigilance**
- **Quality controls**
Cells/Tissues
Afssaps Authorizations and Responsabilities

All types of products covered

• **Simple Processes**
  • Autologous HSC frozen/ stored /shipped prior re-administration

• **Complex Processes**
  • Cell therapy: selection, propagation, differentiation, incorporation into a matrix...
  • Gene therapy i.e. viral vectors: banking system, culture, purification and lyophilisation

• **Proprietary medicinal products**
  • Recombinant viral vectors
  • Allogeneic fibroblasts (diabetic fore-foot ulcer)

• **Non proprietary medicinal products**
  • Autologous: Hematopoietic stem cell (cancer), Keratinocytes (burned patients)
  • Allogeneic: pancreatic cells (diabetes patients), fetal neurons (Parkinson, Huntington)
Cells/Tissues
Afssaps Authorizations and Responsibilities

- **Cell therapy**
  - Hematopoietic stem cells (allogeneic, autologous) in 35 Establishments (cell banks)
  - Other cells: only clinical trials

- **Gene therapy**
  - No product on the market in France. Only clinical trials

- **Tissues**
  - Establishments authorized: 40
  - Products authorized (or ongoing): Corneas, Bones (cryopreserved or viro inactivated), Skin, Cardiac valves, vessels
  - Clinical trials: Amniotic membrane in vascular ulcer, trachea replacing aorta, ovarian tissue autotransplant (chemotherapy situation)

- **Organs**
  - Clinical Trials: Face transplantation, Hand transplantation
Pharma. Establishments
or non Pharma. Est. (public/private)

Same manufacturing steps
- Starting materials
- Bulk active ingredient
- Finished medicinal product

Same requirements
- QA system
- Starting materials (quality/traceability)
- Process validated and reproducible
- QC of the product to be administered

Proprietary
or
non Propr
Med. Prod
Concept of viral safety based on **3 complementary levels**

1. Quality of starting material and other raw materials (ie ancillary products PTA)

2. Efficacy of the production process to eliminate/inactivate viruses

3. Virological in-process controls

The respective importance of each parameter is related to the type of product
### Viral Safety

#### Starting materials and reagents
- **Rec Products**
  - Cell banks
  - Bov.serum
- **Plasma DMP**
  - Donor selection
  - Tests for infection
- **Cell Therapy/Tissues**
  - Donor selection
  - Ancillary products

#### Product/intermediate
- **Rec Products**
  - Testing (harvest)
- **Plasma DMP**
  - Testing (pool)

#### Process
- **Rec Products**
  - Eliminat°/inactiv°
  - Validation (spik.)
- **Plasma DMP**
  - Eliminat°/inactiv°
  - Validation (spik.)
- **Cell Therapy/Tissues**
  - If any

---

**Benefit / risk**
### Donor Selection

<table>
<thead>
<tr>
<th>Clinical selection</th>
<th>Exclusion criteria regarding transmissible infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological selection</strong></td>
<td></td>
</tr>
<tr>
<td>HIV ½ Ab + AgP24 or RNA-HIV 1</td>
<td></td>
</tr>
<tr>
<td>HCV Ab</td>
<td></td>
</tr>
<tr>
<td>AgHBs + Anti-HBc Ab + Anti-HBs Ab</td>
<td></td>
</tr>
<tr>
<td>HTLV I/II Ab</td>
<td></td>
</tr>
<tr>
<td>T. Pallidum (serology)</td>
<td></td>
</tr>
<tr>
<td>CMV Ab</td>
<td></td>
</tr>
<tr>
<td>EBV Ab</td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis serology</td>
<td></td>
</tr>
<tr>
<td><strong>Cells / Tissues</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cells only</strong></td>
<td></td>
</tr>
</tbody>
</table>

| Regulatory Framework | |
|----------------------| |
| European Directive 2006/17/CE | |
| Décret et arrêté du 21/12/05 | |
| Arrêté du 14/01/04 | |
Ancillary products: Examples

- Foetal bovine serum (FBS)
- Trypsin
- Milk derivatives (casein...)
- Insulin
- Cytokines
- Amino-Acids (component of some culture media...)
- Human albumin or transferrin

......
Ancillary products: Documentation to be submitted

Conventional viruses aspects
- quality of starting material (geographical origin, species, tissue), viral testing if appropriate
- main steps of the manufacturing process dedicated to viruses inactivation/removal (ie. autoclaving)

TSE aspects (for products derived from ruminants)
- CEP TSE delivered by EDQM should be provided or appropriate documentation according NFG EMEA/410/01
OVERVIEW

• Products defined as ATMP

• European Bodies and Procedures

• EC Regulation on ATMP (1394/2007/EC -13 Nov 2007)

• Cell/Tissues at National level: ex of France
  • National authorizations
  • Clinical trials
  • Biovigilance
Clinical Trials in France

Cell Therapy

- **Since 1996** ~ 230 trials submitted

- **Sponsors**
  - 80% public establishments
  - Others: pharmaceutical companies

- **Type of cells**
  - 60% Hematopoietic stem cells
  - 75% autologous
Clinical Trials in France
Cell Therapy

- **Haematopoietic stem cells**: marrow, peripheral, placental
  - Hematology: lymphoma, leukemia (ALL, AML...)
  - Cardiomyoplasty, lower limb arteriopathy
- **Immune cells**: Macrophages, dendritic, dexosomes, T cells
  - Immunotherapy of cancers (melanoma, lung, kidney, ovarian...) and infectious diseases
- **Chondrocytes**
  - Knee articular cartilage injuries
- **Keratinocytes/ Fibroblasts**
  - Venous ulcer, diabetic forefoot ulcer, second and third degree burns
- **Nervous cells**
  - Parkinson, huntington diseases
- **Myoblasts**
  - Severe postinfarction left ventricular dysfunction
- **Pancreatic islets**
  - Diabetis mellitus
Clinical Trials in France
Gene Therapy

- Since 1993 ~ 70 trials submitted
- Sponsors
  - 1/3 public establishments
  - 2/3 pharmaceutical companies
- Vectors
  - Viral: Retrov, Adenov, Lentiv, AAV, Pox
  - Non viral: Plasmids
- Strategies
  - ¾ In vivo - ¼ Ex vivo
- Clinical Phase
  - Phase I-II mostly (phase III <5)
OVERVIEW

• Products defined as ATMP

• European Bodies and Procedures

• EC Regulation on ATMP (1394/2007/EC - 13 Nov 2007)

• Cell/Tissues at National level: ex of France
  • National authorizations
  • Clinical trials
  • Biovigilance
To supervise and assess:

- the risk of event and events in relation with products and activities (procurement, processing, testing, storage...)
  
  Examples: microbiological contamination, incomplete serological data, viral inactivation, process failure....

- adverse reactions in the living donor or patient

  Examples: allergic reaction, keratitis, fever, infectious diseases, anaphylactic reaction, neurological disorders
### Biovigilance Products Covered

<table>
<thead>
<tr>
<th>Products included in the biovigilance field</th>
<th>Products excluded from the biovigilance field</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Human organs, tissues or cells intended for therapeutic application as well as ancillary products</td>
<td>• Gamets <em>(Biomedecine Agency)</em></td>
</tr>
<tr>
<td>• Cellular therapy preparations</td>
<td>• Labile blood products</td>
</tr>
<tr>
<td>• Medical devices including human derived products</td>
<td>• Cell and gene therapy products requiring marketing authorization</td>
</tr>
<tr>
<td>• Ancillary products</td>
<td>• Other medical devices</td>
</tr>
<tr>
<td></td>
<td>• Human derived medicinal products (blood derived medicinal products, « extractive protein »)</td>
</tr>
<tr>
<td></td>
<td>• In vitro diagnosis devices</td>
</tr>
</tbody>
</table>
In Establishments in charge of:

- procurement or donation: public or private health establishments, blood establishments, ...

- processing, testing, preservation, storage, distribution, importation, exportation
  - tissue and cell establishments
  - manufacturer of ancillary products ...

- graft and administration: public or private health establishments...
No regional level

Wide range of application fields

variety of products and activities

variety of interlocutors

Not only one manufacturer (except for organs)

Wide variety of medical practices

Few notifications, far less than in Haemovigilance: nb events or reactions

**Cells/Tissues/organs** ~ 4200 organs grafted,
3000 autologous HSC,
1200 allogeneic HSC,
20 000 tissues

**Labile Blood Products** ~ 2 500 000 distributed

\[
\text{nb events or reactions}
\]
ensures organization of the Biovigilance system at a national level
- coordination of Biovigilance local contacts network
- assessment of Biovigilance notifications
- coordination of national Biovigilance actions (alerts, informations, recommendations..)

ensures that procedures are implemented in tissues establishment and in health establishments

the aim is to improve the safety of human organs, tissues, cells and ancillary products
1-SARs with organs

- very likely melanoma disease transmission by organs from one donor to the 4 recipients (1st case described in France)
- bibliographic research (similar cases described) and meeting with experts, ABM and Afssaps: official recommendations to health professionals

2-SARs with cell preparations: after autologous HSC infusion

- assessment by experts: reactions from multicausal origin (disease of the patient, chemotherapy, composition of graft, flow infusion,...)
- first hypothesis: SARs could be related to the amount of granulocytes in the aphaeresis product
- information of the professionals concerned
3-Events with ancillary products

- quality defect of a cornea preservation solution (abnormal color of the medium)
- no contamination, not batch-related, occurs only after thawing in the surgery block: some cornea lost
- investigations (manufacturer + Afssaps): the packaging was not adapted and moreover not in accordance with the specifications
- a new prototype of transport is proposed: event over
300 biovigilance correspondants appointed

notification form

working groups

- methodological aspects: guide of biovigilance, annual report format
- scientific aspects: melanoma, adverse reactions after HSC infusion

national commission: 1st meeting on the 21st March 2007

regional meeting on site with professionals of the network: in progress
Conclusions

• The framework published in Europe November 2007 for Advanced Therapy Medicinal Products will allow an harmonized marketing authorization throughout Europe for these products aiming at facilitating free circulation through member states. It will guarantee a high level of health protection for European patients.

• EMEA is setting up guidelines to harmonize evaluation criteria.

• For products which are outside the scope of the regulation, they will continue to be regulated at national level with still possible divergencies between members states. In France, the legal framework makes the Afssaps the authority responsible for all cells and tissues, even if they do not respond to the definition of Medicinal products (called “preparations”).