資料3－1

cell/tissue engineered products

- French experience
- European experience

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- *I attend this conference as an individual expert* and, although being a member of the CAT and BWP, my presentation might not be the view of the EMA and any of their Committees or working parties and neither of the French Medicines Agency (Afssaps).

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Presentation outlook

- ✓ The two regulatory status in Europe for « cell/tissue [engineered] products »
  - Tissues and cells directive
  - Advanced therapy medicinal products
- ✓ French experience and organisation
- ✓ European approach for ATMP
- ✓ CAT activities
  - Dossier evaluation
  - Classification
  - Scientific advice
  - Technical guidelines
  - Certification
- ✓ Conclusion

« cell/tissues [engineered] products » What are we speaking about?

- ✓ In Europe, two distinct regulatory systems:
  - Human tissue and cells → Directive 2004/23
  - Advanced Therapy Medicinal products → Regulation 1394/2007

Human tissues and cells Directive -1-

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 31 March 2004
on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

And subsequent directives

- DIRECTIVE 2006/17/EC on technical requirements for the donation, procurement and testing of human tissues and cells
- DIRECTIVE 2006/86/EC on traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

This Directive shall apply to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications.

Human tissues and cells Directive - 2-

The main chapters of Tissues and cells directive:

Article 3 : Definitions

- Tissue establishment: means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells;

Human tissues and cells Directive - 3-

The main chapters of Tissues and cells directive:

- Article 4 : National competent authorities responsible for implementing the requirements
- Article 5 : Supervision of human tissue and cell procurement
- Article 6 : Accreditation, designation, authorisation or licensing of
  - tissue establishments
  - tissue and cell preparation processes
- Article 7 : Inspections and control measures
- Article 8 :Traceability: from the donor to the recipient and vice versa.
- Article 9: Import/export of human tissues and cells
- Article 10: Register of tissue establishments and reporting obligations:
  - record of activities by tissues establishments
  - competent authorities to maintain a publicly accessible register of tissue establishments
- Article 11: Notification of serious adverse events and reactions:
  - Member States shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions

→ It is the Member States responsibilities to put in place the necessary regulatory framework to authorise, follow-up and monitor activities in the field of "tissues and cells".... Which are not considered as "medicinal products".

Human tissues and cells Directive - 4-

- The « Human tissues and cells » directive
  - Covers tissues and cells obtained from donation (autologous or allogeneic), intended for human application
  - Introduce the notion of
    - donation and procurment
    - testing and processing
    - preservation, storage
    - distribution of human tissues and cells
  - Introduce the definition and concept of
    - « tissue Establishment » authorised by National Competent Authorities,
    - National competent authorities responsible for accreditation, inspection, of the establishment(s) on their territory and vigilance → National duties for implementation of the Directive
- Human tissues and cells are not considered as medicinal products (and thus not all pharmaceutical requirements are applicable)
- However, « manufactured products » can be derived from those tissues and cells collected in « tissue establishments » and will be regulated by other regulation
- Human Tissues and Cells are under the responsibilities of tissue establishments and the "market" is relatively limited to national territory and use.... More for hospital use and for "conventional application".
- This contrast with the other types of "medicinal products" which may be derived from Human Tissues and Cells, designated as "advanced therapy medicinal products" (ATMPs) and covered now by the pharmaceutical legislation

Advanced Therapy Medicinal Products (ATMP)

✓ Second regulatory status possible in Europe for « cell/tissue [engineered] products »

✓ Regulation 1394/2007

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REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF

Regulation 1394/2007

Article 1

Subject matter

This Regulation lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

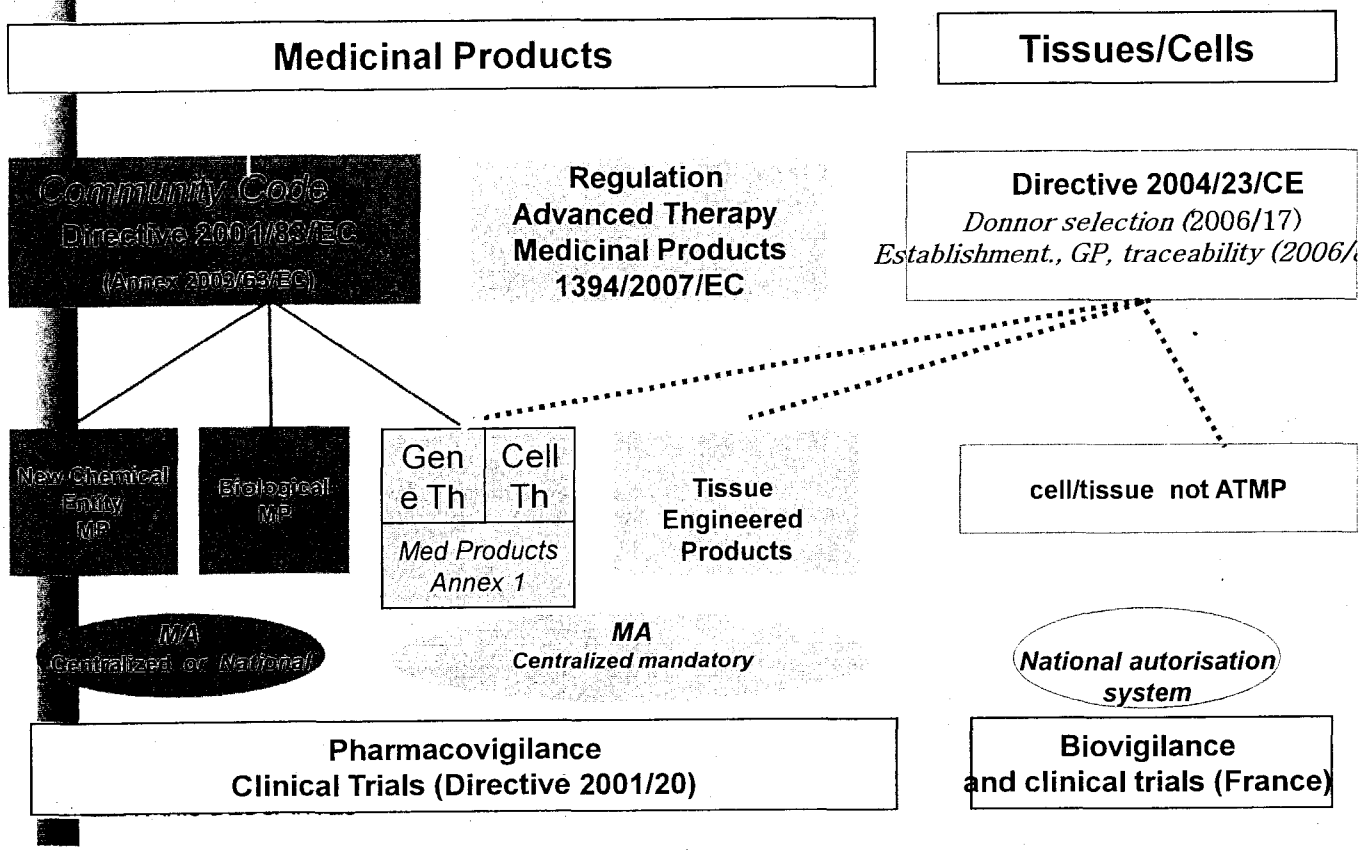
✓ Classifying tissue-based or cell-based products as medicinal products → pharmaceutical legislation applies in all aspects of the product life cycle:
- Development and Clinical trials
- GMP for the production/quality control
- Pharmacovigilance
- With additional requirements (long term follow up –art.14)

✓ EMA responsible for the regulatory framework

✓ One centralised Marketing Authorisation

✓ One scientific Committee to deal with the submission : CAT

European Regulatory Framework for tissues and cells products



The two regulatory status

	Dir. 2004/23 → National responsibilities	Reg. 1394/2007 → European framework
Product	Not considered as « medicinal product » but - Cell preparations - Tissues	Medicinal products: ATMP
Authorisation	National Authorisation(s)	EU centralised Marketing Authorisation
Establishment	« Tissue establishment » National accreditation (for France Tissues or cells establishment)	Pharmaceutical establishment Authorisation by National competent Authorities
Manufacturing practice	Based on the principles of cGMP with adaptation for Tissues and Cells (Dir. 2006/86) At the discretion of National authorities	GMP mandatory ATMP production covered in annex 2 of the EU cGMP (public consultation on going)
Dossier	National decision (in France adaptation of the CTD)	CTD format
Vigilance	National decision (in France « Biovigilance » is mandatory)	Pharmacovigilance + long term follow up
Clinical trials and GCPs	National decision (in France case by case, well established use or clinical trial evidence)	Mandatory to establish the risk-benefit profile and claimed indication(s)

Importance of classifying those products

- Importance of the definition /classification chosen, examples given:
  - T2c001™: Autologous bone marrow-derived mononuclear cells
    - a bone marrow aspirate followed by a ficoll centrifugation,
    - Acute myocardial infarction: cardiac re-injection in the left ventricle
    - → considered as ATMP, cell therapy
  - Chondroselect ™:
    - autologous chondrocytes, expanded from a cartilage biopsy
    - reimplanted in the cartilage defect
    - → ATMP, cell therapy
  - freeze-dried thrombocytes,
    - for application is any wound healing (orthopedics, dental surgery)
    - → not considered as medicinal product, to be regulated by Dir. 2004/23

- The « process » and final product and its claim(s) → qualify or not as « medicinal products »
- The autologous origin of the cells is not the only criteria to justify not being classified as medicinal product and not being imposed clinical trials and clinical evidence

Presentation outlook

- French experience and organisation

French organisation for « tissues and cells »

- In France, Afssaps is the Competent Authorities for regulating the two status

- The same department in Afssaps is in charge of dealing with the two types of products

Afssaps mandates and responsabilities

- Afssaps is in charge of authorising or accrediting
  - Tissues or cells Establishments
    - Private or Public organisations
  - Pharmaceutical establishment for ATMP

- Products to be authorised by Afssaps
  - Tissues or cells preparations (according to Dir. 2004/23): authorisation for a "preparation" (cells) or a "process" (tissues)
  - ATMP under the "hospital exemption" status

- Clinical trials
  - During the development of ATMPs
  - For qualification of the "tissue" or "cell preparation" to be authorised for use in France

- Other Responsabilities:
  - Inspection
    - Manufacturing sites for medicinal products (including ATMPs)
    - Tissue establishments
    - Academic/hospital labs involved in preparation of tissues or cell preparations used in clinical trials
  - Vigilance
    - Pharmacovigilance for medicinal products
    - Biovigilance for tissues and cells
- Quality controls of the products on the market

Cell "Preparation" Authorizations

- Cell establishments : 36
  50% public establisments (EFS) – 50% hospital
- Dossiers : around 140 applications for hematopoietic stem cells
  - Peripheral blood (majority)
    - Autologous
    - Allogeneic
  - Bone marrow
    - Autologous
    - Allogeneic
  - Umbilical cord blood (30 % but increasing number)
    - Allogeneic
  - CD 34+ (allogeneic peripheral HSC) only few
- Scientific data required for Quality, Safety, Efficacy (mainly well established use)

Tissue "Process" Authorizations

- Tissue establishments : 41
  50% held by the state establishment (EFS)
  40% hospital
  10% Private
- Dossiers : around 210 dossiers
  - Bones cryopreserved or viro inactivated
    - massive bone
    - femoral head
    - Others : iliac crest, skull bone flap...
  - Corneas
    - Keratoplasty
    - Cornea stopper
  - Skin
  - Amniotic membranes
  - Arteries, veins, valves
- Scientific data required for Quality, Safety, Efficacy (mainly well established use)

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
  - Veinous ulcer, diabetic forefoot ulcer, second and third degree burns
- ✓ Nervous cells
  - Parkinson, huntington diseases
- ✓ Myoblasts
  - Severe postinfarction left ventricular dysfunction
- ✓ Pancreatic islets
  - Diabetes mellitus

Clinical Trials in France
Tissues

- ✓ Amniotic membrane in corneal ulcer
- ✓ Trachea replacing aorta
- ✓ Ovarian tissue auto-transplant (chimotherapy situation)
- ✓ Face transplantation
- ✓ Forearm transplantation

French activities for ATMPs

- Essentially during the development stage of those « candidate » medicinal products
  - Authorisation for Clinical trials
  - Assistance for innovation development and Scientific advice
- Contribution to EMA and CAT activities for centralised authorisations
- Other contributions
  - joint discussion with official labs, inspectors,
  - « hospital exemption » autorisation → National competences

Presentation outlook

- European approach for ATMP

Consequence of the regulation -1-

- For products fulfilling the definitions (Gene therapy, cell therapy, tissue engineered):
  - Marketing authorisation before launching
  - Assessment of the Quality, Safety & Efficacy
  - Post-authorisation vigilance; specific obligation for safety and for efficacy
- Authorisation via the centralised procedure
- Same dossier as for a medicinal product (CTD) with technical adaptations)

Consequence of the regulation -2-

- Technical requirements:
  - Pre-authorisation:
    - Compliance with 'Essential Requirements' for combined products incorporating medical devices
    - Specific guidelines on
      - GMP (Good Manufacturing Practice)
      - GCP (Good Clinical Practice)
    - Specific rules for labelling/packaging
  - Post-authorisation requirements
    - Follow-up of efficacy and adverse reactions, and risk management: long term follow up → art. 14
    - Traceability