France Legal & Regulatory Framework For Cell/Tissue-based Products and Its Relationship With The European System

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Glossary for the presentation

- Cell/Tissue-based products

  Broader wording which includes all types of products whatever the status (medicinal or not)

- Tissue and Cell Directive

  Refers strictly to a specific EU Directive and its 2 annex directives.

- Tissue 'Processes' and Cell 'Preparations'

  French Wording specific to non-medicinal products

- ATMP : Advanced Therapy Medicinal products

  EU Regulation : Cell therapy MP; Gene therapy MP; Tissue engineered products

- MP : Medicinal Products
- MS : Member States which are part of the EU (27)
- National Competent authorities (NCA) : EU terminology
  - For Medicinal products : NCA is a Drug agency in the 27 MS (Afssaps in France)
  - For Non-ATMP : NCA varies from country to country (Afssaps in France)

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OVERVIEW

- Afssaps and European systems
- Cell/Tissue-based product legal framework: Relationship between European and National (France) levels
- Afssaps responsabilities for ATMP and non-ATMP Cell/Tissue
  - Product authorizations
  - Clinical trial authorizations
  - Scientific evaluation and Scientific advice

French Health Products Safety Agency Afssaps*

- **A public administrative organisation under Health Minister authority**
- **A global Public Health mission**

  for the safety, the quality and the proper use of health products.
- **Independence, expertise and transparency criteria**

  with the contribution and participation of scientific expert committees

~ 1000 employees
~ 2000 external experts

http://afssaps.sante.fr

* Agence Française De Sécurité Sanitaire Des Produits De Santé

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Afssaps
3 Locations

Afssaps
Headquarters and Laboratories
143/147, boulevard Anatole France
93285 SAINT-DENIS CEDEX - FRANCE
33-1.55.87.30.00

Afssaps Laboratories
321, avenue Jean Jaurès
69007 LYON - FRANCE

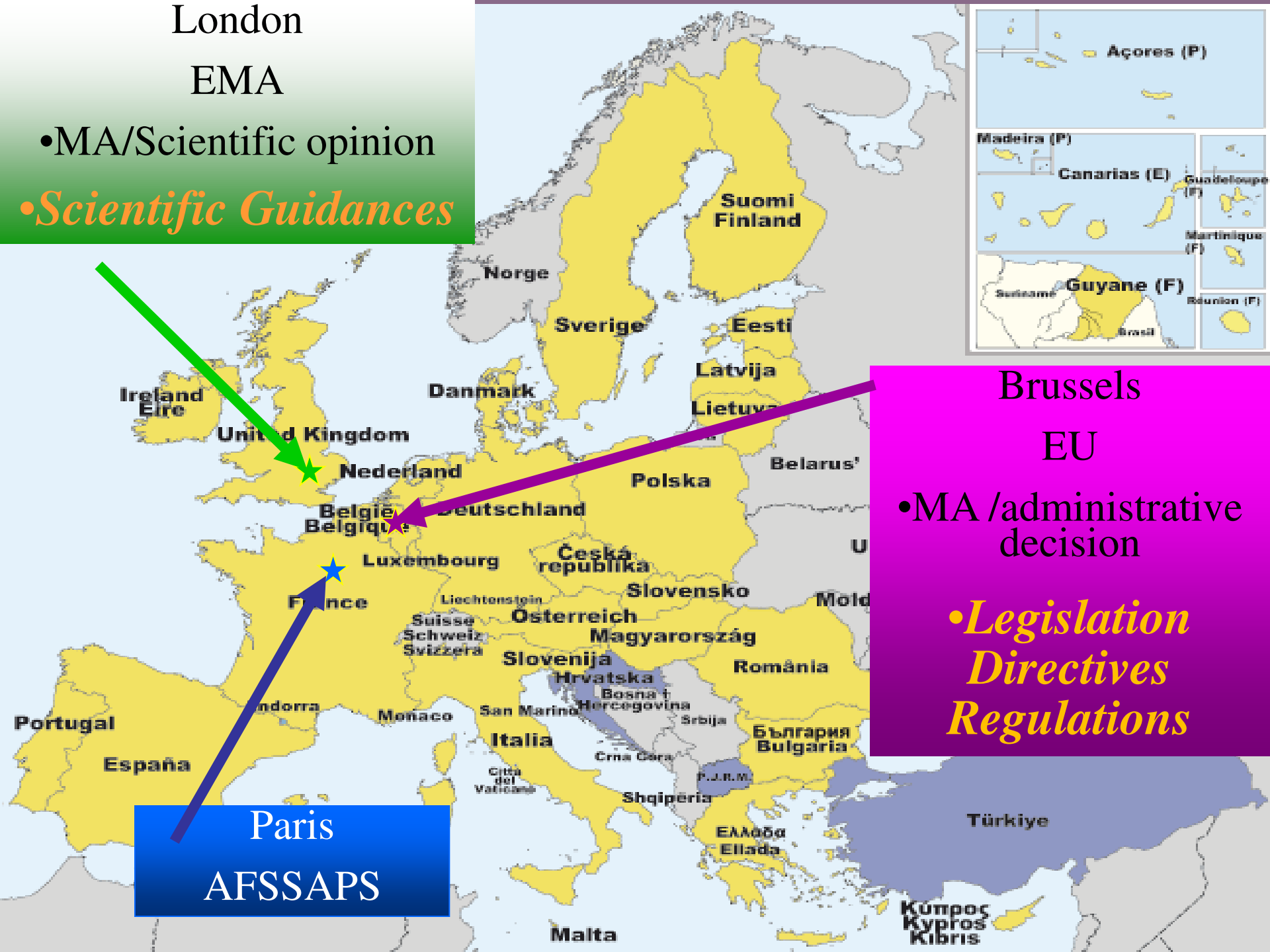
Afssaps Laboratories
635, rue de la Garenne
37740 VENDARGUES - FRANCE

Afssaps
Four Core Missions for health products

- **Evaluation** before and after product marketing
- **Quality control** in laboratories
- **Establishment authorizations** and site **inspections**
- **Information** to health professionals and general public

Afssaps
Biological Products

- Cell therapy products
- Gene therapy products
- Human tissues
- Media in contact with organs, tissues or cells ‘Therapeutic ancillary products’
- Recombinant proteins
- Extractive Products
- Vaccines
- Sera, Allergens
- Blood-derived medicinal products
- Blood products for transfusion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Malta

European Legal framework

European Union adopts legislation in the form of

Regulations	Directives
Binding requirements, directly in force in the 27 member states	**Common Minimal requirements nationally implemented by each member state** ***NB : MS can introduce more stringent protective measures***
Examples ***ATMP***	***Tissues/Cells*** ***Clinical Trials***

REGULATION (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

ATMP

- Classifying tissue-based or cell-based products as medicinal products → pharmaceutical legislation applies in all aspects of the life cycle of those products:
  - Clinical trials
  - GMP for the production/quality control
  - Pharmacovigilance
  - With additional requirements (long term follow up –art.14)
- One centralised regulatory system → EMA
- One centralised Marketing Authorisation
- One scientific Committee to deal with the submission : CAT

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DIRECTIVE 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human Tissues and Cells

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

Tissues and Cells

- Member state shall designate the National Competent Authority(ies) which will authorize Tissue Establishment
- 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

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Products Covered

ATMP Regulation	Tissue/Cell Directive
-Gene therapy MP **-Somatic cell therapy MP** **-Tissue engineered product (cell or tissue of human or animal origin. Cells may be viable or non-viable)**	**- Cell an Tissues products which are not ATMP, named 'preparation' and 'process' in the French system** Products not covered -Tissues and cells used as an autologous graft within the same surgical procedure -Blood and Blood components -organs or part of organs if it is their fonction to be used for the same purpose as the entire organ in the human body

NB : the provisions of the Tissue/Cell Directive, for donation, procurement and testing are applicable to ATMP

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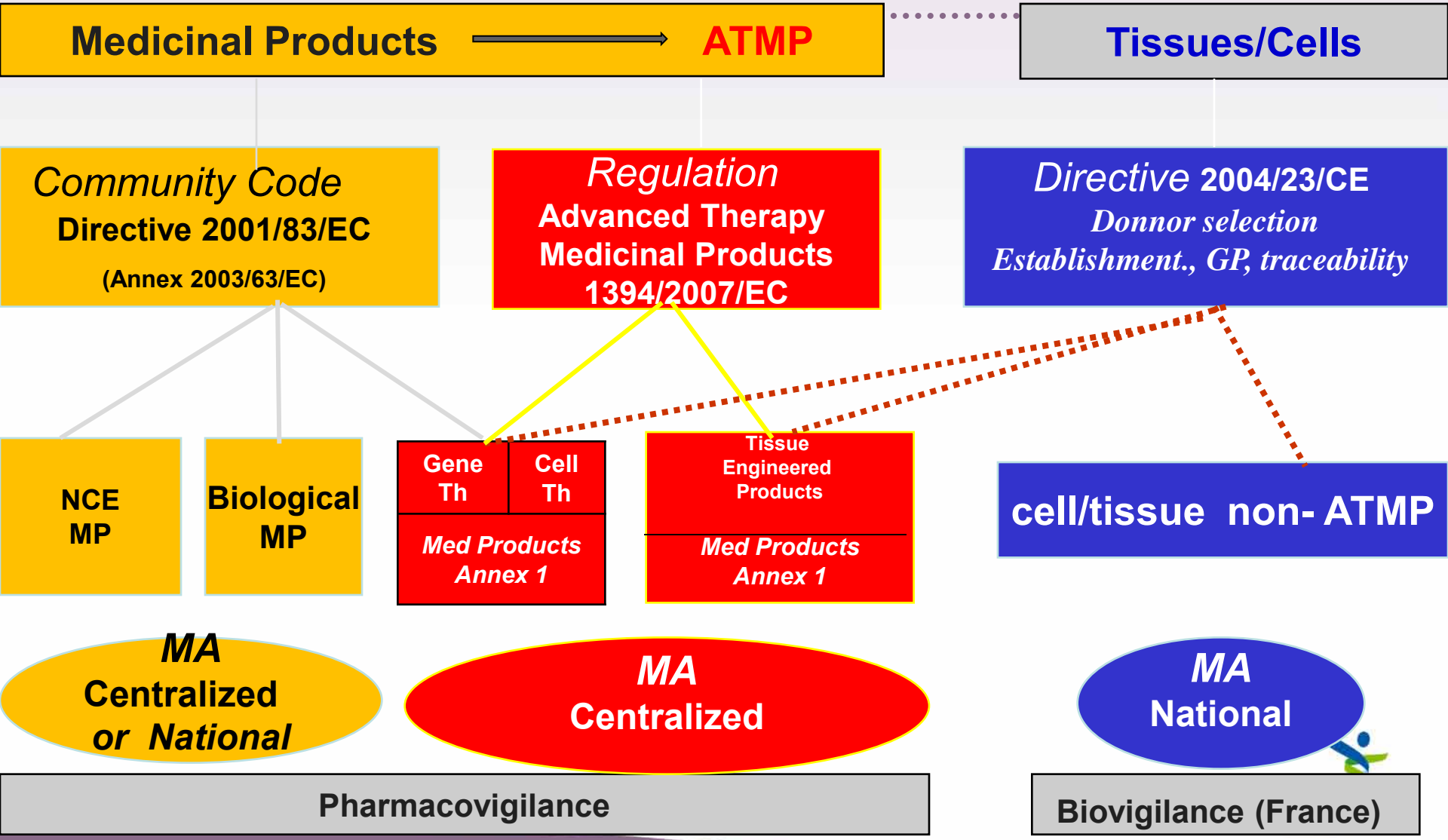
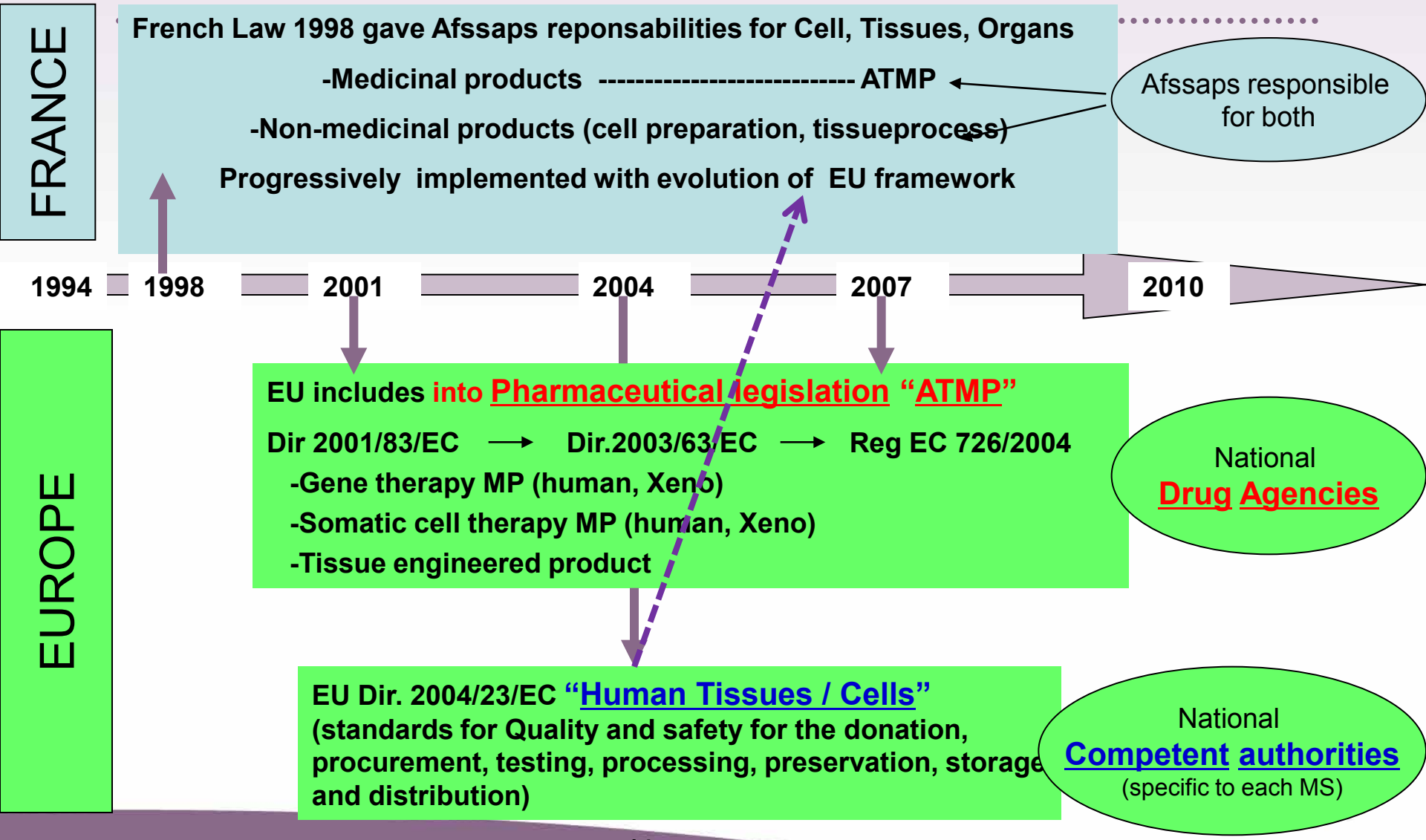
Cell/Tissue-based products
European Regulatory Framework



Complexity of the legal framework, as the national and european levels are continuously interactives



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Cell/Tissue-based products
Various situations in France

- **ATMP** : EU Centralized authorization
- **ATMP exemption** : Afssaps authorization as a MP
  - ATMP prepared in a non-routine basis,
  - Used within the same member state, in an hospital, for an individual patient

  ⇒ Traceability, pharmacovigilance requirements, specific quality standards at national level should be equivalent to the regulation

- **Not a MP /ATMP** : Afssaps gives authorization as
  - "**Preparation**" when Cell Therapy products are concerned
  - "**Process**" when Tissues are concerned

Examples

ATMP

CHONDROCELECT
autologous chondrocytes, expanded from a cartilage biopsy and reimplanted in the cartilage defect

EU marketing authorization 2009

Non-ATMP

Haematopoietic stem cells (autologous, allogeneic)
In hematopoietic reconstitution

Afssaps Authorization

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Non-MP /Non-ATMP

Afssaps Authorizations & Responsabilities

Afssaps has set up a system for Cells and Tissues which are not ATMP, built on the same principles as for Medicinal Products with appropriate adaptations

- Establishment authorization and Inspection
- Product authorization ‘Cell preparation’, ‘Tissue process’

NB: In some other MS, establishment authorization stand for product authorization as well.

- Clinical trial authorization
- Biovigilance
- Quality controls

Product Status in France

	If ATMP	If Non- ATMP
EU framework	ATMP regulation EU centralized authorization	Tissues and Cells Directive National Authorization
Product status	Medicinal Product	"Cell Preparation" "Tissue Process"
Competent authority	Afssaps	Afssaps
Type of establishment	Pharmaceutical establishment Afssaps Authorization	Non Pharmaceutical Cell /Tissue establishment Afssaps Authorization
GMP	European cGMP; recent integration of ATMP (public consultation ongoing)	Good practices but less stringent than cGMP + Dir. 2006/86/CE (French text to be finalized)
Dossier	CTD format +EMA technical guidelines	Adaptation from CTD format +EMA technical guidelines
Efficacy demonstration	Mandatory to establish indications for the marketing authorisation in GCP conditions	"Well established use" GCP not requested (case by case)
Vigilance	Specific vigilance	Obligation of "Biovigilance" French text adopted in 2003
Long term follow up for safety and efficacy	Mandatory	Not envisaged in the legislation

Cell “Preparation” Authorizations

- Cell establishments : 36

  50% public establisments (EFS) – 50% hospital

- Dossiers : around 140 HSC (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% public establisment (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')

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Clinical Trial Authorizations in France

Sponsor submission *	as a Medicinal Product	not as a Medicinal Product
French Regulatory framework	Same as other medicinal products : requirements based on CT European Dir 2001/20/EC implemented in France (2006) + Tissue/Cell Dir (donation, procurement, testing)	Specific French regulation includes principles of Dir 2004/23/EC (Tissues/Cells)
Type of establishment	Pharmaceutical	Non Pharmaceutical
GMP	Based on European GMP; recent integration of ATMP (public consultation ongoing)	GMP principles but less stringent + Tissue/Cell Dir French text to be finalized:
GCP	GCP for ATMP	French text to be finalized : GCP not requested (case by case)
Dossier	Based on CT Dir. and ATMP Reg.	French text to be finalized :based on principles CT Dir +Tissue/Cell Dir
Vigilance	Specific vigilance	Specific vigilance (same as MP)

NB : The sponsor can submit a clinical trial for cell-tissue based product as MP or non-MP; but if the clinical trial is aimed at supporting a marketing authorization application for an ATMP (centralized or exemption) it will have to comply with all requirements for a MP*

Clinical Trials in France
Cell Therapy

- Since 1996 **~ 285 trials submitted**

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

- Type of cells
  - 60% Haematopoietic stem cells
  - 75% autologous

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Clinical Trials in France
Cell Therapy

- Haematopoietic stem cells **: Bone 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

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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)

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Clinical Trials in France
Tissues

- Amniotic membrane in corneal ulcer
- Trachea replacing aorta
- Ovarian tissue autotransplant (chemotherapy situation)
- Face transplantation
- Forearm transplantation

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Scientific Evaluation by Afssaps for MA and Clinical Trials

- Whatever the type of product, ATMP and non-ATMP
- Same criteria are applied for evaluation (MA /Clinical Trial)
  - Quality, Safety, Efficacy
- The same team is leading the evaluation
- Expert group meetings are organized on regular basis with participation of
  - Internal assessors
  - External assessors : all field of expertise represented
- Training for reviewers is operate nationally or through EMA

Scientific Advice

- Dedicated unit in Afssaps « INNOVATION » Coordinated by Stephane Paliès palies@afssaps.sante.fr
- Frequent situations for these products (cell therapy, gene therapy, ancillary products, tissues)
- Stages :Development, CT, MA…
- Applicants are private or public or associations…
- Different from EMA "scientific advice"
  - No fees, not legally binding
- Some rules for applicants
  - Identified questions, submitted in advance
  - Centered on regulatory issues
  - Knowledge of the regulatory framework
  - No to be considered as advice for development

Acknowledgment

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  - Sandrine Jacob
  - Stephanie Jambon
  - Dominique Labbé
  - Sophie Lucas
  - Caroline Matko
- Jean Hugues Trouvin : BWP chairman
  CAT France representative at EMA

Annexes

Technical Guidances available
Cell therapy

- Human cell-based medicinal products CHMP/410869/06
- Points to Consider on Xenogeneic Cell Therapy CHMP/1199/02
- Potency testing of cell based immunotherapy medicinal products for the treatment of cancer CHMP/BWP/271475/06
- Revision of the Points to Consider on Xenogeneic Cell Therapy Medicinal Products CHMP/165085/07
- Xenogeneic Cell-based medicinal products CHMP/CPWP/83508/09
- Reflection paper on *In-Vitro* cultured chondrocyte containing products for cartilage repair of the knee CAT/CPWP/288934/09

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

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Technical Guidances available
Gene therapy

- Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products CPMP/BWP/3088/99 Apr 2001 Oct 2001
- Development and Manufacture of Lentiviral Vectors CHMP/BWP/2458/03
- Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer EMEA/273974/05
- Development of a guideline on the quality, pre-clinical and clinical aspects of medicinal products containing genetically modified cells CHMP/GTWP/405681/06
- Non-clinical studies required before first clinical use of gene therapy medicinal products CHMP/GTWP/125459/06
- Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products CHMP/GTWP/125491/06
- Environmental Risk Assessments for Medicinal Products containing, or consisting of, Genetically Modified Organisms (GMOs) (EMEA/CHMP/473191/06)
- Quality, non-clinical and clinical issues relating specifically to recombinat adeno-associated viral vectors CHMP/GTWP/587488/07
- Follow-up of patients administered with gene therapy medicinal products CHMP/GTWP/60436/07
- ICH Oncolytic Viruses CHMP/GTWP/607698/08
- ICH General Principles to Address Virus and Vector Shedding CHMP/ICH/449035/09

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

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