

# 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 )

# OVERVIEW

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

# French Health Products Safety Agency Afssaps\*

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- **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



# Afssaps

## 3 Locations

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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

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- **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

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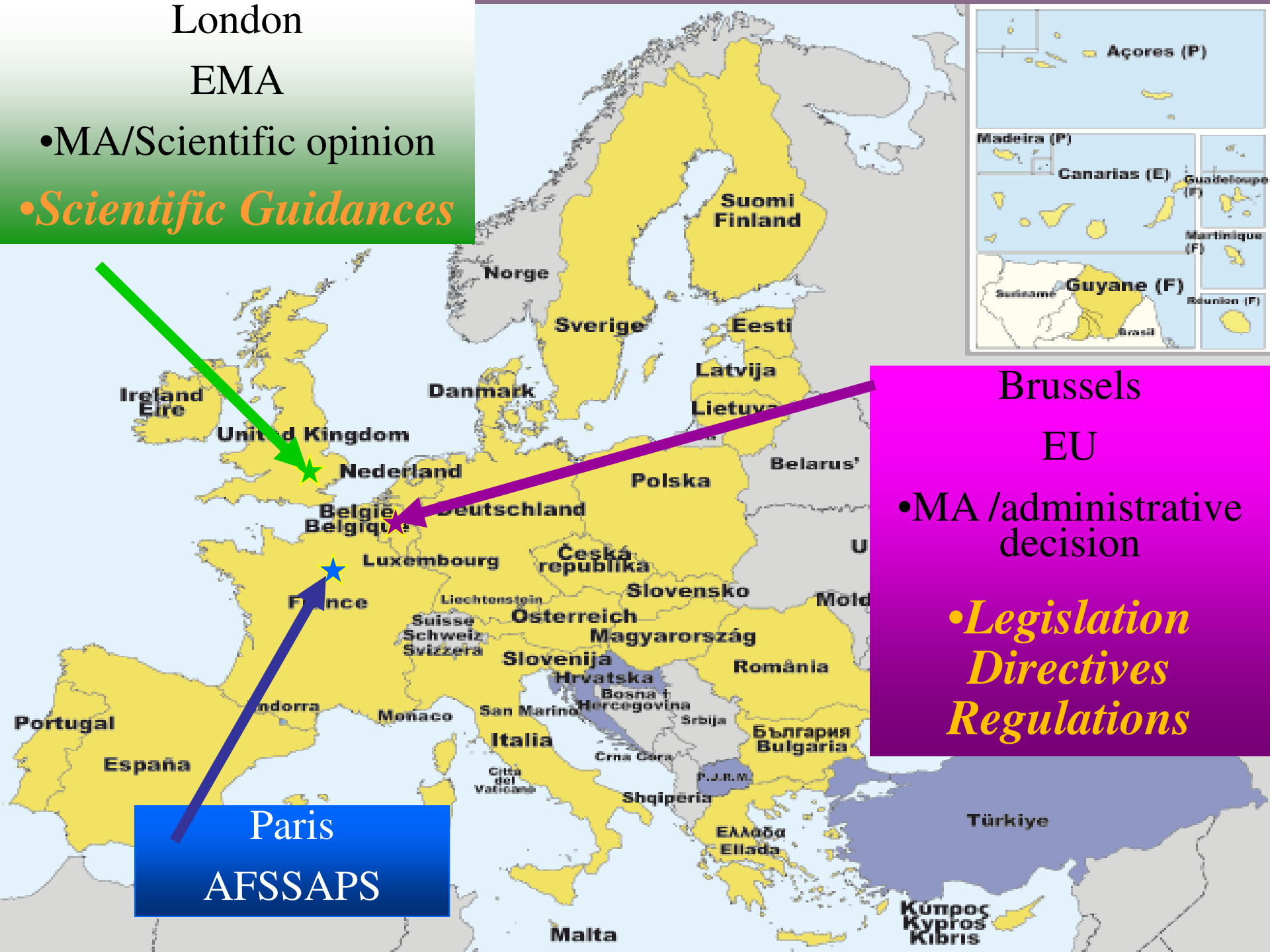
- Cell therapy products
- Gene therapy products
- Human tissues
- Media in contact with organs, tissues or cells  
'Therapeutic ancillary products'
- Recombinant proteins
- Extractive Products
- Vaccines
- Sera, Allergens
- Blood-derived medicinal products
- Blood products for transfusion

London

EMA

- MA/Scientific opinion

- Scientific Guidances*



Brussels

EU

- MA /administrative decision

- Legislation*  
*Directives*  
*Regulations*

Paris

AFSSAPS



# European Legal framework

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European Union adopts legislation in the form of

## Regulations

**Binding requirements,  
directly in force in the 27  
member states**

***ATMP***

## Directives

**Common Minimal requirements  
nationally implemented by each  
member state**

*NB : MS can introduce more  
stringent protective measures*

***Tissues/Cells  
Clinical Trials***

***Examples***

**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

**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

# Products Covered

<b>ATMP Regulation</b>	<b>Tissue/Cell Directive</b>
<ul style="list-style-type: none"><li>-Gene therapy MP</li><li>-Somatic cell therapy MP</li><li>-Tissue engineered product (cell or tissue of human or animal origin. Cells may be viable or non-viable)</li></ul>	<ul style="list-style-type: none"><li>- Cell an Tissues products which are not ATMP, named 'preparation' and 'process' in the French system</li></ul> <p><u>Products not covered</u></p> <ul style="list-style-type: none"><li>-Tissues and cells used as an autologous graft within the same surgical procedure</li><li>-Blood and Blood components</li><li>-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</li></ul>

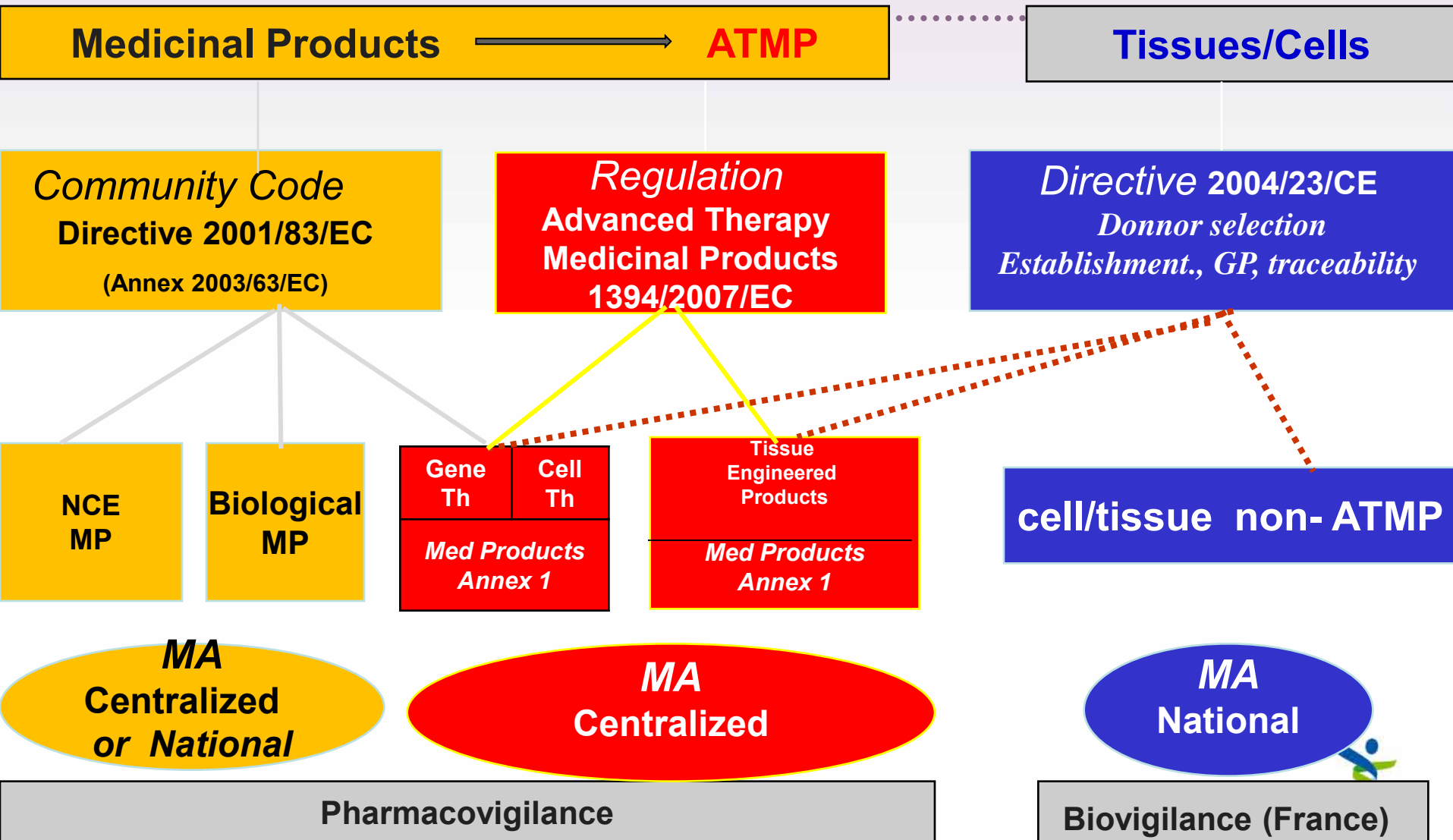
NB : the provisions of the Tissue/Cell Directive, for donation, procurement and testing are applicable to ATMP

# OVERVIEW

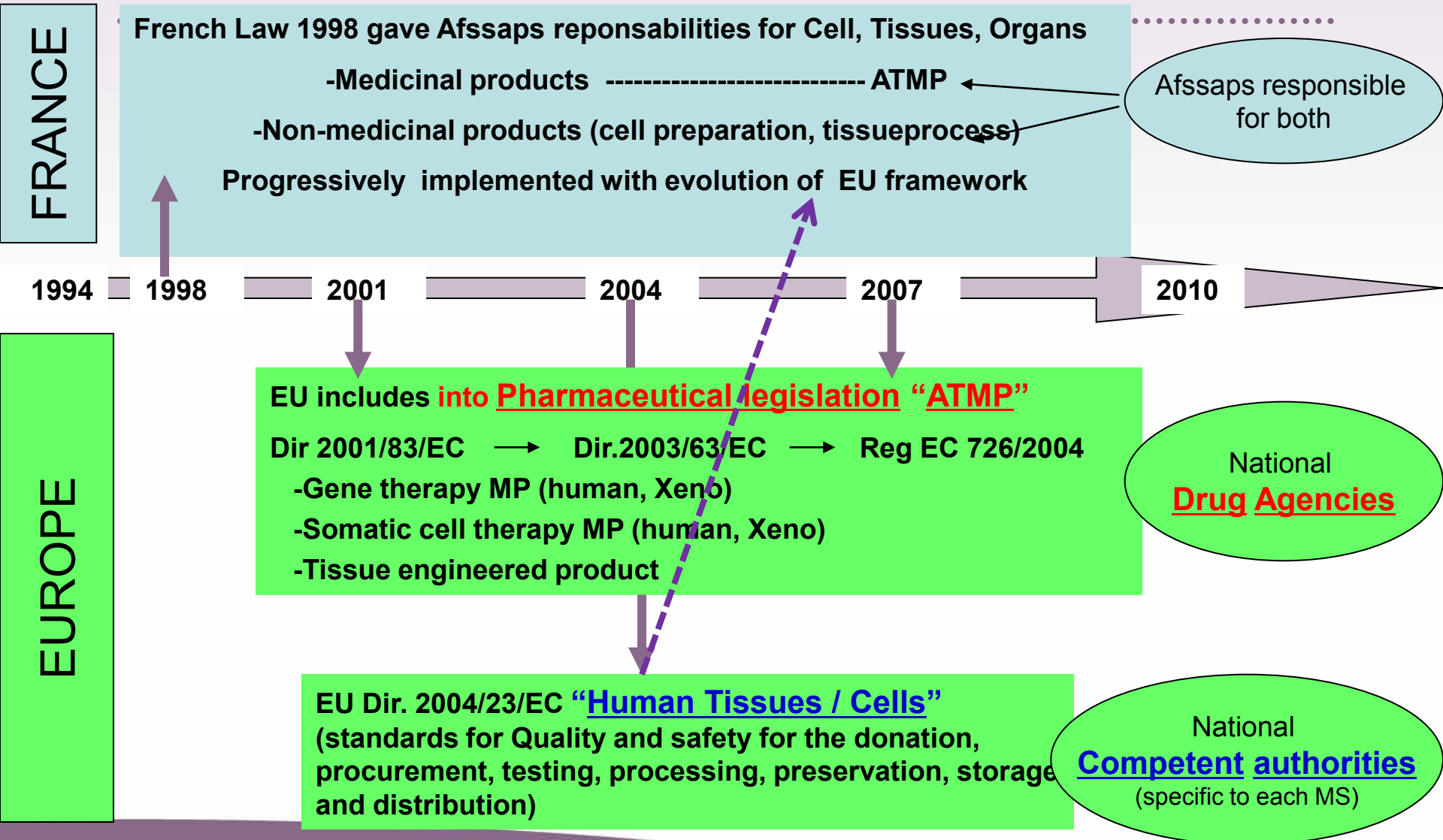
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# Cell/Tissue-based products European Regulatory Framework



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



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# Cell/Tissue-based products

## Various situations in France

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- **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

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## 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

# Non-MP /Non-ATMP

## Afssaps Authorizations & Responsibilities

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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

	<b>If ATMP</b>	<b>If Non- ATMP</b>
<b>EU framework</b>	ATMP regulation EU centralized authorization	Tissues and Cells Directive National Authorization
<b>Product status</b>	Medicinal Product	“Cell Preparation” “Tissue Process”
<b>Competent authority</b>	Afssaps	Afssaps
<b>Type of establishment</b>	Pharmaceutical establishment Afssaps Authorization	Non Pharmaceutical Cell /Tissue establishment Afssaps Authorization
<b>GMP</b>	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)
<b>Dossier</b>	CTD format +EMA technical guidelines	Adaptation from CTD format +EMA technical guidelines
<b>Efficacy demonstration</b>	Mandatory to establish indications for the marketing authorisation in GCP conditions	“Well established use” GCP not requested (case by case)
<b>Vigilance</b>	Specific vigilance	Obligation of “Biovigilance” French text adopted in 2003
<b>Long term follow up for safety and efficacy</b>	Mandatory	Not envisaged in the legislation

# Cell “Preparation” Authorizations

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- Cell establishments : 36
  - 50% public establishments (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

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- Tissue establishments : 41
  - 50% public 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’)

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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

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- Since 1996 ~ **285 trials submitted**
- Sponsors
  - 80% public establishments
  - Others : pharmaceutical companies
- Type of cells
  - 60% Haematopoietic stem cells
  - 75% autologous

# Clinical Trials in France

## Cell Therapy

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- 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

# Clinical Trials in France

## Gene Therapy

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- 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
  - $\frac{3}{4}$  In vivo -  $\frac{1}{4}$  Ex vivo
- Clinical Phase
  - Phase I-II mostly (phase III <5)

# Clinical Trials in France

## Tissues

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- 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

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- 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

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- Dedicated unit in Afssaps « INNOVATION » Coordinated by Stephane Paliès [paliès@afssaps.sante.fr](mailto:paliès@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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## ✓ Afssaps Biological Evaluation Departement

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



# Annexes

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# Technical Guidances available

## Cell therapy

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- 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](http://www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm)



# Technical Guidances available

## Gene therapy

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- 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 recombinant 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](http://www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm)

