

# EMBRYONIC STEM CELLS

## FRENCH REGULATORY FRAMEWORK

S.LUCAS

Washington 14/06/07

# EMBRYONIC STEM CELLS



- **Present situation in France**
- **Future situation in Europe/in France**

- **Present situation based on the French bioethical law (2004)**
  - Basic research is possible
  - Clinical application is forbidden
  
- **Tomorrow : next revision of the French bioethical law (2009)**
  - After revision of the bioethical law, it should be possible that the legislator will give the possibility to use this type of cell in clinical trial for a human application
  - Cell therapy products derived from embryonic stem cells will be submitted to clinical trial

- **Basic research is possible with embryo but :**
  - restricted to a period of 5 years
  - each research protocol must be authorised by the BioMedecine Agency
  - goal of research protocol : to enable major therapeutic progress impossible to be performed by any other method

## Objectives of 5 years for basic research



- **Knowledge improvement of cell potentiality**

- Self renewal potentiality (cellular physiology, teratogenic potential...)
- Differentiation Potentiality (pertinent cell markers...)
- Apoptosis phenomena
- Genetic mutation phenomena (translocations...)
- Phenomena causing immunological reactions

- **Improvement of cell culture conditions**

- Adapted medium (feeder cells, matrix...)
- Cell selection methods (differentiated cells...)
- Adaptation of culture conditions for clinical application (MCB, WCB, differentiated cells ...)
- Controls of all parameters of process preparation

- **The next step** : Cell therapy products derived from embryonic stems cells will be submitted to clinical trial

# **European Regulatory Framework**

**Differentiated  
cells**



**European directive 2001/83/CE  
and  
European Proposal on TEP**



**Embryonic  
stem cells**

## Cell therapy : Definition (2001/83/CE Directive)



- **Somatic cell therapy medicinal product** shall mean the use in human of autologous, allogeneic or xenogeneic somatic living cells, **the biological characteristics of which have been substantially altered as a result of their manipulation** to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means.
- This manipulation includes the expansion or activation of autologous cell population *ex vivo*, the use of allogeneic and xenogeneic cells associated with medical devices used *ex vivo* or *in vivo*

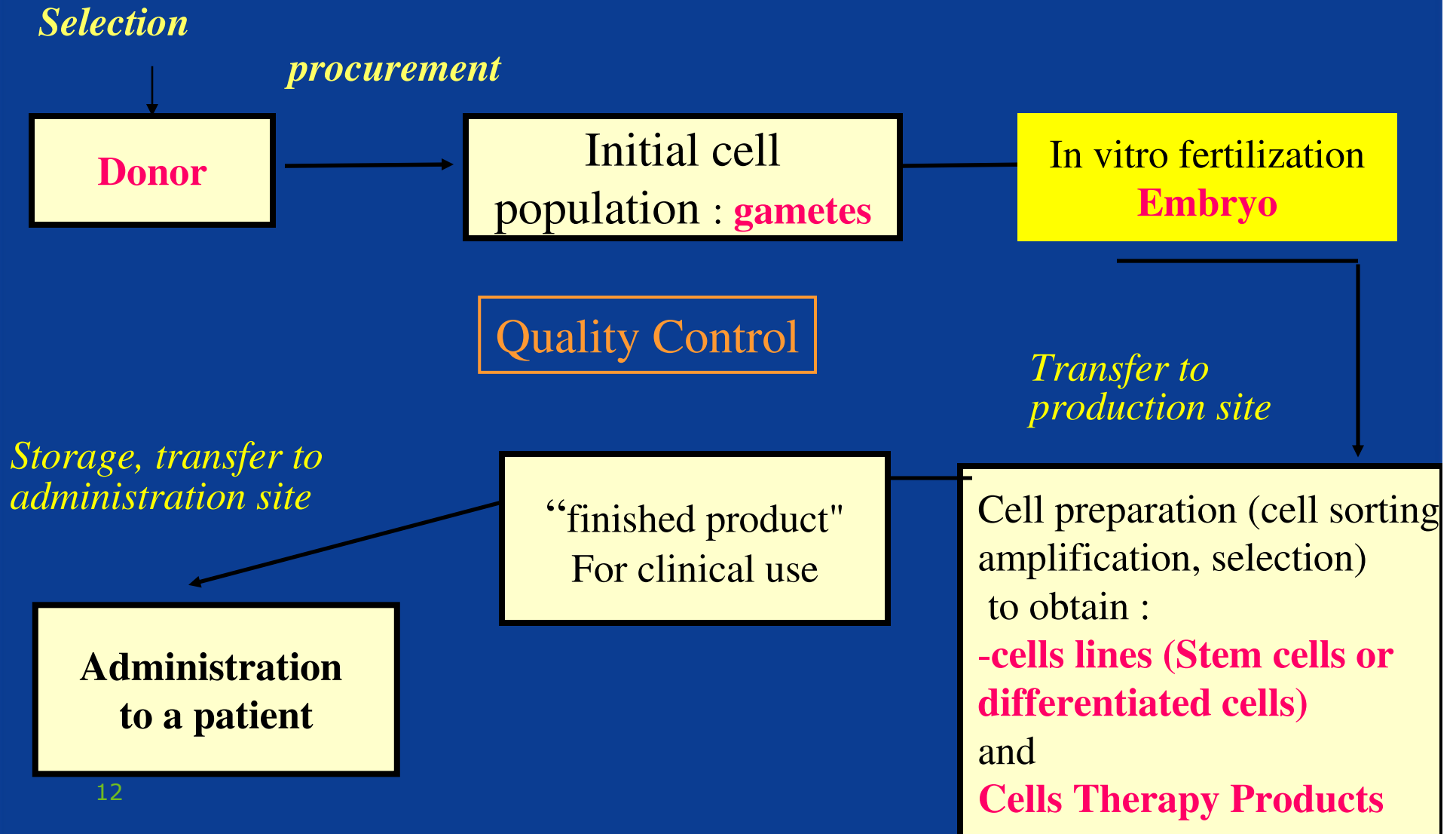
- **Cell therapy medicinal product**

# Evaluation criteria for a cell therapy product



- **Quality data (production, storage and controls)**
- **Non clinical data (proof of concept, animal model, and toxicity)**
- **Clinical data (safety and efficacy)**
  - **Benefit / Risk Ratio**

# Cells therapy process : the main steps



# Cell therapy products : the main steps



## *Main steps*

- Donor/Gametes
- Embryo
- Cell lines
- Cell therapy products



## *Critical points*

- Starting materials
- Ancillary products
- Cell preparation process
- Quality controls
- « finished product »

### Three key steps

#### **1 - Starting materials : materials from which the “active substance” is manufactured**

- Donor/Gametes, Embryo, stem cells lines

#### **2 -Bulk of active ingredient**

- pool of differentiated cells for therapeutic purposes

#### **3 - Finished product**

- Active ingredient formulated in its final immediate container for the intended medical use : Cell therapy products.

- **Issues** : which requirements for the steps prior to embryo ?
  - Donor selection
  - Culture condition (in vitro fertilization procedure)

## Main steps from the embryo to cells lines



- **Starting materials**

- embryo and ancillary products (feeder cells, culture medium with or without serum, growth factor...)

- **cell lines**

- Cell lines characterisation (purity stability, ...)
- Traceability data on cells lines (history of the cells lines, available documentation on cells culture conditions...)

- **preparation process**

- description, identification of critical steps, validation

- **Quality controls**

- Starting materials : embryo and ancillary products
- control of intermediates and finished products
- Viral safety

## Examples of cell lines characterisation



<b>Identity</b>	<b>Morphology, Genotypicals and Phenotypical markers (oct-4, SSEA3...),</b>
<b>Impurities linked to the medium</b>	<b>Residual medium</b>
<b>Impurities linked to the product</b>	<b>« Engaged » cells, fragments cells</b>
<b>Microbiological controls</b>	<b>Sterility, mycoplasmas, endotoxins</b>
<b>viability</b>	<b>Cell numbers</b>
<b>Propriety - Functionality :</b>	<ul style="list-style-type: none"> <li>-differentiated cells (endo, meso and ectoderme),</li> <li>-integration in tissues in development comprising germinal cell lines</li> <li>-capability of teratoma development (immunocompromised mice)</li> <li>-capability of long term self renewal</li> <li>- High telomerase activity</li> <li>- caryotype : Normal (chromosomic rearrangements), diploïde</li> </ul>
17	

# Main steps from cell lines to cell therapy products



- **Starting materials**

- Differentiated cells lines and ancillary products (feeder cells, culture medium with or without serum, growth factor...)

- **preparation process**

- description, identification of critical steps, validation

- **Quality controls**

- Starting materials : embryo
- Ancillary products
- controls of intermediates and finished products
- Viral safety

18 ● **Cell therapy products**

## Examples of cell therapy product characterisation



<b>Identity</b>	<b>Morphology genotypic/phenotypic markers</b>
<b>Impurities linked to the process</b>	<b>Residual medium</b>
<b>Impurities linked to the product</b>	<b>undifferentiated cells,</b>
<b>Microbiological controls</b>	<b>Sterility, mycoplasmas, endotoxins</b>
<b>viability</b>	<b>Number of cells</b>
<b>propriety/functionality</b>	<ul style="list-style-type: none"> <li>- Cell functionality according to cell type specificity (nervous, cardiac cells....)</li> <li>- immunogenicity</li> <li>- senescence</li> <li>- <b>caryotype</b> Normal, diploïde</li> </ul>

\*only some controls will be kept for regular controls

## Conclusion - Requirements for the first clinical trial



- **Quality Data**
  - Reproducibility of the process
  - A final product : defined
- **Non-Clinical Data**
  - Proof of concept on animal model
  - Knowledge on toxicity
- **Clinical Data :**
  - Clinical protocol

- **Assessment of safety and therapeutic purposes**

at pre-clinical stage

- ➡ discussion with Afssaps
- ➡ Scientific opinion

- assessment of quality (microbiological controls, ...)
- integrity and functionality of administered products
- safest used and clinical efficacy