Legal aspects of banking stem cells in Europe

ICAST 2015
June 9, 2015, Zurich (CH)

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Lawyer in Verona
There isn’t a specific regulation

Directive 2004/23/EC
CELLS AND TISSUES BANKING

STEM CELLS ... ARE CELLS!!!
DIRECTIVE 2004/23/EC
standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

DIRECTIVE 2006/17/EC
technical requirements for the donation, procurement and testing of human tissues and cells

DIRECTIVE 2006/86/EC
technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells
Directive 2004/23/EC

- Technical Directive 2006/17/EC;
  - “Donation, Procurement, Testing” from November 2006
    - Training
    - Tissue Establishments
    - Consent
    - Selection criteria
    - Testing criteria
Directive 2004/23/EC

Technical Directive 2006/17/EC;

Testing

- HIV 1&2, HepB, HepC, Syphilis, HTLV
- (Optional) RhD, HLA, Malaria, CMV, Toxoplasma, EBV, Trypanosome Cruzi

National interpretation
Directive 2004/23/EC

- Technical Directive 2006/86/EC;
- “Processing, Preservation, Storage, Distribution” from October 2006
- Adverse Events and Traceability
- Accreditation of “Tissue Establishments”
- Identification of “Responsible Person”
Directive 2004/23/EC

- Technical Directive 2006/86/EC;
  - Quality Systems basis
  - Communications between Competent Authorities and European Commission
  - Templates for Adverse Events
  - TRACEABILITY
Directive 2004/23/EC

“In the absence of other legislation”

Article 2 – Donation, Procurement, Testing

Tissue/Cells Banks – borderline with other legislation
Regulation 1394/2007

- Advanced Therapy Medicinal Products Regulations (ATMPs)
- Gene Therapy, Somatic Cell Therapy, Tissue Engineering
- “Mode-of-Action”
- Viable vs. Non-Viable
Regulation 1394/2007

- Requirements within ATMP Regulation (1);
  - Clinical data according to 2001/20/EC; amendments to GCP being considered,
  - Good Manufacturing Practice to be followed,
  - Combination products considered as ATMPs,
  - Committee for Advanced Therapies (CAT) within EMA;
Regulation 1394/2007

Requirements within ATMP Regulation (2);

- Pharmacovigilance and Traceability,
- Scientific Advice
- Certification of Quality and pre-clinical data,
- Fee waivers
- Transition period;

- On market before 30/12/08 – registered by 30/12/12
- Not on market before 30/12/08 – registered by 30/12/11
These are part of whole blood

Blood stem cells

Art. 2 Directive 2004/23/EC

The Directive shall not apply to:

Blood and blood components as defined by Directive 2002/98/EC
'allogeneic use' means cells or tissues removed from one person and applied to another;

ART. 2 DIRECTIVE 2004/23 /EC

ALLOGENEIC USE

THE BANK IS ALWAYS NECESSARY

STEM CELLS UTILIZATION
ONE STEP SURGERY PROCEDURES
cells used as an autologous graft within the same surgical procedure: Directive 2004/23/EC shall not apply

STEM CELLS UTILIZATION

TWO STEP SURGERY PROCEDURES
DIRECTIVE 2004/23/EC SHALL APPLY
The role of STEM CELLS BANK

1. PROCUREMENT of the cells

2. PROCESSING/STORAGE of the cells

3. DISTRIBUTION for therapeutic use

4. VALIDATION, SAFETY AND QUALITY ASSURANCE for the patients
STEM CELLS BANK

1. PROCUREMENT (donation testing)
   Always Directive 2004/23/EC

2. PROCESSING/STORAGE
   It all depends on final product legal aspects

3. DISTRIBUTION
   It all depends on final product legal aspects

4. VALIDATION, SAFETY AND QUALITY ASSURANCE
   It all depends on final product legal aspects
Where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A as defined in the current European Guide to Good Manufacturing Practice (GMP), Annex 1 and Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue/cell concerned but at least equivalent to GMP Grade D in terms of particles and microbial counts.
A less stringent environment than specified in point 3 may be acceptable where:

(a) a validated microbial inactivation or validated terminal sterilisation process is applied;

(b) or, where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned;

(c) or, where it is demonstrated that the mode and route of application of the tissue or cell to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with cell and tissue transplantation;

(d) or, where it is not technically possible to carry out the required process in a Grade A environment (for example, due to requirements for specific equipment in the processing area that is not fully compatible with Grade A).
THE GMP RULES

STANDARDS OF STEM CELLS BANKING

THE GMP ACCREDITATION IS NOT NECESSARY
THIS IS TRUE IF THE FINAL PRODUCT WILL BE A GRAFT!!
MINIMAL Manipulation

Directive 2004/23/EC

SUBSTANTIAL Manipulation

Directive 2001/83/EC

EU Regulations 1347/2007 on Tissue Engineering Products: THE PRODUCT IS CONSIDERED A DRUG

BORDER LINE LEGISLATIONS
STEM CELLS
UTILIZATION

OMOFUNCTIONAL USE

Cells used for the same essential function in the recipient as in the donor

GRAFT (DIRECTIVE 2004/23/EC)

BORDER LINE LEGISLATIONS

NO OMOFUNCTIONAL USE

Cells not used for the same essential function in the recipient as in the donor

DRUG (EU Regulation 1394/2007)
FOR A MODERN TISSUE BANK IN COMPLIANCE WITH EU REGULATIONS IT’S VERY IMPORTANT TO CONSIDER NOT ONLY THE RAW MATERIAL (CELLS) BUT ALSO:

1) THE FINAL PRODUCT;
2) THE USE OF THE FINAL PRODUCT!
SOURCES OF MSC

Marrow

Adipose tissue

Cord blood

Dental pulp

Blood
ADIPOSE TISSUE

TISSUE
FILTERING, SEPARATION, SOAKING

WHAT KIND OF MANIPULATION IS IT?
MINIMAL MANIPULATION

STEM CELLS
CELULAR MANIPULATION STARTING FROM SVF

DEFINITION

SVF
Vascular Stromal Fraction

ENZYMATIC DIGESTION

SUBSTANTIAL MANIPULATION

STARTING FROM SVF

VASCULAR STROMAL FRACTION
IT'S CONSOLIDATED
THE AUTOLOGOUS USE IN ONE STEP SURGERY PROTOCOLS

BY JURIDICAL POINT OF VIEW
IT'S A TISSUE GRAFTING
ADIPPOSE TISSUE
for LIPOFILLING

| 1 | AUTOLOGOUS USE IN ONE STEP SURGERY |
| 2 | TISSUE GRAFTING |
| 3 | MINIMAL MANIPULATION |
| 4 | OMOFUNCTIONAL USE |
| 5 | "used for the same essential function in the recipient as in the donor" |
| 6 | MANIPULATION WITH DEVICES IN ASEPITC CONDITIONS |

...with these conditions NO GMP rules for processing, NO GCP for the clinical application, NO Ethical Committee approval
<table>
<thead>
<tr>
<th>AUTOLOGOUS USE IN ONE STEP SURGERY</th>
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<td>TISSUE GRAFTING</td>
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- Directive 2004/23/EC not applied
- NO ADVANCE THERAPY PRODUCT
- NO TISSUE ENGINEERING PRODUCT
- SAFE MANIPULATION
THE ADIPOSE TISSUE (CELLS) BANKS NOT ONLY FOR PLASTIC USE
ENZYMATIC DIGESTION

OPEN ISSUES ON ADIPOSE TISSUE

THE CONCEPT OF OMOFUNCTIONAL or HOMOLOGOUS USE

2015 OPEN ISSUES
FDA POSITION

"processing that does not alter the relevant biological characteristics of cells or tissues" (21 C.F.R. 1271.3)

COLLAGENASE alters the relevant biological characteristics of the adipose tissue, the final product is a DRUG.
FIRST ISSUE
ENZYMATIC DIGESTION

ENZYMATIC DIGESTION
IS IT A SUBSTANTIAL MANIPULATION?

SEPARATION IS
MINIMAL MANIPULATION
(REG. EU. 1394/2007, ANNEX I)

THERE IS NOT DISTINCTION
between chemical or physical manipulation
WE APPLY THE EUROPEAN RULES

REG. EU. 1394/2007, ANNEX I
Enzymatic digestion of tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts.
Committee for Advanced Therapies (CAT)
Reflection paper on classification of advanced therapy medicinal products
The same essential function for a cell population means that the cells when removed from their original environment in the human body are used to maintain the original function in the same anatomical or histological environment. An example of this category is bone marrow cells used for haematopoietic reconstitution. All other clinical uses of bone marrow cells are considered to be ATMPs.

HOMOLOGOUS USE
Cells used to maintain the original function in the same anatomical or histological environment
Pag. 14. It is possible that cell-based products administered in the same anatomical location fall under the definition of ATMP on grounds that it is for non-homologous use. This can be encountered when the mode of action of the cells is not identical to the one attributed to the cells by the scientific knowledge. As an example, injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use.
New REGULATORY RATIONALE for the homologous use of the cells/tissues

Cells used with the same original function

Same mode of action of the cells

SECOND ISSUE
OMOFUNCTIONAL USE
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<tr>
<td>1</td>
<td>It’s only an “opinion document” that explain the EMA/CAT position</td>
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<td>2</td>
<td>It isn’t definitive the stakeholders and the scientific associations have sent a lot of proposals of modification</td>
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<td>3</td>
<td>Autumn 2015 we will have probably the final document</td>
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<td>4</td>
<td>Today the only official document is the EU reg. 1394/2007</td>
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Situation at 2015.06.09
CONCLUSIONS
THE EU AUTHORITIES are oriented to an extension of the legal limits of ATMP
In the next future
many products based on cells will be considered an ATMP (DRUG)
The European Cells Banks should obtain the GMP accreditation and should be in compliance with EU regulations about ATMP products.
The FAT is a very interesting source of STEM CELLS but in my opinion, the Banks of ADSC will have a primary role in the utilization of the FAT’s final product...
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