EU regulations for import and export of cellular therapy products

Ineke Slaper-Cortenbach
Aims /Role of JACIE

1. Accreditation of Individual Centres
   • Assistance
   • Inspection
   • Certification

2. Information / Education
   • QM courses
   • Training courses
   • Sample documents

3. Regulatory Issues
   • updating standards
   • adjust to regulations
     • International harmonisation
Countries represented on JACIE Board:
How did AHCTA start?

- Representatives of JACIE, WMDA, EBMT, ISCT-Europe (and support of FACT) had a meeting on March 9, 2006 with the European Commission:
  - import and export of cells
  - position of Donor Leukocyte Infusions
  - Air quality
  - European coding system
ORIGIN OF STEM CELL PRODUCTS SPECIFIED PER EU COUNTRY

UNRELATED STEM CELL PRODUCTS IN EUROPE

WMDA Annual Report 2005
Import Bone Marrow/PBSC/Cord in the year 2005

<table>
<thead>
<tr>
<th>Country</th>
<th>BM/PBSC</th>
<th>Cord</th>
<th>Total</th>
<th>% of total transplants coming national donor</th>
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<tbody>
<tr>
<td>France</td>
<td>303</td>
<td>97</td>
<td>400</td>
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<td>Italy</td>
<td>252</td>
<td>30</td>
<td>282</td>
<td>37</td>
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<td>Spain</td>
<td>74</td>
<td>45</td>
<td>119</td>
<td>21</td>
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<tr>
<td>UK</td>
<td>181</td>
<td>43</td>
<td>224</td>
<td>57</td>
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</table>
EU Directive 2004/23/EC: Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

- This Directive should apply to tissues and cells including hematopoietic peripheral blood, umbilical-cord (blood) and bone marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells, and adult and embryonic stem cells.

- It was published in the Official Journal of the European Union on April 7, 2004 and entered into force.

- Implementation in Members States before April 7, 2006.
Article 9: Import/export of human tissues and cells

3.

a. The import or export of tissues and cells referred to in Article 6(5) (directly distributed) may be authorised directly by the competent authority or authorities

b. In case of emergency, the import or export of certain tissues and cells may be authorised directly by the competent authorities

c. The competent authority or authorities shall take all necessary measures to ensure that imports and exports of tissues and cells referred to in subparagraphs (a) and (b) meet quality and safety standards equivalent to those laid down in this Directive
EU Directives

  - quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
  - donation, procurement and testing of tissues and cells
  - traceability requirements
  - serious adverse reactions and events
  - coding, processing, preservation, storage and distribution of human tissues and cells
- Implementing Directives in progress
  - Import/export: established in 2008
  - A single European coding system: Effective Sept 1, 2008
2006/17/EC: technical requirements for donation, procurement and testing of tissues and cells

- Article 2: Requirements for the procurement of human tissues and cells
- Article 3: Selection criteria for donors of tissue and cells
- Article 4: Laboratory tests required for donors
- Article 5: Procurement procedures
- Article 6: requirements for distribution
- Article 7/8: transposition & entry into force

- staff must be properly trained;
- the facilities must be maintained to prevent contamination;
- proper, sterile instruments must be used for procurement;
- SOP’s for
  - the donation and testing process;
  - during transport;
  - at the point of reception in tissue establishments
- selection of tissue and cell donors (live or deceased)
- A unique identifier code for proper identification and traceability.
1. Biological tests required for donors

1.1. The following biological tests must be performed for all donors as a minimum requirement:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>HIV 1 and 2</td>
<td>Anti-HIV-1,2</td>
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<tr>
<td>Hepatitis B</td>
<td>HBsAg</td>
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<td></td>
<td>Anti-Hbc</td>
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<tr>
<td>Hepatitis C</td>
<td>Anti-HCV-Ab</td>
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<tr>
<td>Syphilis</td>
<td>See 1.4 (below)</td>
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</tbody>
</table>

1.2. HTLV-1 antibody testing must be performed for donors living in or originating from high-incidence areas or with sexual partners originating from those areas or where the donor’s parents originate from those areas.

1.3. When anti-Hbc is positive and HBsAg is negative, further investigations are necessary with a risk assessment to determine eligibility for clinical use.

1.4. A validated testing algorithm must be applied to exclude the presence of active infection with *Treponema Pallidum*. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. A donor whose specimen tests reactive on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use.

1.5. In certain circumstances, additional testing may be required depending on the donor’s history and the characteristics of the tissue or cells donated (e.g. RhD, HLA, malaria, CMV, toxoplasma, EBV, *Trypanosoma cruzi*).
Towards a **Global Standard** for Donation, Procurement, Testing, and Distribution of HSC and Related Cellular Therapies

Position Paper from the Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA).

AHCTA represents JACIE, EBMT, WMDA, ISCT-Europe, FACT, FACT-Netcord, ISCT, EFI, ASBMT and AABB.
Issues affecting quality and safety of tissues and cells

• Donor assessment
• Procurement
• Storage (in case of cord blood banks)
• Transport and distribution
  – including reception at the tissue establishment
  – in case of direct distribution, at the clinical facility
• Labelling
Information provided in workshops 2 and 5 at this meeting
CEN/ISSS Workshop:

The Workshop will have four plenary meetings (including the kick-off meeting).

The following timetable is proposed:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Milestone</th>
<th>Month</th>
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<tbody>
<tr>
<td>Workshop announcement</td>
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<td>12 February 2007</td>
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<tr>
<td>Launch call for experts</td>
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<td>February 2007</td>
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<tr>
<td>Approval of Business Plan, appointment of Workshop Chair</td>
<td>Kick-Off meeting</td>
<td>13 April 2007</td>
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<td>Selection PT</td>
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<td>End April 2007</td>
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<tr>
<td>First draft of CWA</td>
<td>Second plenary</td>
<td>Mid September 2007</td>
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<tr>
<td>Interim Report to EC</td>
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<td>End September 2007</td>
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<td>Ws comment on first draft CWA</td>
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<td>Oct 2007</td>
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<tr>
<td>Second draft CWA including comments received</td>
<td>Third plenary</td>
<td>Mid Nov 2007</td>
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<td>Public comment period (60 days)</td>
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<td>Mid Nov 2007-Mid Jan 2008</td>
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<td>Third draft CWA</td>
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<td>Mid Feb 2008</td>
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<td>Approval CWA by Workshop</td>
<td>Fourth plenary</td>
<td>Early March 2008</td>
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<td>Closure WS</td>
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<td>Mid March 2008</td>
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CEN/ISSS Workshop

Minimal information:

(a) Donation identification:
   — Unique ID number
   — Identification of the tissue establishment

(b) Product identification:
   — Product code (basic nomenclature)
   — Split number (if applicable)
   — Expiry date
Mission statement:

• Harmonisation of respective standards
• Ultimately achieve a single set of quality, safety and professional requirements for cellular therapy including haematopoietic stem cell (HSC) transplantation.
• All aspects of the process from donor recruitment to transplantation and clinical outcome.
• Supported by
  – complementary standards and guidelines,
  – promotion of the concept of a global set of standards
• Inform and support authorities in the area of cellular therapy regulation
<table>
<thead>
<tr>
<th>EU 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.</th>
<th>FACT-JACIE STANDARDS 3rd ED DRAFT FEB06 Section B Clinical and Donor Evaluation Section C Collection Facility</th>
<th>COMMENTS</th>
<th>To be Updated</th>
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<tr>
<td>Whereas:</td>
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<td>WMDA STANDARDS version December 15-2005</td>
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<td>(1) The transplantation of human tissues and cells is a strongly expanding field of medicine offering great opportunities for the treatment of as yet incurable diseases. The quality and safety of these substances should be ensured, particularly in order to prevent the transmission of diseases.</td>
<td>FACT-JACIE sets standards for quality and safety in all aspects of stem cell transplantation.</td>
<td>Consistent</td>
<td>WMDA sets standards for quality and safety as they relate to the international exchange of hematopoietic stem cells. The standards include guidelines for health screening of donors to prevent transmission of diseases.</td>
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<tr>
<td>(2) The availability of human tissues and cells used for therapeutic purposes is dependent on Community citizens who are prepared to donate them. In order to safeguard public health and to prevent the transmission of infectious diseases by these tissues and cells, all safety measures need to be taken during their donation, procurement, testing, processing, preservation, storage, distribution and use.</td>
<td>FACT-JACIE standards cover donation, procurement, testing, processing, preservation, storage, distribution and use.</td>
<td>Consistent</td>
<td>WMDA standards cover health testing of donors, testing for histocompatibility, donation, international transport, and use. They do not cover processing and storage.</td>
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<tr>
<td>(3) It is necessary to promote information and awareness campaigns at national and European level on the donation of tissues, cells.</td>
<td>FACT-JACIE does not have a role in promoting information and awareness of donation but can assist by assuring safety of donation.</td>
<td>Consistent</td>
<td>WMDA supports registry activities that provide information and awareness of donation. WMDA standards ensure the anonymity of donors and donor...</td>
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More information:

1. *AHCTA*: www.ahcta.org
2. *EU Tissues and cells*:
   http://europa.eu.int
3. *Advanced Therapies*
   http://pharmacos.eudra.org/F2/advtherapies/index.htm
4. European LRA committee: see ISCT webpage
Advanced cell therapy products

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);

(b) **tissue engineered product** means a product that:

   – contains or consists of engineered cells or tissues; and

   – is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue;
Medicinal products based on

- Genes: gene therapy
- Cells: cell therapy
- Tissues: tissue engineering
## Today’s regulatory patchwork

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- autologous products
- allogeneic products

Ref: Joint Research Centre, European Commission 2004
The regulatory gap

Legislation

- Medical Devices 93/42/EEC
- Medicinal Products 2001/83/EC

Advanced Therapies

- Medical Devices
- Tissue Engineering
- Cell Therapy
- Gene Therapy
- Biotech
- Chemicals
Regulatory levels of the overall approach

1. Existing Legislation on Tissues & Cells, Medical Devices and Medicines
2. Regulatory framework Regulation on Advanced Therapies
3. Technical Requirements
4. Guidelines

Proposal!
Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA)

Members:

- American Association of Blood Banks (AABB)
- American Society for Blood & Marrow Transplantation (ASMBT)
- European Group for Blood & Marrow Transplantation (EBMT)
- European Federation of Immunogenetics (EFI)
- Foundation for the Accreditation of Cellular Therapy (FACT)
- International Society for Cellular Therapy (Europe) (ISCT)
- International NETCORD Foundation
- Joint Accreditation Committee ISCT-EBMT (JACIE)
- World Marrow Donor Association (WMDA) (incl NMDP)