INTERNATIONAL REGULATIONS FOR TISSUES & CELLS

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Fact: Tissue and Cell therapy is a field in which an intensive worldwide exchange takes place.

Need: Safeguard public health

Goal: worldwide standards
Bone Grafts Distributed/Exported by USA

Tissue grafts/devices are exported to 45 countries

Haematopoietic Stem Cells
EUROCET data for 2008

- **Import by EU Member States** - 1122 units of HSC (Belgium, Bulgaria, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Italy, Lithuania, the Netherlands, Portugal, Romania, Slovenia, and the United Kingdom).

- **Export by EU Member States** - 269 units of HSC (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Ireland, Spain, France, Italy, Cyprus, the Netherlands, Portugal, Romania and the United Kingdom).

EUROCET (European Registry for Organs, Tissues and Cells, http://www.eurocet.org/)

*In many cases data concerning volumes of exports is not available.*
To Safeguard Public Health

- Common quality standards
- Common glossaries.
  (Harmonisation and comparable data to disseminate reliable information)

International Regulations

Tissues? Cells?

- Bone marrow
- Peripheral Blood Stem cells
- Cord blood
- Skeletal
- Skin
- Vascular
- Ocular
- Amniotic membrane
- Reproductive cells
EU directives on Tissues and Cells

- **2004/23** of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells


- **2006/86** implementing Directive 2004/23/EC of the European Parliament and of the Council as regards 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

Stem cells?

- Adult
- Embryonic
- Allogeneic
- Autologous
- Haematopoietic
- Somatic

Same provisions in regulations
<table>
<thead>
<tr>
<th><strong>Apply to</strong></th>
<th><strong>Do not apply to</strong></th>
</tr>
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<tbody>
<tr>
<td>- Procurement</td>
<td>- In vitro research</td>
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<tr>
<td>- Testing</td>
<td>- Tissues &amp; cells used as autologous graft within the same surgical procedure</td>
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<td>- Processing</td>
<td>- Hospital exemption products</td>
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<tr>
<td>- Storage</td>
<td>- Blood and blood products (2002/98/EC)</td>
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<tr>
<td>- Distribution</td>
<td>- Organs or parts of organs</td>
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<tr>
<td>- Export/Import</td>
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<td>- Clinical use of tissues &amp; cells</td>
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• Advanced therapy medicinal products

**Directive 2004/23 EU**

- Applies to tissues and cells including haematopoietic peripheral blood, umbilical cord blood and bone marrow stem cells.
- Lays down the standards of quality and safety for human tissues and cells intended for human applications, in order to ensure a high level of protection of human health.
The Competent Authorities
Responsibilities

- Supervision of tissue and cell procurement and testing
- Accreditation, designation, authorisation/licensing of tissue establishments
- Inspections and control measures to ensure compliance
- Vigilance and Surveillance of activities
- Report to the EU Commission on activities undertaken in relation to the provisions of the Directives
- Report to the EU Commission on SAEs/SARs and notify other competent authorities for tissues/cells that are distributed

Tissue establishment Responsibilities

- Voluntary unpaid donation (donors may receive compensation strictly limited to expenses and inconveniences)
- Consent
- No unauthorised disclosure of donor or patient personal data
- Donor evaluation and selection is carried out under specified conditions
But also...

- Quality system based on the principles of good practice
  1. Standard operating procedures
  2. Guidelines
  3. Training and reference manuals
  4. Reporting forms
  5. Donor records
  6. Information on the final destination of tissues and cells
  7. Ensure traceability from donor to recipient
  8. Validation of processes
  9. Processing of tissues/cells while exposed to environment must be in grade A air quality with a background air of at least quality D

As well as...

- Designated responsible person
- Appropriately trained personnel
- Written agreements with third parties in order to ensure that the quality of tissues/cells is not compromised
- Ensure the quality of tissues/cells during distribution
- Report and/or investigate serious adverse events to the competent authority
Criteria for SARs reporting to the Competent authorities

- Any unintended response, including a communicable disease, in the donor or recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

  (infection, hypersensitivity, malignancy, toxicity, mismatch, genetic abnormality or other transmission)

Criteria for SAEs reporting to Competent Authorities

Deviations should not be reported as SAEs to CAs unless:

- Inappropriate tissues or cells have been released for clinical use, even if not used
- The event could have implications for other patients or donors because of shared practices, services, supplies or donors
- The event resulted in the loss of any irreplaceable autologous tissues or cells or any highly matched (i.e., recipient specific) allogeneic tissues or cells
- The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.
Movement of tissues and cells

- **Transport**: between tissue establishments
- **Distribution**: between a tissue establishment and a site of human application
- **Import/Export**: EU Member State and a Third country. The CA can introduce prohibition of or restriction on the importation of human tissues and cells to ensure a high level of health protection.
- Tissue establishments that receive such imports/send such exports shall ensure that these meet standards of quality and safety equivalent to the ones described in this Directive. Movement of tissues and cells between countries within European Economic Area actually falls within the definition of transport and distribution and not import and export. If a tissue establishment imports tissues and cells and supplies other tissue establishments, the responsibility resides with this first establishment as the original place of entry.
Advanced Therapy Medicinal Products for human use

- Gene therapy medicinal product
- Somatic cell therapy medicinal product
- Tissue engineered medicinal product

Cells or tissues have been subjected to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or placement are achieved. AND/OR

Cells or tissues that are not intended to be used for the same essential function/functions in the recipient as in the donor.

- Substantial manipulation is not considered cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilisation, irradiation, cell separation, filtering, lyophilisation, freezing, cryopreservation, vitrification.

EU Regulation and Directive on Advanced Therapy Medicinal products

  (Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of those cells or tissues shall be made in accordance with Directive 2004/23/EC)

  (The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council, as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells)
Committee for Advanced Therapies

- The Committee for Advanced Therapies (CAT) was established in accordance with Regulation (EC) No 1394/2007 for ATMPs. It is a multidisciplinary committee, gathering together some of the best available experts in Europe to assess the quality, safety and efficacy of ATMPs, and to follow scientific developments in the field.

- The main responsibility of the CAT is to prepare a draft opinion on each ATMP application submitted to the European Medicines Agency, before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the granting, variation, suspension or revocation of a marketing authorisation for the medicine concerned. At the request of the Agency’s Executive Director or of the European Commission, an opinion is also drawn up on any scientific matter relating to ATMPs.

Hospital Exemption Products

- This is a custom-made cell-containing product that is prepared on a non-routine basis according to specific quality standards. It is made available to an individual patient in a European hospital under the exclusive responsibility of a doctor.

- It is authorised for use by the regulatory authority of the Member State where the product is made.
In the USA.....

- The Centre for Biologics Evaluation and Research (CBER) at the FDA, regulates HCT/Ps under 21 CFR, parts 1270 and 1271.

- The FDA’s revised regulations are contained in Part 1271 and apply to tissues recovered after 2005, which are the current tissue rules. Examples of tissues regulated are musculoskeletal tissue, skin, corneas, heart valves, haematopoietic stem cells and reproductive cells.

The 3 FDA rules......

- **Registration and listing** - Requires tissue establishments to register and list their HCT/Ps with the FDA. This includes the types and uses of the products that will be regulated by these rules. Also, all foreign establishments importing HCT/Ps into the US must register and list such HCT/Ps.

- **The donor eligibility rule** - Requires HCT/P establishments to screen and test tissue and cell donors for relevant communicable disease agents or diseases.

- **Current good tissue practices** - The requirements that govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including all steps in recovery, donor screening and testing, processing, labelling, packaging and distribution. Also included are the requirements for process validation, labelling, tracking, complaint files and adverse reaction reporting. In general CGTP ensures that HCT/Ps do not contain communicable disease agents, are not contaminated and that they do not become contaminated during manufacturing.
In Australia......

- **Therapeutic Goods Act 1989** - therapeutic goods which are imported into Australia, supplied for use in Australia or exported from Australia, conform with a standard applicable to the goods. The Act includes non-cord blood HPCs.


The future.....

Implementation of European/Global Surveillance and Vigilance system

- **Role of Regulators, engagement of Clinicians, role of Professional Societies, clarity in reporting requirements, openness, transparency and non-punitive culture, effective communication, patient focus, system standardisation, education of stakeholders**

Implementation of a European Coding System
Ευχαριστώ για την προσοχή σας

Thanks for your attention