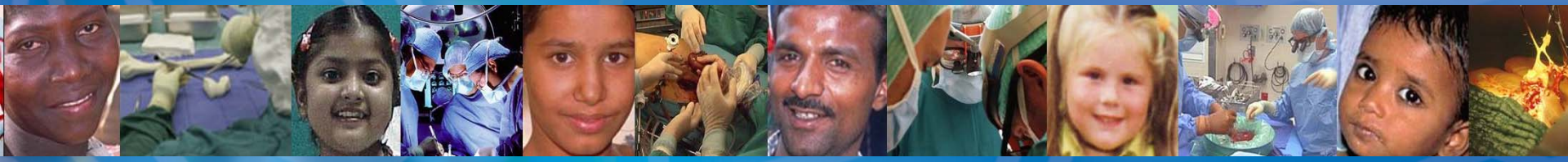
World Health Organization

ESSENTIAL HEALTH TECHNOLOGIES

Eustite

Public Health

Safety Vigilance and Surveillance of Human cells and Tissues for Human Application



Luc Noel (WHO) Deidre Fehily (CNT)

10th European Hæmovigilance Seminar

Frankfurt am Main, Germany, 28 February-1 March 2008

Vigilance and Surveillance, V&S

- Vigilance:

  Latin, vigilare "to keep awake or alert, to care for".

  An attitude

- Surveillance:

  French, from surveiller "to watch over".

  A method

  " Systematic, ongoing collection, collation, and analysis of data and the timely dissemination of information to those who need to know so that action can be taken."

First Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation

Ottawa, 29 Nov to 1 Dec 2004

- 29 countries
- Clinicians, practitioners and regulators
- Reports from individual countries
- Reports from professional organisations
- Reports from regulators

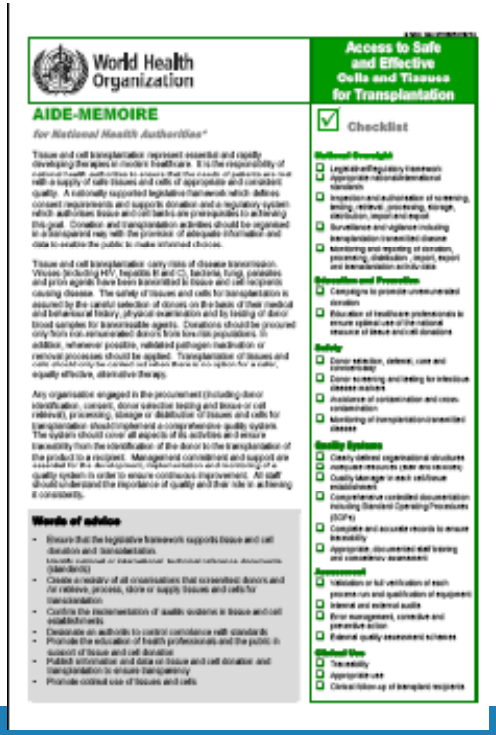
Focus on Quality and Safety of Cells and Tissues for Transplantation

Vigilance and surveillance:

- Should be incorporated at an early stage
  - Human origin - Risk of transmissible agents - Susceptibility to microbial contamination - Limited experience in clinical trials of processing methods or clinical use
- Not only adverse event and reaction reporting, but should include active and comprehensive vigilance and surveillance
- Opportunity for valuable collaboration of clinicians, operators, regulators and policy makers
- Requires international collaboration

Access to Safe and Effective Cells and Tissues for Transplantation

Cell and tissue transplantation carries the risk of disease transmission. Viruses (including HIV, hepatitis B and C), bacteria, fungi, parasites and prion agents have been transmitted to tissue and cell recipients causing disease.


World Health Organization

Access to Safe and Effective Cells and Tissues for Transplantation

AIDE-MEMOIRE

*for National Health Authorities**

Checklist

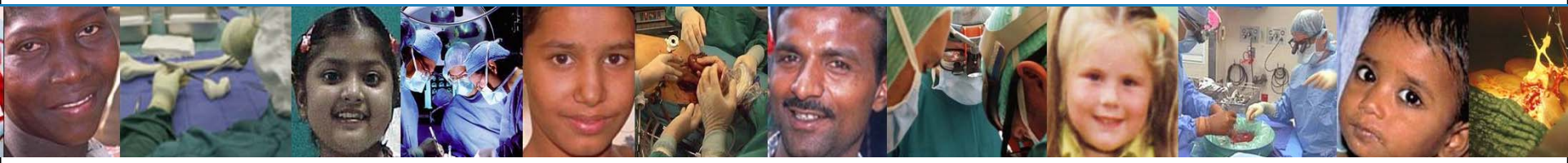
Words of advice

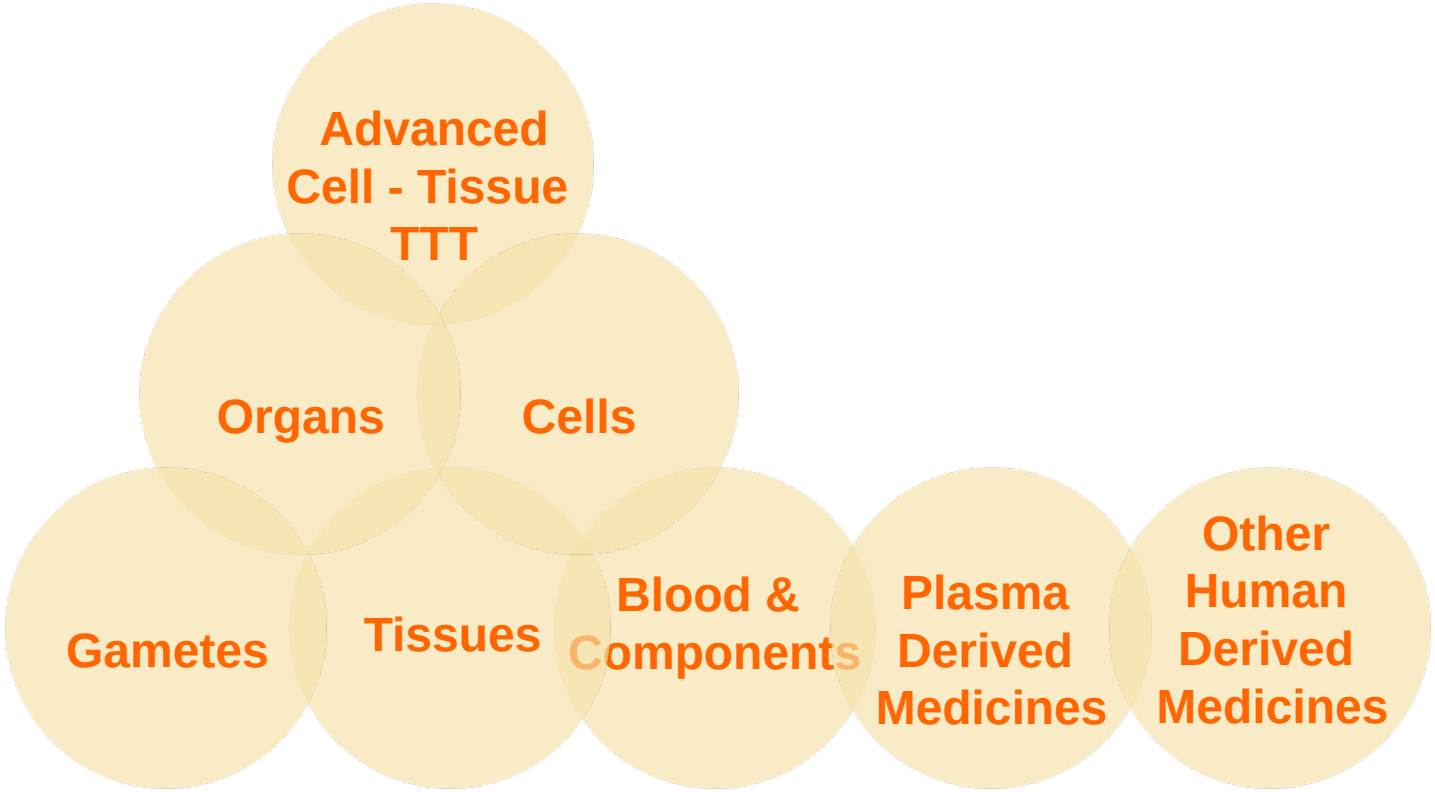
- Ensure that the legislative framework supports tissue and cell donation and transplantation.
- Create a registry of all organisations that screen/test donors and /or retrieve, process, store or supply tissues and cells for transplantation.
- Confirm the implementation of quality systems in tissue and cell establishments.
- Designate an authority to control compliance with standards.
- Promote the education of health professionals and the public in support of tissue and cell donation.
- Publish information and data on tissue and cell donation and transplantation to ensure transparency.
- Promote optimal use of tissues and cells.

- ❑ Monitor adverse reactions in patients to allow corrective and preventive action

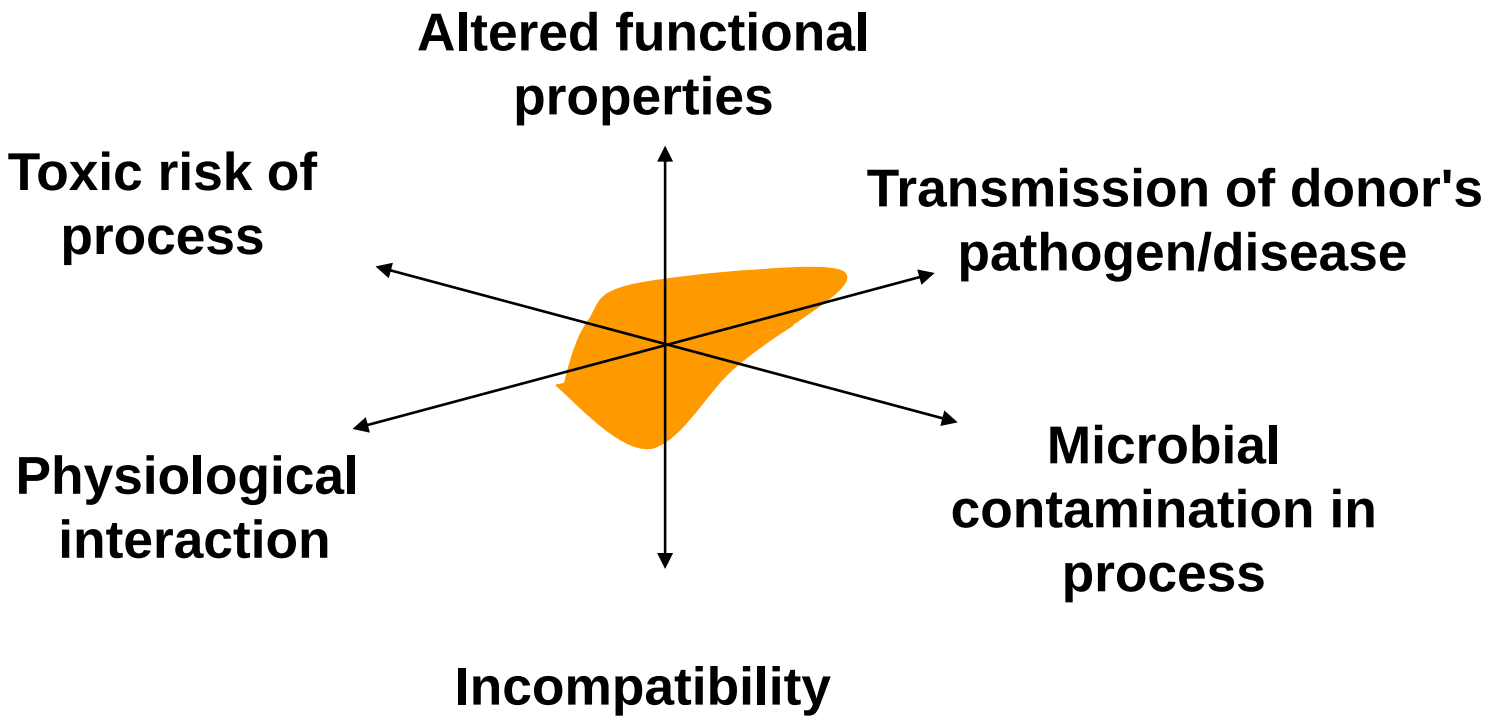
http://www.who.int/transplantation/cell_tissue/en/

Therapeutic Products of Human Origin





Variety of Shared Safety Risks of Human Cell and Tissue products



Global Circulation of Human Tissue and Cells
Some Examples

- AATB survey (2002, 59 banks) – 23,000 donors – tissues distributed to the US and to 39 other countries
- 40% of unrelated bone marrow donations are transplanted in a country other than the one where they were donated
- Canada – 100% of dental bone and 70% of other tissues implanted are imported
- 36,000 (of 46,000) corneas distributed by Sri Lanka Eye Bank to over 61 countries

Second Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation

Geneva, June 2006

Towards

Global Harmonization

through

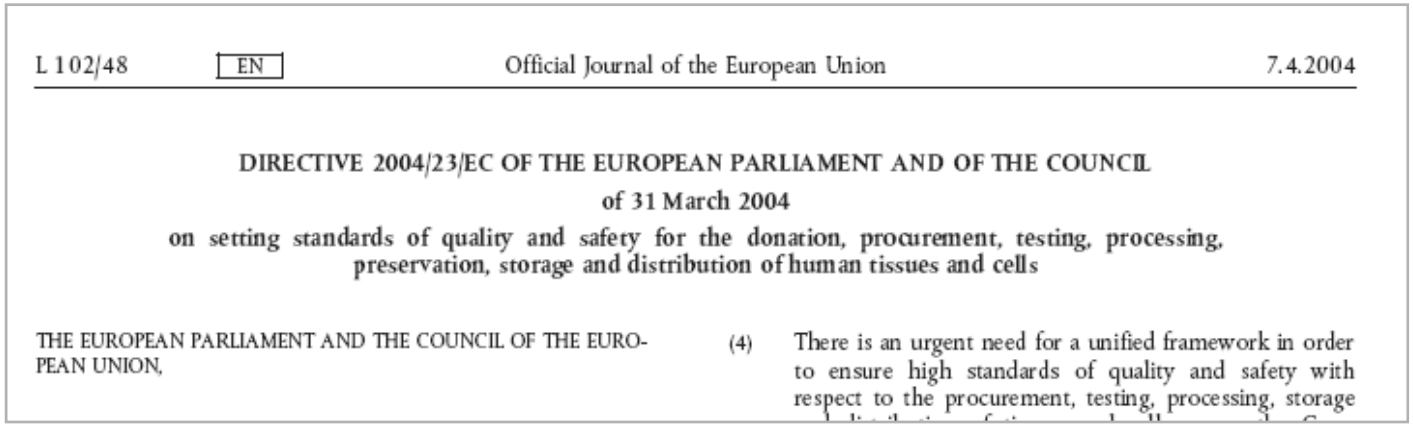
Graduated Standards

Second Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation
Geneva, June 2006

Vigilance and surveillance:

- Many countries are in the process of developing systems for vigilance and surveillance
- There needs to be a global aspect to vigilance to ensure that risks and events are communicated and acted on appropriately
- Tools for inter-communicability between national/regional programmes are required. WHO's GKT will evolve to provide a global source of information on risk
- There was recognition of the pioneering value of the participation of WHO in the EUSTITE project and regulatory approaches and systems for vigilance and surveillance generally

V&S for Human Tissue and Cells in the European Union



L 102/48 EN Official Journal of the European Union 7.4.2004

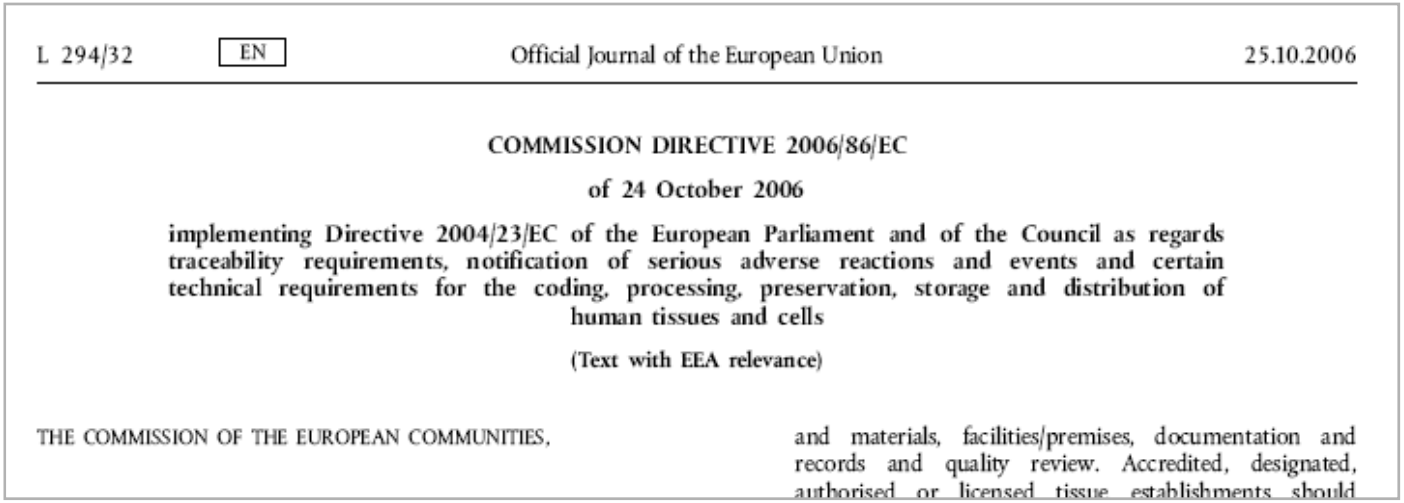
DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

(4) There is an urgent need for a unified framework in order to ensure high standards of quality and safety with respect to the procurement, testing, processing, storage



L 294/32 EN Official Journal of the European Union 25.10.2006

COMMISSION DIRECTIVE 2006/86/EC

of 24 October 2006

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

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

and materials, facilities/premises, documentation and records and quality review. Accredited, designated, authorised or licensed tissue establishments should

EU Directive Definitions

'Serious Adverse Event' means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity

'Serious Adverse Reaction' means an unintended response, including a communicable disease, in the donor or in the 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

The EUSTITE Project

European **U**nion **S**tandards and **T**raining in the **I**nspection of **T**issue **E**stablishments

- 12 Partners
- 2.5 M Euro (co-funding)
- December 2006 – November 2009
- Website: ***www.eustite.org***

The EUSTITE Consortium
Competent Authorities for Inspection
Gametes and Embryos - Tissues and Cells

- **Centro Nazionale Trapianti - Italy (Co-ordinator)**
- **Irish Medicines Board Inspectorate Department**
- **Federal Ministry of Health and Women/ Unit III/A/4 Austria**
- **National Transplant Organisation (ONT) Spain**
- **Agence de la Biomedecine, France**
- **AFSSAPS, France**
- **University Hospital in Bratislava, Slovakia**
- **National Centre for Tissue and Cell Banking Poland**
- **Human Fertilisation and Embryology Authority UK**
- **Bulgarian Executive Agency for Transplantation**
- **Danish Medicines Agency**
- **WHO Essential Health Technologies - Clinical Procedures**

Vigilance and Surveillance in EUSTITE

Objectives: Development of a model for the reporting and investigating of adverse events and reactions associated with the quality and safety of tissues and cells in the EU (Work Package 4(b))

- ➔ month19 Development of the model
- ➔ month 20-32 Pilot implementation July 2008 to July 2009
- ➔ month 33-36 Report and Recommendation to SANCO

WHO is the main partner

V&S Medical Advisory Committee (VSMAC) Permanent Members

Project Partners

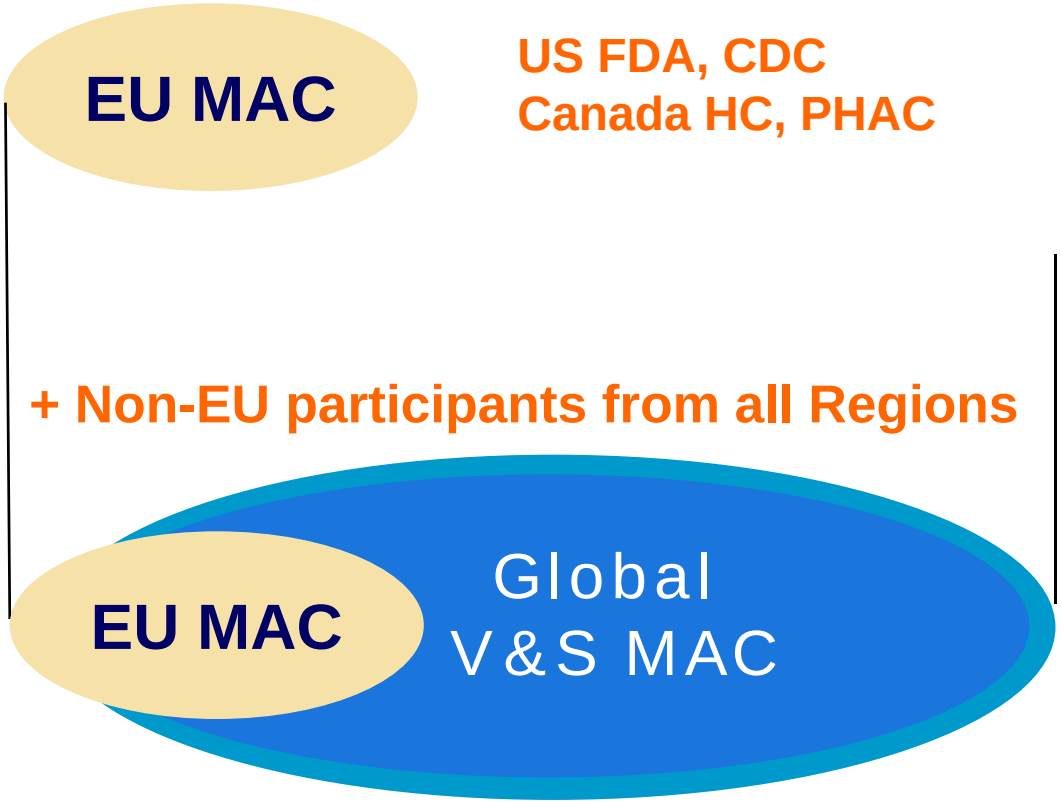
- Agence de la Biomedecine, France
- AFSSAPS, France
- Bultransplant, Bulgaria
- Central Tissue Bank, Slovakia
- Centro Nazionale Trapianti, Italy
- HFEA, UK
- ONT, Spain
- WHO

External Experts

- ECDC
- EBMT
- LUMC, Netherlands
- Paul-Ehrlich Institut, Germany
- University College London, UK

EUSTITE Vigilance and Surveillance
EU and Global V&S Medical Advisory Committee

- Madrid, March 2007
- Rome, July 2007



Expected Outcomes

- **EUSTITE:**
  - **A model for the definition, notification, classification and management of SAE and SAR**
  - **Tool kit and reporting system**
  - **Generic and specific to meet EU Directive requirements**
  - **Validated by pilot implementation in EU**
- **WHO**
  - **Global guidance for V&S, with generic tools**

Component of the EUSTITE V&S Tool Kit (1)

- Roles of structures and flows of information
- Who to declare in the complexity of international circulation
- What to report
  - SAE SAR with recipients , with live donors (threat to supply= threat to product)
  - To Tissue Establishment
  - To Competent authorities
- Why is Communication with Stakeholders essential to identify SAE SAR
  - Clinical Users
  - Organ procurement organizations
  - Other vigilance systems
  - Testing laboratories

Component of the EUSTITE V&S Tool Kit (2)

- How to assess SAE and SAR
  - Severity grading system for SARs with guidance on which level to report to CA (based on ISBT system for blood)
  - Imputability grading system for SARs
  - Impact grading system (risk matrix including wider system implications) for SAEs and SARs
  - Guidance on applying these tools
- Guidance on management of SAEs and SARS that have cross-border implications

Component of the EUSTITE V&S Tool Kit (3)

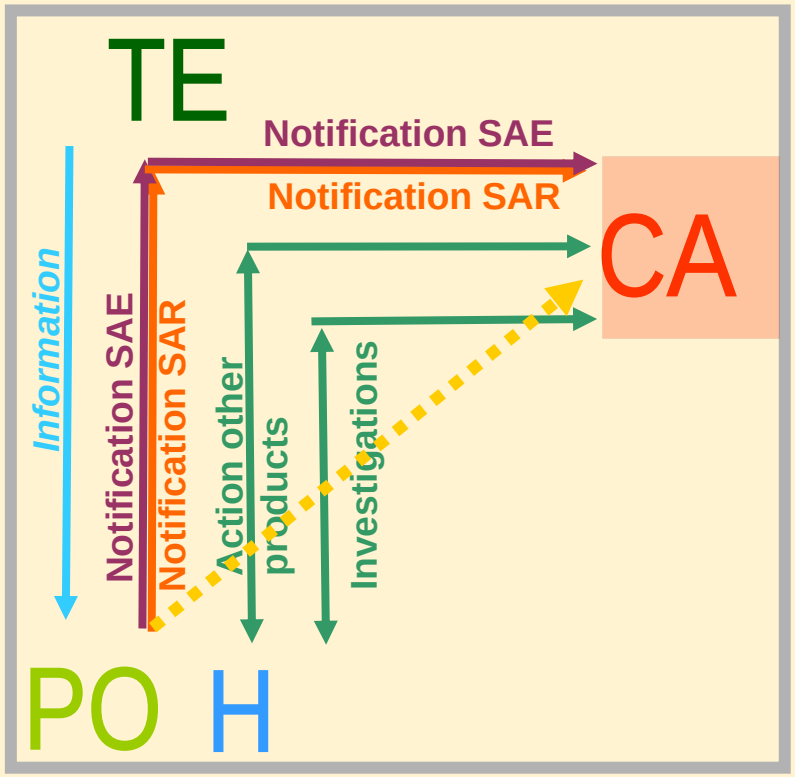
- **How Competent Authorities respond to SAR/E by**
  - **Rapid Alerts**
    - **Incident of a serious or potentially serious nature**
    - **Potential risk to other individuals across member states**
    - **Wider public health implications**
  - **Regulatory Action Notices**
    - **Based on serious incidents or trends**
    - **Lessons learnt from investigations of SAR/E shared throughout the professional community**
  - **Routine Responses to SAE/R Reports**
    - **within on week**
- **21 criteria for the evaluation of a V&S**

Implementation Options agreed for EUSTITE V&S

- **Beyond the Directive**
  - CA to include report of allogeneic donors harmed by a donation process with no detrimental impact on the quality or safety of the specific tissues or cells
  - Report to own CA when SAR/E is associated to a product imported directly from another EU Member State, simultaneously to notifying the TE
  - All adverse events and reactions that are suspected of being caused by the tissues or cells should be notified to TEs to allow trends in minor events and reactions to be monitored for continuous improvement purposes.
- **Illustrative example**s are extensively used for each type of product (categories, grading…etc)
- **Users involvement** at EU level, e.g. through concerted information through scientific and professional journals and meetings.
- **Risk surveillance**, horizon scanning is an integral component to be shared.

V&S Information Flow within an EU Member State

Key role of Tissue Establishments,



TE: Tissue Establishment

H: Organization Responsible for Human Application

PO: Procurement Organization

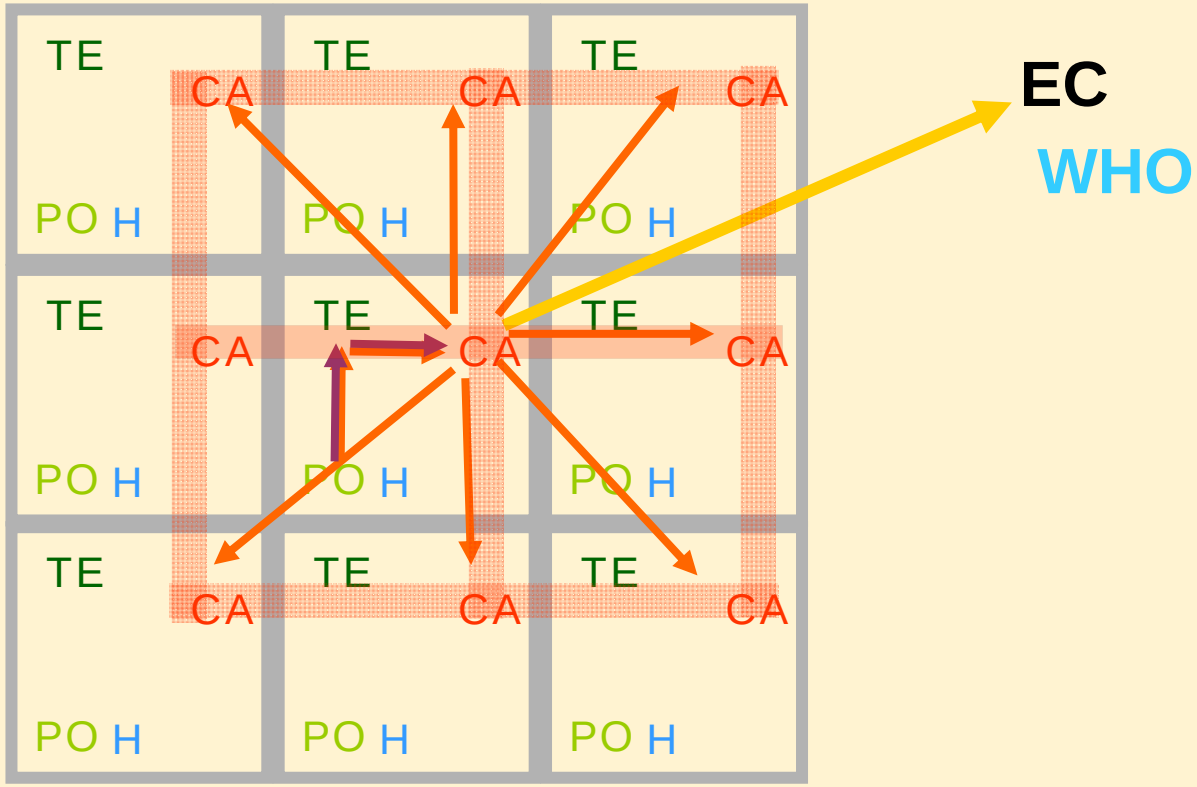
CA: Competent Authority

EC: European Commission

Exceptionally, if TE not contactable or mistrust of TE. Direct SAE/R report to CA which would involve the TE in the ensuing investigation and measures.

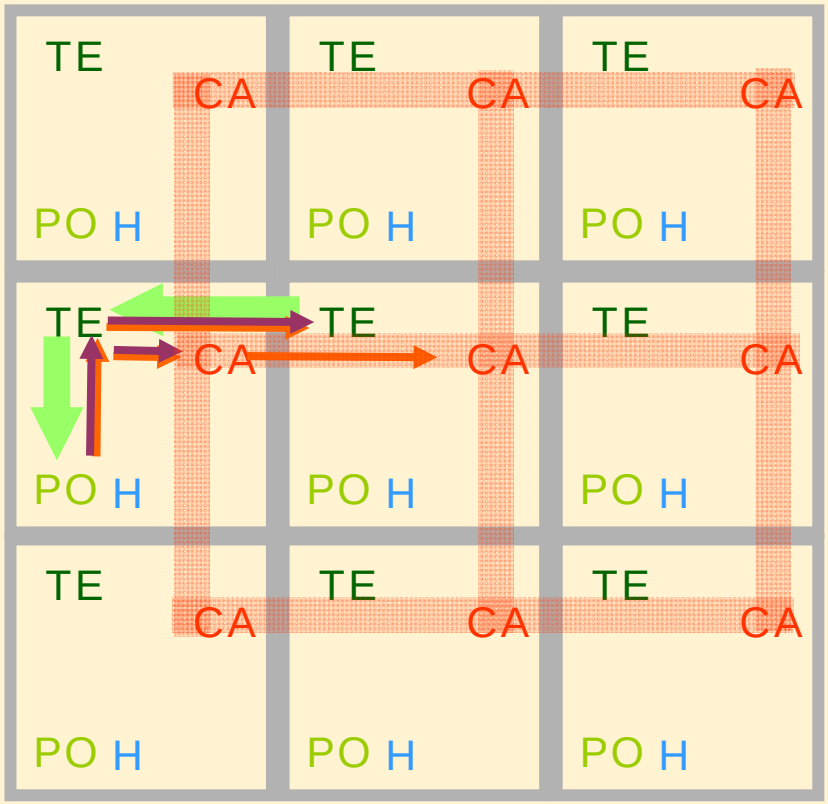
V&S Information Flow within EU Member States (1)

Key role at EU level of Competent Authorities to "communicate to each other and to the Commission such information as is appropriate with regard to SAR and SAE."



V&S Information Flow within EU Member States (2)

Tissues/cells from a TE in another EU Member State, through an importing TE: report to this TE and to own CA.



V&S Information Flow within EU Member States (3)

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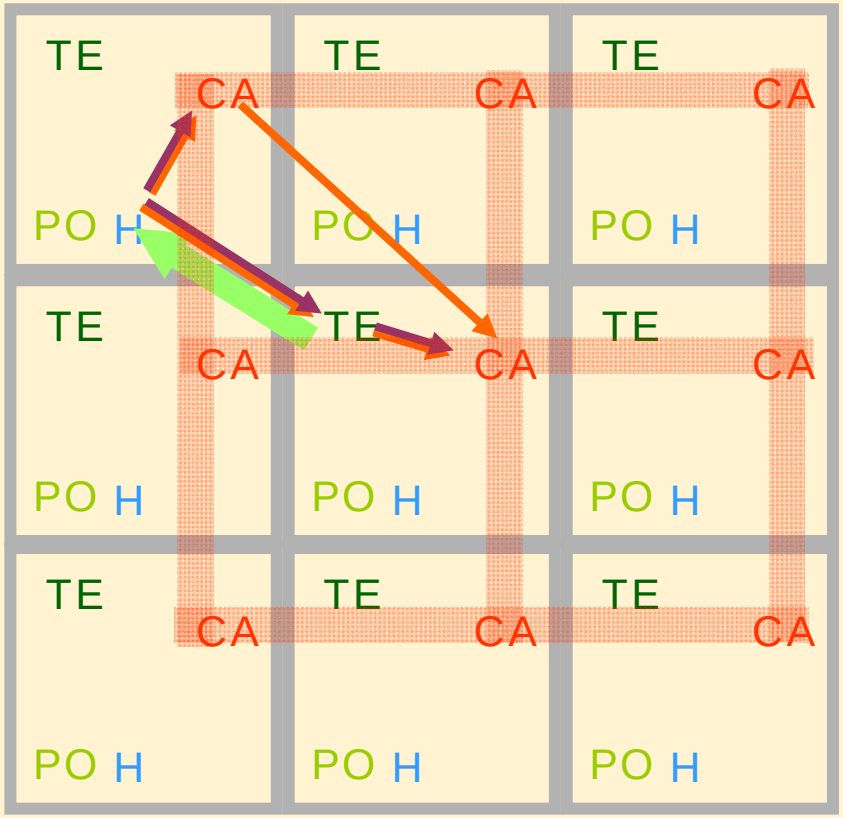
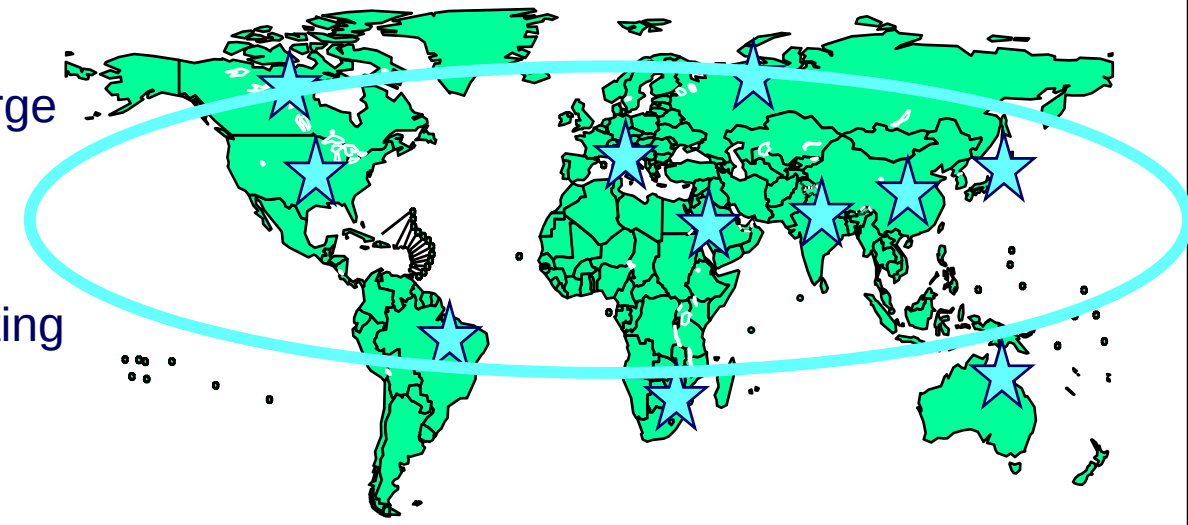


Beyond EUSTITE for EU: Global V&S

- A tool kit for V&S activities in the EU
- Generic tools as a basis for Global V&S
- EU as an example for very large countries or sub-regional collaborations
- A global network of collaborating centres on Vigilance and Surveillance for CTO transplantation



1991

WHO Guiding Principles for Transplantation

1. **Consent for deceased donation**
2. **No conflict for physicians determining death**
3. **Deceased but also live consenting donors**
4. **Minors and incompetent persons protected**
5. **No sale or purchase**
6. **Promotion of donation no advertising nor brokering**
7. **Physician responsibility on origin of transplant**
8. **Justifiable professional fees**
9. **Allocation rules**

Draft Guiding Principle 10

Quality of care, safety and efficacy of procedures are mandatory for donor and recipient alike. The long-term outcomes of cell, tissue and organ donation and transplantation should be assessed for both the donor and the recipient in order to document the benefit and harm for recipients and any harm to living donors.

The level of safety, efficacy and quality of human cells, tissues and organs for transplantation, as health products of an exceptional nature, has to be maintained and optimized on an ongoing basis. This requires implementation of quality systems including traceability and vigilance with adverse events and reactions reporting.

Draft Guiding Principle 11

The organization and execution of donation and transplantation activities, as well as the clinical results of such activities, must be transparent and open to scrutiny, while assuring that donors' and recipients' anonymity is always protected.

Thank you

Luc Noel
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Health Technology and Pharmaceuticals

Essential Health Technologies

World Health Organization