

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



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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

First Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation Ottawa, December 2004

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

AIDE-MEMOIRE
*for National Health Authorities**

Tissue and cell transplantation represent essential and rapidly developing therapies in modern health care. It is the responsibility of national health authorities to ensure that the needs of patients are met with a supply of safe tissues and cells of appropriate and consistent quality. A nationally supported legislative framework which defines consent requirements and supports donation and a regulatory system which addresses tissue and cell banks are prerequisites to achieving this goal. Donation and transplantation activities should be organized in a transparent way with the promise of adequate ethical and data to enable the public to make informed choices.

Tissue and cell transplantation carry risks 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. The safety of tissues and cells for transplantation is ensured by the careful selection of donors on the basis of their medical and behavioural history, physical examination and by testing of donor blood samples for transmissible agents. Donations should be processed only from non-remunerated donors from low-risk populations. In addition, whenever possible, validated pathogen inactivation or removal processes should be applied. Transplantation of tissues and cells should only be carried out when there is no option for a safer, equally effective, alternative therapy.

Any organisation engaged in the procurement (including donor identification, consent, donor selection testing and tissue or cell retrieval, processing, storage or distribution) of tissues and cells for transplantation should implement a comprehensive quality system. The system should cover all aspects of its activities and ensure a traceability from the identification of the donor to the transplantation of the product to a recipient. Management commitment and support are essential to the development, implementation and monitoring of a quality system in order to ensure continuous improvement. An audit should underpin the importance of quality and their role in achieving it consistently.

Words of advice

- Ensure that the legislative framework supports tissue and cell donation and transplantation.
- Develop national or international technical reference documents (standards).
- Create an inventory of all organisations that harvest donors and/or retrieve, process, store or supply tissues and cells for transplantation.
- Clarify 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 respect of tissue and cell donation.
- Publish information and data on tissue and cell donation and transplantation to ensure transparency.
- Provide control use of tissues and cells.

Access to Safe and Effective Cells and Tissues for Transplantation

☒ Checklist

General framework

- ☒ Legislative/regulatory framework
- ☒ Legitimate non-commercial standards
- ☒ Inspection and authorization of screening, testing, storage, processing, transport, distribution, recipient input
- ☒ Surveillance and vigilance including transplantation-associated disease
- ☒ Monitoring and reporting of reactions, post-mortem examination, impact, report and information availability

Selection and Prevention

- ☒ Campaigns to promote unremunerated donation
- ☒ Education of healthcare professionals to ensure optimum use of the tissue and ensure of tissue and cell donation

Safety

- ☒ Donor selection, selection, care and consent
- ☒ Donor screening and testing for infectious diseases
- ☒ Assessment of contamination and cross-contamination
- ☒ Monitoring of transplantation-associated disease

Quality Systems

- ☒ Clearly defined organizational structures
- ☒ Competence resources (staff and security)
- ☒ Quality management system
- ☒ Comprehensive validated documentation including Standard Operating Procedures (SOPs)
- ☒ Complete and accurate records to ensure integrity
- ☒ Appropriate, documented self-testing and external audits

Assessment

- ☒ Selection or full verification of each process and quality of equipment
- ☒ Internal and external audit
- ☒ Error management, correction and preventive action
- ☒ External quality assessment schemes

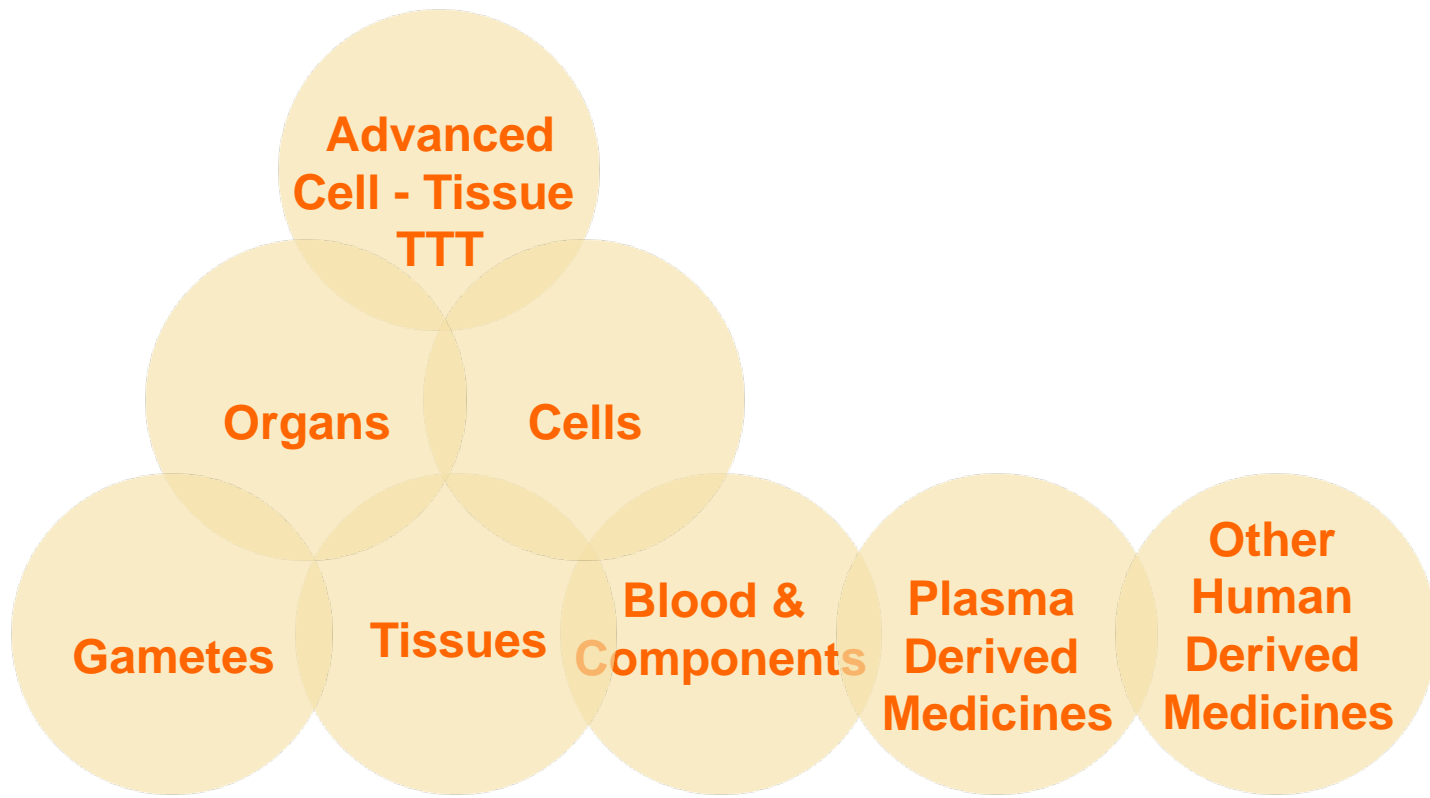
Ethical Use

- ☒ Transparency
- ☒ Appropriate use
- ☒ Close follow-up of transplant recipient

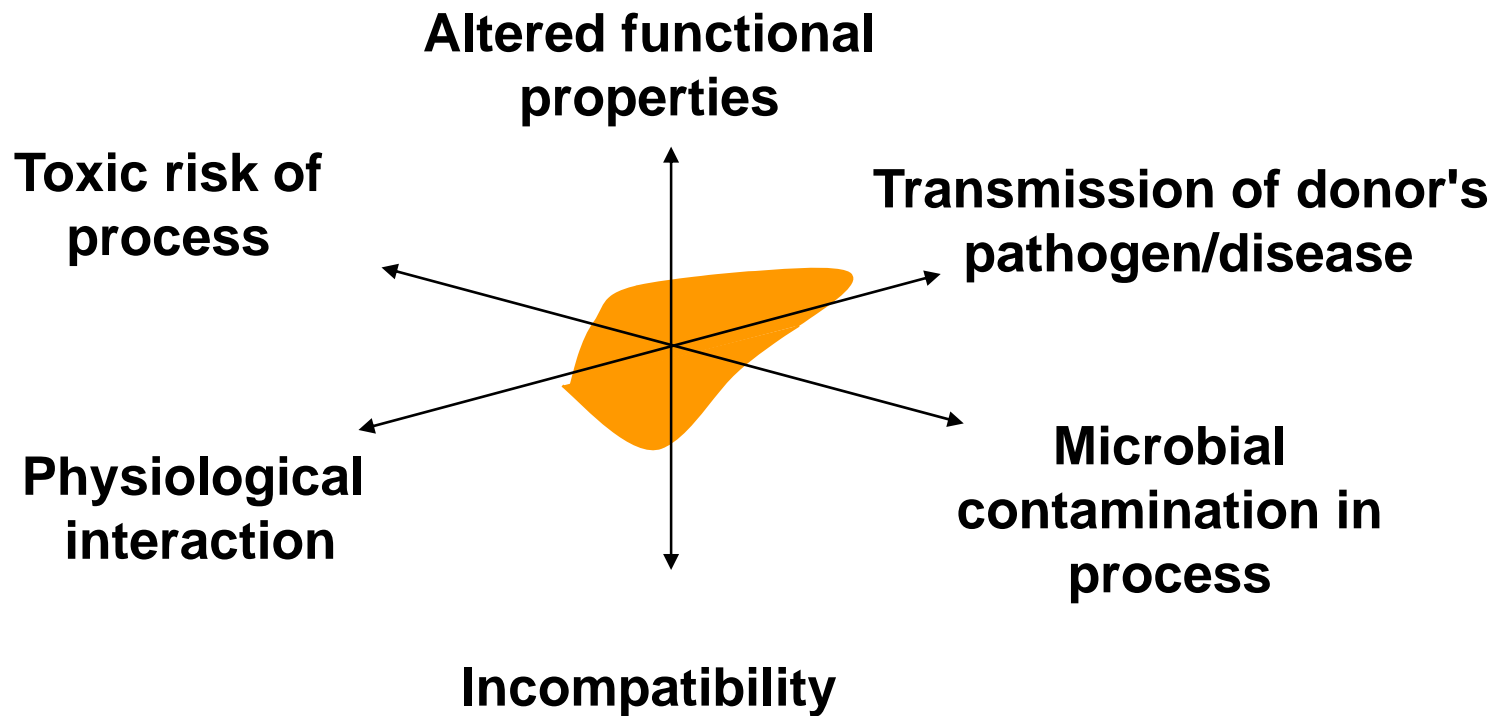
☐ Monitor adverse reactions in patients to allow corrective and preventive action

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 EURO-
PEAN 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 Union Standards and Training in the Inspection of Tissue Establishments



CENTRO NAZIONALE TRAPIANTI

- 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))

- ➔ month 19 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

EU MAC

**US FDA, CDC
Canada HC, PHAC**

- Rome, July 2007

+ Non-EU participants from all Regions

EU MAC

Global
V&S MAC



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**



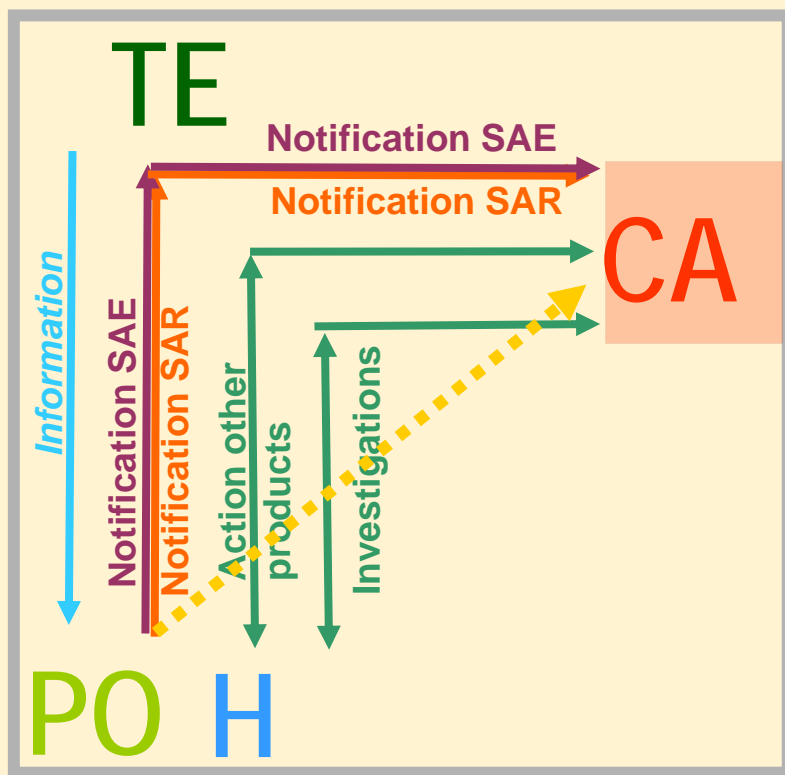
Implementation Options agreed for EUSTITE V&S

- **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 examples** 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,

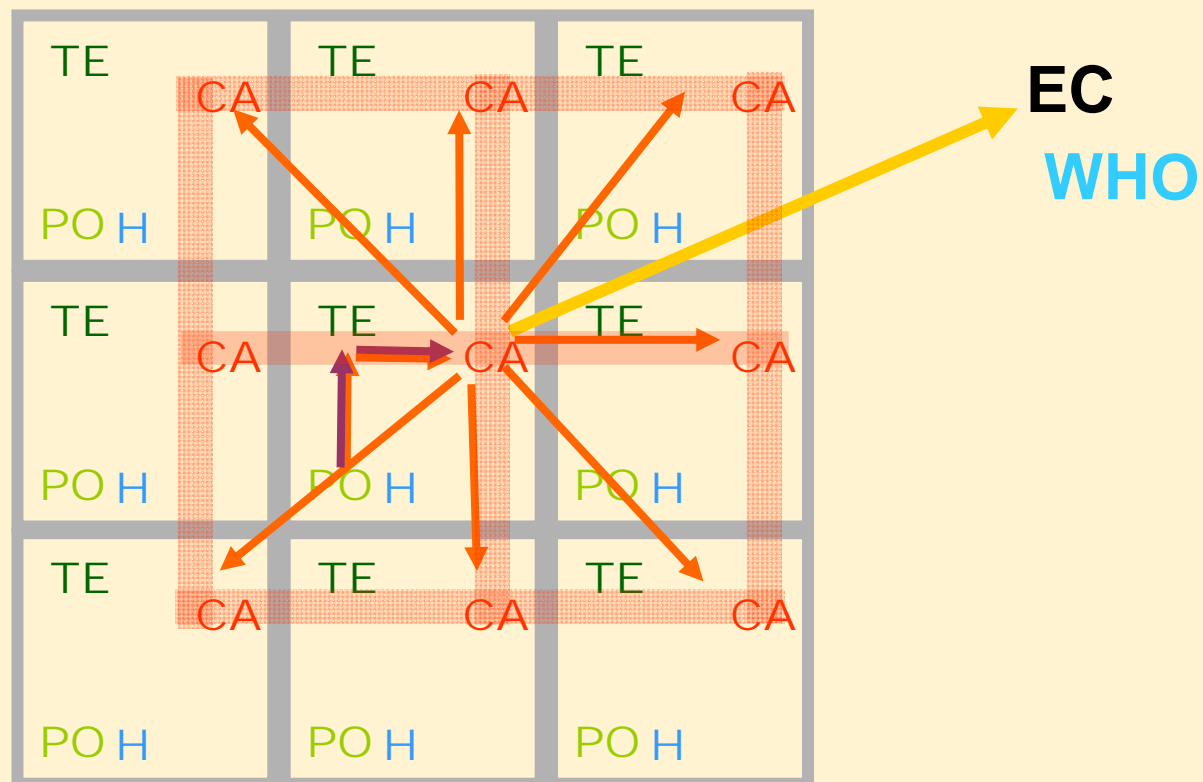


- TE:** Tissue Establishment
- H:** Organization Responsible for Human Application
- PO:** Procurement Organization
- CA:** Competent Authority
- EC:** European Commission

➡ *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.*

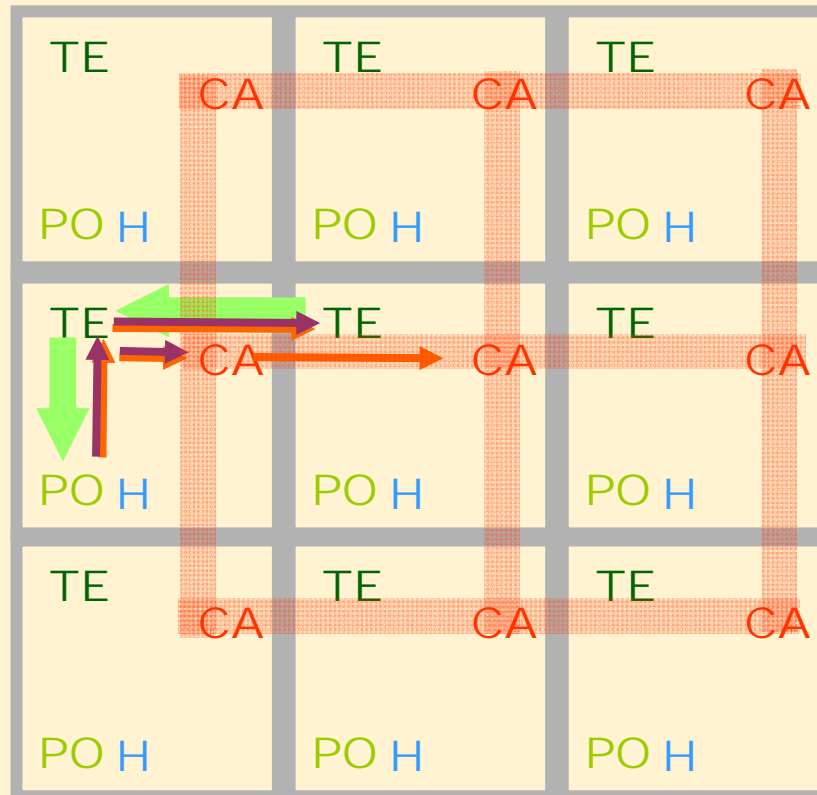
V&S Information Flow within EU Member States (1)

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."



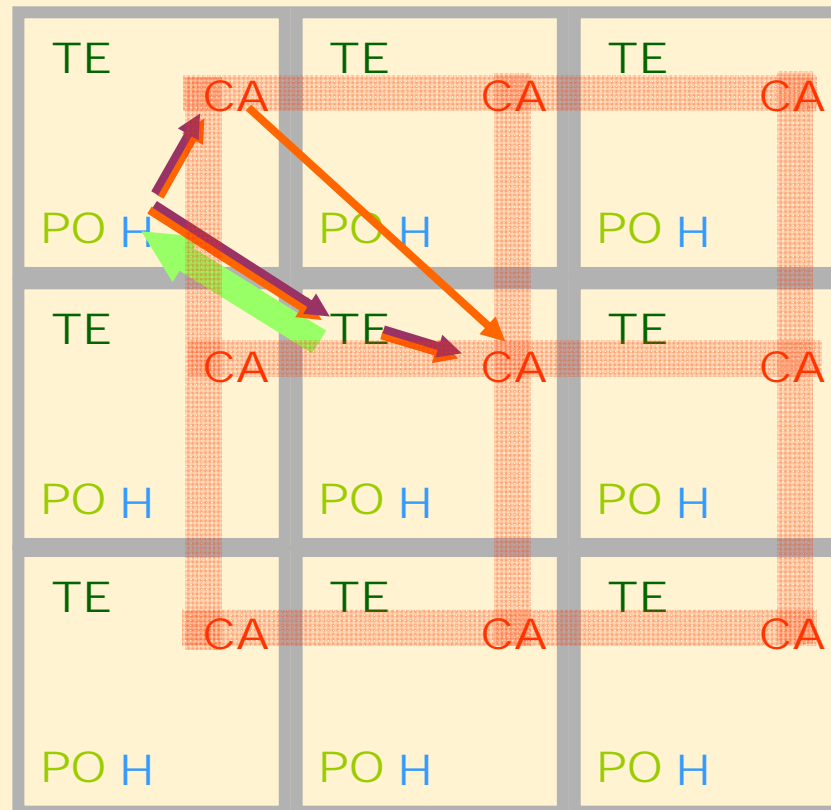
V&S Information Flow within EU Member States (2)

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)

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



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

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**Health Technology
and Pharmaceuticals**

**Essential Health
Technologies**



**World Health
Organization**