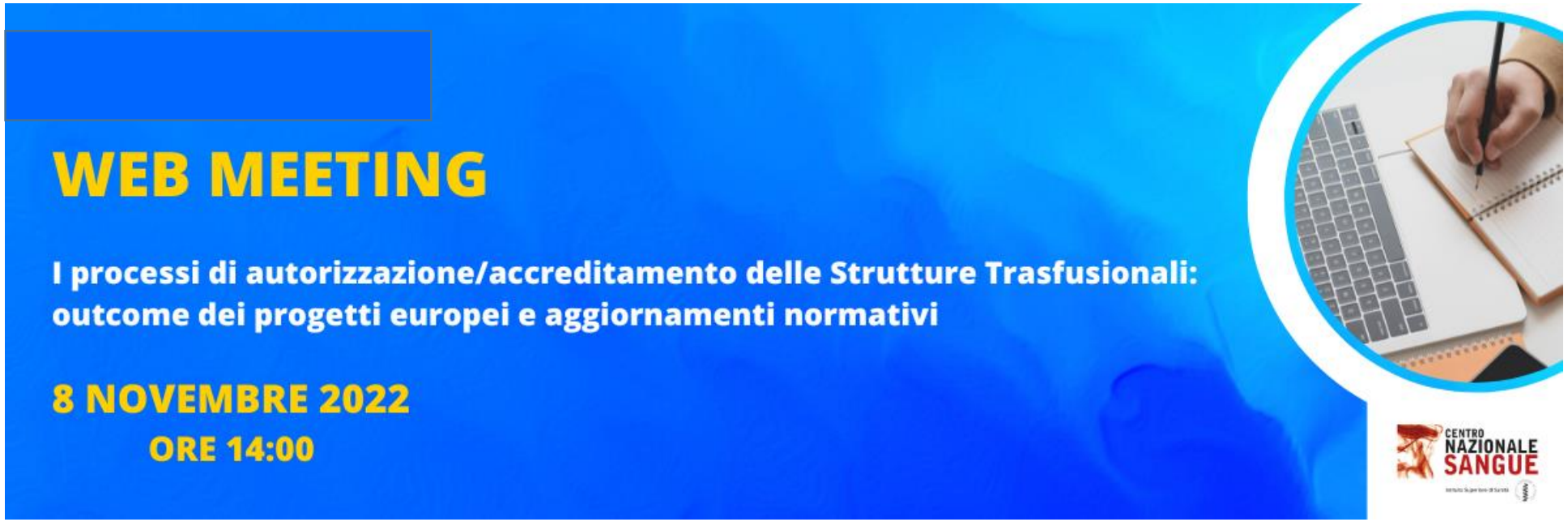
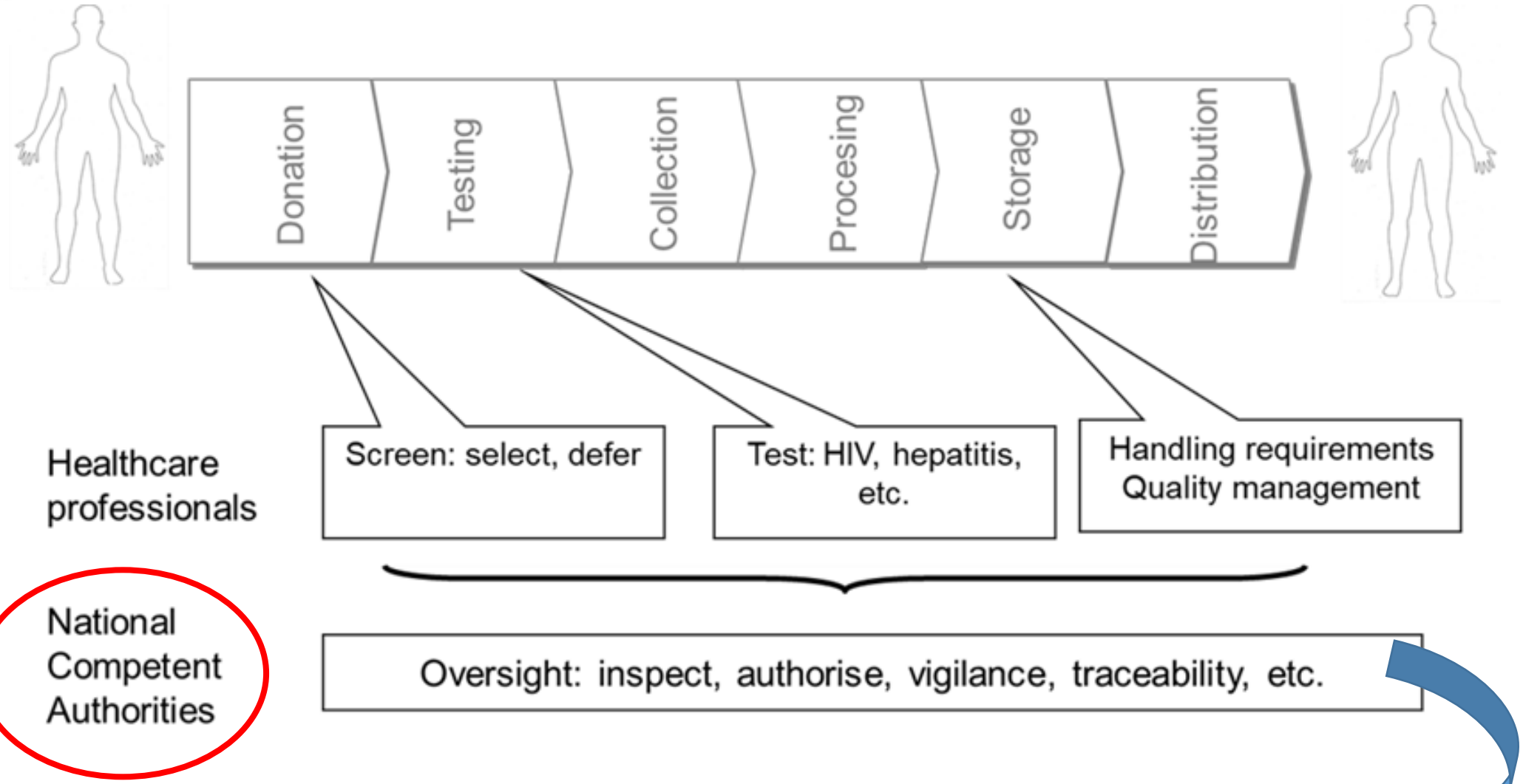



# Inspection guidelines for EU competent authorities responsible for inspection and authorisation of blood and tissue establishment (VISTART): introduzione, gestione della qualità e tool sviluppati, prospettive future

Dott.ssa Simonetta Pupella

CENTRO NAZIONALE SANGUE

# OBIETTIVI DELLE DIRETTIVE BTC




**VIGILANZA E CONTROLLO**

# I PRINCIPI

**Direttiva 2002/98/CE del Parl. Europeo e del Consiglio**

CAPO II
OBBLIGHI DELLE AUTORITÀ DEGLI STATI MEMBRI
Articolo 5
Designazione, autorizzazione, accreditamento o concessione di una licenza per i centri ematologici

Articolo 6
Banche del sangue degli ospedali

Articolo 7
Disposizioni relative ai centri già esistenti

Articolo 8
Ispezioni e misure di controllo

**Direttiva 2004/23/CE del Parl. Europeo e del Consiglio**

CAPO II
OBBLIGHI DELLE AUTORITÀ DEGLI STATI MEMBRI
Articolo 5
Vigilanza sull'approvvigionamento dei tessuti e delle cellule umani

Articolo 6
Accreditamento, designazione, autorizzazione o rilascio di licenza per gli istituti dei tessuti e per i procedimenti di preparazione dei tessuti e delle cellule

Articolo 7
Ispezioni e misure di controllo

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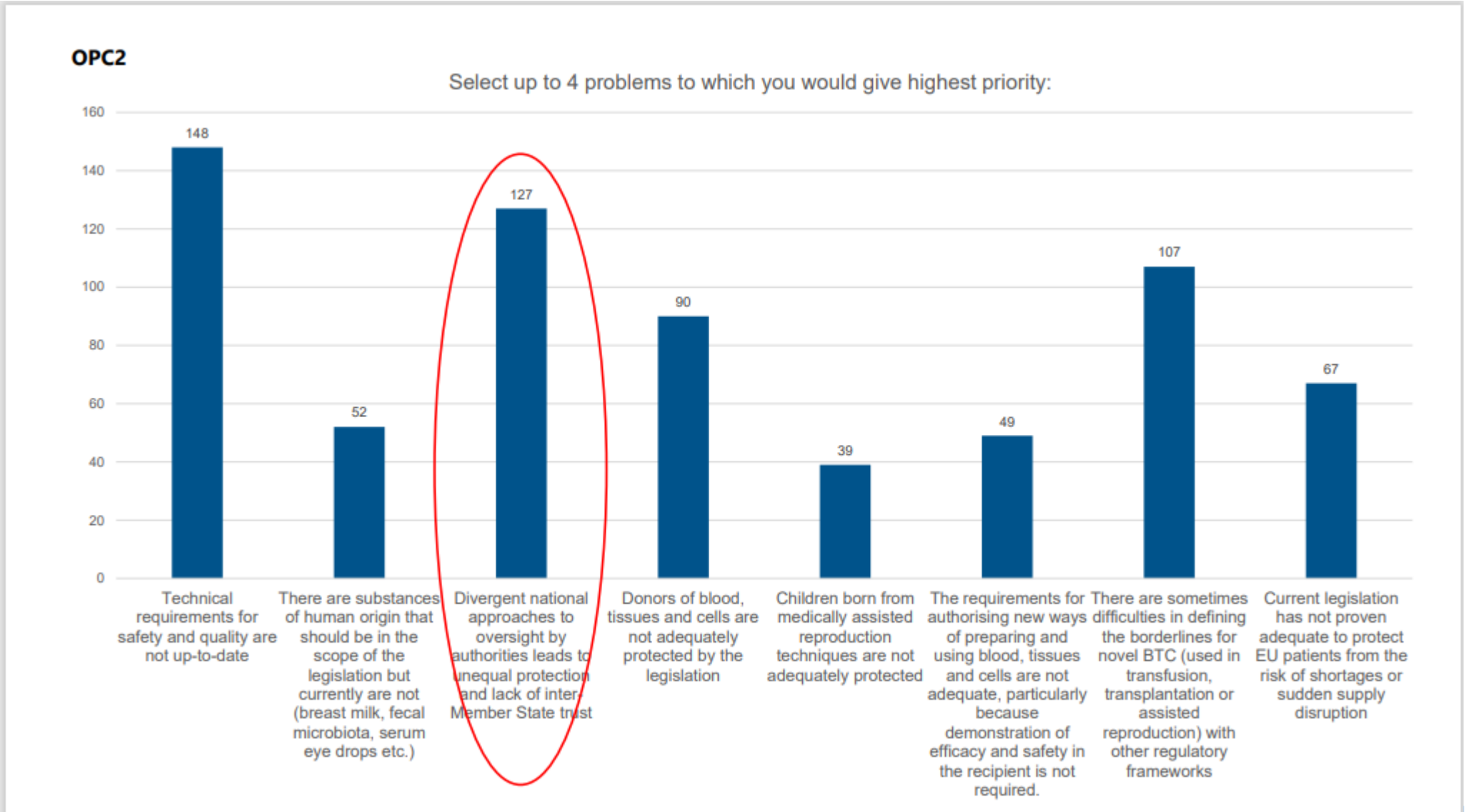
# IMPACT ASSESSMENT



# PERCHE' UNA REVISIONE DELLA LEGISLAZIONE BTC

## GAP/LIMITI

**1. Patients are not fully protected from avoidable risks**

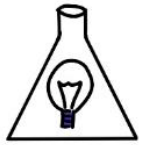
EU safety and quality requirements are incomplete and have failed to remain up to date with frequently changing scientific and epidemiological developments. The outdated provisions are technical in nature

**2. Avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos**

Donor adverse reactions (including serious ones) are not systematically reported and the requirements for testing egg and sperm donors for genetic conditions are limited.

**3. Divergent approaches to oversight cause unequal levels of safety and quality and barriers to the exchange of BTC across the EU**

Lack of general principles, provisions for verification of effective implementation of inspection, authorisation, vigilance.



**4. BTC legislation lags behindinnovation**

Limited clinical data on safety and efficacy of new ways of processing donations. Difficulties in defining the borderlines for novel BTC with other regulatory frameworks

**5. EU vulnerable to interruptions in supply of some BTC**

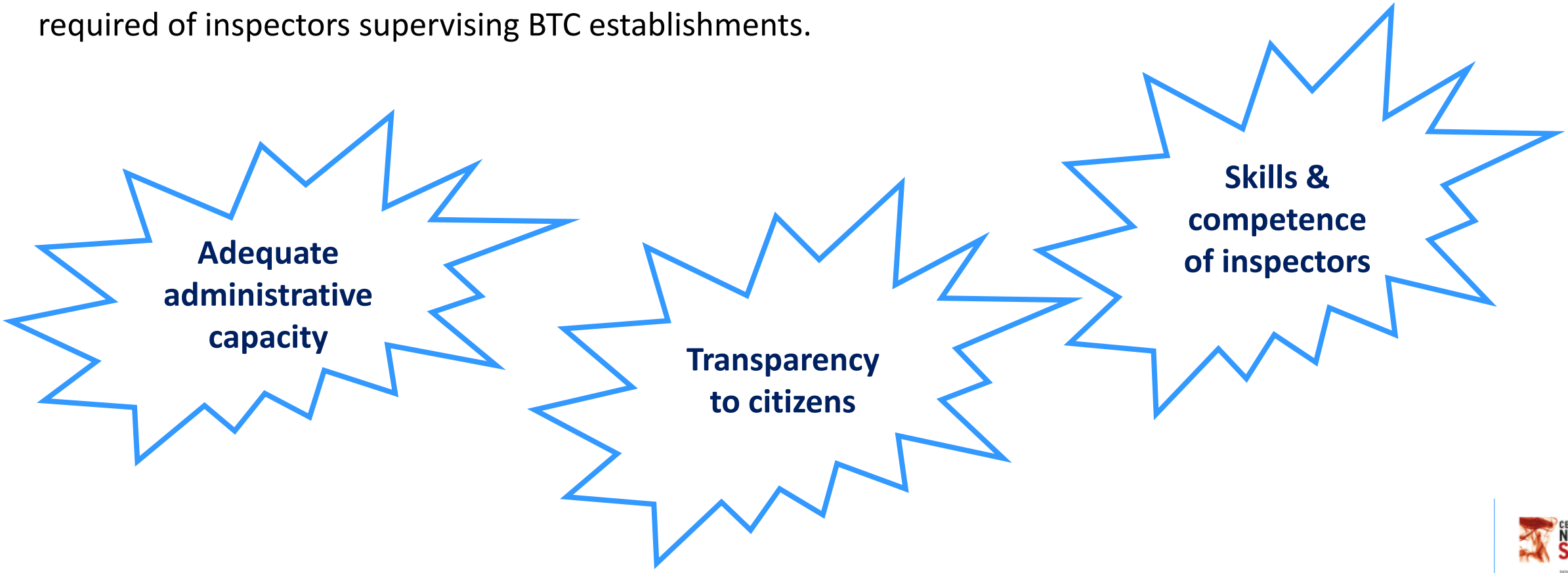
High dependence on plasma import. Lack of supply monitoring for crisis management

# BACKGROUND

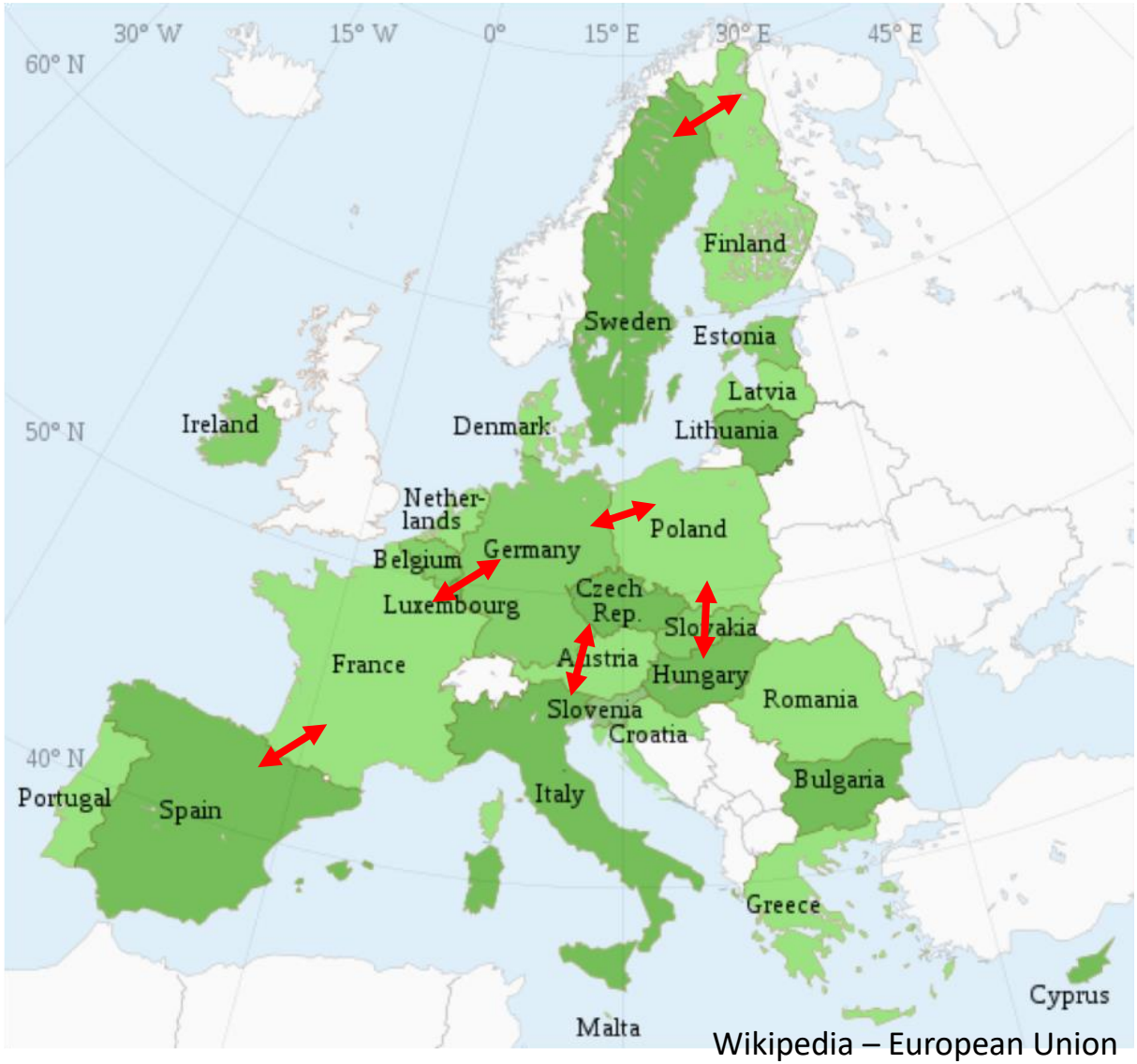
**Problem to be addressed:**

The BTC evaluation identified a need to **strengthen oversight of the BTC sector** in order to achieve a standard approach to the implementation of the rules. Divergent approaches to oversight cause **unequal levels of safety and quality** and **barriers to the exchange of BTC across the EU**….

These differences reflect the **lack of common provisions** for verification of effective implementation of inspection, authorisation and vigilance, and inconsistency in the levels of capacities, skills and independence required of inspectors supervising BTC establishments.



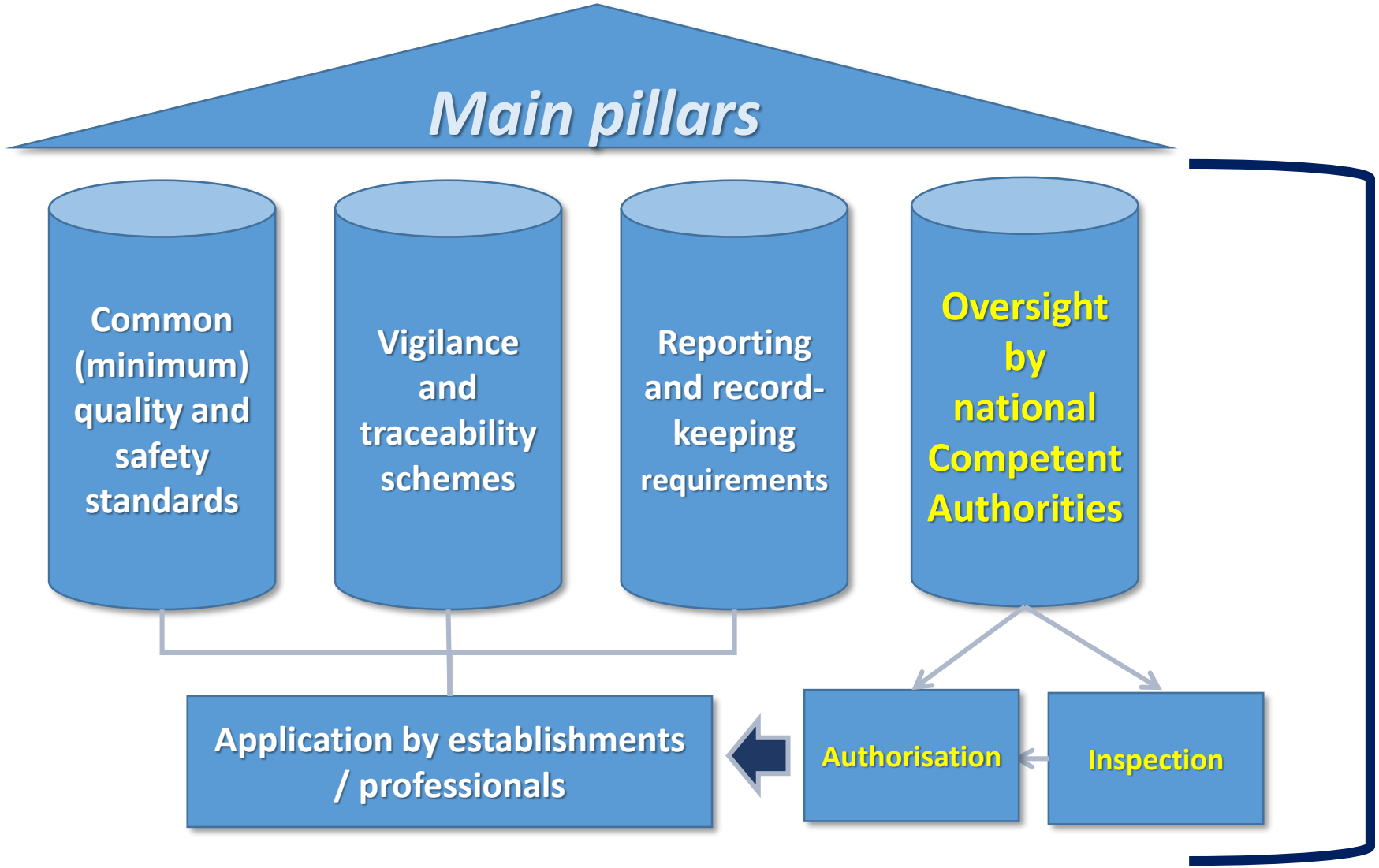
# SINGLE MARKET WITH FREE CIRCULATION OF GOODS




Wikipedia – European Union

**Presentation by Lea Joos, Regional Inspectorate, Germany**

# I PILASTRI DELLA LEGISLAZIONE COMUNITARIA IN MATERIA DI BTC



VISTART
VIGILANCE AND INSPECTION FOR THE SAFETY OF TRANSFUSION ASSISTED REPRODUCTION AND TRANSPLANTATION

# Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation

- ✓ Data di inizio: 10/10/2015
- ✓ Data di fine: 09/02/2019

## Obiettivi generali

- ✓ Promuovere e facilitare l'**armonizzazione** dei sistemi di ispezione, autorizzazione e vigilanza nei settori sangue, tessuti e cellule.
- ✓ Incrementare la **collaborazione** e la fiducia nei programmi di ispezione e vigilanza tra gli SM.

*"This presentation is part of the joint action '676969 / VISTART' which has received funding from the European Union's Health Programme (2014-2020). The content of this presentation represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for any use that may be made of the information it contains."*

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# Pacchetti tecnici

**WP 4**
Vigilance reporting for blood, tissues and cells

Portogallo

**WP 5**
**International Collaboration for Vigilance Communication and Preparation Process Development**

Italia (CNT)

**WP 6**
Inspection Guidelines for the Competent Authorities on Blood, Tissues and Cells

Francia

**WP 7**
Training of blood, tissues and cells inspectors with sharing of expertise across Member States

Italia (CNS)

**WP 8**
Establishment of a framework for joint inspections

Croazia

**WP 9**
A Voluntary Programme of Inter-MS Inspection System Auditing

Irlanda

**WP 10**
Implementation of the Single European Coding system in tissue establishments

Italia (CNT)

**OBIETTIVO:**

- ✓ **Produzione di Linee Guida sulle ispezioni per le AC europee responsabili dell'ispezione e dell'autorizzazione dei servizi trasfusionali (ST) e degli istituti dei tessuti.**


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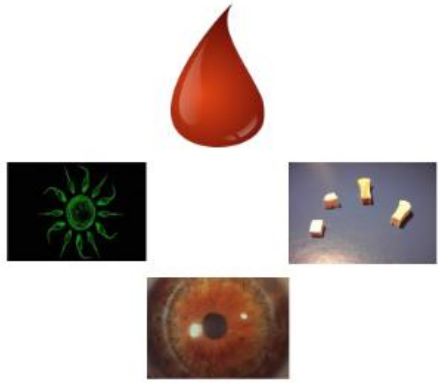
VISTART
VIGILANCE AND INSPECTION FOR THE SAFETY OF TRANSFUSION ASSISTED REPRODUCTION AND TRANSPLANTATION

Funded under the Joint Action 'Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation (VISTART)' by the European Commission, Directorate General Sante and the Consumers, Health and Food Executive Agency (Grant Agreement No. 676969)

# INSPECTION GUIDELINES FOR EU COMPETENT AUTHORITIES RESPONSIBLE FOR THE INSPECTION AND AUTHORISATION OF BLOOD AND TISSUE ESTABLISHMENTS



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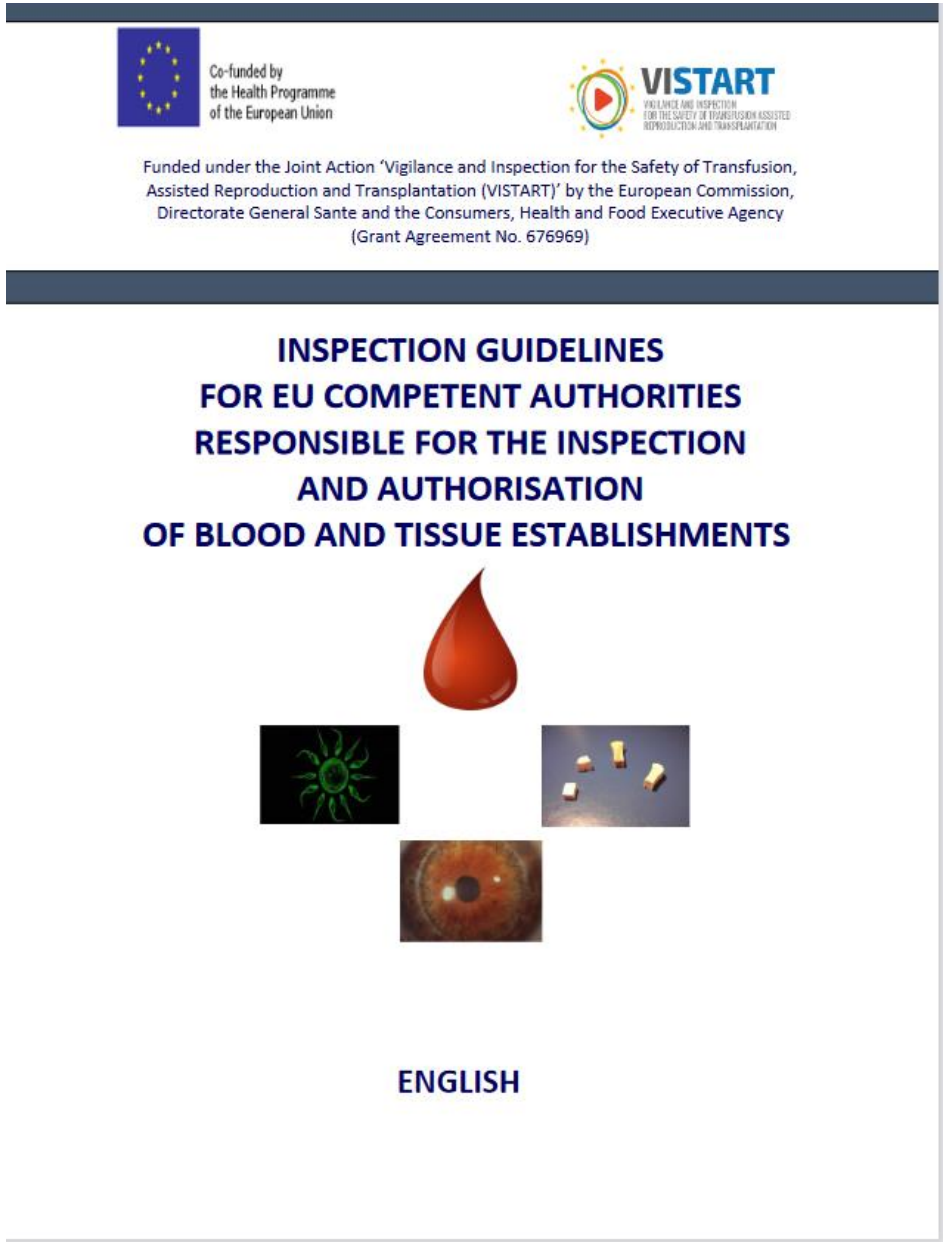


# OBIETTIVI DELLE GUIDELINE

- General governance and quality management principles for CAs,
- Key procedures and documents for licensing blood and tissue establishments,
- Authorisation of processing methods,
- Scheduling, preparation, conduct and follow-up of inspections,
- Recruitment, training and management of inspectors,
- Control of import and export.

## References


- Competent Authority Training of Inspections in Europe (developed by EU funded project CATIE),
- Common Criteria for the Inspection of Blood Establishments (developed by EU funded project EUBIS – European Blood Inspection Project),
- European Union Standards and Training in the Inspection of Tissue Establishments (developed by EU funded project EuSTITE),
- Inspection of tissue and cell procurement and tissue establishments - Operational Manual for Competent Authorities (developed by EU funded project),
- Compilation of Community Procedures on Inspections and Exchange of Information (EMA/572454/2014 Rev 17),
- EN ISO 17020.


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# COMPITI DELLE AUTORITA' COMPETENTI (CAs)

# LA GOVERNANCE DELLE CAs

- Programmare, pianificare e condurre le ispezioni
- Reclutare e formare gli ispettori
- Gestire le misure di controllo
- Identificare le attività illegali
- Autorizzare i BTC establishments
- Revocare o sospendere le autorizzazioni


Adeguate risorse umane per numero e competenze

Disponibilità delle informazioni per i cittadini

# SISTEMA DI GESTIONE PER LA QUALITA' (SGQ)

**Quality policy and manual**

**Documentation and change control**

**Control and access to records**

**Internal and external audit**

**Quality improvement**


**Management of risks arising from the activities of an inspectorate**

# SISTEMA DI GESTIONE PER LA QUALITA' (SGQ)

**Procedures for taking urgent measures for the protection of public health**

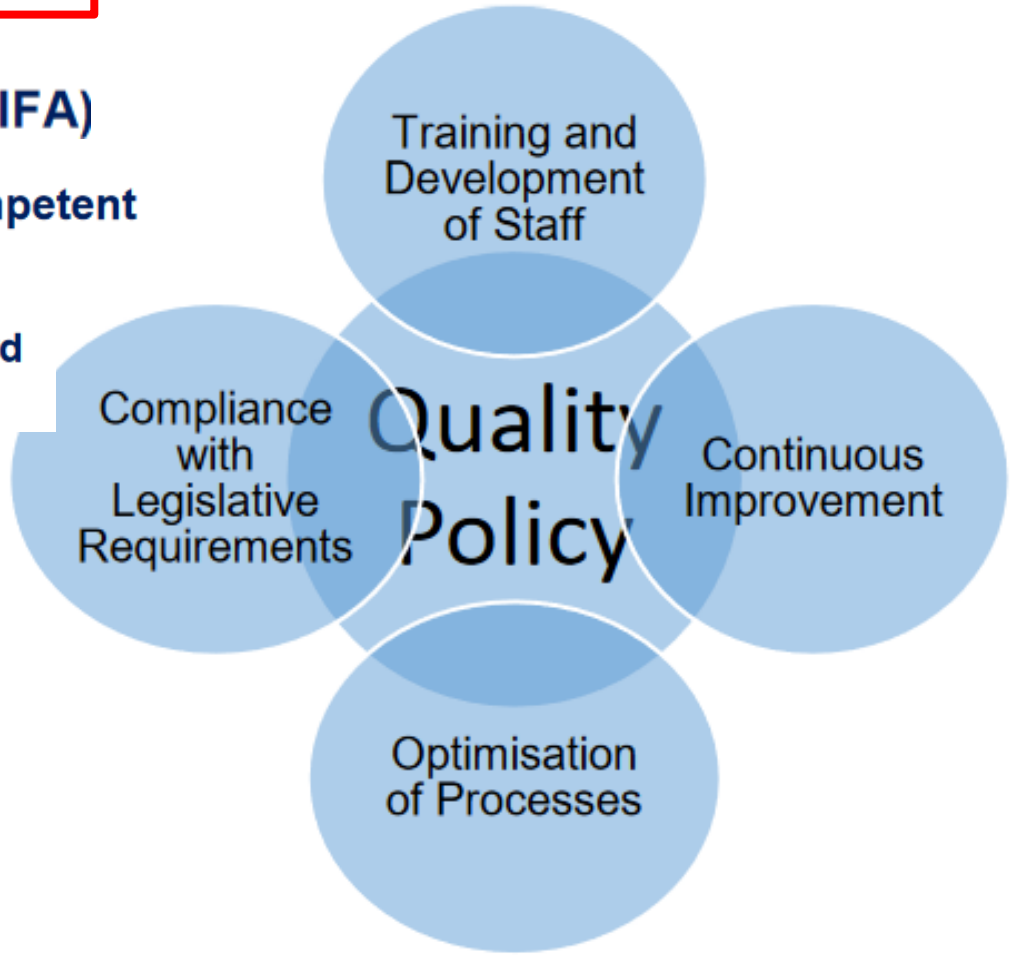
**Procedures for identifying illegal and fraudulent activity (IFA)**

**Exchange of information between EU Member States/Competent Authorities**

**Exchange of information with other regulatory authorities or third countries**

**Management of complaints**

**Management of conflicts of interest**



# Management of risks arising from the activities of an inspectorate

**Table 1:** Example of a Risk Register

| Risk | Causes | Effects | Mitigating Factors | Additional Actions Taken |
|---|---|---|---|---|
| Inconsistency of inspectors in applying legislation, regulations or standards. | • Insufficient training of inspectors<br>• Inadequate guidance/procedures for inspectors to follow. | • Loss of stakeholder confidence.<br>• Increased risk of challenges to regulatory decisions.<br>• Risk to public health. | • Quality assurance of inspection reports.<br>• Mentoring new inspectors.<br>• Continuous training and development. | • Audit of inspection reports.<br>• Audit of Inspection Evidence Forms.<br>• Review of training programme. |

# AUTORIZZAZIONE DEI PROCESSI DI PREPARAZIONE DI BTC

Directive 2005/62/EC Article 6.4 (2), requires that

*The processing of blood components shall be carried out using appropriate and validated procedures including measures to avoid the risk of contamination and microbial growth in the prepared blood components.*

Directive 2006/86/EC Annex 11, requires

*Competent authorities to authorise each tissue and cell preparation process after evaluation of the donor selection criteria and procurement procedures, the protocols for each step pf the process, the quality management criteria, and the final quantitative and qualitative criteria for cells and tissues. The evaluation must comply at least with the requirements set out in the annex.*

# AUTORIZZAZIONE DEI PROCESSI DI PREPARAZIONE DI BTC

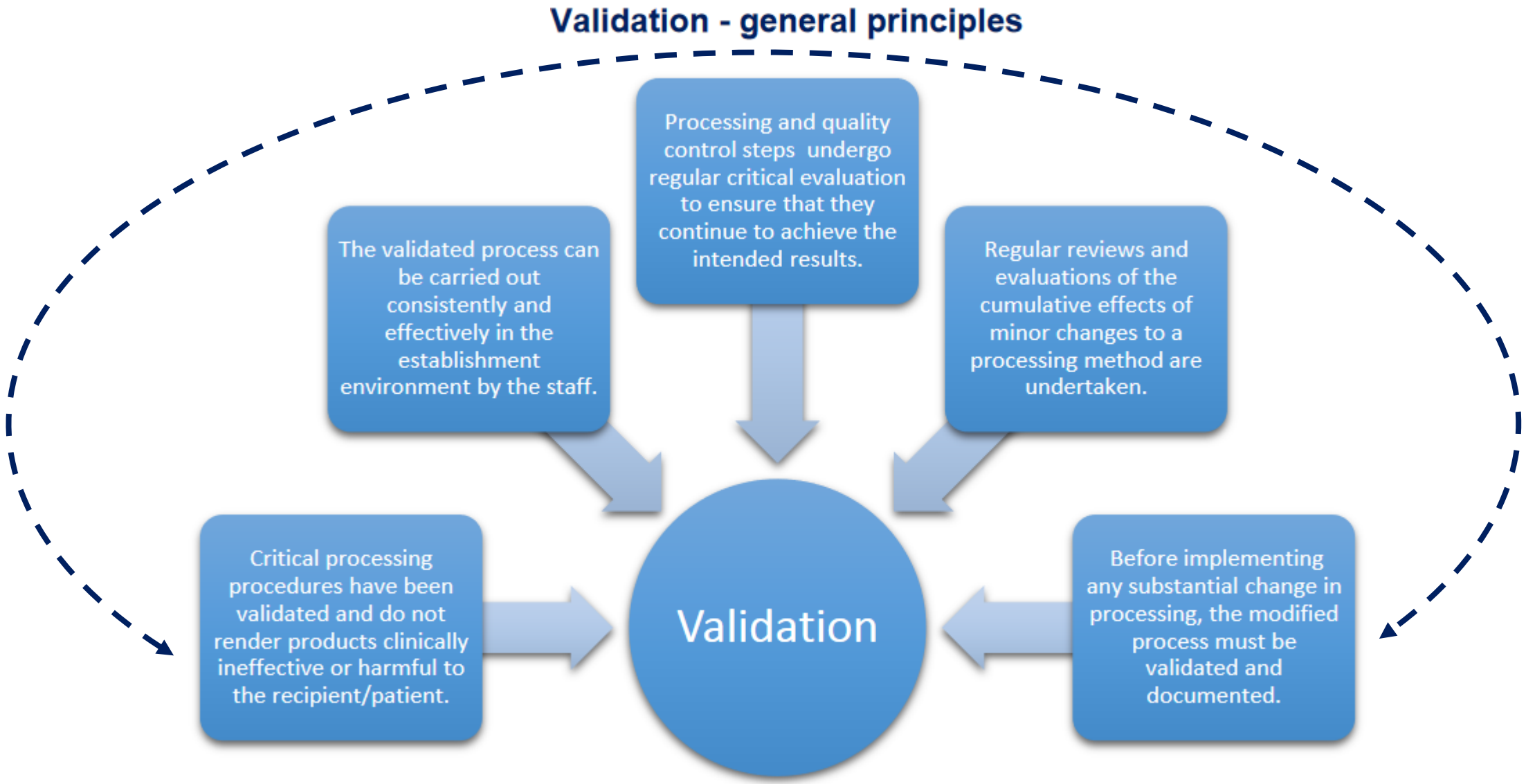



**Figure 2:** Principles of validation

# 4 Inspections

**Blood Directive 2002/98/EC, Article 3 defines an inspection as:**

*Inspection shall mean formal and objective control according to adopted standards to assess compliance with this Directive and other relevant national legislation and to identify problems.*

- general systems inspections,
- thematic inspections,
- desk-based reviews,
- inspections of third parties,
- EU joint inspections,
- re-inspections.

# Implementing a risk-based approach to inspection scheduling

## Risk rating

# Quality Risk Management Tools
## Intrinsic risk

- Two factors
  - Complexicity of the site, processes and products.
  - Criticality of the products, services, etc.


| | Criticality | | |
|---|---|---|---|
| Complexity | 1 | 2 | 3 |
| 1 | 1 (Low) | 2 (Low) | 3 (Medium) |
| 2 | 2 (Low) | 4 (Medium) | 6 (High) |
| 3 | 3 (Medium) | 6 (High) | 9 (High) |


A total score of 1 or 2 represents a **Low** Intrinsic Risk
A total score of 3 or 4 represents a **Medium** Intrinsic Risk
A total score of 6 or 9 represents a **High** Intrinsic Risk

# Quality Risk Management Tools
## Compliance related risk

| Deficiency Profile | Compliance-related Risk Score |
|---|---|
| 1 or more Critical Deficiencies or more than 5 Major Deficiencies | High |
| From 1 to 5 Major Deficiencies | Medium |
| No Major or Critical Deficiencies | Low |

High Compliance-related Risk Score may need to be inspected again very soon after the inspection that identified the poor state of compliance → Non routine inspection

# Quality Risk Management Tools
## Overall Risk Rating

- Intrinsic rate risk
- Non compliance related rate risk

| | Intrinsec Risk | | |
|---|---|---|---|
| Compliance risk | Low | Medium | High |
| Low | Risk Rating = A | Risk Rating = A | Risk Rating = B |
| Medium | Risk Rating = A | Risk Rating = B | Risk Rating = C |
| High | Risk Rating = B | Risk Rating = C | Risk Rating = C |

There are three possible risk ratings, A, B & C. ('A' represents a relatively low risk site and 'C' represents a relatively high risk site).

# Quality Risk Management Tools
## Inspection Frequency

**FATTORI DI RISCHIO**

- intrinsic risk (e.g. blood, blood components will always be considered high risk[10]; for tissues and cells, new or complex processes may indicate a high intrinisic risk),
- complexity of activities performed,
- the compliance history of the site,
- the criticality of the establishment to supply.

Scoring 1-4 with 4 representing highest risk rating

Establishment *000000* – Risk Rating

| Intrinsic Risk | Compliance History | Complexity | Supply | Overall Risk Rating |
|---|---|---|---|---|
| 4 | 2 | 3 | 1 | 10 |

Overall Risk Rating

1-4 = Low Risk, 5-9 = Medium Risk, 10 or more = High Risk

| Overall Risk Rating | Suggested Onsite Inspection Frequency |
|---|---|
| Low | Reduced Frequency, ≥25 months ≤ 48 months* |
| Medium | Normal Frequency ≤ 24 months |
| High | Increased Frequency ≤18 months |

# Inspection preparation

## Pre-inspection document review

**Licence status and history**

- Establishment Dossier
- Previous Inspection Report
- Non-compliances and follow-up
- Preparation process dossier (where relevant)
- Significant changes since the last inspection e.g. premises, equipment, perso

**Activities**

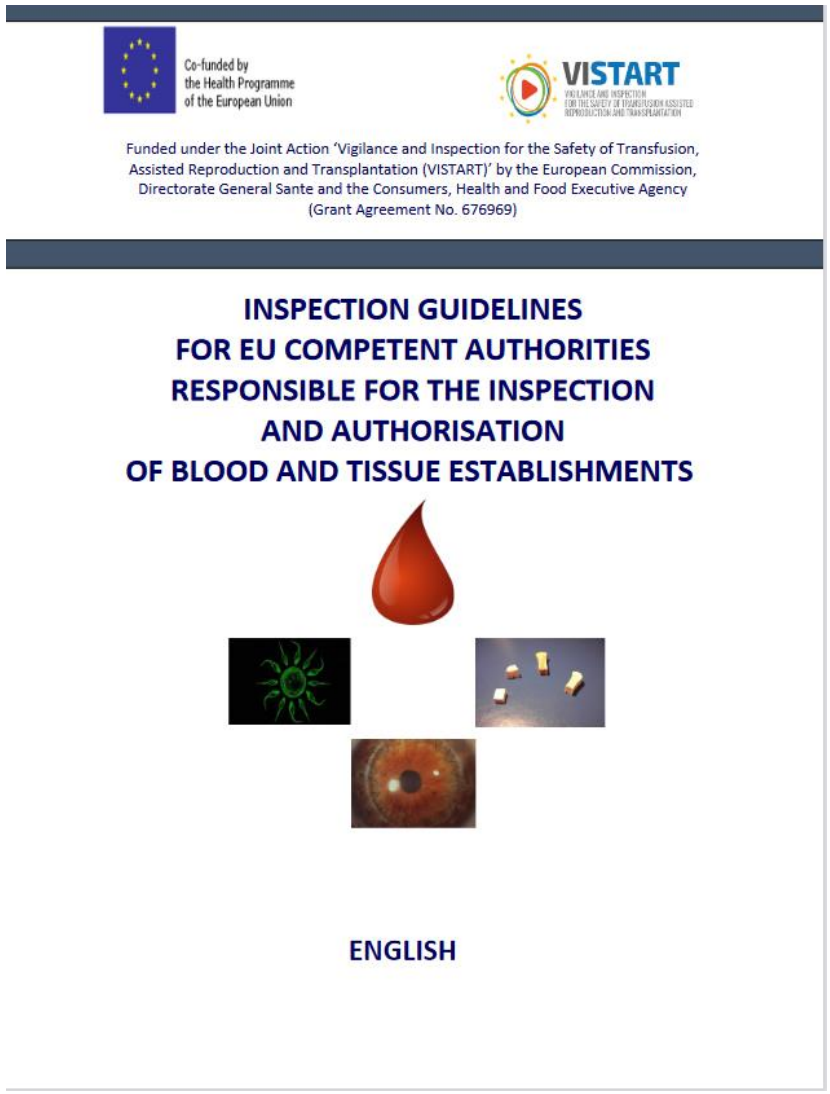
- Volume and Complexity
- Processes and products
- Procurement and testing arrangements
- Import
- Third parties/sub-contractors

**Other**

- Serious Adverse Events and Reactions, Recalls
- External intelligence e.g. from another regulator
- Complaints/whistleblowing
- Annual activity data

## Gathering evidence during an inspection

# INSPECTION GUIDELINE TOOLS



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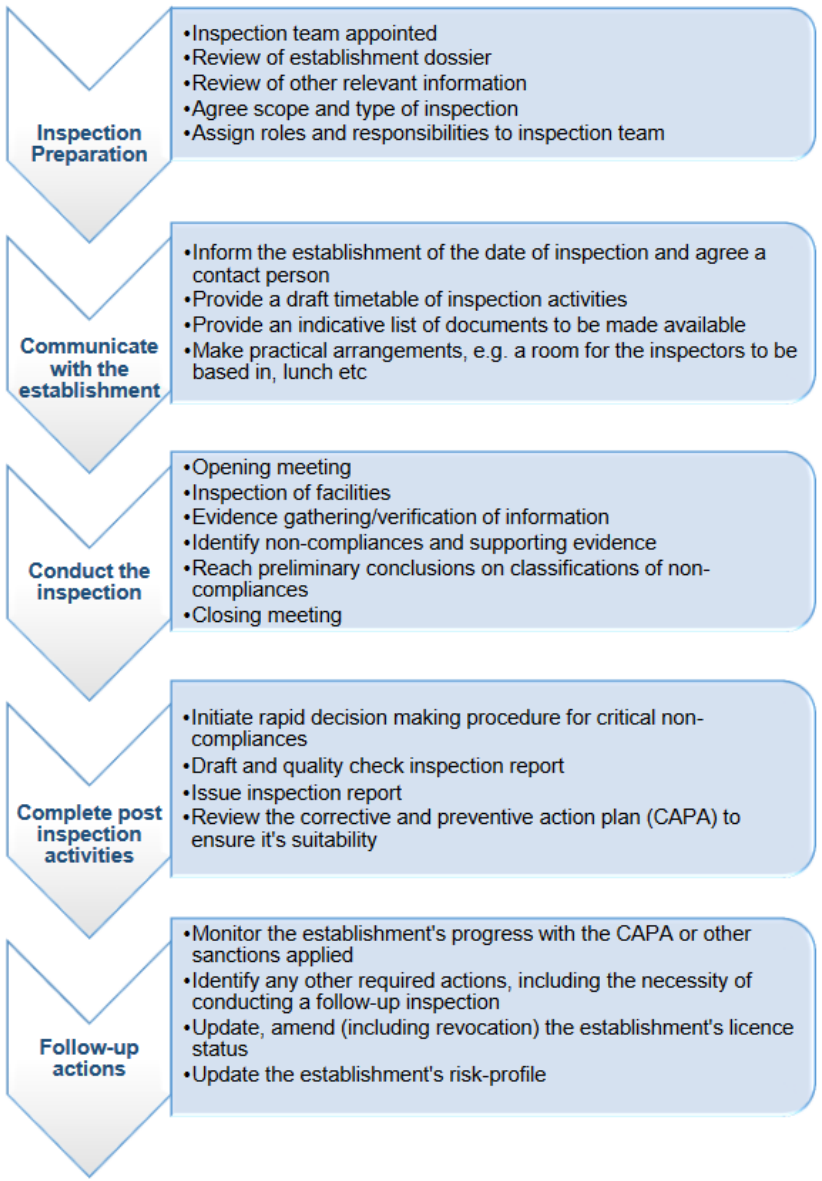
INSPECTION GUIDELINES
FOR EU COMPETENT AUTHORITIES
RESPONSIBLE FOR THE INSPECTION
AND AUTHORISATION
OF BLOOD AND TISSUE ESTABLISHMENTS

ENGLISH

# Inspection procedure flow chart: common tools

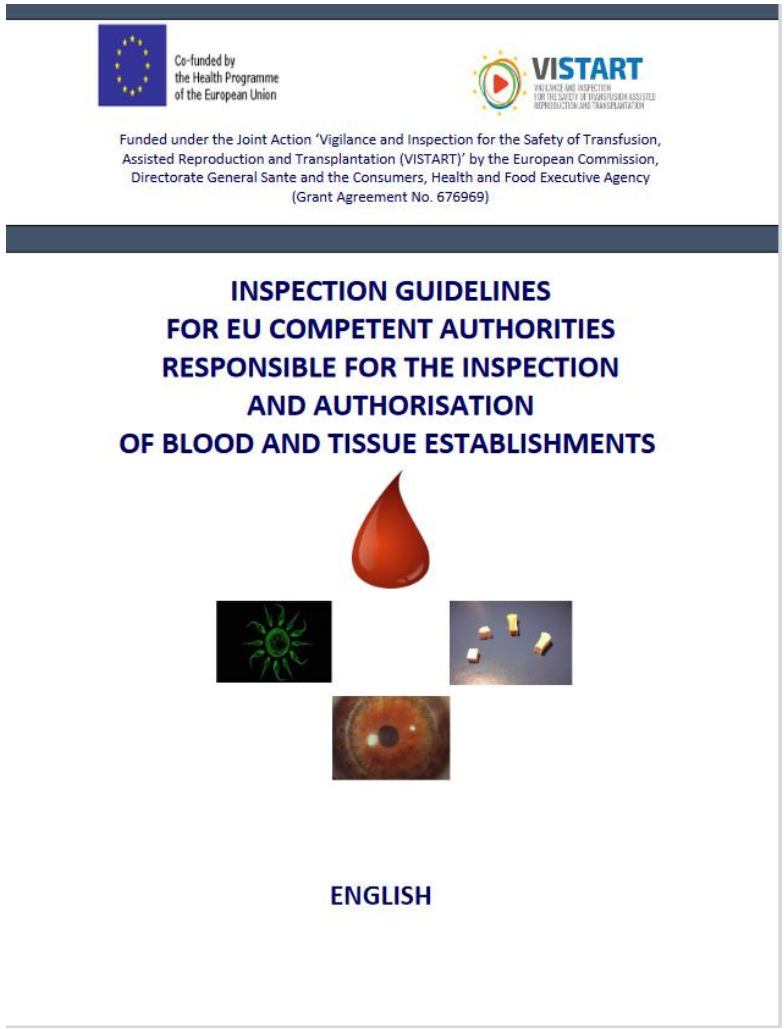



**Annex 1: Proposed Format for a Blood Establishment Dossier (BED)**
**Annex 2: Proposed Format for a Tissue Establishment Dossier (TED)**
**Annex 3: Proposed Format for a Preparation Process Dossier for BTC**

- procurement and processing records,
- staff training records,
- equipment and facilities maintenance records,
- audits,
- traceability of the blood, tissues and cells
- change control documentation.

**Classification of non-compliances**

**Annex 5: Proposed Format for an Inspection Evidence Form**




https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b1d517f8&appId=PPGMS

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# Grazie dell'attenzione!