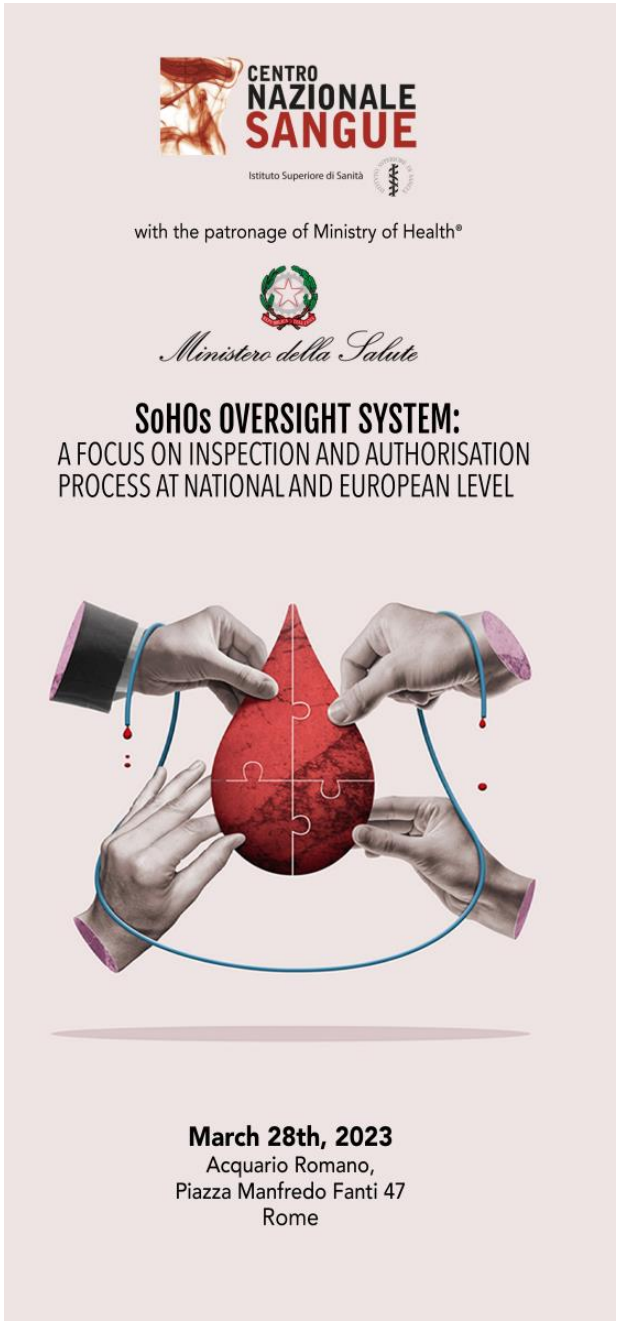


The inspection and authorisation processes of the Italian tissue, cells and MAR systems

Letizia Lombardini

Centro Nazionale Trapianti
ISTITUTO SUPERIORE DI SANITÀ

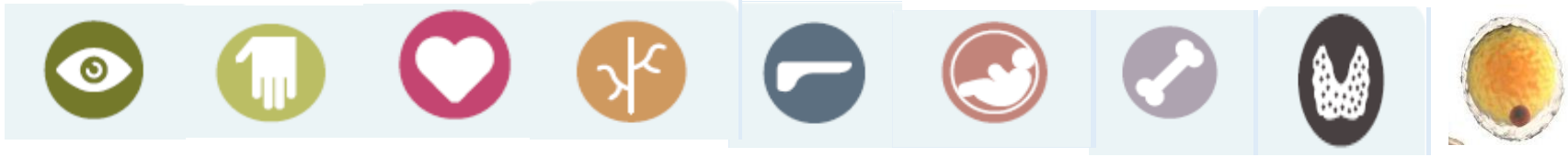
Rete Nazionale Trapianti

Rome, 28th March 2023

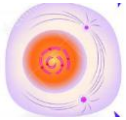
Italian network of Tissue Establishments

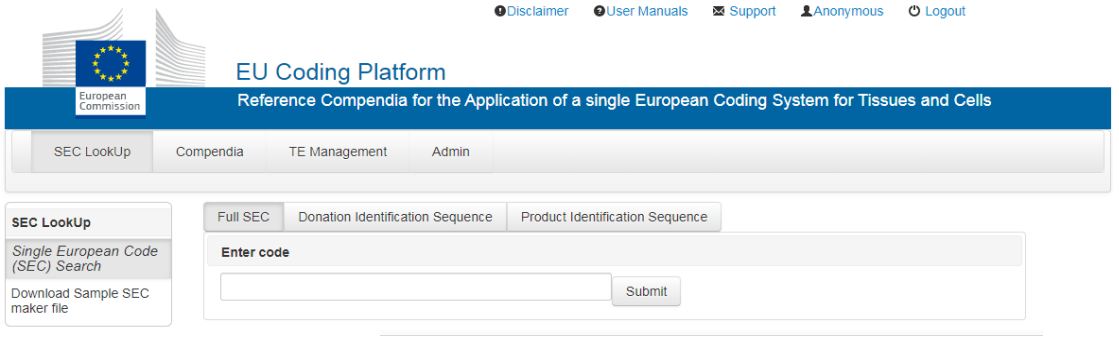
29 tissue banks

- 14 mono tissue
- 15 multi tissue

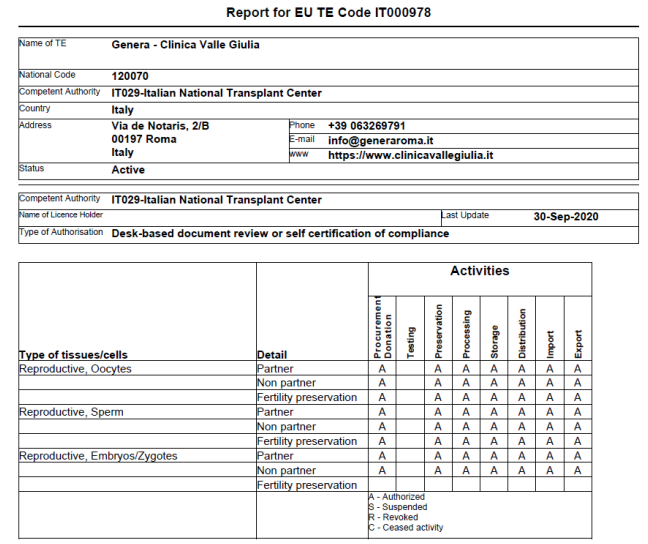


77 Processing Units Hematopoietic Stem Cells (HSC)





18 Cord Blood Banks



Report for EU TE Code IT000978

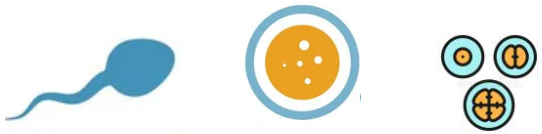
Name of TE	Genera - Clinica Valle Giulia
National Code	120070
Competent Authority	IT029-Italian National Transplant Center
Country	Italy
Address	Via de Notaris, 2/B 00197 Roma Italy
Phone	+39 063269791
E-mail	info@generaroma.it
www	https://www.clinicavallegiulia.it
Status	Active

Competent Authority	IT029-Italian National Transplant Center
Name of Licence Holder	
Last Update	30-Sep-2020
Type of Authorisation	Desk-based document review or self certification of compliance

Type of tissues/cells	Detail	Activities							
		Procurement Donation	Testing	Preservation	Processing	Storage	Distribution	Import	Export
Reproductive, Oocytes	Partner	A		A	A	A	A	A	A
	Non partner	A		A	A	A	A	A	A
	Fertility preservation	A		A	A	A	A	A	A
Reproductive, Sperm	Partner	A		A	A	A	A	A	A
	Non partner	A		A	A	A	A	A	A
	Fertility preservation	A		A	A	A	A	A	A
Reproductive, Embryos/Zygotes	Partner	A		A	A	A	A	A	A
	Non partner	A		A	A	A	A	A	A
	Fertility preservation								

A - Authorized
S - Suspended
R - Revoked
C - Ceased activity

170 Medically Assisted Reproduction (MAR) centres



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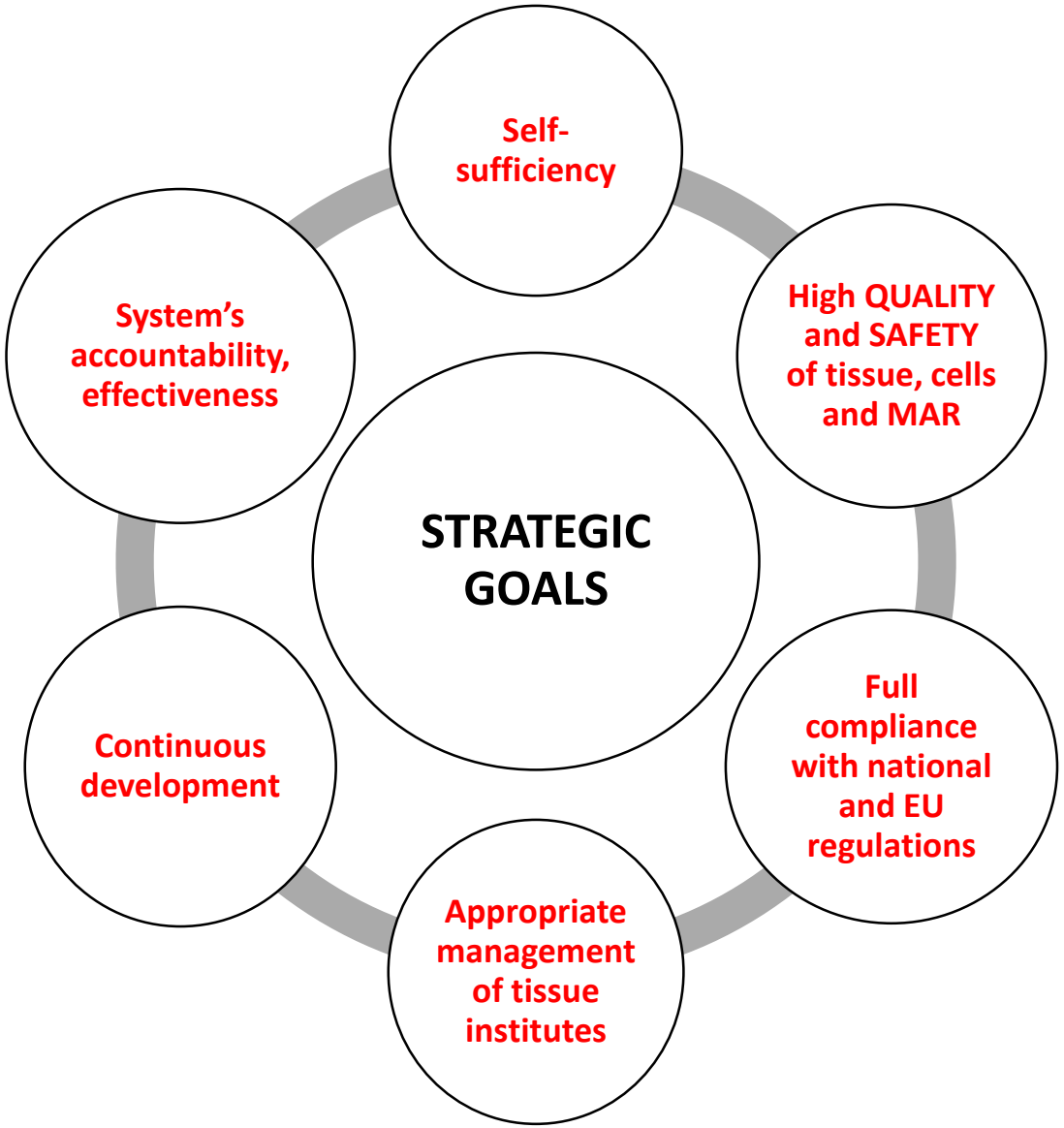
THE ITALIAN TRANSPLANT SYSTEM



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TISSUE/CELLS AND MAR SYSTEMS GOVERNANCE IN ITALY

Ministry of Health	National Transplant Centre (CNT)	Regional Transplant centres (CRT)	Regional MAR office
• Political decisions • Strategic goals	• Technical body of the MoH • Coordination and technical and scientific control of the national transplant network	• Technical bodies of regional health authorities • Coordination and technical and scientific control of the regional transplant network	• Coordination and technical control of the regional MAR network
		⇩	⇩
		Tissue and cells	**Law 19 February 2004, n. 40**

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THE REGULATORY FRAMEWORK

Law 1 aprile 1999, n. 91
Provisions concerning the procurement and transplantation of organs and tissues

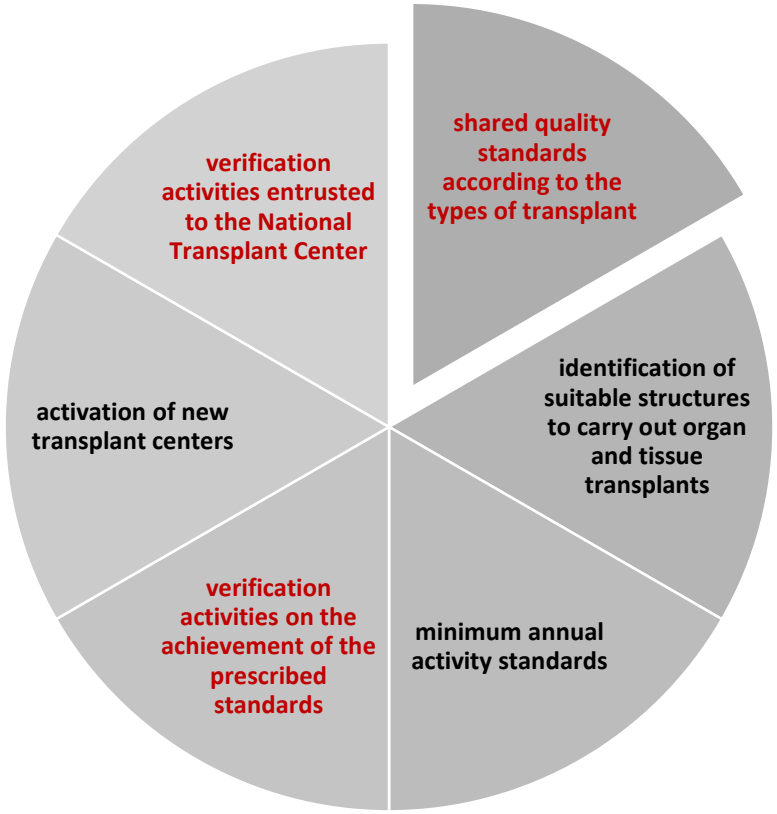
Reference law

Art. 15.
(Structures for the conservation of the collected tissues)

1. The regions, having consulted the regional or inter-regional centre, identify the **public health structures with the task of conserving and distributing the tissues withdrawn, certifying their suitability and safety**

Act by Permanent Conference for relations among State, Regions and Autonomous Provinces of Trento and Bolzano - February 14 2002

Agreement between the Minister of Health, the regions and the autonomous provinces of Trento and Bolzano on the **requirements of the structures suitable for performing organ and tissue transplants and on the minimum standards of activity** referred to in art. 16, paragraph 1, of the law of 1 April 1999, n. 91, containing "**Provisions concerning the procurement and transplantation of organs and tissues**".



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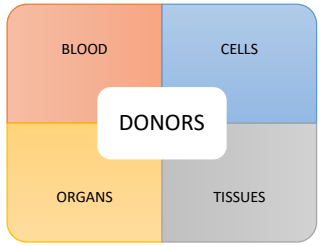
Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells	**DECRETO LEGISLATIVO 6 novembre 2007, n.191** Attuazione della direttiva 2004/23/CE sulla definizione delle norme di qualità e di sicurezza per la donazione, l'approvvigionamento, il controllo, la lavorazione, la conservazione, lo stoccaggio e la distribuzione di tessuti e cellule umani.
Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells	**DECRETO LEGISLATIVO 25 gennaio 2010, n.16** Attuazione delle direttive 2006/17/CE e 2006/86/CE, che attuano la direttiva 2004/23/CE per quanto riguarda le prescrizioni tecniche per la donazione, l'approvvigionamento e il controllo di tessuti e cellule umani, nonché per quanto riguarda le prescrizioni in tema di rintracciabilità', la notifica di reazioni ed eventi avversi gravi e determinate prescrizioni tecniche per la codifica, la lavorazione, la conservazione, lo stoccaggio e la distribuzione di tessuti e cellule umani.
Commission Directive 2006/86/CE 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	

FOCUS ON QUALITY AND SAFETY



of any Substance of human origin intended to be applied to humans

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«Licensing» in the EU regulatory framework

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

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 and distribution of tissues and cells** across the Community and **to facilitate exchanges** thereof for patients receiving this type of therapy each year. It is essential, therefore, that Community provisions ensure that human tissues and cells, whatever their intended use, are of **comparable quality and safety**. The establishment of such standards, therefore, will help to reassure the public that human tissues and cells that are procured in another Member State, nonetheless carry the same guarantees as those in their own country.

With due regard to the principle of transparency, **all tissue establishments accredited, designated, authorised or licensed** under the provisions of this Directive, including those manufacturing products from human tissues and cells, whether subject or not to other Community legislation, should have access to relevant tissues and cells procured in accordance with the provisions of this Directive, without prejudice to the provisions in force in Member States on the use of tissues and cells.

An **accreditation system for tissue establishments and a system for notification of adverse events and reactions** linked to the procurement, testing, processing, preservation, storage and distribution of human tissues and cells **should be established in the Member States**.

Member States **should organize inspections and control measures**, to be carried out by officials representing the competent authority, **to ensure that tissue establishments comply with the provisions of this Directive**. Member States should **ensure that the officials involved in inspections and control measures are appropriately qualified and receive adequate training**

Keywords

Quality and Safety Standards

Legislative Decree 6 November 2007, n.191

Art. 6.
Licensing and accreditation of tissue establishments and tissue and cell preparation processes

definition of the minimum organizational, structural and technological requirements of tissue institutes and the guidelines for accreditation

- **CNT**
- **CNS**

Legislative Decree 25 January 2010, n. 16

Art. 8
Requirements for the authorization and accreditation of tissue establishments

ANNEX V

- **A. Organization and management**
- **B. Personal**
- **C. Equipment and materials**
- **D. Services and rooms**
- **E. Documentation and records**
- **F. Quality check**

Art. 9
Requirements for the authorization and accreditation of the performance of tissue and cell preparation processes

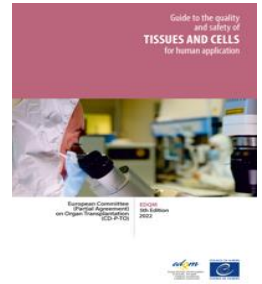
ANNEX VI

- **A. Reception of tissues and cells**
- **B. Processing**
- **C. Storage and release of tissues and cells**
- **D. Distribution and withdraw**
- **E. Final labeling for distribution**
- **F. External labeling of the shipping container**

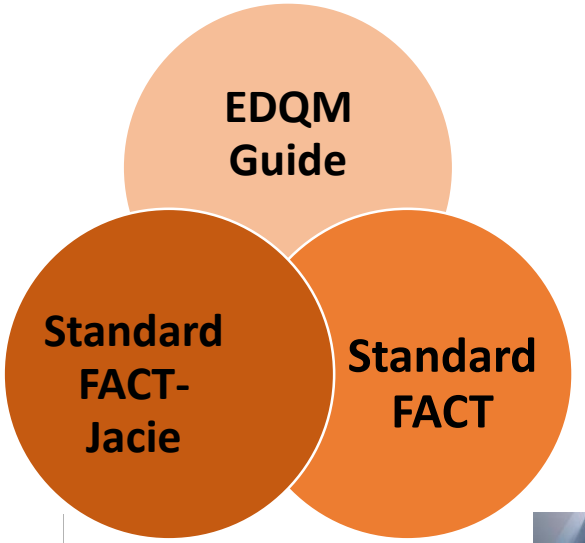
Centro Nazionale Trapianti

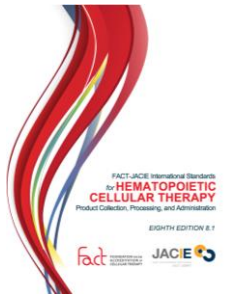
Quality and Safety Standard

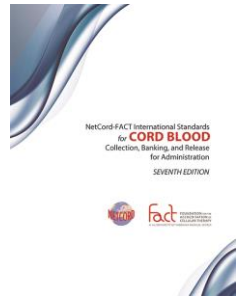
Minimum requirements and guidelines for accreditation



Tissue/Cells	→	ASR n. 66 del 08/03/2018
Haemopoietic Stem Cells	→	ASR n. 49 del 05/05/2021
MAR	→	ASR n. 59 del 15/03/2012







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Inspection and control measures

Legislative Decree 6 November 2007, n.191

Art. 7.
Inspections and control measures

Region or Autonomous Provinces

organize inspections and adequate control measures at tissue establishments, even in case of serious adverse events/reactions

With support of the for the specific areas of competence CNT or the CNS

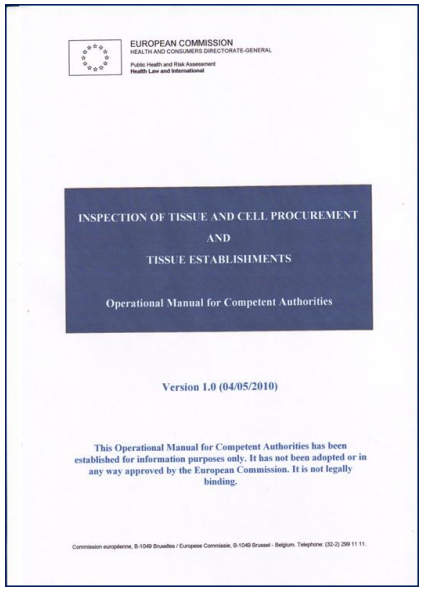
implemented at regular time intervals and in any case not greater than that at two years.

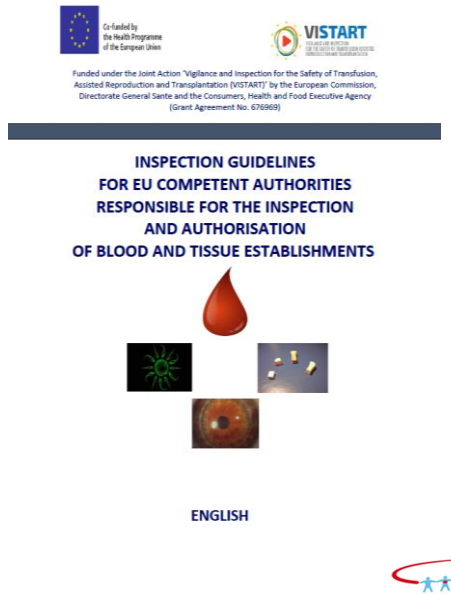
Are established, also in accordance with the indications provided by the European bodies, the criteria relating to the performance of inspections and control measures

Training for Inspectors

COMMISSION DECISION of 3 August 2010 establishing guidelines concerning the conditions of inspections and control measures, and on the training and qualification of officials, in the field of human tissues and cells provided for in Directive 2004/23/EC of the European Parliament and of the Council (notified under document C(2010) 5278) (Text with EEA relevance) (2010/453/EU)

- **Responsibility of Inspectors**
- **Qualification of Inspectors**
- **Inspector training**
- **Types of inspections**
- **Inspection scheduling**
- **Conducting the inspection**





MAR

ASR . n. 58 del 25/03/2015

"Criteria for verification visits of the structural, technological and organizational requirements of medically assisted procreation centers (MAP), pursuant to legislative decrees n. 191/2007 and no. 16/2010, and for the training and qualification of the assessors involved in these verification visit".

- **Methods for identifying PMA regional evaluators**
- **Training by the CNT**
- **Joint regional/CNT team**
- **Inspection mode**

National lists of inspectors

Decreto 8 luglio 2021, n. 13

Istituto Superiore di Sanità

Centro Nazionale Trapianti

Decreto per l'istituzione e gestione: "Elenco degli ispettori per le visite di verifica delle Banche dei Tessuti e dei Centri PMA svolte dal Centro Nazionale Trapianti".

Decreto del Direttore 8 luglio 2021 n. 12

Istituto Superiore di Sanità

Centro Nazionale Trapianti

Decreto per l'istituzione e gestione: "Elenco degli ispettori addetti alle visite di verifica dei programmi di trapianto di cellule staminali ematopoietiche _CSE svolte dal Centro Nazionale Trapianti.

Accreditation
Designation
Authorisation
Licensing

Legislative Decree 6 November 2007, n.191

Art. 6.
Licensing and accreditation of tissue establishments and tissue and cell preparation processes

authorization and accreditation

- **Regions and Autonomous Provinces**

Region or Autonomous Provinces

authorizes and accredits the TE, and indicates the activities the exercise of which is permitted, providing for them conditions.

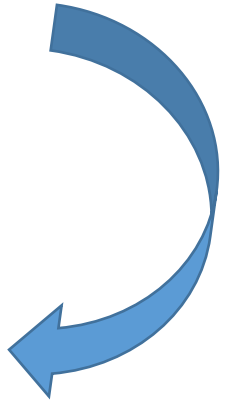
authorizes and accredits the activities related to tissue and cell preparation procedures, which the tissue establishment can carry out in compliance with current legislation in the sector.

suspend or withdraw the authorization and accreditation of a TE or a tissue and cell preparation procedure if the inspection or the implemented control measures show that this institute or procedure does not meet the stipulated requirements.

«Authorisation/accreditation» in the Italian regulatory framework

AUTHORIZATION
General authorization requirements fixed by law (references in the D.P.R. of 14 January 1997)

INSTITUTIONAL ACCREDITATION
Demonstration of compliance with additional requirements (references in Legislative Decree 229/99)

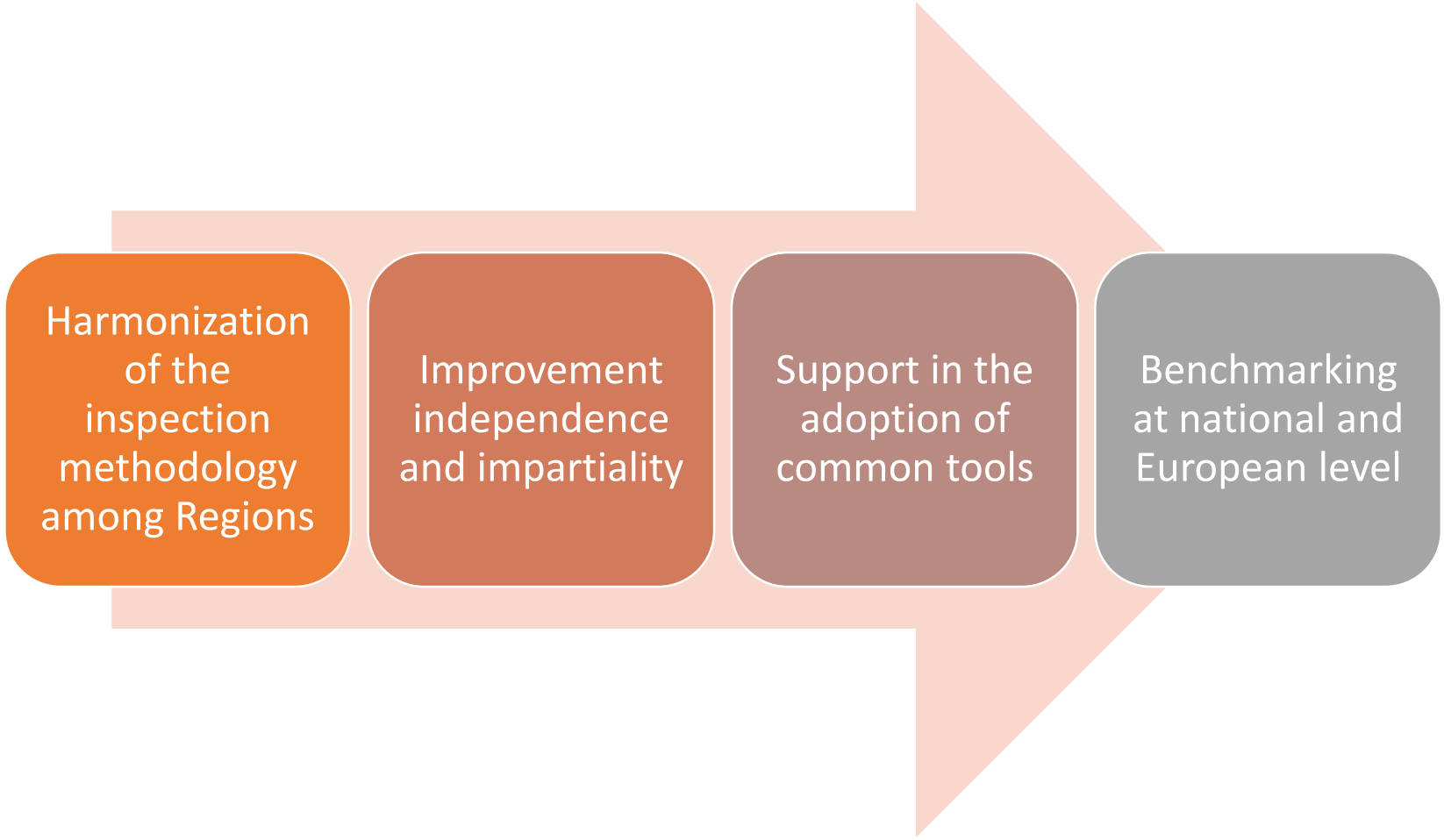


- It defines the minimum requirements for authorization to carry out healthcare activities for all types of Structure.

- It clarifies how the requirements necessary for accreditation are additional to the minimums, identifying in the Regions and P.A. the subjects responsible for processing them on the basis of the general criteria contained in the deed itself.

The inspection and authorisation processes of the Italian tissue, cells and MAR systems

General principles



THE INSTITUTIONAL FRAMEWORK OF THE ITALIAN TRANSPLANT SYSTEM

Phase 1

- Visiting program
- Assessment of documentation

Phase 2

- On site Visit
- Report

Inspection team
Regional + CNT/CNS

Phase 3

- Corrective plan
- Release of authorisation/accreditation/certificate of conformity

document review or self-certification of conformity

The CNT issues a certificate of compliance with current legislation

Authorisation new preparation processes

DOSSIER FOR NEW PREPARATION PROCESSES

CNT.POS.03 All 5

Dossier dei Processi di lavorazione (PPD)

Sezione A – Informazioni sulla struttura

Denominazione della Struttura	
Indirizzo della struttura	
Nome della persona responsabile	
Numero di Telefono	Numero di Fax
Indirizzo di posta elettronica	

Sezione B – Processi di lavorazione – Informazioni generali

processo di preparazione	
Descrizione dei tessuti o delle cellule ai quali si applica il processo di lavorazione	
Dettagliare ogni specifico requisito aggiuntivo per la selezione del donatore o per i test sierologici che deve essere applicato ai donatori di tessuti o cellule processati con questo metodo	
Dettagliare ogni specifico requisito di prelievo/raccolta che deve essere applicato per il prelievo di tessuti o cellule processati con questo metodo	
Si prega di fornire una breve descrizione dei processi di preparazione	

CNT.POS.03 All 5

(allegare una flow-chart descrittiva del processo)	

Sezione C – Materiali e attrezzature

Si prega di elencare tutti i materiali e le attrezzature utilizzate nel processo fornendo i dettagli del fornitore per ognuno

Reagenti o material che vengono in contatto con le cellule/tessuti	Specifiche	Fornitore

Attrezzature	Specifiche	Fornitore

Sezione D – test per controlli di qualità (inclusi test microbiologici)

Test	Descrizione del campione (analita)	Criteri per il rilascio

Sezione E – Validazione del processo

Come sono stati validati i metodi di lavorazione applicati per dimostrare che non rendono il tessuto clinicamente inefficace o tossico per il ricevente ?	a) con studi eseguiti dalla struttura stessa SI ☐ NO ☐ Se si, si prega di **allegare una copia del report di validazione** b) con dati di studi pubblicati da altri SI ☐ NO ☐ Se si, si prega di **allegare copia delle pubblicazioni più rilevanti** c) con valutazione retrospettiva dei risultati clinici ? SI ☐ NO ☐ Se si, si prega di **allegare un report dei dati raccolti** d) altro (si prega di specificare)
Se il processo ha portato ad un brevetto registrato, si prega di fornire il numero di registrazione	
Se il processo comprende un passaggio di sterilizzazione o inattivazione virale, si prega di fornire una breve descrizione della validazione e copie degli studi di in attivazione virale sui quali la	Si prega di inserire una copia del report di validazione

CNT.POS.03 All 5

validazione è basata.

Sezione F – Etichettatura finale e documentazione di accompagnamento

Si prega di inserire qui una copia dell'etichetta finale applicata al contenitore primario dei tessuti o cellule che sono state processate utilizzando questo metodo.

Si prega di inserire una copia del modulo di accompagnamento che è inviato agli utilizzatori insieme ai tessuti o cellule.

Si prega di inviare la scheda completata al seguente indirizzo email :

cnt@iss.it

Si prega di controllare che tutti gli allegati richiesti siano stati acclusi.

Region and CNT

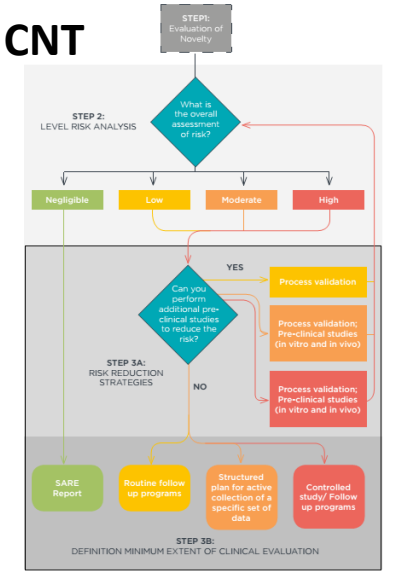
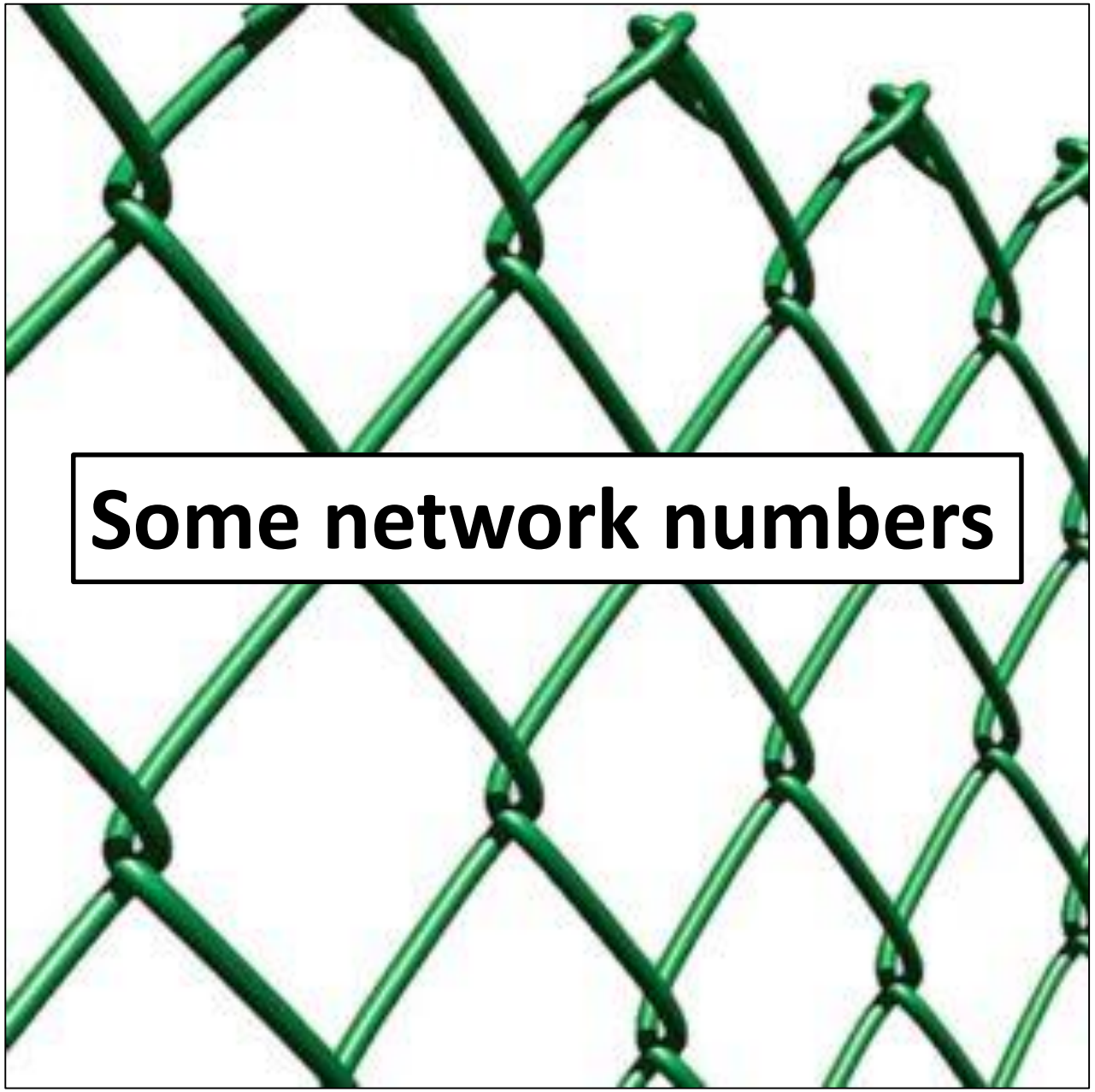


Figure 2.5.: The risk reduction and determination of the extent of studies required

Joint action EUROGTP II (Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products - http://goodtissuepractices.eu/) and Joint action GAPP


Some network numbers

TISSUE BANKS INSPECTION ACTIVITY

Start of inspections: year 2004

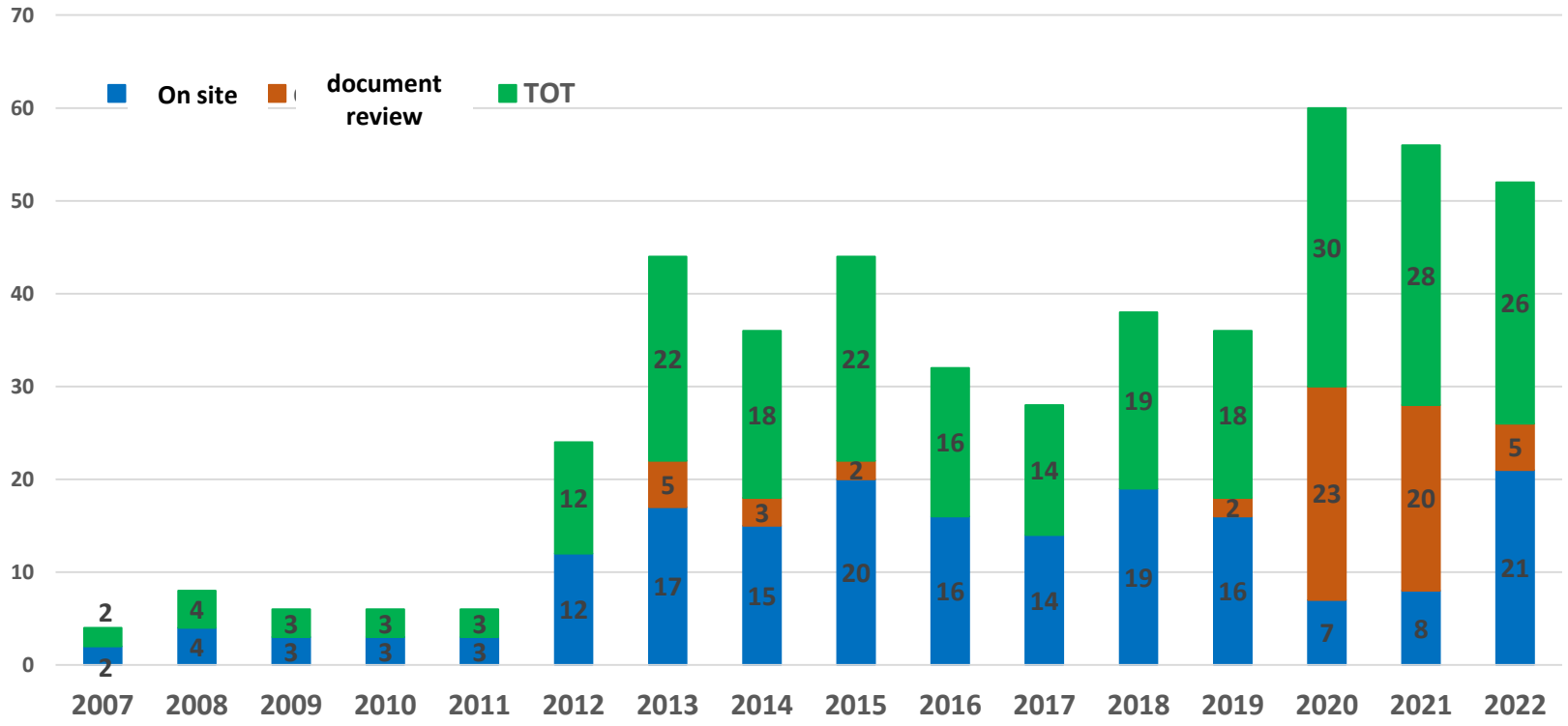
Number of inspections/year

From 2004 to 2022, 213 inspections were carried out

2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
9	10	16	10	15	10	11	12	10	14	15	11	10

2017	2018	2019	2020	2021	2022
12	10	8	9	11	10

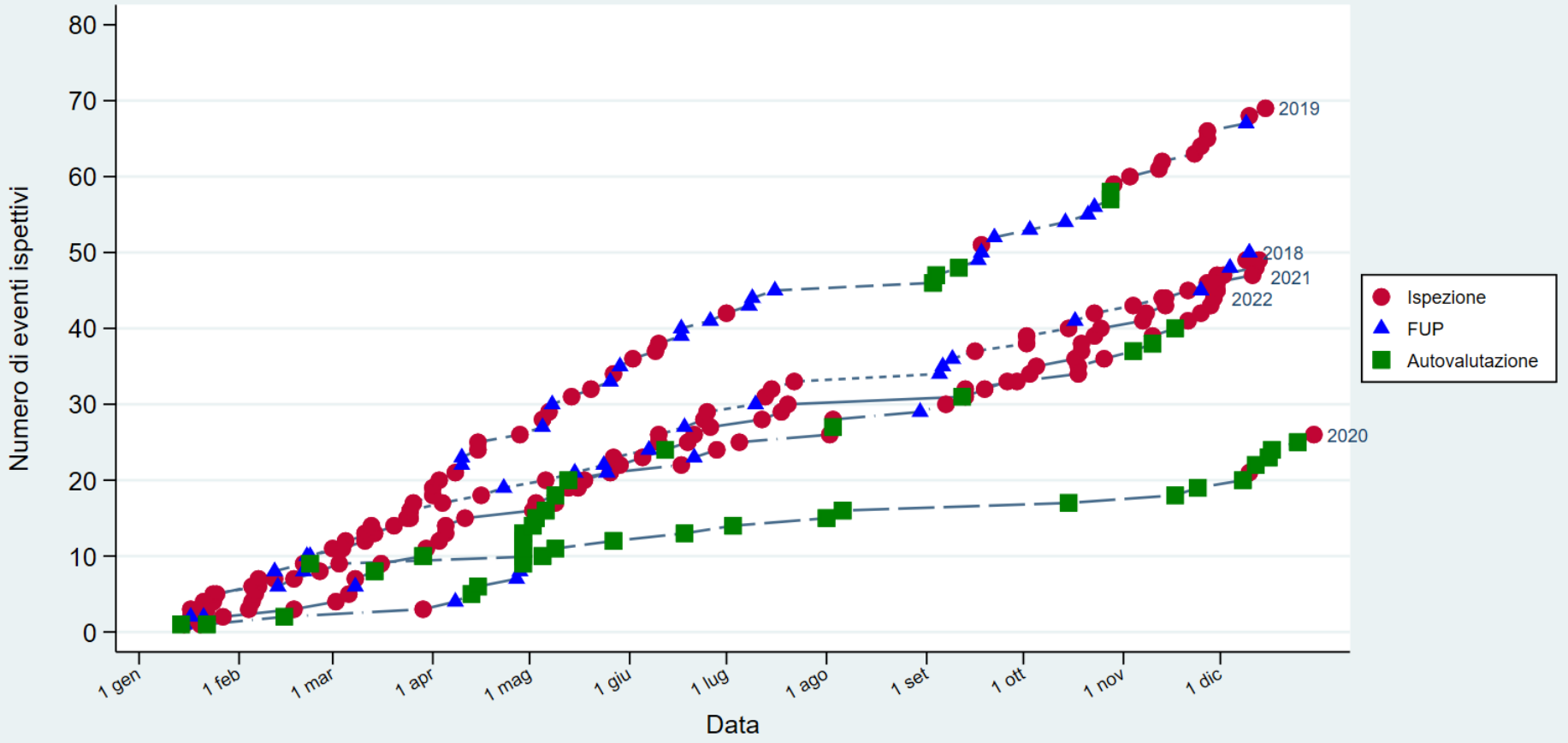
HSC PROCESSING UNIT INSPECTION ACTIVITY



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	TOT
On site	2	4	3	3	3	12	17	15	20	16	14	19	16	7	8	21	180
document review	-	-	-	-	-	-	5	3	2	-	-	-	2	23	20	5	60
TOT	2	4	3	3	3	12	22	18	22	16	14	19	18	30	28	26	240

MAR centers inspected
(at 31/12/2022)

n. 187

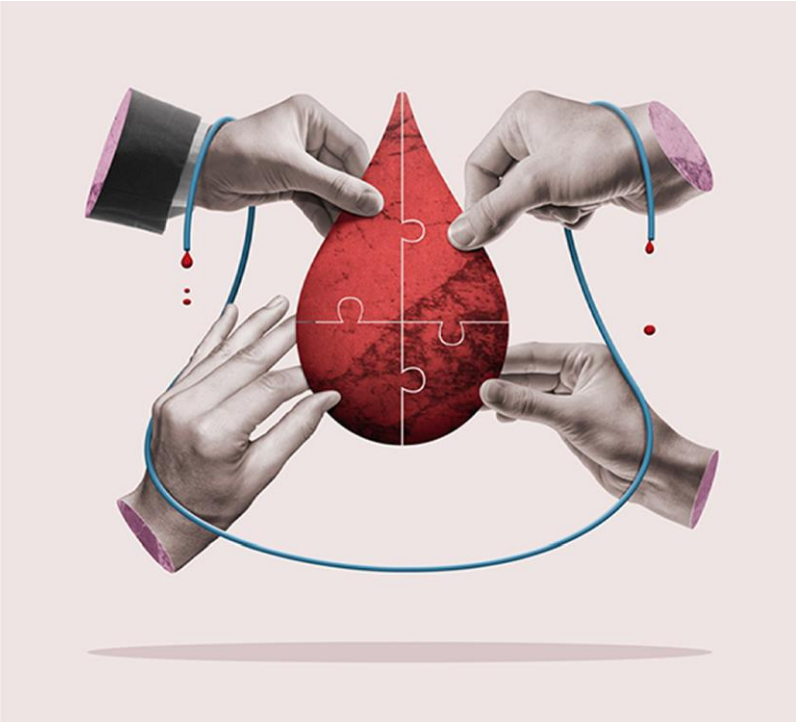


Conclusions

✓ All Tissue Institutes have been inspected and are included in the European Compendium of Tissue Institutes reaching HIGH QUALITY and SAFETY levels

✓ Requests for new manufacturing/processing that require additional checks are increasing

In the light of the current ongoing revision of the European legislation, the new EUROPEAN REGULATION of cells and tissues will certainly have an IMPACT on the management of audits



Thanks for your attention