Health and Youth Care Inspectorate
Ministry of Health, Welfare and Sport

A healthy sense of trust

Inspection Focus:

Equipment
&
Climate Control

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TRIP Symposium 2017

Goal of this presentation

Give insight in inspection findings with respect to equipment and climate control

Emphasize notifications to TRIP and their recommendations in their annual report

Take advantage of the information presented today and evaluate the procedures in your laboratory

Not to discuss regulations/interpretations

Not to provide solutions

Helpful references how to comply with regulations

Change of Organization Name:

Health Care Inspectorate / Inspectie voor de Gezondheidszorg (IGZ)

Youth Care (Jeugdzorg)

Health and Youth Care Inspectorate (IGJ)

https://www.igj.nl/documenten/videos/2017/10/01/het-verhaal-van-igj-gezond-vertrouwen

Ministry of Health, Welfare and Sports

Inspectorate of Health and Youth Care (Location Utrecht)

A huge variety of sectors are covered by IGJ
(https://www.igj.nl/zorgsectoren)

<u>Department of Products and Oral Health Care</u>

- **Blood & Tissues**
- GLP
- Opiates
- Medicines Advertising Control Unit
- Oral Health Care

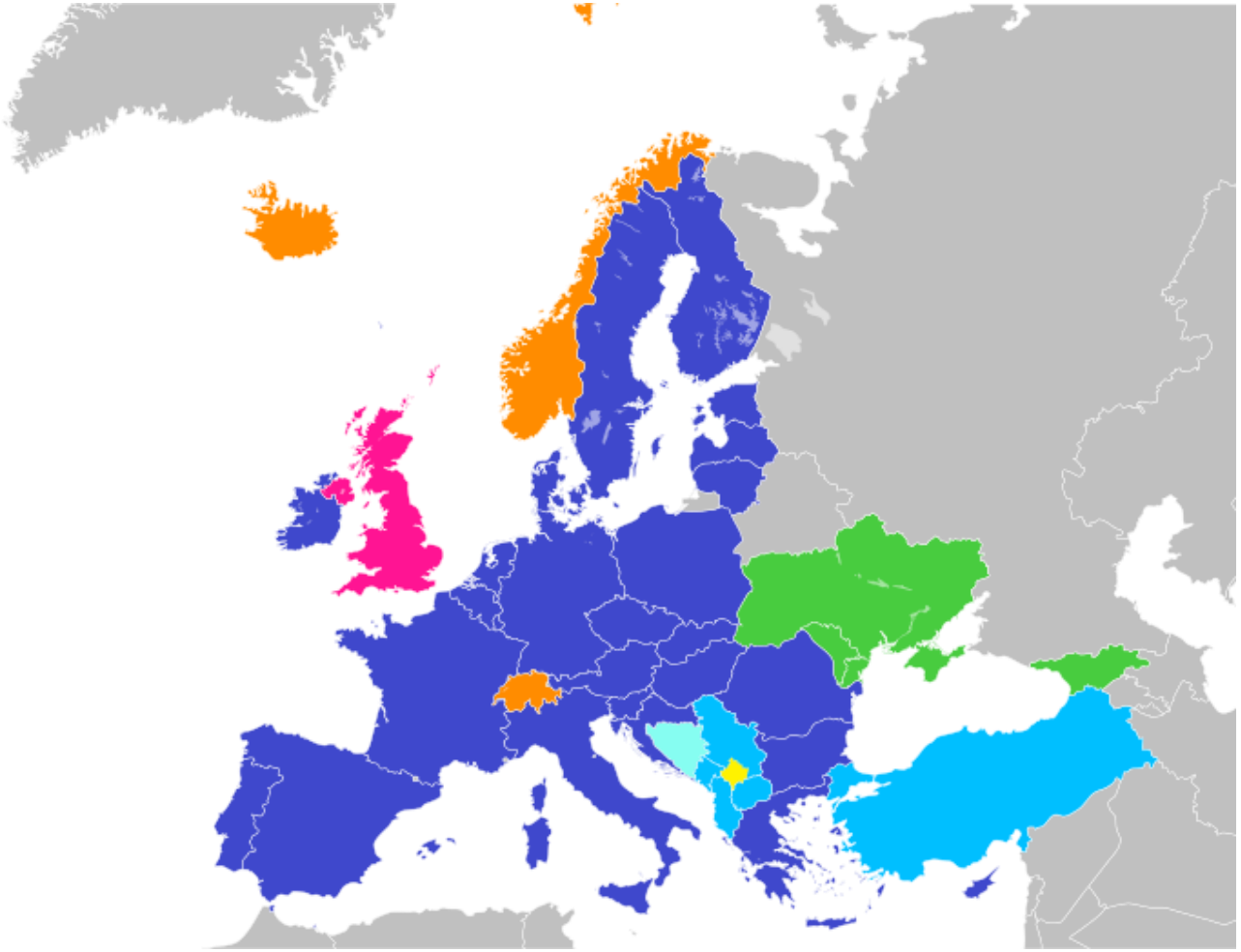
Legislation in The Netherlands for Human Tissues and Cells

1998 Act on Organ Donation

1999 Royal Degree on Safety of Tissue Banks (Post Mortem donors)

2007 Act of Quality and Safety of Human Body Materials
2007 Degree on Human Body Materials

(Technical) European Directives covering Tissues and Cells



28 countries

1 EU Directive

Every country can set higher standards

28 significant deviations in harmonized regulations

https://en.wikipedia.org/wiki/Future_enlargement_of_the_European_Union#/media/File:Further_European_Union_Enlargement.svg

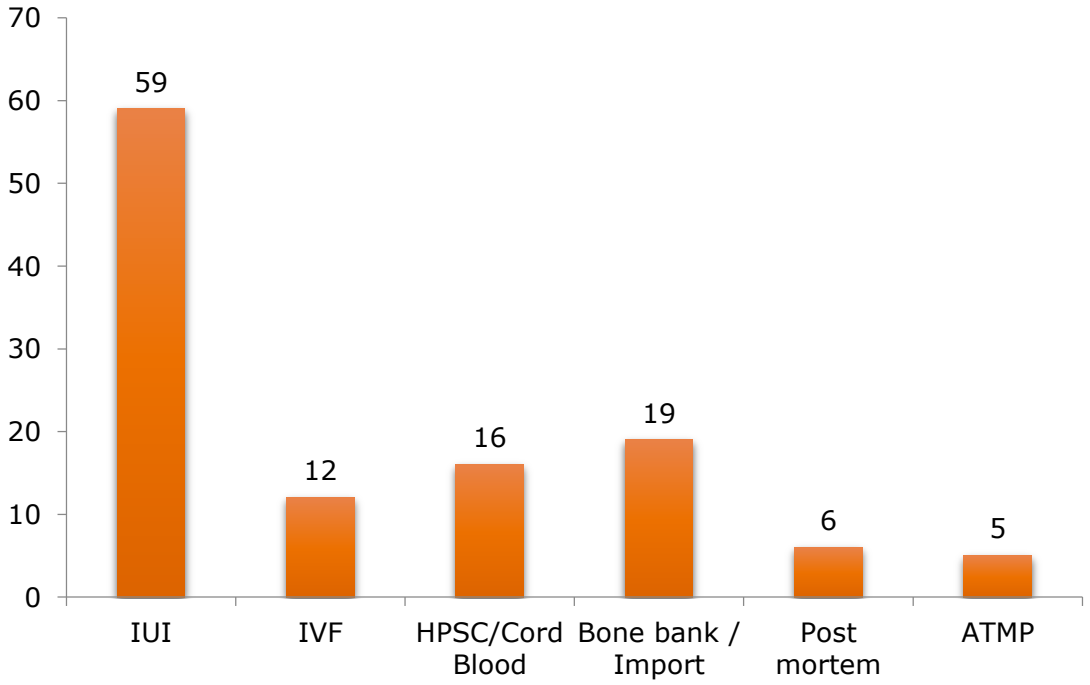
Examples of different regulations within EU

- Serology (additional NAT testing)
- Distribution of tissues from one EU country to another must go through another registered tissue bank, not directly to hospital
- More stringent contra-indications such as onset cooling diseased donor or criteria for malignancies
- Processing environment (processing in Grade A with background environment Grade B in stead of Grade D)




TE Licenses in The Netherlands

As per November 2017: **117 TE Licenses** in total



Activities to be licensed:

- Receipt of tissues and cells (donation, procurement, testing)
- Processing
- Storage
- Distribution

  tissue movement from a TE located within a hospital is not considered to be distribution in NL

  Movement of reproductive tissue by the patient from one TE to another is considered distribution in NL

Specific Designation:

Import
Export

<u>Many activities require essential/critical equipment and climate controlled premises</u>

Inspection Results

Building – Materials etc.			
	Critical	**Major**	**Minor**
Premises		3	26
Equipment		13	31
Materials		17	56
Traceability		3	3
Documents		9	6

Data presented during TRIP symposium 2010

FACILITIES
&
PREMISES

2006/86/EG, Facilities / Premises

1. A tissue establishment must have **suitable facilities** to carry out the activities
2. Processing of tissues and cells must take place in an environment with **specified air quality and cleanliness** in order to minimize the risk of contamination, including cross-contamination between donations. **The effectiveness of these measures must be validated and monitored**.
3. []
4. Unless otherwise specified, processing of tissues and cells should be performed in a GMP **Grade A** environment with a background at least equivalent to GMP **Grade D**

5. It must be **demonstrated and documented** that the chosen environment achieves the quality and safety required. **Appropriate garments and equipment for personal protection** and hygiene must be provided with **written hygiene and gowning instructions**.
6. []
7. **Critical parameters** (e.g. temperature, humidity, air quality) must be **controlled, monitored and recorded**
8. **Written** policies and procedures for **controlled access, cleaning and maintenance, waste disposal**

Observations during inspections

- Grade A Laminar Flow Cabinet placed in a unqualified/unclassified background environment

- Laboratory is not state-of-the-art, processing on a table in a quiet room, particles are measured once a year:
  - No Grade A present. Background is insufficient monitored to control potential contamination risks. In addition the quality of the area is influenced by window blinds, non-smooth walls/ceiling, floor uneven/broken, presence of a utility sink, unnecessary art/paintings/decoration/plants

- Laboratory is not state-of-the-art, processing on a table in a quiet room, particles are not measured
  - The working environment and background is uncontrolled. The environment is insufficient monitored to control potential contamination risks

Other observations (might be tissue specific!)

- No (documented) risk-based decision on the air quality specifications
- No (documented) monitoring particle concentration
- No (documented) microbiological monitoring
- No (documented) temperature control/humidity control
- Insufficient or no pressure differences
- No documented system for cleaning and disinfection
- No documented system for gowning and laundry
- No gowning procedure
- No documented training for gowning
- No limited access

Common operational errors

Pictures provided by courtesy of Johann Kurz

Also in 2006/86/EG, Annex I, D: exemptions

4. A less stringent environment than specified in point 3 may be acceptable where:

(a) a validated microbial inactivation or validated terminal sterilisation process is applied;

(b) or, where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned;

(c) or, **where it is demonstrated that the mode and route of application of the tissue or cell to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with cell and tissue transplantation**;

(d) or, where it is not technically possible to carry out the required process in a Grade A environment (for example, due to requirements for specific equipment in the processing area that is not fully compatible with Grade A).

Deviation from Grade A processing facilities (with Grade D background)

Meaning:

Processing in Grade A with Grade B or C background, or
Processing in less than Grade A with a Grade D background

The specification of the air quality of the processing facilities should be **decided on the basis of the particular type of tissue or cell and the processing method that is being applied**.

Based on a (documented) **risk assessment**, several factors should be taken into consideration **when determining the air-quality specifications**, especially, when less stringent conditions are applied.

Most important findings during the inspection when less than Grade A

- Not **demonstrated <u>and documented</u>** that the chosen environment achieves the quality and safety required
- No (documented) critical parameters specified
- No (documented) **risk assessment**
- **Critical parameters** (e.g. temperature, humidity, air quality) are not set and they are not sufficient **controlled, monitored, and recorded**
- **The effectiveness** of these measures must be **validated and monitored with <u>appropriate time intervals</u>**

From the Guide to the Quality and Safety of Tissues and Cells (EDQM):

Validation of cleanrooms and laminar hoods is required

The specified acceptance criteria set for your facilities should be verified

therefore testing of certain parameters and specifications should be performed (time intervals).

Time interval example of tests for Grade A with Grade D background

Table 8.3. **Qualification tests for cleanrooms, clean zones and laminar flow hoods**

Tests	Specification	Recommended time interval
Airborne particle count (classification test)	The total count of airborne particles (viable and non-viable) performed at rest and in operation, to determine cleanliness class	6 months if classification is ≤ ISO 5 12 months if classification is > ISO 5
Airflow test	Average airflow velocity and air changes per hour	12 months
Air pressure difference	Differential pressure between different areas	12 months
Installed filter system leakage test	Detection of leaks in the absolute filter and integrity testing of seals between filter and mounting arrangements	24 months or if the resistance across the filter changes abnormally
Temperature and relative humidity		12 months
Recovery test	The time required for a clean room to recover after a particle-generation event – normally tested for clean rooms classified as Grade A or B. Maximum delay given by GMP Annex 1 is 15-20 min	24 months
Airflow direction test and visualisation	Airflow pattern type, i.e. unidirectional, non-unidirectional or mixed	24 months
Containment leak test	Detection of leaks on structure	24 months
Laminar airflow velocity (laminar flow hoods)	The average velocity must meet the specified acceptance criteria	12 months

From: EDQM 3rd edition

EQUIPMENT

EUROPEAN DIRECTIVE 2006/86/EG

Annex I, C. EQUIPMENT AND MATERIALS

1. All equipment and material must be **designed and maintained** to suit its intended purpose and must minimize any hazard to recipients and/or staff.
2. All **critical** equipment and technical devices must be **identified and validated**, regularly **inspected** and **preventively maintained** in accordance with the manufacturers' instructions. Where equipment or materials affect **critical processing or storage parameters** (e.g. temperature, pressure, particle counts, microbial contamination levels), they must be **identified** and must be the subject of **appropriate monitoring, alerts, alarms** and corrective action, as required, to detect malfunctions and defects and to ensure that the critical parameters are maintained within acceptable limits at all times. All equipment with a critical measuring function must be **calibrated** against a traceable standard if available.
3. **New and repaired equipment** must be tested when installed and must be **validated before use**. Test results must be **documented**.
4. **Maintenance, servicing, cleaning, disinfection and sanitation** of all **critical equipment** must be performed **regularly and recorded** accordingly.
5. Procedures for the operation of each piece of critical equipment, detailing the action to be taken in the **event of malfunctions** or failure, must be available.

Observations during inspections:

- No list of critical/essential equipment
- No periodic maintenance, or not recorded

- No disinfection/cleaning of equipment or not recorded

- No (clear) contract between TE and maintainer, no clear defined criteria what to maintain/ what to check
- After maintenance, operational procedure using this equipment starts directly without a procedure to release the equipment for operational use

- No continuous temperature control and alarm
- Temperature sensor in too much buffer compared to the amount of minimum volume stored in the fridge
- No temperature mapping of the fridge or freezer
- No trend analysis of critical parameters over time (appropriate monitoring to detect (to be soon expected) malfunctions)

- Alarm can be overruled without further action
- Reason of alarm not recorded

TRIP Recommendations (annual reports based on SAE/SARE)

2014 **Tissue establishments should not rely solely on the validation process of the manufacturer**.

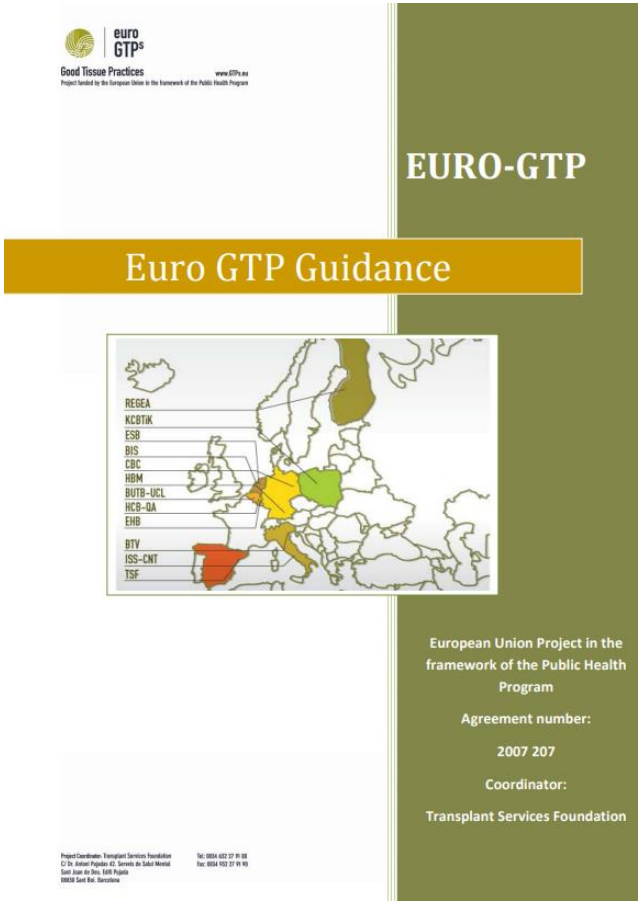
2013: **Equipment needs frequent checking** and needs an effective alarm system.

2012 Validated **transportation conditions** are necessary for assuring the quality of transported tissues or cells. If validation of these processes has not been performed this should be undertaken.

Essential **equipment** like transportation boxes, incubators, cryopreservation devices and storage devices **needs an adequate fail-safe alarm system** to prevent quality loss or avoidable loss of tissues or cells in case of breakdown.

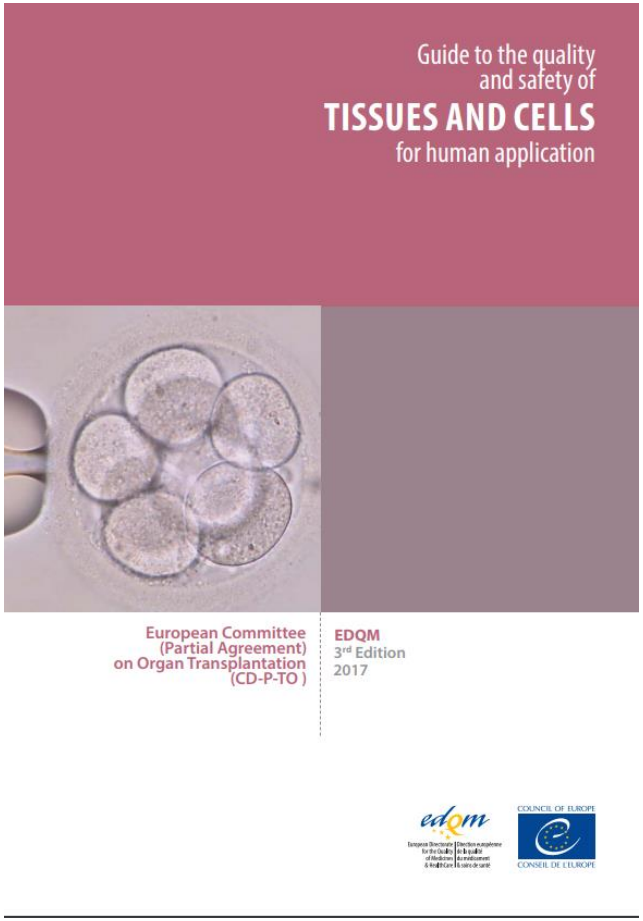
2010 Particular alertness is advised after **maintenance or repair of essential equipment**. The **recommissioning should be laid down in a standard operating procedure**.

Guidance document: Euro Good Tissue Practices



Download for free
http://www.goodtissuepractices.eu/images/outcomes/EuroGTP_Final_Delivery.pdf

Guidance document:



Council of Europe / EDQM
(European Directorate for the Quality of Medicines & Healthcare)

3rd Edition (download for free):
https://www.edqm.eu/en/organ-tissues-cells-transplantation-guides-1607.html

Chapter 2. Quality management, validation and risk management

2.4. **Premises**, **equipment** and materials

2.5. **Contractual arrangements**

2.15. **Validation**

- 2.15.6. Qualification of facilities and equipment
  - Design Qualification (DQ)
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)
- 2.15.7. Qualification of software
- 2.15.8. Test method validation
- 2.15.9. Process validation

Chapter 6. **Procurement**
6.3. Facilities, equipment and materials

Chapter 7. **Processing** and **storage**

Chapter 8. **Premises**

PART B. SPECIFIC REQUIREMENTS (**tissue specific**)

Once again:

You must **demonstrate and document** that the chosen **environment** achieves the quality and safety required for your tissues and cells.

You must **demonstrate and document** that the chosen **equipment** achieves the quality and safety required for your tissues and cells.

Please have a look at the helpful guides to ensure you comply with the regulations!

Questions & Comments are welcome, also after the meeting

Please send your inquiries to

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