JACIE
Processing Standards
7th edition

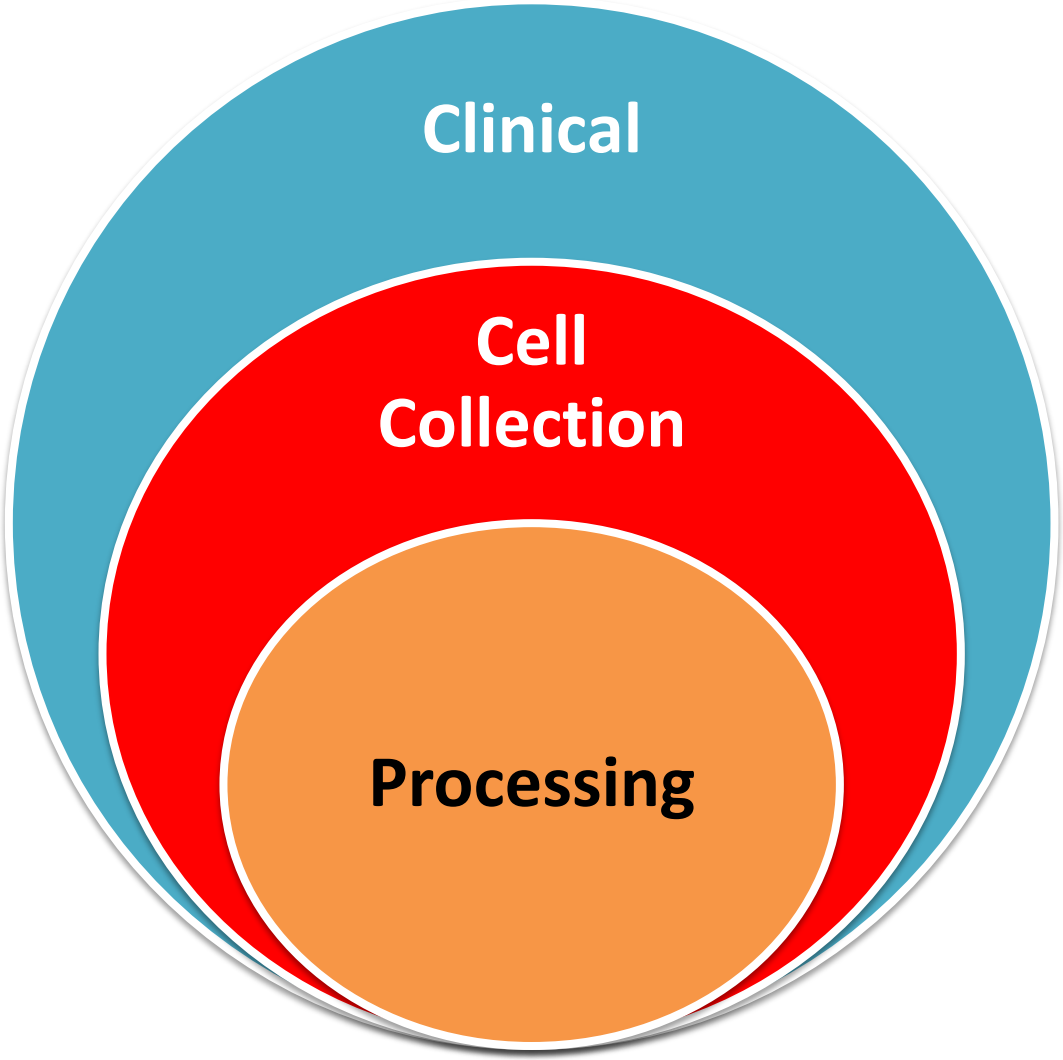
PARTS

- A
  - TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS
- B
  - CLINICAL PROGRAM STANDARDS
- CM/C
  - COLLECTION FACILITY STANDARDS
- D
  - PROCESSING FACILITY STANDARDS

PART B CLINICAL	PART CM MARROW	PART C APHERESIS	PART D PROCESSING
B1 General	CM1 General	C1 General	D1 General
B2 Clinical Unit	CM2 Marrow Collection Facility	C2 Apheresis Collection Facility	D2 Processing Facility
B3 Personnel	CM3 Personnel	C3 Personnel	D3 Personnel
B4 Quality Management	CM4 Quality Management	C4 Quality Management	D4 Quality Management
B5 Policies and Standard Operating Procedures	CM5 Policies and Standard Operating Procedures	C5 Policies and Standard Operating Procedures	D5 Policies and Standard Operating Procedures
B6 Allogeneic and Autologous Donor Selection, Evaluation, and Management	CM6 Allogeneic and Autologous Donor Evaluation and Management	C6 Allogeneic and Autologous Donor Evaluation and Management	D6 Equipment, Supplies, and Reagents
B7 Recipient Care	CM7 Coding and Labeling of Cellular Therapy Products	C7 Coding and Labeling of Cellular Therapy Products	D7 Coding and Labeling of Cellular Therapy Products
	CM8 Process Controls	C8 Process Controls	D8 Process Controls
	CM9 Cellular Therapy Product Storage	C9 Cellular Therapy Product Storage	D9 Cellular Therapy Product Storage
	CM10 Cellular Therapy Product Transportation and Shipping	C10 Cellular Therapy Product Transportation and Shipping	D10 Cellular Therapy Product Transportation and Shipping
B8 Clinical Research			D11 Distribution and Receipt
B9 Data Management			D12 Disposal
B10 Records	CM11 Records	C11 Records	D13 Records
	CM12 Direct Distribution to Clinical Program	C12 Direct Distribution to Clinical Program	

Transplant Programme

"Use cell processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Apheresis Collection Facility"

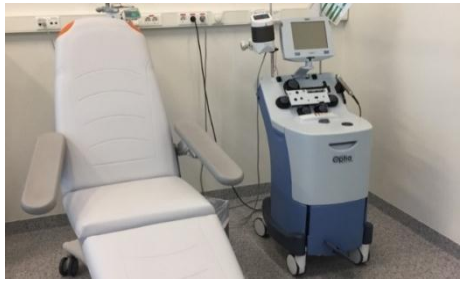


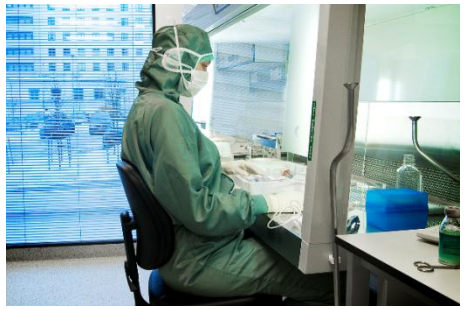
D1 General Requirements

- Comply with applicable laws and regulations
- Shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed
- Compliance with JACIE does not guarantee compliance with all applicable laws and regulations and vice versa

Example: in the EU, the inspector would expect to see:
-tissue establishment license by the Competent Authority
-GMP-manufacturing license if ATMPs are being manufactured at the same site
-product labeled with Single European Code - **SEC**.

D2 Processing Facility

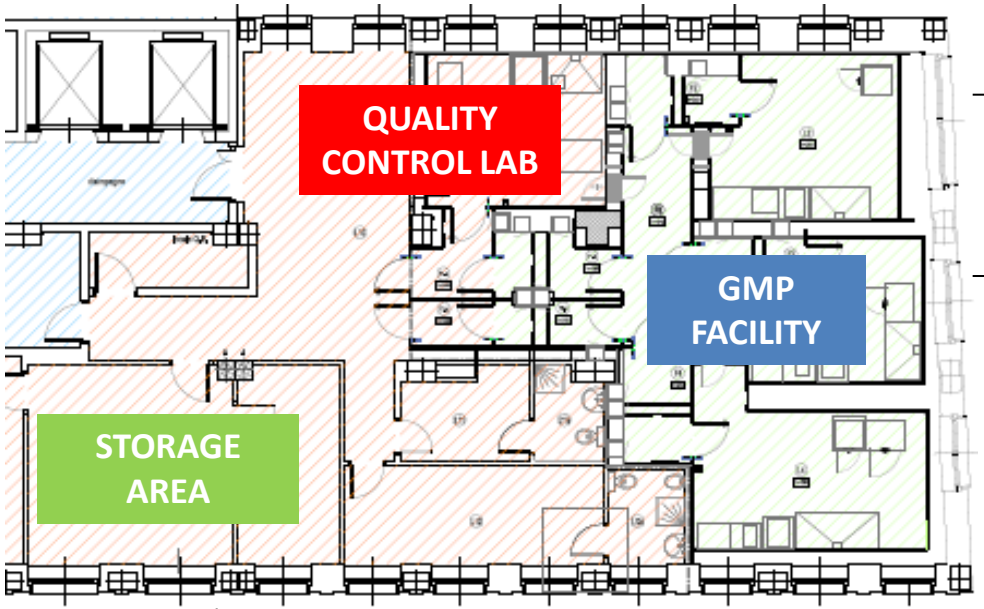




D2 Facilities

Adequate space, design and location

Adequate lighting, ventilation and access to sinks



Divided into defined areas

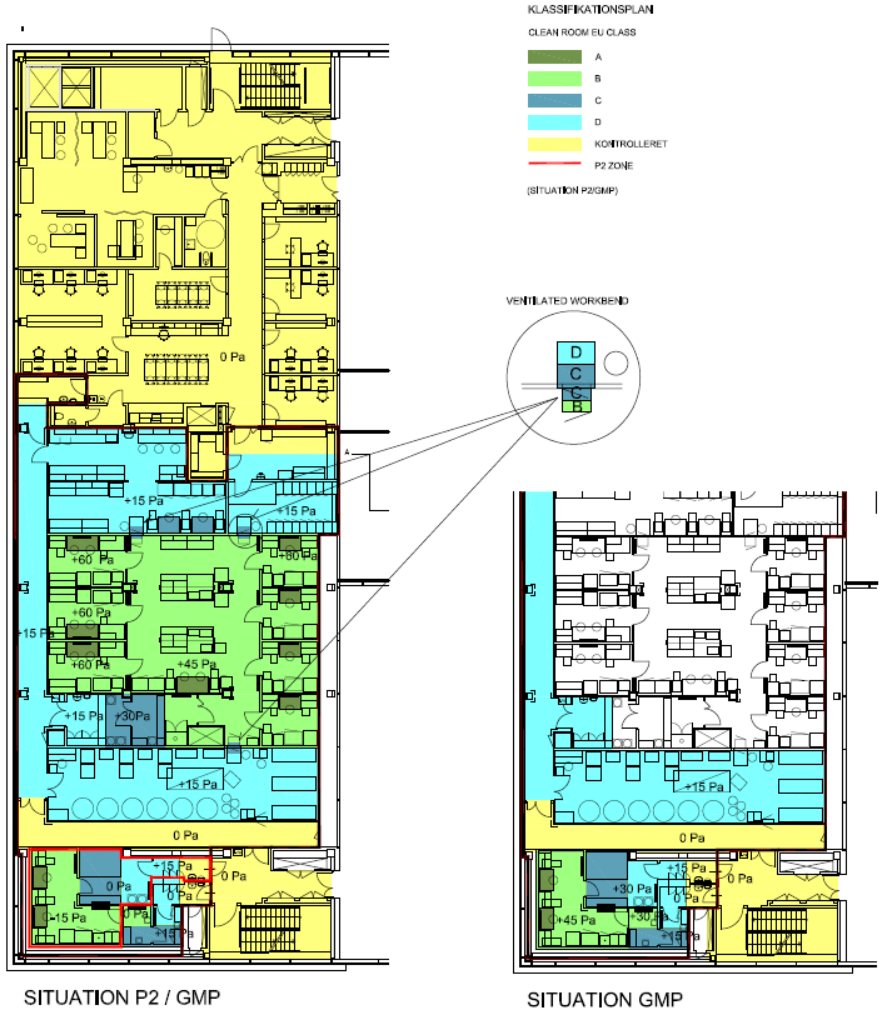
Adequate equipment and materials

Secure Access

Oxygen sensors for LN2 use

Parameters and environmental conditions controlled

Floor Plan:
Cell and Gene Therapy GMP Area



prior to the on-site inspection

-**Floor plan**: preliminary understanding of the designate areas and process flow

on-site inspection

-**Tour the facility,** all location where products are received, processed, and stored

P2 facility

D2 Processing facility: Critical parameters

Parameters identified to be a risk must be controlled, monitored and recorded

- Temperature
- Humidity
- Air quality

- Surface contaminates
- Monitoring for microorganisms

-ask for evidence of monitoring, the actions taken if enviromental conditions were outside the requested ranges

D2.3. There shall be a **written assessment** of critical facility parameters that may affect processing, storage, or distribution.

D2 Cleaning and sanitation

- D2.4 Qualify environmental control systems and validate cleaning and sanitation procedures appropriate for the environmental classification and degree of manipulation performed

- D2.5 Document facility cleaning and sanitation **to ensure adequate conditions for proper operations**

Daily Laboratory / office Cleaning Record Sheet

Format No.:

Date	Lab A	Lab B	Chemical Analysis	Physical Analysis	M.D. Offce	Computer Room	Sample Test Office	Kitchen	Measuring / Balance	Instrument Storage Room	Store Room	Done By	Checked By
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02													
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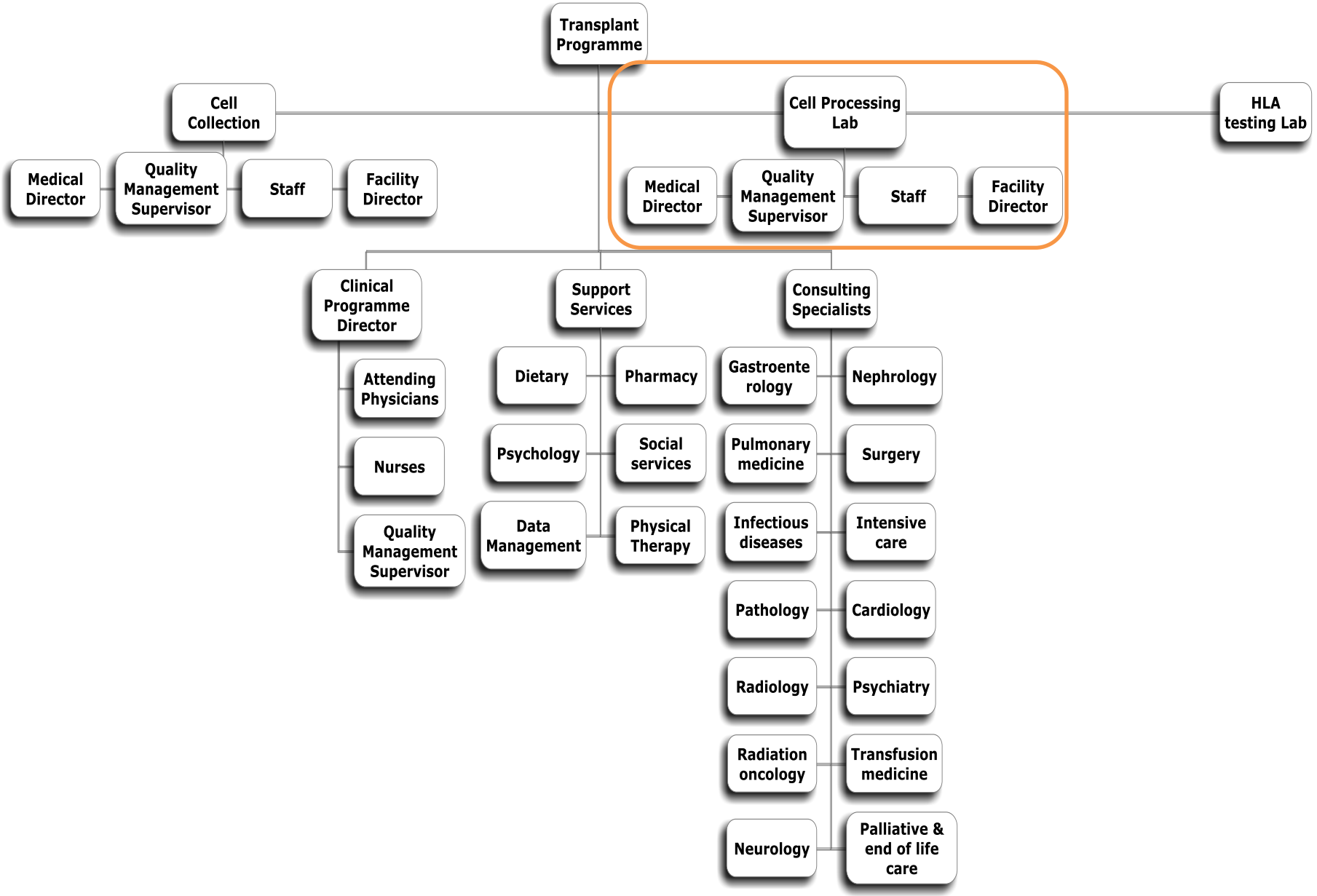
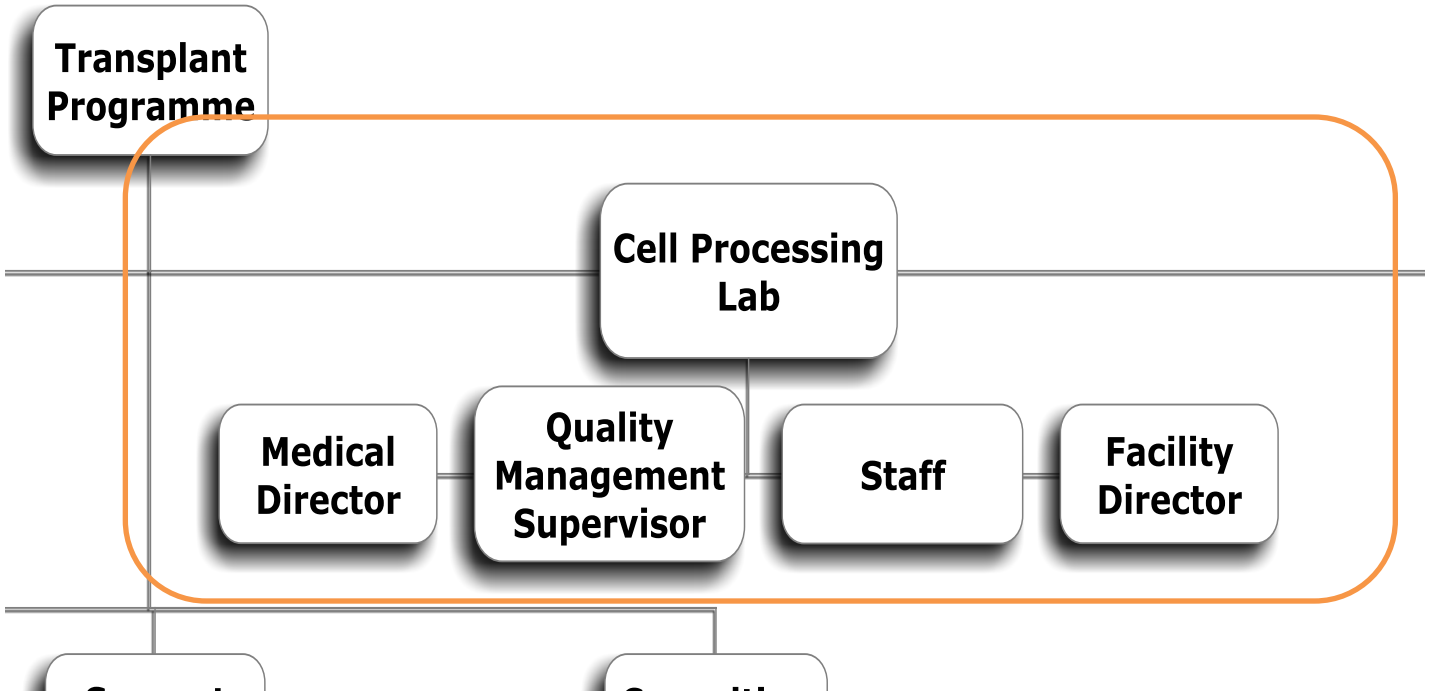
Sign. of LAB.Manager .....

Records of cleaning and sanitation activities and concomitant microbial monitoring within the Processing Facility should be available for inspector review

D3 Personnel



D3 Personnel



organizational chart with names gives overview of the roles and responsibilities in lab

D3 Processing Facility Director

License	Education	Experience
• medical / doctoral / equivalet degree in a relevant science	• Participate regularly in educational activities related to the field of HPC transplantation	• qualified by minimum of 2 years training and experience for the activities carried out in the PF

responsibilities

All procedures

Administrative operations

Quality Management Program

Compliance with Standards and laws and regulations

verify that the PF Director has a sufficient on-site physical presence, and is available to the personnel when needed

D3.1.3 The PF Director shall have **performed or supervised** a minimum of **five (5) cellular therapy product processing procedures** per year

D3 Processing Facility Medical Director

Licensed	Education	Experience
• Licensed or certified **physician** with postgraduate training • Postgraduate training	• Participate <u>regularly</u> in educational activities related to the field of HPC transplantation	• Min. of 2 years postgraduate training and practical and relevan experience for the scope of activities carried out in the preparation and clinical use of products

RESPONSIBILITY

- directly responsible for all medical aspects related to the processing facility: authorization for the distribution of non-conforming products due to urgent medical need, review and approval of SOPs, authorization for product discard

Evidence of availability may be confirmed by examining documents, records, audits, and other records requiring the director's review

D3.2.3 The PF Medical Director shall have **performed or supervised** a minimum of **five (5) cellular therapy product processing procedures** per year

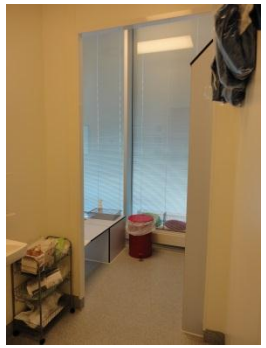
D3.4 Staff

- The Facility shall have an **adequate** number of trained staff for the number of procedures performed

HOW MANY IS “ADEQUATE”?

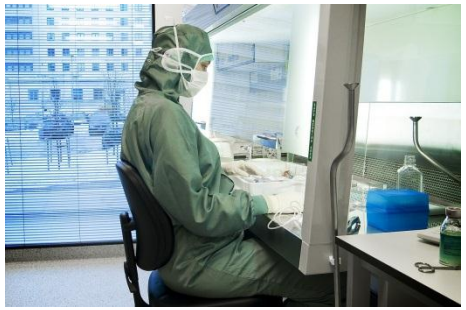
Minimum of one designated trained individual with an identified trained backup to maintain sufficient coverage

3 ½ hours work in the cleanroom before and after production



Daily activites before and after production:

Slucing in of material:	1 person ½ hour
Slucing in and out of personel:	½ time per person
Preparation of the room:	1 person 1 hour
Contamination control and cleaning of the working area:	1person ½ hour
Slucing out of production material :	1 person ½ hour
Product documentation :	1 person ½ hour



D3 Personnel

Inspection Tip

- **Qualifications?**
- **Educational history, employment history, memberships, publications, meeting attendance**
- **Training/competency?**
- **Review initial training or authorization documents**
- **Review records for current competency assessments**
- **Interview the most recently employed technician and go through training records**
- **Workload?**
- **Review most recent volume statistics.**

Organizational Chart

Professor Dr Gunnar Kvalheim Director
Substituted by: Dag Josefsen MD PhD

Head of Staff *
– Biomedical Scientists:
(Merete Djupedal)

Quality Management
Cecilie Nguyen

Cleanroom Facility

Facility Manager:
Simon Echmann

Analysis Laboratory

Responsible Biomedical Scientists:
Sissel Nygren
Marianne Dyrhaug

Somatic Stem Cells
Dag Josefsen

Collection/ Processing
M. Lundby
G.Andreassen

Biomedical Scientists
N= 9 + 2

DC Production
NK Production

Production Leader:
Lisbeth Skoge
Kirsti Hønnåshagen

Biomedical Scientists
N= 2 + 3 (shared w. RNA prod. and Stemcell team)

T-cell Production
HSC selection

Production Leader:
Marianne Lundby

Biomedical Scientists
N=0

RNA Production
S. Sæbøe Larssen

Biomedical Scientists
N=1+1

Immune monitoring/ Clinical
Else Marit Inderberg

Biomedical Scientists Research scientists
N=5+1

Immune monitoring/ R&D
Sébastien Wälchli

Research Scientists Biomedical Scientists
N=5

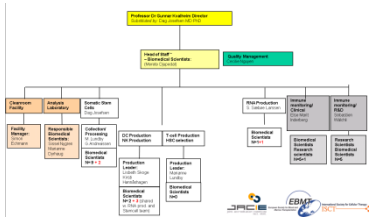
to review in an organigram?

- Key positions
- Relationships between departments
- *does it portray the reality?*
- *-tools: Interview and supporting documentation*

is important for the inspection?

- Key document to prepare the agenda timetable
- It can be used as the guiding theme for the inspection:
  - understanding responsibilities
  - areas to be inspected
  - interrelationship between departments
  - document control pathways

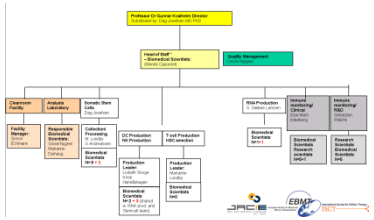
WHEN to use it?



PRE-INSPECTION → INSPECTION → POST-INSPECTION

identification kye personnel → verification → report writing

“Difficulties” encounterd by inspectors



- the organigram provided by the facility is not updated
- names are not included in the organigram so specific persons can not be identified (it si not a requirement)
- the information provided in the organigram does not correspond with the CVs in the pre-inspection documentation

D4.10 Errors, accidents, biological product deviations, serious adverse events, and complaints

- Investigation – root cause
- Documentation
- Reportin
- Corrective and Preventive action

The review of records of nonconformities will show you how quality system deals with this issues

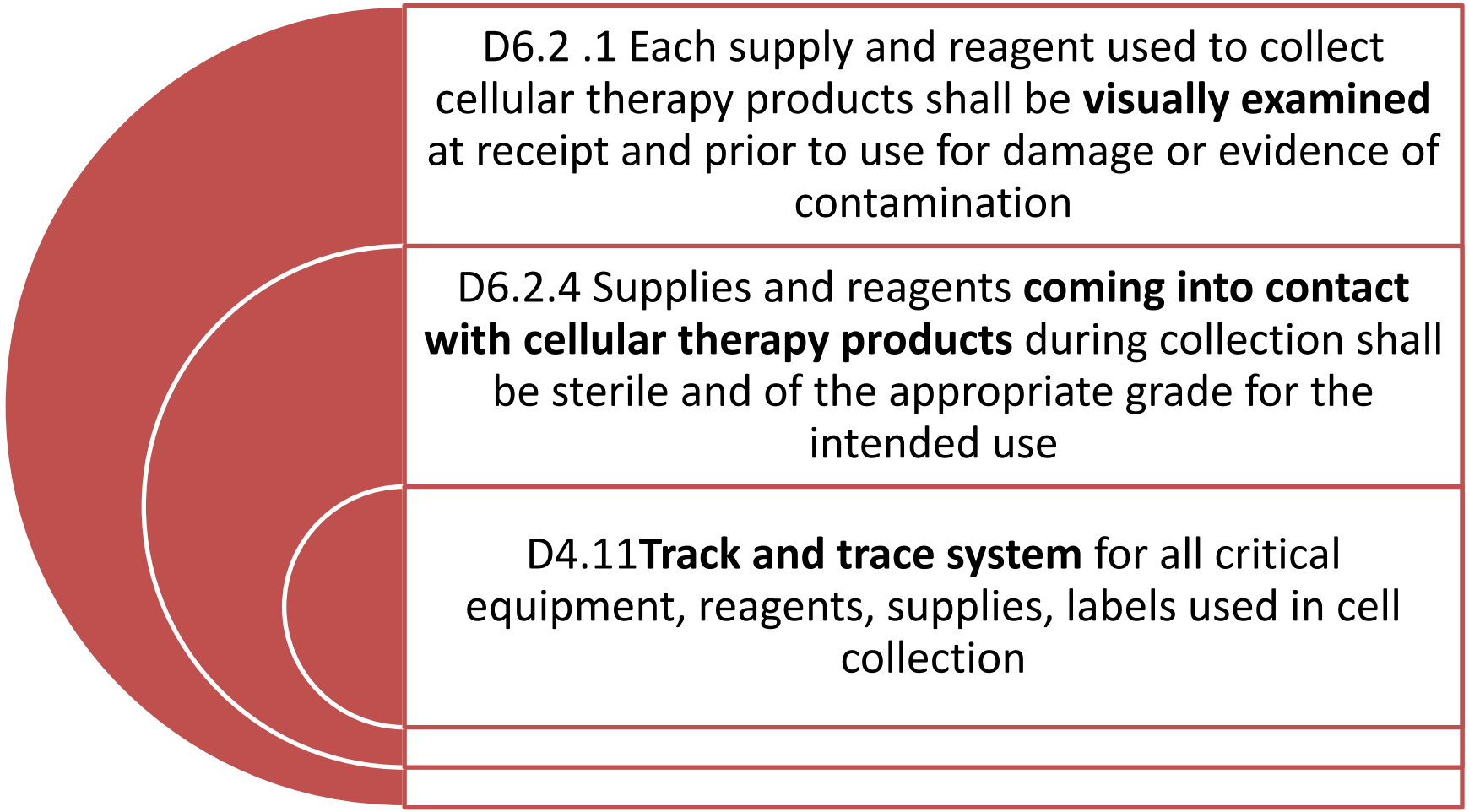
D6 Equipment, Supplies and Reagents

- Stock / inventory control
- Use supplies and reagents according to manufacturers instructions
- Track using of equipment and critical reagents
- Plan and record cleaning, calibration and equipment maintenance
- Record equipment failure
- Procedure to link reagents /supplies/equipment used in processing of each cellular therapy product

D5.1.14 Critical reagent and supply management
D6.2 Materials Management System for Consumables&Reagents

- Records include :
  - consumable or reagent type,
  - quantity
  - manufacturer
  - lot number
  - date of receipt, acceptability,
  - if applicable, expiration date.

D6 Equipment, Supplies and Reagents



D6 Equipment, Supplies and Reagents

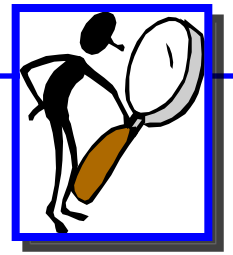
D6.2.4.2 **Where there are no** suitable clinical or pharmaceutical grade reagents available, reagents shall undergo **lot-to-lot** functional verification

e.g. suitable grades of DMSO do not need to undergo lot-to-lot verification

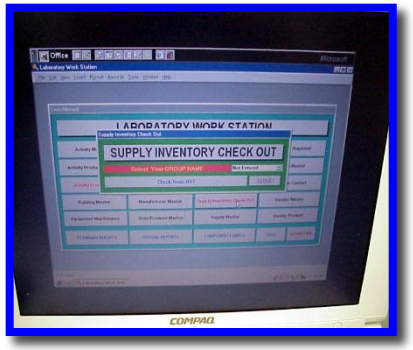
Suitable grade explained in the manual: Examples of statements that are used on **COAs** of reagents considered to be of the appropriate grade include:

- "A Sterile and Endotoxin Free (According to Ph.Eur./USP) Non pyrogenic cryopreservative solution."
- "Complies with USP" or "Complies with Ph.Eur."
- "This batch complies with the specifications of the USP and Ph.Eur."
- "**Grade: USP**" or "**Grade: Ph.Eur**."
- "Cryoprotectant for the cryopreservation of human cells and tissues for transplantation."

D6.2.4.3 **Lot-to-lot** functional verification shall include **acceptance criteria** to confirm that new lots perform as expected compared to the previous lots



D6.2 Materials management system



Observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer

D6 Equipment

D6.6 Standardised and calibrated according to manufacturer's specifications on a regular basis

- Use of traceable standards

D6.8 Conform to applicable laws and regulations

- CE Marking
- Electrical safety testing

D6.4 Cleaning, Disinfection, Calibration & Maintenance

- D6.4 Equipment used ... shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

- D6.5 The equipment shall be inspected for cleanliness prior to each use and verified to be in compliance with the maintenance schedule daily prior to use.

-evidence that equipment is evaluated for cleanliness
-visual inspection that equipment can be easily accessed for cleaning, disinfection, and maintenance.
-sampling of calibration records

D7 Labels

In the 6th ed., active implementation of ISBT 128 was accepted

Evidence:

- Organizations must, minimally, demonstrate a clearly documented infrastructure including:
  1. Registration with ICCBBA.
  2. Identification or creation of appropriate product codes.
  3. Label designs according to the requirements of ICCBBA for Cellular Therapy Products.
  4. Label validation.
  5. Use of scanned information at the time products are released from collection, received into the laboratory, and at distribution from the processing facility.

- It is understood that some organizations may have difficulty with active implementation early after the effective date of these standards. Organizations may be requested to provide updates throughout the accreditation cycle via interim reporting.

ISBT 128
More than Identification

D7 Labels

In the 6th ed., active implementation of ISBT 128 was accepted**, but now… 7th edition**

Evidence:

- Organizations must, minimally, demonstrate a clearly documented infrastructure including:
  1.
  2.
  3.
  4.
  5.

D7.1.1 Cellular therapy products **shall** be identified according **to ISBT 128 Standard Terminology or Eurocode**

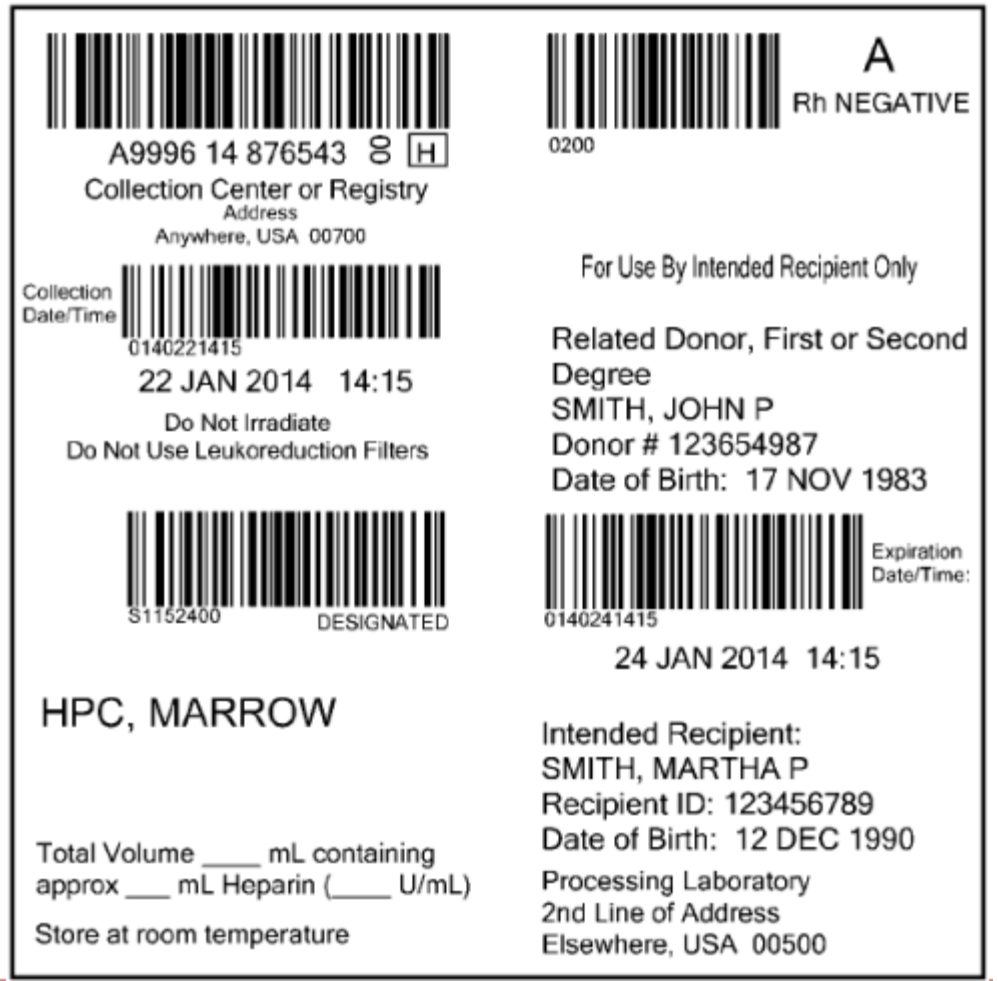
D7.1.2 Coding and labeling technologies **shall be implemented** using **ISBT 128 or Eurocode**

- It is understood that some organizations may have difficulty with active implementation early after the effective date of these standards. Organizations may be requested to provide updates throughout the accreditation cycle via interim reporting.

C7.1 ISBT 128 & EUROCODE

ISBT 128
ICCBBA is a nongovernmental organization in official relations with the World Health Organization

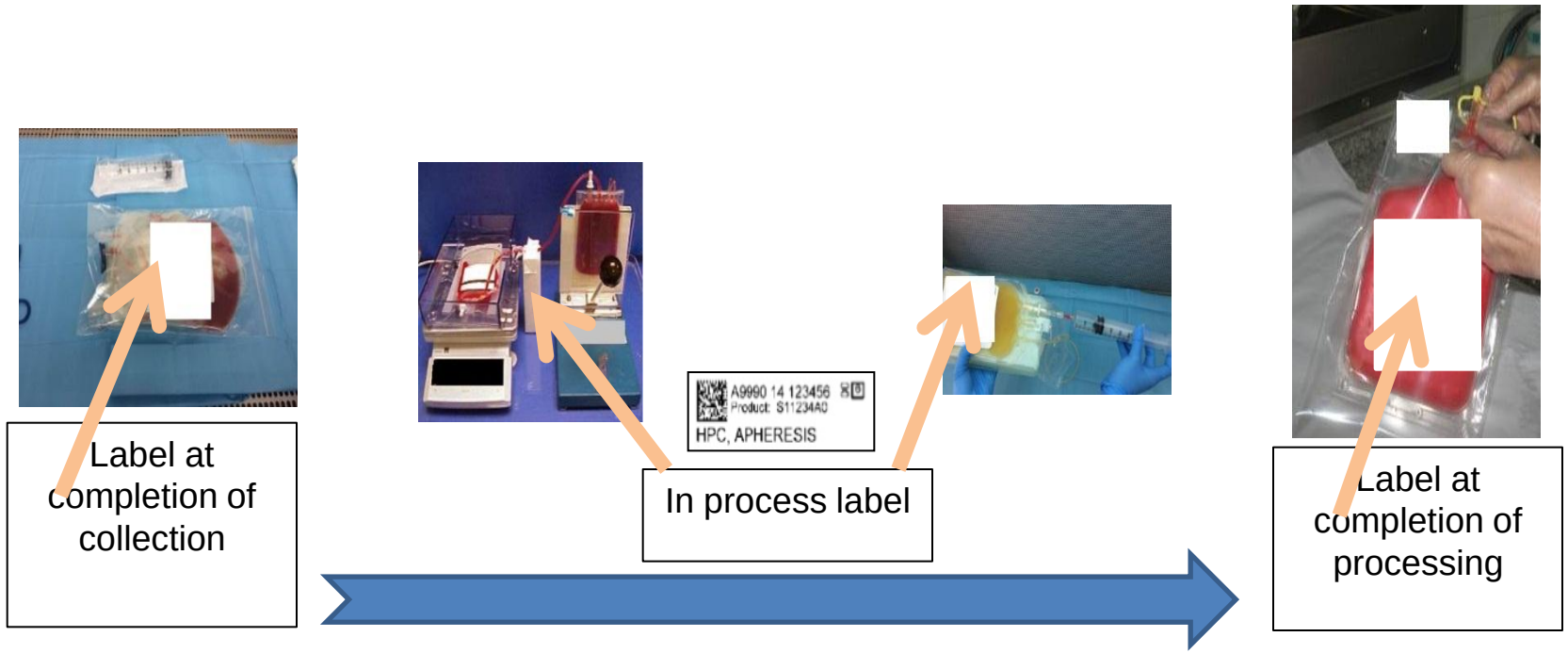
https://www.iccbba.org/



EUROCODE-IBLS

http://www.eurocode.org/index.html

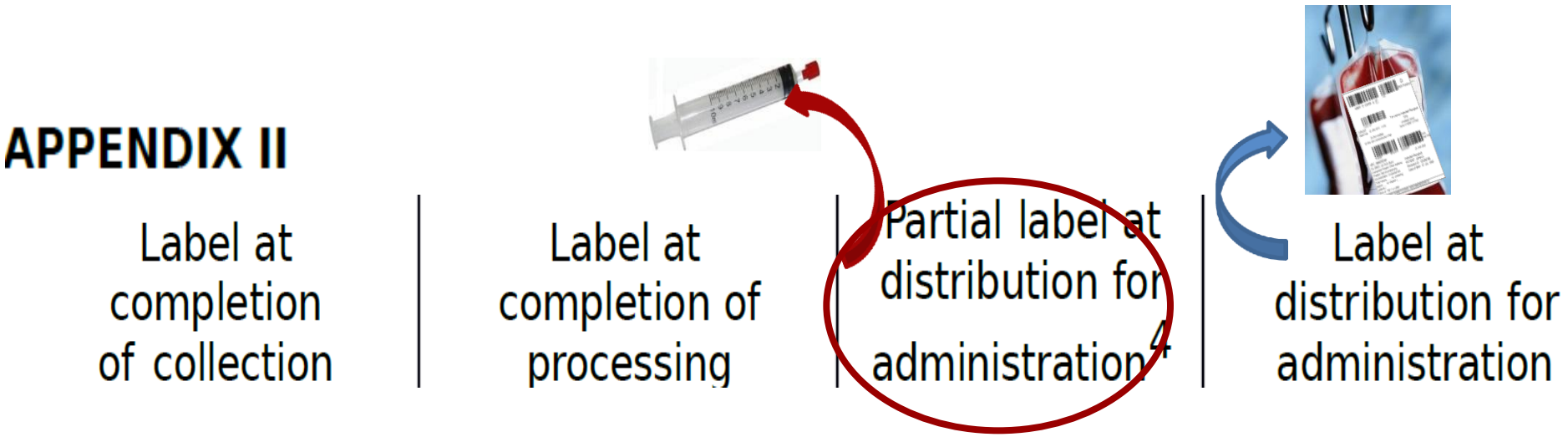
- D7.4.1 **At all stages of processing**, the cellular therapy product shall be **labeled** with the **proper name** of the product and the unique numeric or **alphanumeric identifier**, at a minimum



- ***Before inspection: check labeling SOP and examples of labels***
- ***During the inspection: real case or mock case***

- Appendix II – Cellular Therapy Product Labeling

Partial label at distribution for administration: a label that **because of the size of the product containe**r or other constraints, does not contain all of the required information



- D7.4.4 Any container bearing a partial label at the time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix II. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.

- ***Before inspection: check labeling SOP and examples of labels***
- ***During the inspection: real case or mock case***

D8.1 Process controls: Processing

Process for controlling and monitoring the manufacturing of cellular therapy products to ensure products **meet predetermined release specifications.**

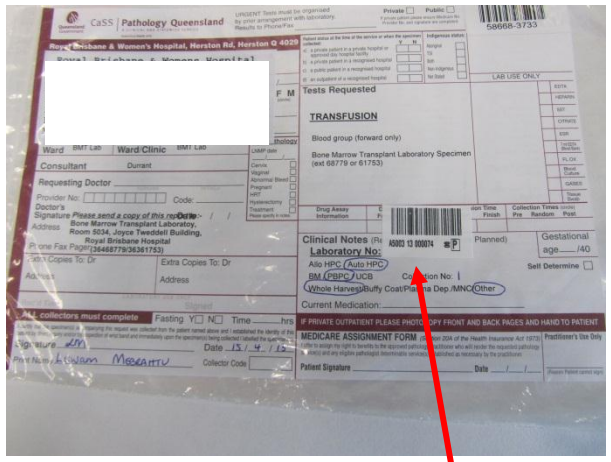
PF will be requested to provide SOP(s) describing the procedures to be followed during the manufacturing of cellular therapy products.

D8.1.2 Process controls: Processing

Documented system for the **identification** and **handling** of test samples so that they are accurately related to the corresponding cellular therapy product, donor, or recipient, as applicable.

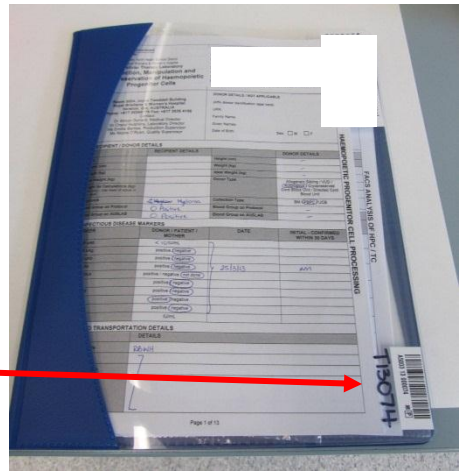
Mechanism to identify the **individual** obtaining the sample, the date, the time (if appropriate), and the sample source.

D8.1.2 Identification of Test Samples



Sample must be representative of CT product

- Sample source
- Date & time of collection
- Collector



Donation Identification Number – DIN
On every page of processing record, request forms & specimens

D8.1.4 Overview of requirements for tests performed within the Processing Facility

- Process for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments including
  - Use of controls
  - Calibration and standardization of reagents and equipment
  - Staff training and proficiency testing

New lots must be verified before use to:

- Ensure comparable results to current lots
- Produce results in agreement with suitable reference material

Controls (D8.1.4.3)

Must be used each day of testing

Must give results within the defined range established for that material

Only required if reference material is available

- Control cells must be appropriate for the instrument in use

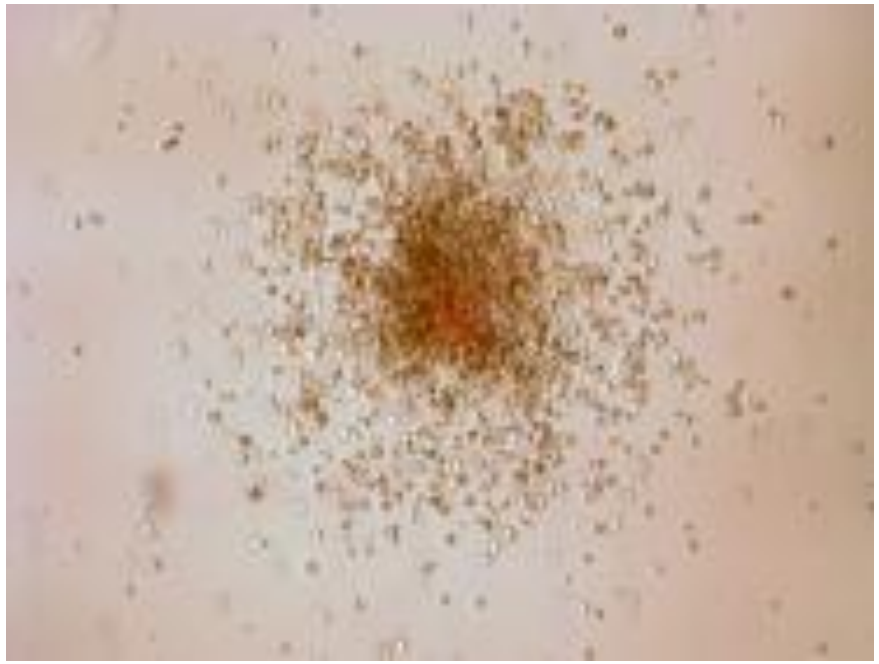
Proficiency Testing (D8.1.4.5)

- Must have documentation of ongoing proficiency testing
  - Processing Facility Director responsible for determining schedule
- Results must be reviewed by the Director and outcomes reviewed with the staff
- Availability of proficiency testing:
  - **Administered by external organizations**
  - Established internally if no external test is available

Proficiency Testing (D8.1.4.5)

Tests with available proficiency testing programs:

- automated cell counting
- colony assays
- flow cytometry



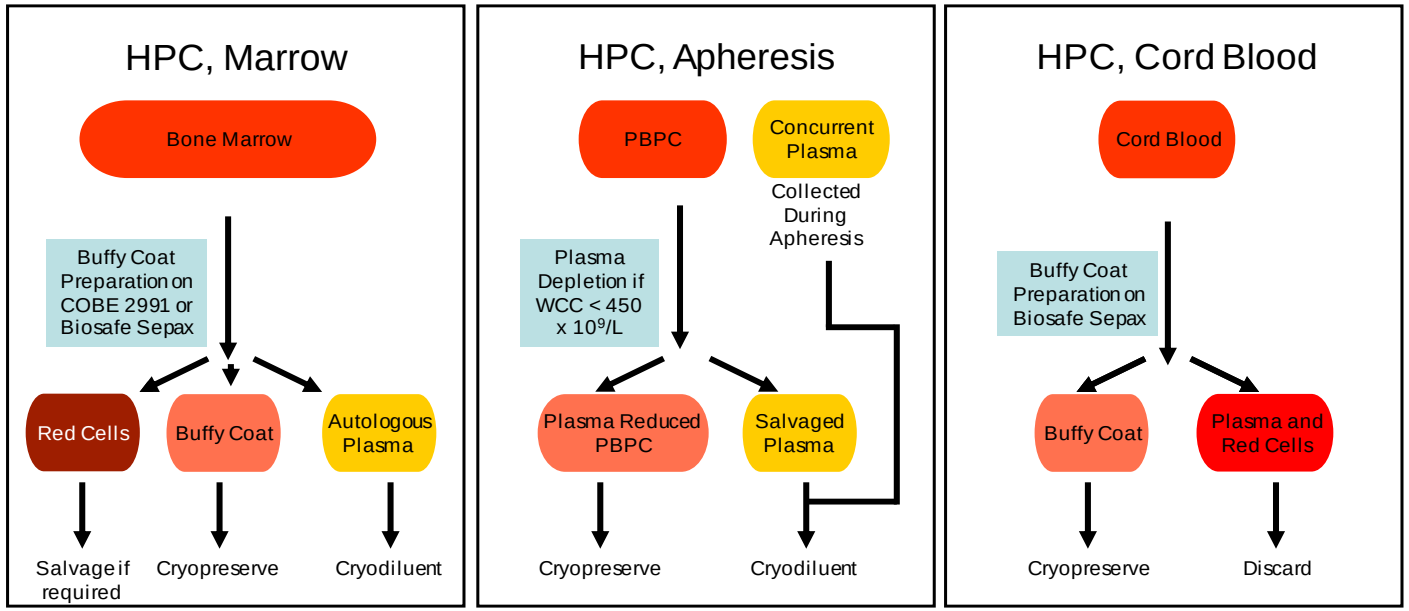
- College of American Pathologists (CAP)
- Stem Cell Technologies
- Center for Communicable Diseases
- National Institute for Allergies and Infectious Disease
- United Kingdom National External Quality Assessment Schemes (NEQAS)
- Internal if external proficiency test is unavailable.

Testing Performed by an External Laboratory (D8.1.5)

- Laboratory must be certified or accredited by appropriate laboratory regulatory agency (D8.1.5)
- Documentation must be available to inspector
  - However, actual certificates are not required to be on-site at Processing Facility

D8.5 Critical Control Points

SOPs should specify when during processing testing should be performed and the end points and /or range of results expected post processing



D8.4 Validation of Processing Procedures

Processing procedures shall be validated in the processing facility and documented to result in acceptable target cell viability and recovery

- ✓Retrospective, concurrent or prospective
- ✓Ongoing evaluation of processing results, data analysis
- ✓Expected ranges

Requirements for Validation

Validation of:

- Critical or significant procedures
  - Processing and cryopreservation techniques
  - Labeling
  - Storage
  - Distribution
  - Manufacture of reagents in-house
- Changes to processes
  - Verify or validate changed processes to ensure they do not create an adverse impact anywhere in the operation

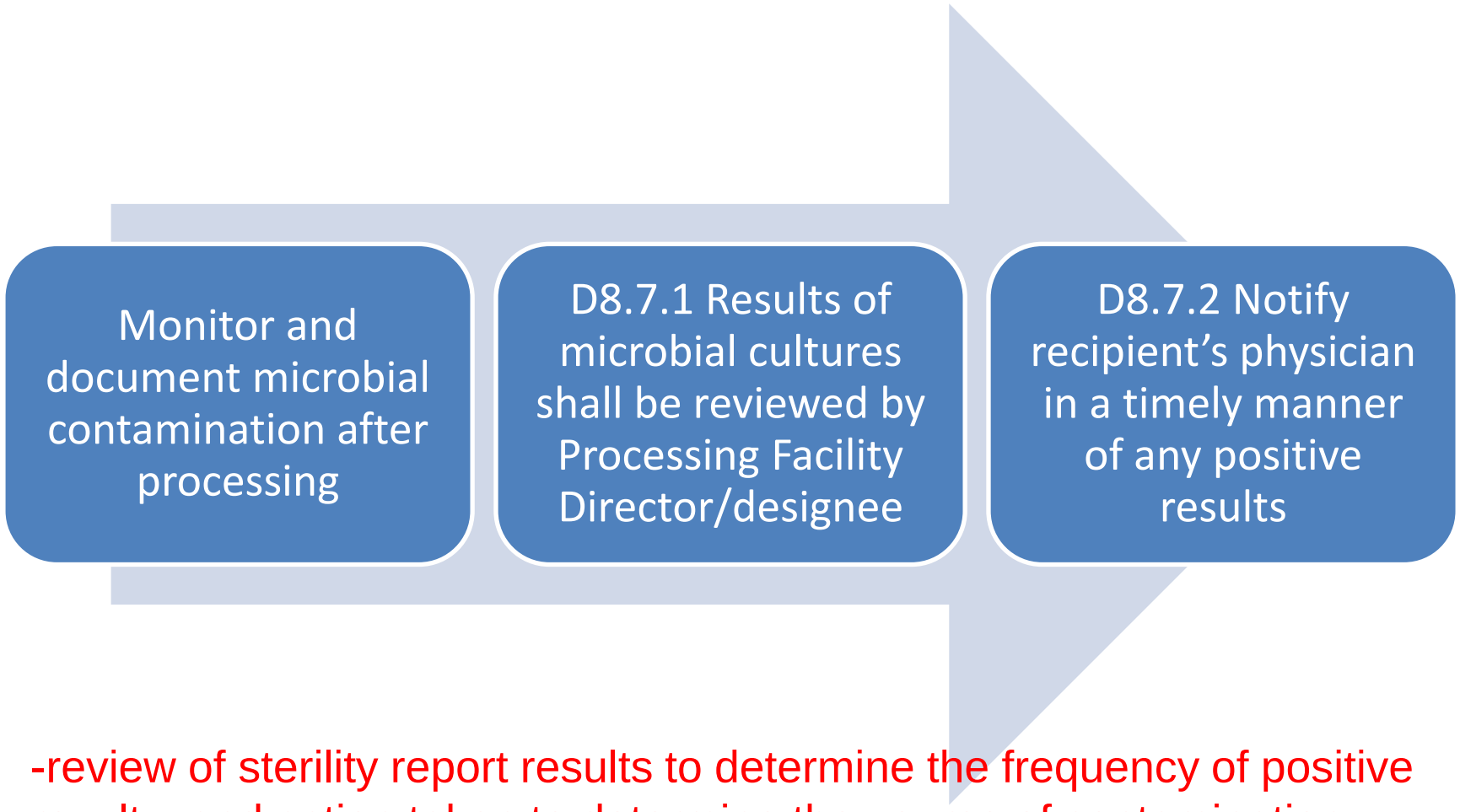
Validation Summary

- Results attached (may be bulky with multiple graphs)
- Deviations from plan (almost nothing goes completely as planned)
- Summary of findings
- Assessment
  - Acceptable
  - Acceptable with limitations
  - Reject
- Comments
- Corrective actions if needed
- Review and Approvals

D8.6 Processing methods shall employ aseptic technique / minimise risk of cross contamination

- Eliminate possibility of product mix-ups and/or cross contamination.
  - Physical separation of records / and products during processing
  - Labelling
- Specify cleaning and disinfection pre and post-processing
- Use of disposable closed systems

D8.7 Microbial contamination

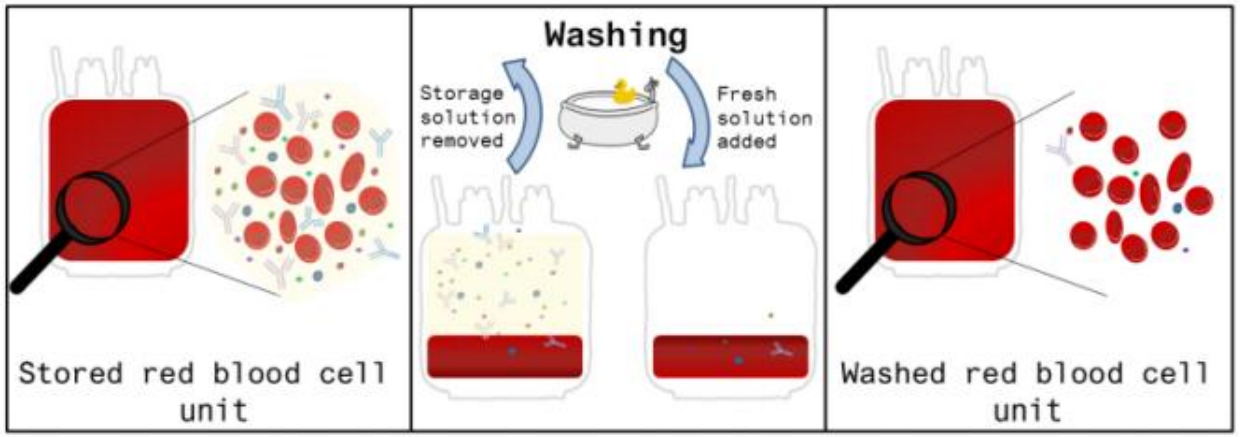


-review of sterility report results to determine the frequency of positive results, and action taken to determine the source of contamination

Cord blood units

- D8.4.3 Cord blood units that <u>have not</u> been red cell reduced prior to cryopreservation <u>shall</u> be washed prior to administration.

- D8.4.4 Cord blood units that <u>have</u> been red cell reduced prior to cryopreservation <u>should</u> be diluted <u>or</u> washed prior to administration.



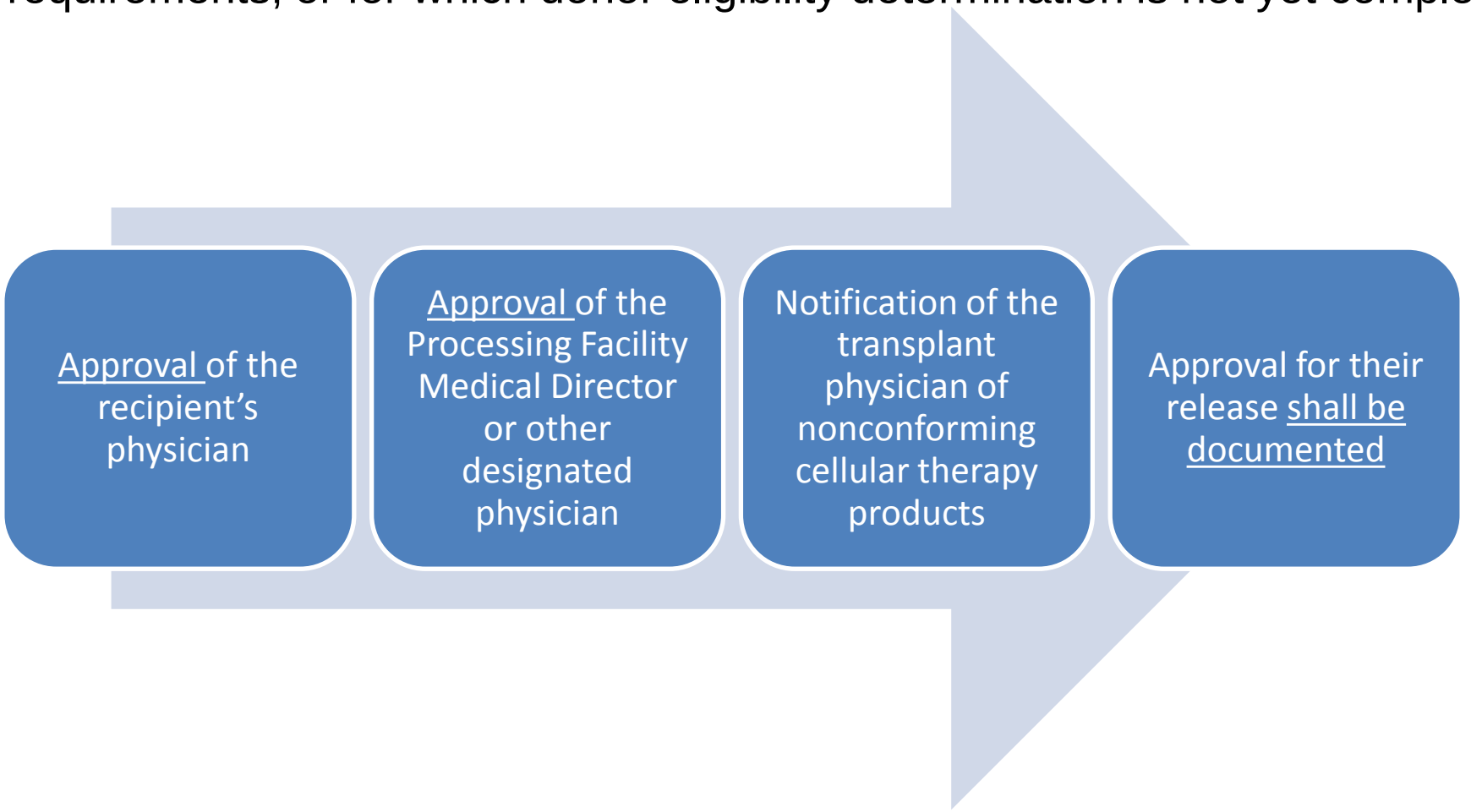
D8.9 Review of Processing Records

The Processing Facility Director or designee shall review the **processing record for each** cellular therapy product **prior** to release or distribution

- D8.10 Notification of the recipient's physician and the Processing Facility Medical Director when the clinically relevant processing end-points are **not met**.
- Documentation of notification and any remedial actions in processing record.

D8.1.7 Urgent medical need

Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which donor eligibility determination is not yet complete



D8.12 Testing of ABO Group & Rh Type for allogeneic cellular therapy product containig red blood cells

- Standards require testing on 2 independently collected specimens
  - Donor work up (PB)
  - Donor PB at time of collection / Specimen from HPC

Evidence:

-look for records of ABO and Rh typing results and antibody screening in the processing chart records.

- SOPs for
  - Processing HPC products when ABO major or minor mismatch
  - Management of CT products in case of infusion reaction

D9 Cellular Product Storage

- Duration and temperature of storage must maintain viability and function and inhibit infectious agents

- Products must not be stored with other materials that may adversely affect the products

- **Quarantined** products must be stored in a manner that minimizes cross-contamination

- Storage units must be monitored and have alarm systems

- An inventory control system must be used to manage supplies, reagents, and cell products

D9 Storage Area Tour

- Temperature
- Quarantine system
- Alarm systems
- Back-up storage plan
- Inventory control system

D9.2.2 Storage

Written stability program that evaluates	Minimally annually
• viability • potency	• e.g. retrospective, could use products scheduled for discard, samples stored

D9 Storage

- Alarm systems shall have audible and visible signals or other effective notification methods.

Ask for the records of last recorded alarm, what actions were take?

D9 STORAGE

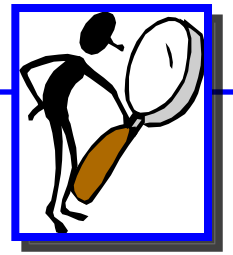
Inspection Tip

- **Observe storage room and tanks.**
- **Look for alarm system warning instructions.**
- **Review inventory records.**
- **Ask staff to locate a component**

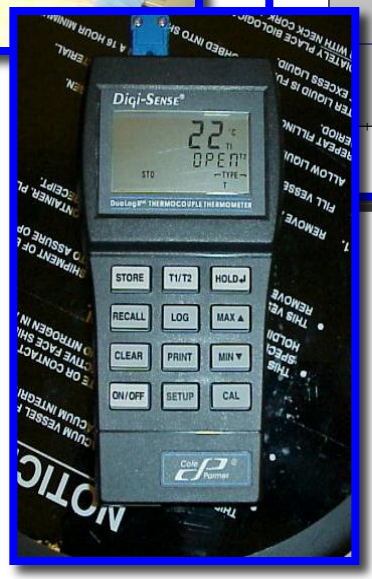
D9 STORAGE

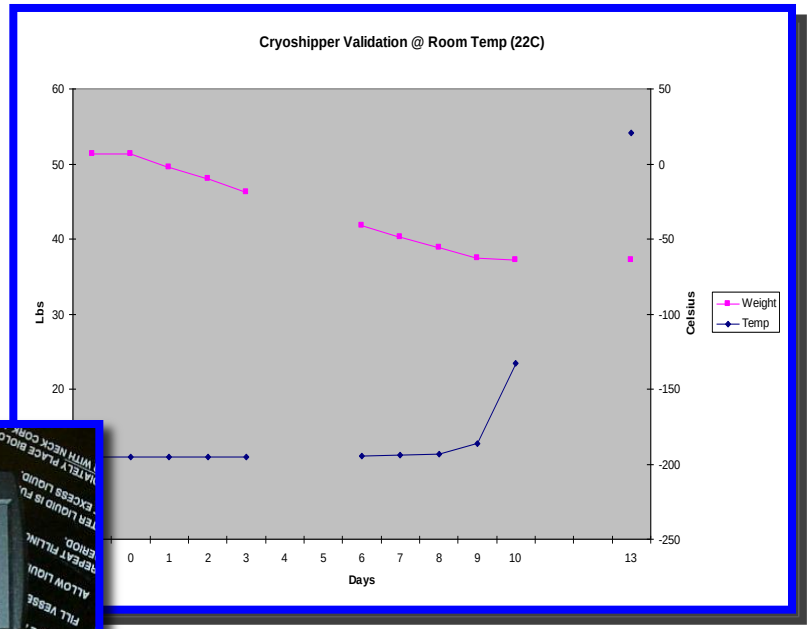
Deficiencies

- Unrestricted access to storage tanks and/or room
- No Discard Policy
- Non-secure inventory records
- No adequate backup in the event of device failure



D10 TRANSPORTATION AND SHIPPING





D10 Transportation and Shipping

-the transferring of cellular therapy product within or between facilities
Transport: *During* transportation the product does not leave the control of trained personnel
Shipping: *During* shipping the product leaves the control of trained personnel at the distributing or receiving facility.

- Procedures in place, risk asessments
- Container validation
- Courier qualifications
- Time limits
- Records kept of transport times and temperature

D10 Transportation and Shipping

D10.5.2.1 The temperature of the shipping container shall be continuously monitored during shipment of cellular therapy products.

D10.5.3 The outer container shall be secured.

D10.5.6 The outer container shall be labeled in accordance with applicable laws and regulations regarding the cryogenic material used and the transport or shipment of biological materials.

✓time at the start of transportation or shipping
✓specification of the conditions of transportation or shipping relevant such as "KEEP COOL," "DO NOT FREEZE"

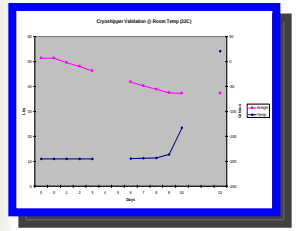
NON-CRYOPRESERVED TRANSPORT

Outer Shipping Container

- **Thermally insulated.**
- **Sturdy construction with absorbent**
- **Must state “Medical Specimen Do not X-Ray”**
- **Must bear biohazard label if positive for infectious disease marker.**
- **Must contain information to identify and contact receiving facility and shipping facility.**
- **Contents must be described, e.g. no. & volume**

CRYO-SHIPPING

- Liquid nitrogen dry shipper required for components stored below -80ºC
- Must maintain temperature for 48 hrs beyond transit
- Temperature monitor required
- Container meets temperature & shipping regs



D11 Distribution and Receipt

Receipt of each cellular therapy product shall include inspection of:

1. Container integrity
2. Appearance
3. Labelling
4. Appropriately transported
5. Temperature of outer container

D11 Distribution and Receipt

- Records for each product must allow tracking and tracing between the donor and the recipient
- Pre-determined release criteria must be met before distribution, unless Director provides authorization
- Each cellular therapy product issued for administration shall be visually inspected by 2 trained persons
- Handling instructions/indications/side effects
- Processing records include written record of distribution
- Distribution records must provide certain details, for example, date, time, and product identifier

D12 Disposal

Procedure/policy for discard and method of disposal of cellular therap product

Policies	Written agreement	Transfer	Records
• for the duration and conditions of storage and indications for disposal	• pre-collection • between the storage facility & designated recipient or the donor • defined lenght of storage	• The option to transfer the CT product to another facility if designated recipient is still alive	• when discarded or transferred, date of discard, method of disposal must be recored

D13 Records

- Records Management
- Tracking product
- Assignment of unique identifiers
- Development/installation/validation
- Maintenance
- Staff training
- Monitoring of data integrity

- D13.4.1.1 **Employee records** shall be mantained in a **confidential** manner, as required by applicable laws and regulations

- D13.2 The Processing Facility shall define and follow **good documentation practices**

  e.g. Completion of all fields (using « not applicable » when necessary)

RECORDS

How, where, and for how long are records stored?

Electronic records

Critical electronic record systems shall include at a minimum systems

- under the control of the Processing Facility
- that are used as a substitute
  - for paper
  - to make decisions
  - to perform calculations
  - or to create or store information used in critical procedures.

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Revised: "Validation of Computerised Systems" Guideline

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AGENDA

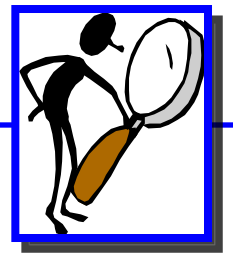
- https://www.edqm.eu/en/news/revised-validation-computerised-systems-guideline

The revised guidelines are the following

- Validation of Computerised Systems - Core Document
- Validation of Computerised Systems Annex 1: Validation of Excel Spreadsheets
- Validation of Computerised Systems Annex 2: Validation of Complex Computerised Systems

Remember

- The ACCREDITATION MANUAL includes examples of what to look for



INSPECTORS

REMINDERS

- Take time
- Many ways to achieve compliance
- Can ask for demonstrations
- Interactive, constructive experience
- Encourage information exchange

INSPECTORS

REMINDERS

- Respect confidentiality
- Provide feedback, not decisions