OVERVIEW OF 6th EDITION CELL PROCESSING SECTION

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FACT-JACIE INTERNATIONAL STANDARDS

for HEMATOPOIETIC CELLULAR THERAPY

Product Collection, Processing, and Administration

SIXTH EDITION

FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPY
JACIE

5th edition
INTERNATIONAL STANDARDS FOR CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION

6th edition
INTERNATIONAL STANDARDS FOR HEMATOPOIETIC CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION

The scope of the Hematopoietic Cell Therapy Standards includes:

- ✓ Collection, processing, and administration of hematopoietic progenitor cells (HPCs), whether minimally or more than minimally manipulated, for hematopoietic indications.
- ✓ Collection, processing, and administration of cellular therapy products for donor lymphocyte infusion (DLI).

6th edition GLOBAL CHANGES

CONTINUING EDUCATION
B3.1.6, B3.2.2, B3.8.4, B3.10.2, CM3.1.5, CM3.2.2, C3.1.5, C3.2.5, C3.3.2, D3.1.3, D3.2.3, D3.3.2

Key personnel (directors, attending physicians, quality managers, and designated pharmacists) must participate in at least **10 hours** of continuing education.
Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and apheresis.

- ✓ Collection quality managers should also have education in cell collection.
- ✓ Processing quality managers should also have education in cellular therapy processing.

D3.1.1 There shall be a **Processing Facility Director** with a medical degree, doctoral degree, or equivalent degree in a relevant science, qualified by a minimum of two (**2**) years training and experience for the scope of activities carried out in the Processing Facility.

D3.2.1 There shall be a Processing Facility Medical Director who is a licensed or certified physician with a minimum of two (**2**) years postgraduate training and practical and relevant experience for the scope of activities carried out in the preparation and clinical use of cellular therapy products.

6th edition GLOBAL CHANGES

OUTCOME ANALYSIS (B4.7, C4.7, D4.7)

Outcome analysis must include evaluation of individual cellular therapy product data and aggregate data for each type of cellular therapy product and/or recipient type.

Clinical Programs **must compare** one-year survival to national or international outcome data, and should achieve survival rates within expected ranges.

NEW REQUIRED ANALYSIS

Clinical Programs:

1. Acute GVHD grade within one hundred (100) days after transplantation.
2. Chronic GVHD grade within one (1) year after transplantation.
3. Central venous catheter infection.

Apheresis Collection and Processing Facilities:

1. Time to engraftment measured by ANC and platelet count

6th edition GLOBAL CHANGES

DEVIATION MANAGEMENT (B4.10, B5.7, CM5.7, C4.10, C5.7, D4.10, D5.7)

PLANNED DEVIATIONS

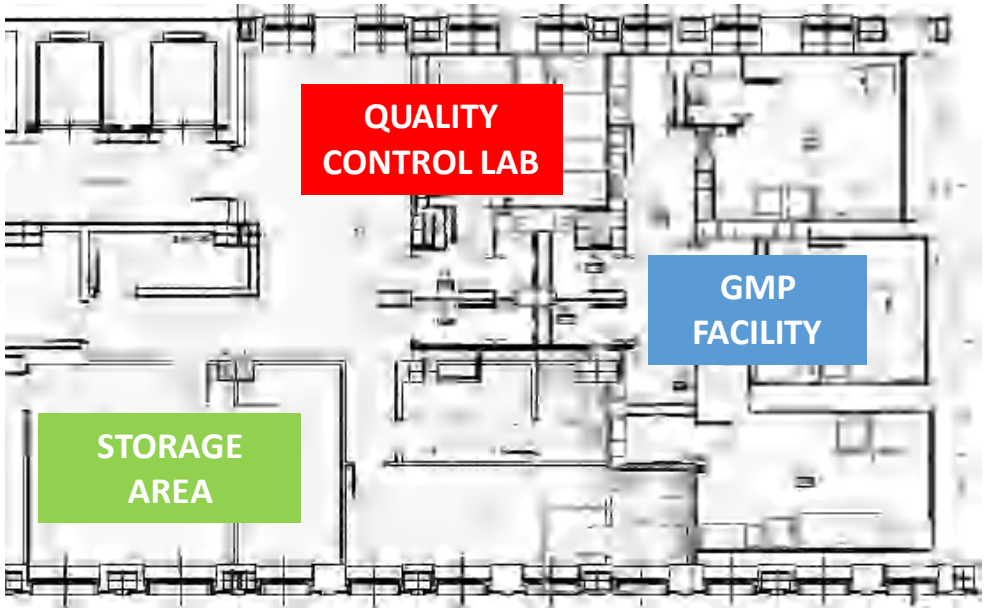
***Biological product deviation*:** Any event associated with the manufacturing of a cellular therapy product, including testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product:
- Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product.
- Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product.

VARIANCES

Variance: A planned deviation from recommended practice or standard operating procedure approved as the best course of action when adherence to the established course or accepted standard was not feasible or possible.

SPECIFIC POINTS FOR *PROCESSING FACILITIES*

D2: PROCESSING FACILITY



- Adequate equipment and materials
- Adequate space, design, and location
- Divided into defined areas
- Oxygen sensors for LN2 use
- Adequate lighting, ventilation, and access to sinks

D2.1.2 Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present.

D2.8 The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, or radiological hazards.

LIQUID NITROGEN SAFETY (B2.15, B2.1.2, B2.8, D2.1.2, D2.8)

Processing Facilities must have oxygen sensors that are appropriately placed and utilized in areas where liquid nitrogen is present and must also specifically address liquid nitrogen exposure in the written safety manual.

NEW

Clinical Program personnel are in the immediate vicinity of liquid nitrogen when a cryopreserved cellular therapy product is brought to the clinical unit. The written safety manual must include action in case of exposure to liquid nitrogen.

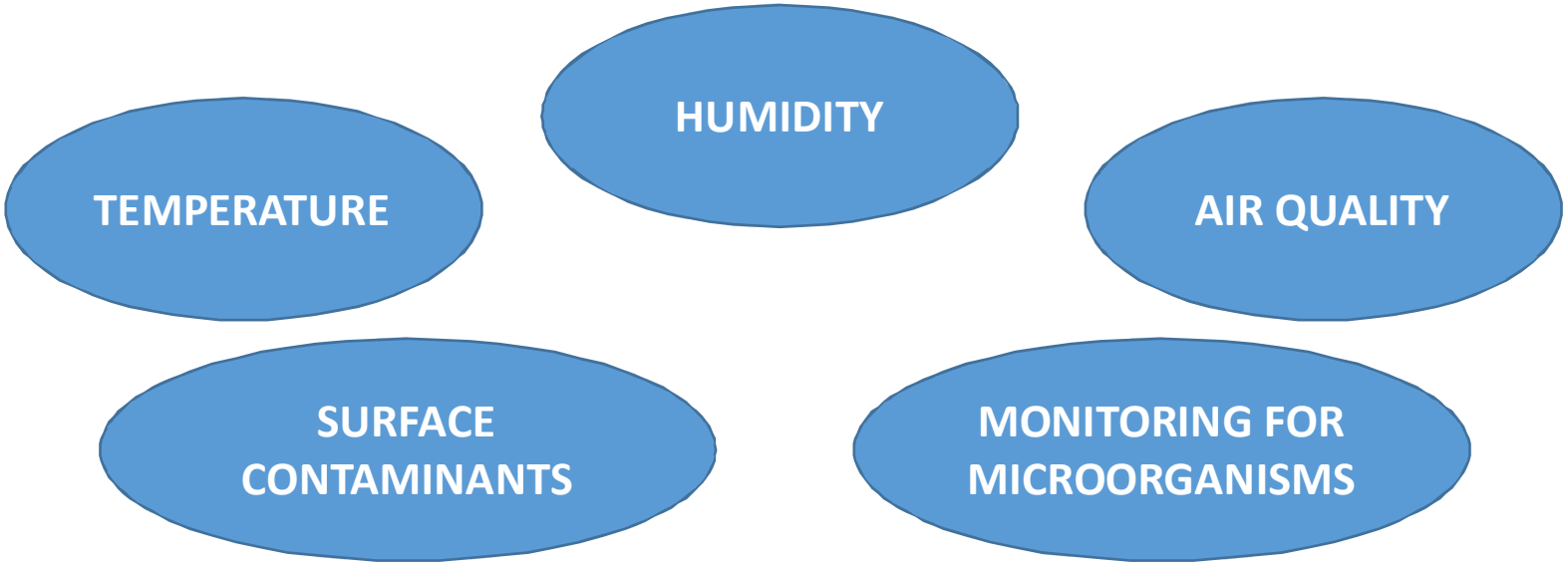
B2.15 –D2.8 The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, or radiological hazards.

D2.2 Processing Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of personnel.

D2.4 When using procedures that may result in contamination or cross-contamination of cellular therapy products or when performing more than minimal manipulation, critical environmental conditions shall be controlled, monitored, and recorded where appropriate for air quality and surface contaminates.

D2.4.1 The Processing Facility shall qualify environmental control systems and validate cleaning and sanitation procedures appropriate for the environmental classification and degree of manipulation performed.

D8.11.1 Processing Facilities must adhere to good manufacturing practices (GMP) appropriate for the degree of cellular therapy product manipulation.



D4: QUALITY MANAGEMENT
(B4, C4, CM4, D4)

D4.2 The Processing Facility shall establish and maintain a written Quality Management Plan.

D4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Processing Facility.

D4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control and management.

D4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.

D4: QUALITY MANAGEMENT
AUDIT MANAGEMENT

D4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a schedule for conducting, reviewing, and reporting audits of the Processing Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

D4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

D4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.

D4.8.3 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements shall be audited annually.

- ✓ ***Audit plan***
- ✓ ***Audit report***
- ✓ ***External audit***
- ✓ ***Follow-up and actions to take after audit***

D4: QUALITY MANAGEMENT
DEVIATION MANGEMENT

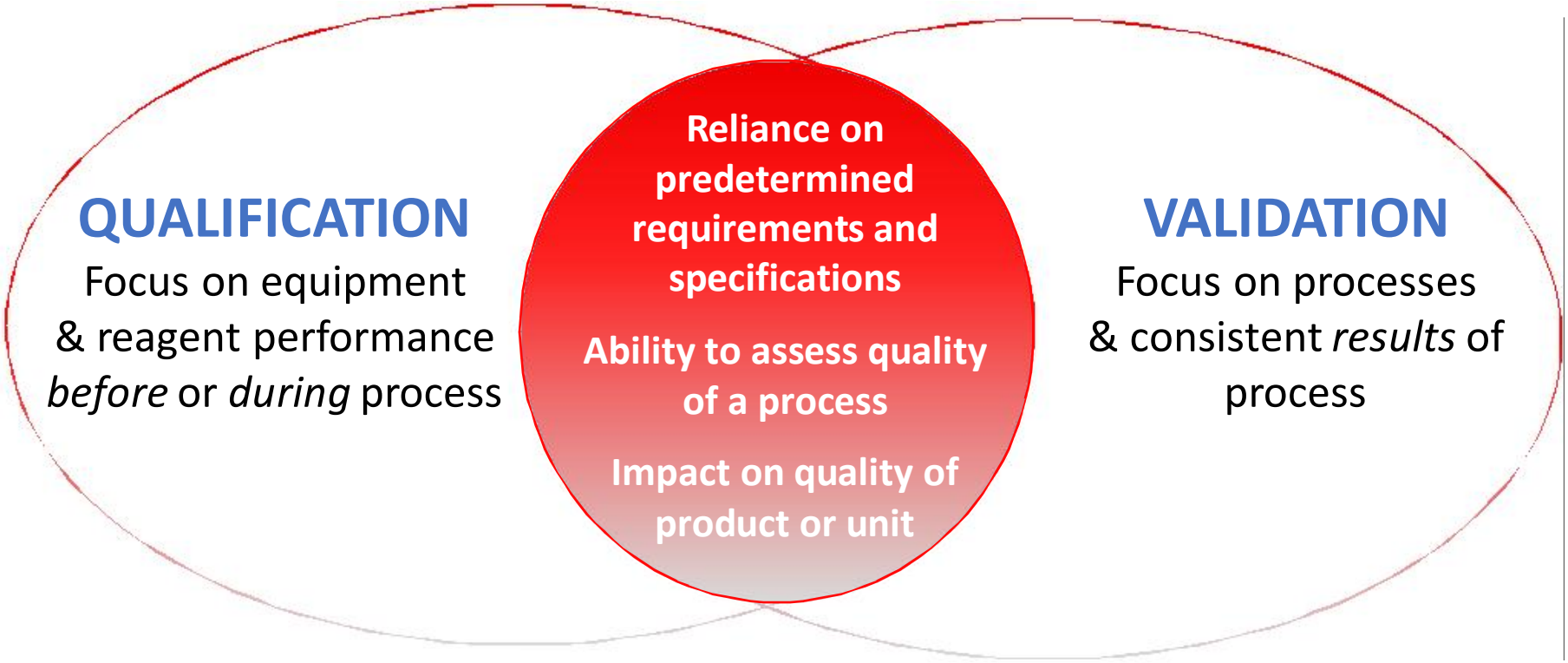
D4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective actions as warranted.

D4.10.3.1 Documentation shall include a description of the event, the involved individuals and/or cellular therapy products, when the event occurred, when and to whom the event was reported, and the immediate actions taken.

D4.10.3.3 Cumulative files of errors, accidents, biological product deviations, serious adverse events, and complaints shall be maintained.

D4.10.5.1 Appropriate corrective action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

D4: QUALITY MANAGEMENT
VALIDATION&QUALIFICATION



QUALIFICATION is documented evidence that the equipment/ facility/ utility / is meeting to the user requirement specification. It is further classified as IQ (Installation Qualification) OQ(Operation Qualification) and PQ(Performance Qualification), Qualification is also extended to the material you are planning to use and personnel qualifcation is essential to confirm that the person has appropriate qualification and training to carry out the assigned activity. Qualification is a pre requisite for Validation.

VALIDATION is a documented evidance which provides high degree of assurance that a specific process will work consistantly to produce predetermined specifications/expectations. The pre requisite to carry out validation is that you need to have qualified equipment, materials, people,facility and utility & Process.

D4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of critical procedures to achieve the expected end-points, including viability of cells and cellular therapy product characteristics.

D4.14.2 Each validation shall include:

- D4.14.2.1 An approved validation plan, including conditions to be validated.
- D4.14.2.2 Acceptance criteria.
- D4.14.2.3 Data collection.
- D4.14.2.4 Evaluation of data.
- D4.14.2.5 Summary of results.

NEW

D4.14.3 Changes to a process shall include evaluation of risk to confirm that they do not create an adverse impact anywhere in the operation and shall be validated or verified as appropriate.

Risk Consequence x Probability		Probability			
		Unlikely	Not very likely	Possible	Probable
Consequence	Very Serious	Hazardous	Hazardous	Very Hazardous	Very Hazardous
	Serious	Moderately Hazardous	Hazardous	Hazardous	Very Hazardous
	Mild	Moderately Hazardous	Hazardous	Hazardous	Hazardous
	Insignificant	Not Hazardous	Not Hazardous	Moderately Hazardous	Hazardous

D5: POLICIES AND PROCEDURES

D5.2 The Processing Facility shall maintain a detailed Standard Operating Procedures Manual that includes a listing of all current Standard Operating Procedures, including title, identifier, and version.

«SOP for SOPs»

D5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.

D5.1.1 Donor and recipient confidentiality.

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NEW

D5.1.4 Processing of ABO-incompatible cellular therapy products to include a description of the indication for and processing methods to be used for red cell and plasma depletion.

D5.1.5 Prevention of mix-ups and cross-contamination.
D5.1.6 Labeling (including associated forms and samples).
D5.1.7 Cryopreservation and thawing.

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D5.1.13 Cellular therapy product disposal.
D5.1.14 Critical reagent and supply management.
D5.1.15 Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.
D5.1.16 Recalls of equipment, supplies, and reagents.
D5.1.17 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.

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D5.1.19 Hygiene and use of personal protective equipment.
D5.1.20 Disposal of medical and biohazard waste.

D6: EQUIPMENT, SUPPLIES, AND REAGENTS

NEW

D6.4 Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

- ✓ Equipment used for product processing or testing must be located to allow access for maintenance and calibration at pre-determined intervals.
- ✓ A schedule for equipment cleaning, sanitation, disinfection, calibration & maintenance is required

D6.6 The equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

- ✓ Standardised and calibrated according to manufacturer's specifications on a regular basis including after a critical repair or move

  - Use of traceable standards

- ✓ Conforms to applicable laws and regulations

  - CE Marking

  - Electrical safety testing

SAFETY MARK
123456-00

D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

D7.1.2 If coding and labeling technologies have not yet been implemented, the Processing Facility shall be actively implementing ISBT 128.

The sixth edition requires that organizations be **actively implementing** ISBT 128 coding and labeling technologies.

The 5th edition required organizations to have a plan for ISBT 128 coding and labeling technology implementation. "Actively implementing" could be demonstrated by registration with ICCBBA, identification or creation of appropriate product codes, label designs, label validation, and/or use of scanned information.

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.

D7.2.7 The information entered on a container label shall be verified by **one** (1) qualified staff member using a validated process to verify the information or **two** (2) qualified staff members prior to distribution of the cellular therapy product.

AF-Affix: To adhere in physical contact with the cellular therapy product container.

AC-Accompany*:* To go, be together with, or be available to the appropriate individual(s) electronically, but not affixed or attached. Written or printed information that must accompany a cellular therapy product must be in a sealed package with, or alternatively, be attached or affixed to, the cellular therapy product container.

AT-Attach: To fasten securely to the cellular therapy product container by means of a tie tag or comparable alternative. Any information required to be attached to a cellular therapy product container may alternatively be affixed.

Element	Partial face	Labeling at completion of collection	Labeling at completion of processing	Labeling at distribution/for administration
Unique numeric or alphanumeric identifier	AF	AF	AF	AF
Proper name of product	AF	AF	AF	AF
Donor/manufacturer			AC	AC
Recipient name and/or identifier		AT	AT	AT
Identity and address of collection facility or donor registry		AT	AC	AC
Date/time collection ends, and (if applicable) time zone		AT	AC	AC
Approximate volume		AT	AT	AT
Nominal quantity of anticoagulant and other additives		AC	AC	AC
Donor identifier and (if applicable) name		AT	AT	AT
Recommended storage temperature range		AT	AT	AT
Distinctive and/or warning labels (as applicable, see CBER's 21 CFR 610)		AT	AT	AT
If applicable: • Statement "WARNING: NOT TESTED FOR INFECTIOUS DISEASES" • Statement "WARNING: Infectious Patient of Communicable Disease Risk" • Statement "WARNING: Possible Infectious Agent (Name of disease agent or illness)"		AT AT AT	AT AT AT	AT AT AT
Identity and address of processing and distribution facilities			AC	AC
Statement "Medical Irradiation"			AT	AT
Expiration Date (if applicable)			AC	AC
Expiration Time (if applicable)			AC	AC
ABO and RhD of donor (if applicable)			AC	AC
HLA compatibility determination (if applicable)				AC
Statement indicating that leukoreduction filter shall not be used				AT
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)		AT	AT	AT
Date of fabrication				AC

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

COMMISSION DIRECTIVE (EU) 2015/565

of 8 April 2015

amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells

Article 1

Commission Directive 2006/86/EC ([1]) is hereby amended as follows:

(1) In Article 2, the following points (k) to (y) are added:

'(k) "Single European Code" or "SEC" means the unique identifier applied to tissues and cells distributed in the Union. The Single European Code consists of a donation identification sequence and a product identification sequence, as further specified in Annex VII to this Directive;

(p) "product code" means the identifier for the specific type of tissue and cell in question. The product code consists of the product coding system identifier indicating the coding system used by the tissue establishment ("E" for the EUTC, "A" for ISBT128, "B" for Eurocode) and the tissues and cells product number foreseen in the respective coding system for the product type, as further defined in Annex VII to this Directive;

DONATION IDENTIFICATION SEQUENCE			PRODUCT IDENTIFICATION SEQUENCE			
EU TISSUE ESTABLISHMENT CODE		UNIQUE DONATION NUMBER	PRODUCT CODE		SPLIT NUMBER	EXPIRY DATE (YYYYMMDD)
ISO country code	Tissue establishment number		Product Coding System identifier	Product number		
2 alphabetic characters	6 alpha-numeric characters	13 alpha-numeric characters	1 alphabetic character	7 alpha-numeric characters	3 alpha-numeric characters	8 numeric characters*

Addition of the SEC to an ISBT 128 label (invented data)

- ✓ ITALY: implementation of EUROCET, a project aiming at setting up a registry on organ, tissue and cell donation and transplantation activity.

- ✓ GERMANY: implementation of EUROCODE

- ✓ OTHER MEMBER STATE: implementation of ISBT 128

D8: PROCESS CONTROL

D8.1.3.3 For cellular therapy products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, shall be employed for evaluation of the viable target cell population before and after the processing procedures.

- ✓ When processing procedure validation demonstrates a loss of CD34 cells and/or a loss in total nucleated cells (e.g., after density gradient separation for mononuclear cell preparation), testing for the affected cell type(s) must be performed at the end of processing and prior to infusion or cryopreservation.

D8.1.7 Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director or other designated physician.

D8.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D8.1.4.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.

Facilities performing in-house testing (e.g. Flow cytometry and automated cell counts) must meet the same general requirements as those for an external accredited testing facility.

- ✓ 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

D8.1.4.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.

D8.1.4.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.

UK NEQAS

- ✓ The facility may establish its own proficiency testing program, particularly for site-specific activities not routinely performed by other laboratories and for which no external proficiency test is available.

- ✓ For tests such as manual cell counts the manual method can be compared with results obtained from a validated hematology analyzer.

D8.1.4.5 For tests performed within the Processing Facility, there shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director or designee and outcomes reviewed with the staff.

D8.1.5 Tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory that is certified, licensed, or accredited by the appropriate laboratory regulatory agency.

- ✓ 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

D4.13.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

PROCESSING REAGENTS
LOT-TO-LOT QUALIFICATION

If a reagent is not of the appropriate grade, it must be of the highest grade (or purity) available and the Processing Facility must validate that the reagent is safe and effective for the specified purpose

Includes DMSO **not** approved for human use

- ✓ *Critical reagent that performs a function (protects cells)*
- ✓ *Failure to function as intended would have dire consequences to recipient*

D9: CELLULAR THERAPY PRODUCT STORAGE

D9.2.2 There **shall be** a written stability program that evaluates the viability and potency of cryopreserved cellular therapy products, minimally annually.

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

D9.4.3.3 Processing Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination as required by applicable laws and regulations.

Many methods for quarantine are acceptable

- ✓ Physical (separate storage, overwrap, etc.)
- ✓ Electronic (flags and warnings in the processing record)
- ✓ Tie tags

D10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

***Transport**:* The physical act of transferring a cellular therapy product within or between facilities. During transportation the product **does not leave** the control of trained personnel at the transporting or receiving facility.

***Shipping**:* The physical act of transferring a cellular therapy product within or between facilities. During shipping the product **leaves** the control of trained personnel at the distributing or receiving facility.

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

- ✓ It is recommended that a copy of the data logger printout be shared with the receiving facility for their records; however, documentation from the shipping facility of the temperature conditions during transport would beacceptable.

NEW

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”

D12: DISPOSAL

D12.1 Disposal of cellular therapy products shall include the following requirements:

D12.1.1 A pre-collection written agreement between the storage facility and the designated recipient or the donor defining the length of storage and the circumstances for disposal of cellular therapy products.

D12.1.2 The option to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

D12.1.3 Documentation of no further need for the cellular therapy product before any product is discarded.

…….

D12.1.7 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the intended recipient is lost to follow-up, the storage facility shall make a documented effort to notify the donor, cellular therapy product manufacturer, or designated recipient's physician and facility about product disposition, including disposal or transfer.

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The impact of improved JACIE standards on the care of related BM and PBSC donors

C Anthias[1,2], ME Ethell[3], MN Potter[3], A Madrigal[1,2] and BE Shaw[1,2,3]

Haematologica 2014; 99(2)

Use of the quality management system "JACIE" and outcome after hematopoietic stem cell transplantation

Alois Gratwohl,[1] Ronald Brand,[2] Eoin McGrath,[3] Anja van Biezen,[2] Anna Sureda,[4] Per Ljungman,[5] Helen Baldomero,[6] Christian Chabannon,[7] and Jane Apperley[8] for the Joint Accreditation Committee (JACIE) of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation, and the European Leukemia Net

Cytotherapy, 2011; 13: 765–766

JACIE celebrates its 10-year anniversary with the demonstration of improved clinical outcome

CHRISTIAN CHABANNON[1,2], DERWOOD PAMPHILON[2,3], CHRISTIANE VERMYLEN[2,4], ALOIS GRATWOHL[5], DIETGER NIEDERWIESER[6], EOIN MCGRATH[2], COR LAMERS[7], FRANCESCO LANZA[8], INEKE SLAPER-CORTENBACH[9], ALESSANDRO MADRIGAL[10] & JANE APPERLEY[8,11]

http://www.jacie.org/about/related-publications

Thank you!