



Session 3: Step's required in quality systems in blood establishments

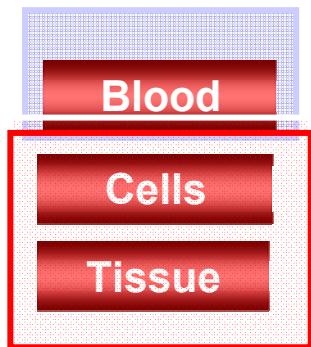
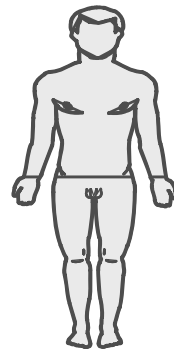
Pilars in the organization and infrastructure of optimal quality systems in blood transfusion services

Prof. Dr Christian Seidl

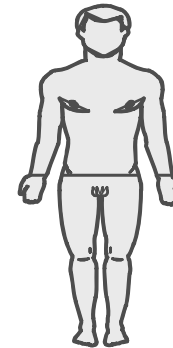
Red Cross Blood Donor Service Baden-Wurttemberg - Hessen (Germany)

Pilars - Levels of quality management

External - Third party
collection center



Donor



Patient

Therapeutic Interventions

- Surgery
- Intensive care
- Traumatology and emergency care
- Hematology and Oncology
- Transplantation medicine
- Pediatrics
- Gynaecology
- Urology

Collection

Production and Testing

Storage and distribution

Issuing and monitoring

Blood establishment

Tissue establishment

Hospital blood bank

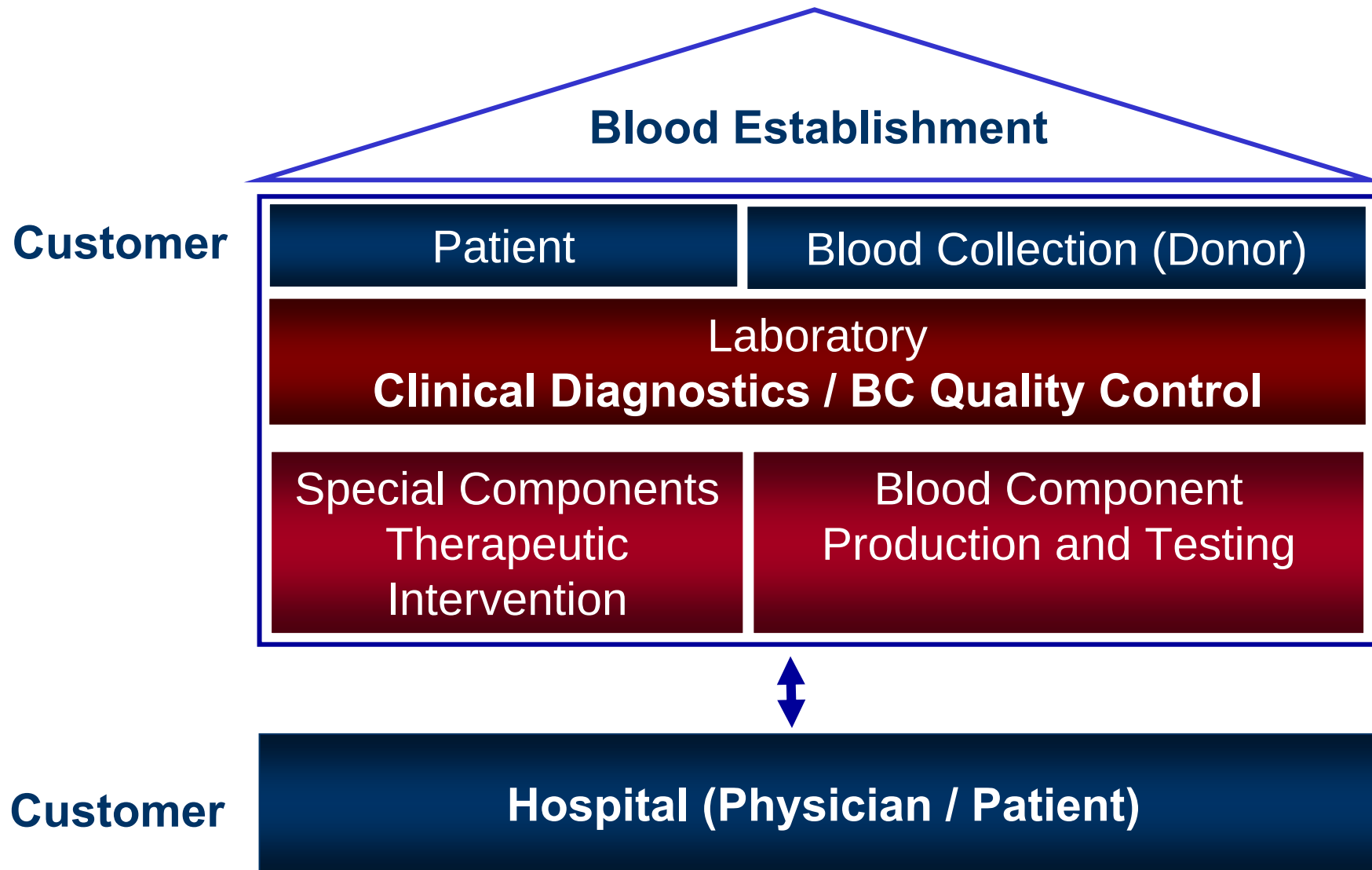
Hospital tissue bank

**Clinical Governance of the 'vein-to-vein-process'
Blood Transfusion Service**

The 5C ,Pilars‘ of Quality Management

- Competence
- Complexity
- Continuity
- Components
- Competition

Competence in Transfusion Medicine



Complexity – Legislation and guidelines

National (DE)

Transfusions Law (TFG)
Guidelines Haemotherapy
Pharmaceutical Law (AMG)
Infectious Protection Law (IFG)
Medicinal Product Law (MPG)

European (EC) / International

EU Blood Directives

2002/98/EC and technical annexes

EU Tissue and Cell Directives

2004/23/EC and technical annexes

EU Pharmaceutical Directives

2001/83/EC

GMP Guidance

International

ISO 9001

ISO 13489

ISO EN 15189

ISO EN 17025

In-vitro-Diagnostics

IVD Directive 98/79/EC

GP Guidelines (GPG) (EDQM)

Eurotransplant / EFI Accreditation

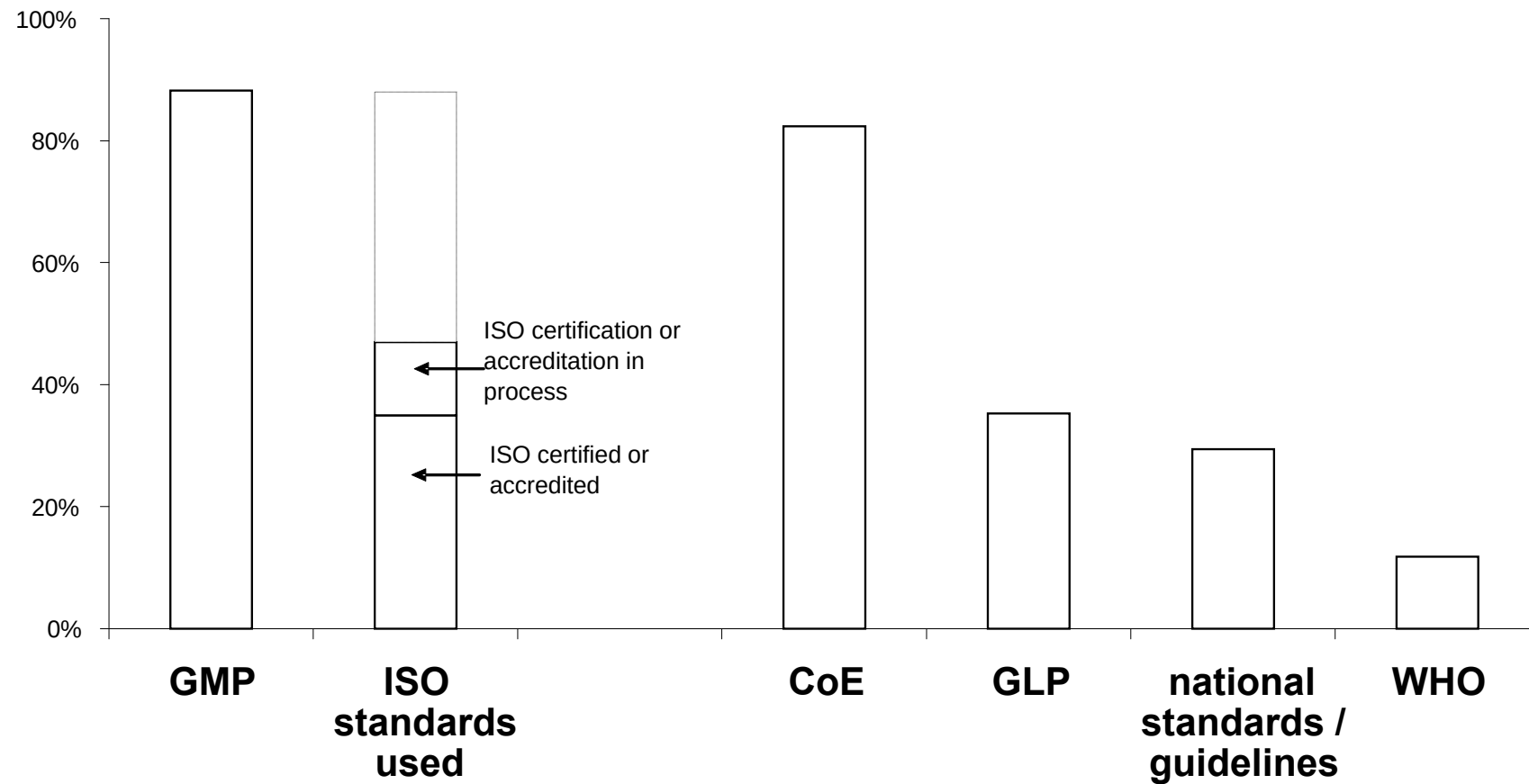
JACIE / FACT Accreditation

NMDP – European MDP

Survey – QMS standards used for blood establishments



Supported by the EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Directorate C - Public Health and Risk Assessment
C6 - Health measures



Continuity – Quality policy

Safety of blood components

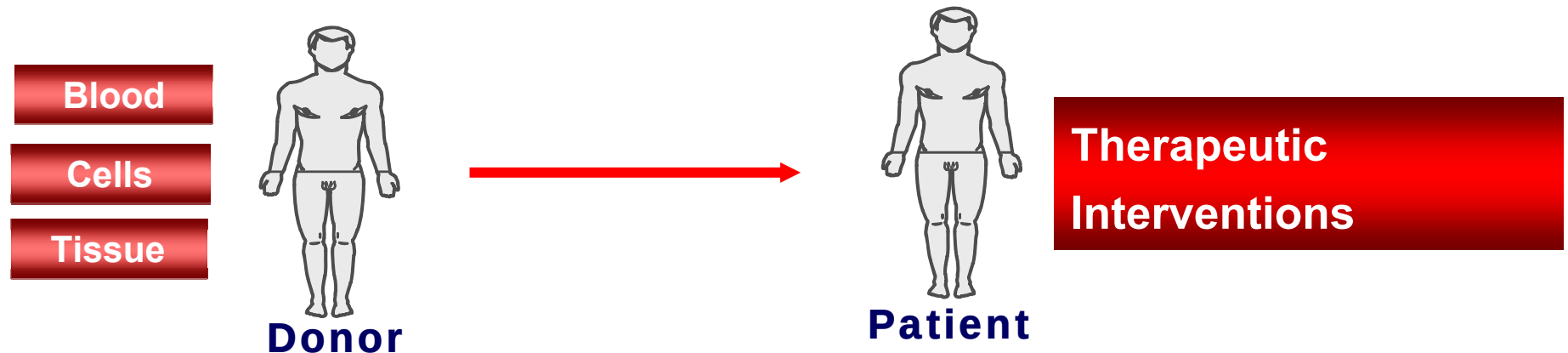
Self-sufficiency

Donor management

R&D

(Development of new technology (testing/production))

Components – Blood [and Clinical Services]



Blood components:

Red Cell / Platelet Concentrates
Fresh Frozen Plasma / Plasma for Fractionation
Autologous Blood

related preparations:

Blood stem cells / Cord blood
Granulocytes, Lymphocytes

Clinical Services

Patient Diagnostics / Reference Laboratory
Organ Transplant Regional Service
Bone marrow donor registry



Q7: Activities carried out by Blood Establishments

Blood Component preparation:

Cellular (erythrocyte and/or platelet concentrates)	100%
Fresh frozen plasma	100%

Related preparations:

Cord blood	25%
Blood stem cells	44%
Granulocytes	48%
Lymphocytes	36%

Source plasma for fractionation	57%
Cryoprecipitate	60%

Autologous blood components	84%
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Competition – Blood [and Clinical Services]

Compatibility between quality systems in hospital and blood establishments

- to safeguard the 'vein-to-vein-process'
- to give transparency of quality processes for the Health Insurance system

Competition in costs and client services effectivity between blood establishments

- e.g. Public versus Private, Germany

Improved resource management for R&D



“HUMAN SUBSTANCES”

(Substances of Human Origin – SoHO)

- **Blood and blood components**
- **Tissues and Cells**
- **Organs**



Directorate-General for
Health & Consumers

EU legislation – substances of human origin

- **Blood Directive (2002/98/EC)**
 - 3 Implementing Directives (2004/33/EC, 2005/61/EC, 2005/62/EC)
- **Tissues and Cells Directive (2004/23/EC)**
 - 2 Implementing Directives (2006/17/EC, 2006/86)
- **Directive on Organ Donation and Transplantation (May 2010)**
(Directive 2010/53/EC)



with kind permission from DG Sanco, EC

Directive 2002/98/EC and its technical annexes.

Article 2 (2005/62/EC). Good practice (GP) guidelines shall be developed by the Commission, .. the Commission shall take fully into account the detailed principles and guidelines of good manufacturing practice (GMP), as referred to in Article 47 of Directive 2001/83/EC.

Directive 2016/1214 – GP Guidelines

Based on Sept. 2013: GP guidelines have been developed by the Council of Europe in discussion with the EC. **TS066 – Appendix 1 ,Elements of Good Practice Guidelines for Blood Establishments and Hospital Blood Banks’ – 18th Ed. CoE**

COMMISSION DIRECTIVE (EU) 2016/1214

of 25 July 2016

amending Directive 2005/62/EC as regards quality system standards and specifications for blood establishments

(Text with EEA relevance)



Blood Regulatory Framework

SOURCE

Collection and testing of human blood and blood components whatever their intended purpose (including starting materials for medicinal products)

Blood Directive

PROCESSING

Processing, Storage and
Distribution

When intended for transfusion

Blood Directive

Proprietary industrially-prepared
medicinal products derived from
human blood or plasma

**Directive 2001/83/EC Community
Code relating to Medicinal
Products for human use**

Legal Framework – Blood and Pharma legislation

Expected and experienced interactions



Directive 2002/98/EC
Directive 2004/23/EC

Directive 2001/83/EC

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COMMISSION DIRECTIVE 2005/62/EC**of 30 September 2005****implementing Directive 2002/98/EC of the European Parliament and of the Council as regards
Community standards and specifications relating to a quality system for blood establishments****1 General Principles****2 Personnel and Organisation****3 Premises****4 Equipment and Materials****5 Documentation****6 Blood collection, testing and Storage****6.1 Donor eligibility****6.2 Collection of blood and blood components****6.3 Laboratory testing****6.4 Processing and validation****6.5 Labelling****6.6 Release of blood and blood components****7 Storage****8 Contract Management****9 Non-Conformance****9.1 Deviations****9.2 Complaints****9.3 Recall****9.4 Corrective and preventive actions (CAPAs)****10 Self-inspection, audits and improvements**

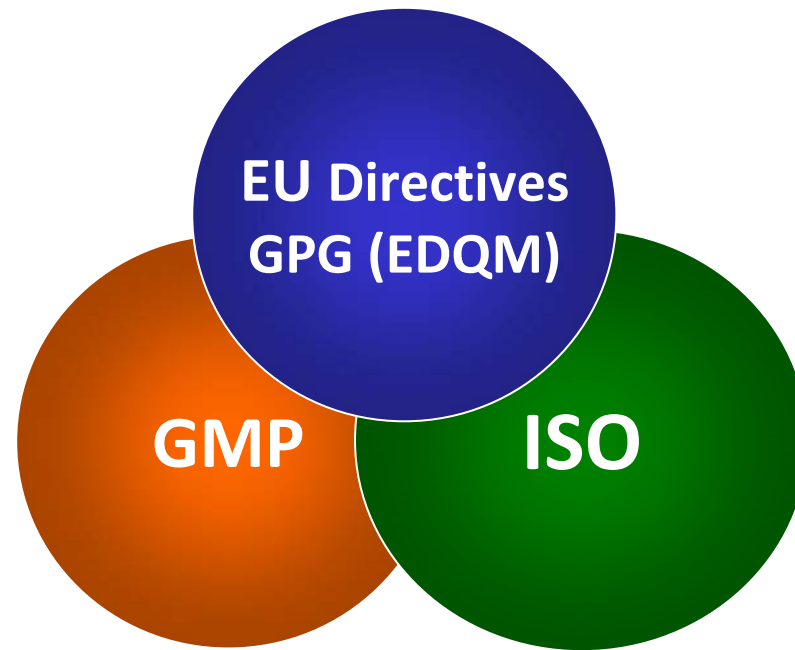
Legal Framework – Substances of Human Origin

Blood components, tissues and cells

- **Supervision of SoHO components collection/procurement, testing, processing, storage and distribution**
- **Designation, authorisation, accreditation or licensing of blood/tissue establishments**
- **Inspection and control measures**
- **Quality systems**
- **Traceability**
- **Notification of Serious Adverse Events and Reactions (SAE/SAR)**

,The tools to reach the best level'

Interaction of International (GMP, ISO) and Regional (EU Directive, GP Guideline) Standards



No Contradiction but Supplementation

Main Objectives

Quality/Safety of Blood/Blood Components
and Optimal Supply/Use
(Quality Policy / Aims)

Quality Manual (QM)
Licensing/Authorisation

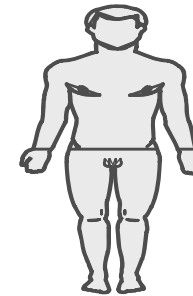
Site-Master File

Operating Procedures
(SOPs, Documentation, etc.)

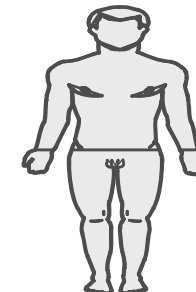
Competence of staff
(Education, Training, Re-Qualification)



Donor Management



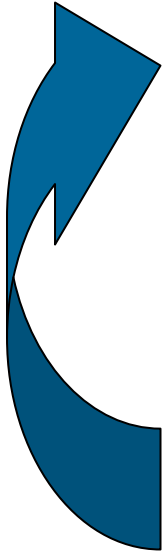
Patient



Donor

Quality Manual (QM)

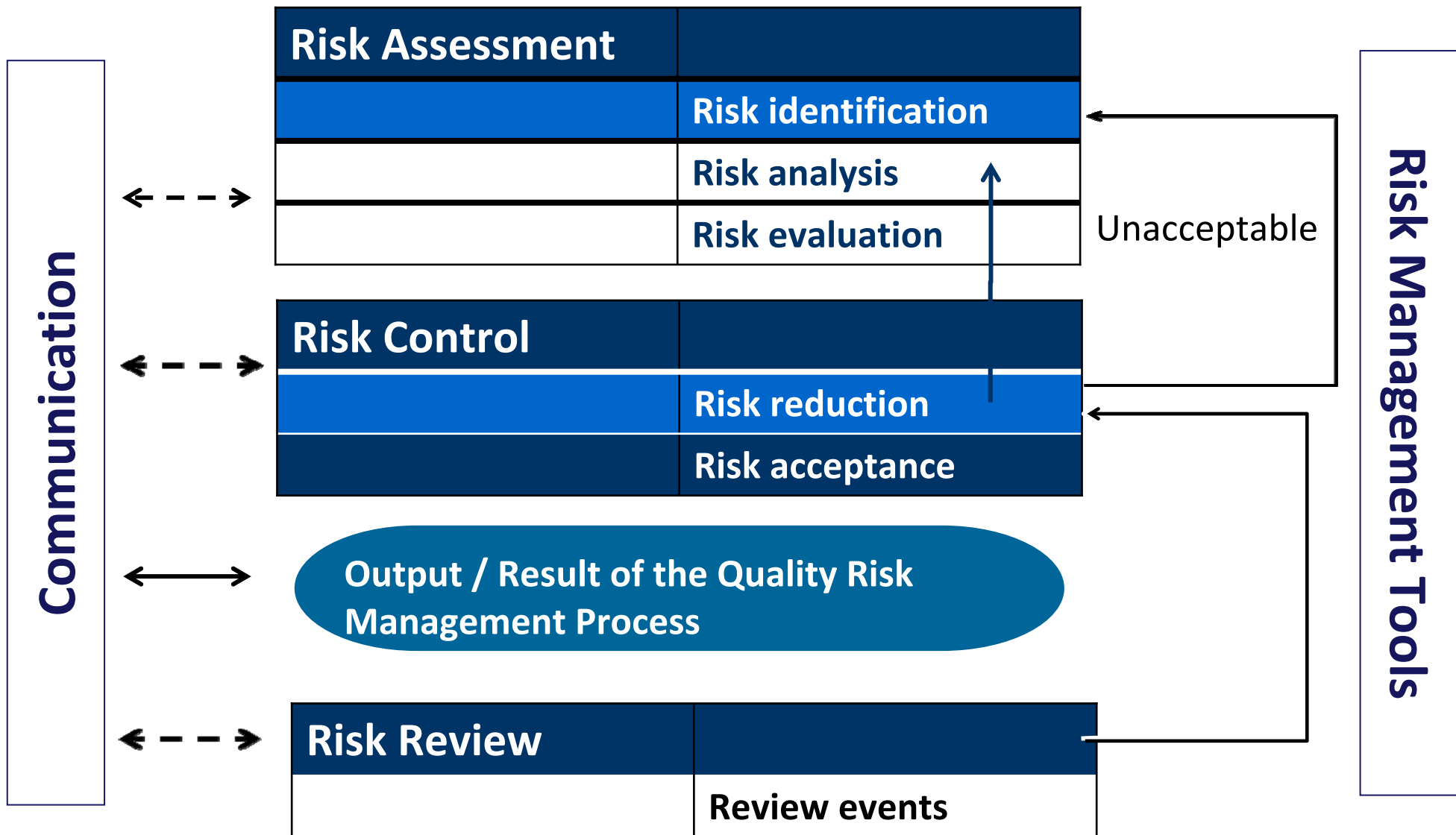
Objective to define the overall function (level Director/Department)

- 
- **Quality Policy**
 - **Regulatory Framework** (e.g GMP)
 - **General Overview of all Processes/Activities**
(Licensing/Authorisation, etc.)
 - **Risk Assessment / Risk Management Guidelines**
 - **Organigramm**
 - **Number of Staff and Level of Qualification**
 - **Job description**
 - **Staff Responsibility and Operational Function**
 - **Facility and Equipment Management**



Management Review

Quality Risk Management Process





Identified Areas/Activities for improvements (I)

ISBT-WP-QM survey/database

Level 1

Personnel and organisation

- Quality policy
- Organigrams and responsibility of staff
- Job descriptions (qualification / re-qualification)

Documentation

- SOP system / Change control of documents
- Continous training of SOPs (documents)

Level 1

Self-Inspection / Continous Improvements

Non-Conformance / Risk-Management

- Deviations
- Complains
- Recall
- Corrective and preventice action



Identified Areas/Activities for improvements (I)

ISBT-WP-QM survey/database

Level 2

Premises

- Donor area, collection area
- processing and testing, storage

Laboratory testing

Processing and validation

Storage and distribution

Assessment of Areas/Activities for improvements

EuBIS guide - content www.eubis-europe.eu

Provides:

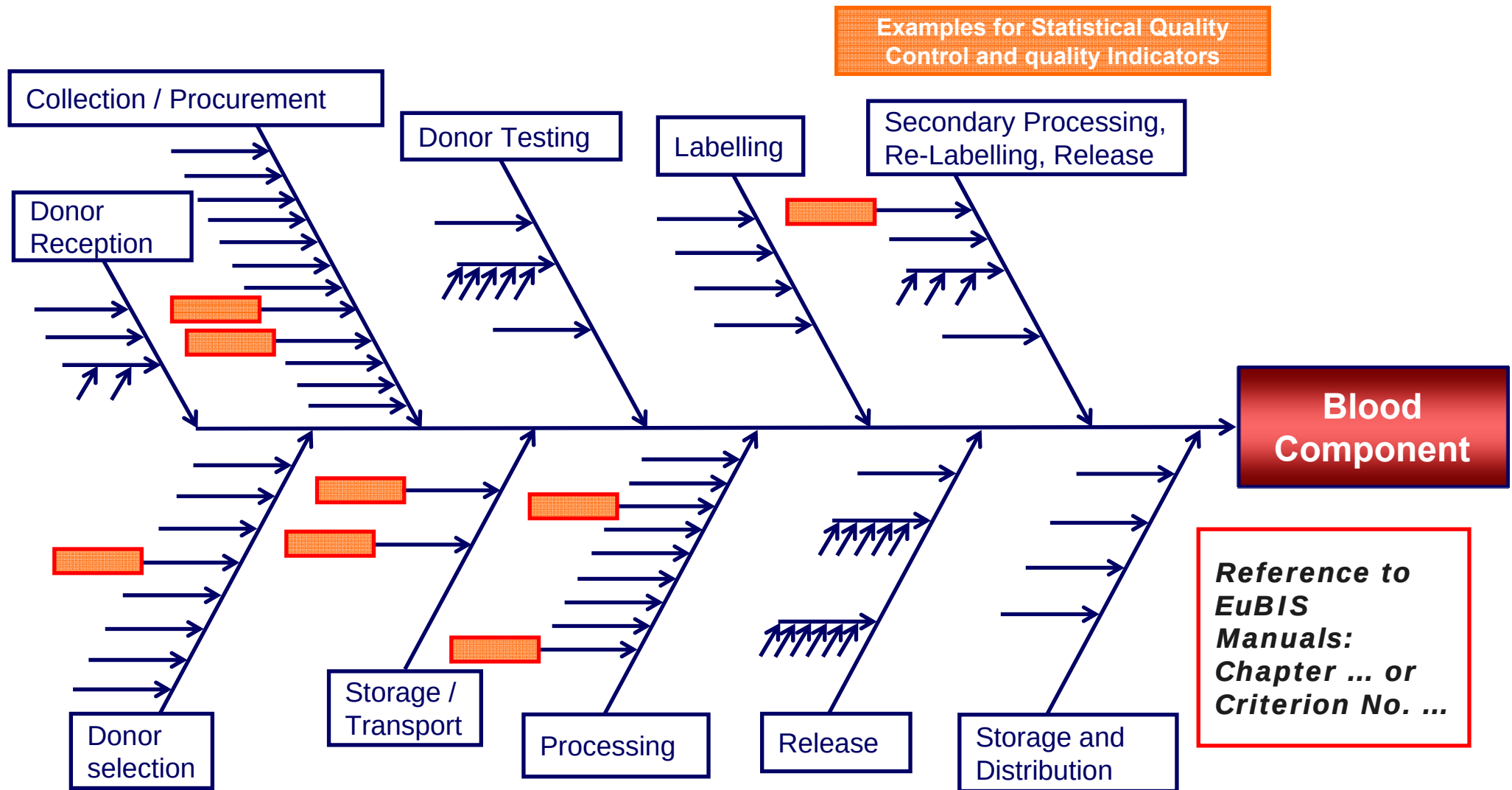
- Critical control points in processes / procedures
 - Example evidence to confirm conformance
- Cross references to audit/inspection standards defined by:
 - EU Blood Directives
 - International: GMP, EDQM (CoE), PIC/S
- Document templates
 - Self inspection record / audit trail.
 - Self inspection summary report

Assessment of Areas/Activities for improvements

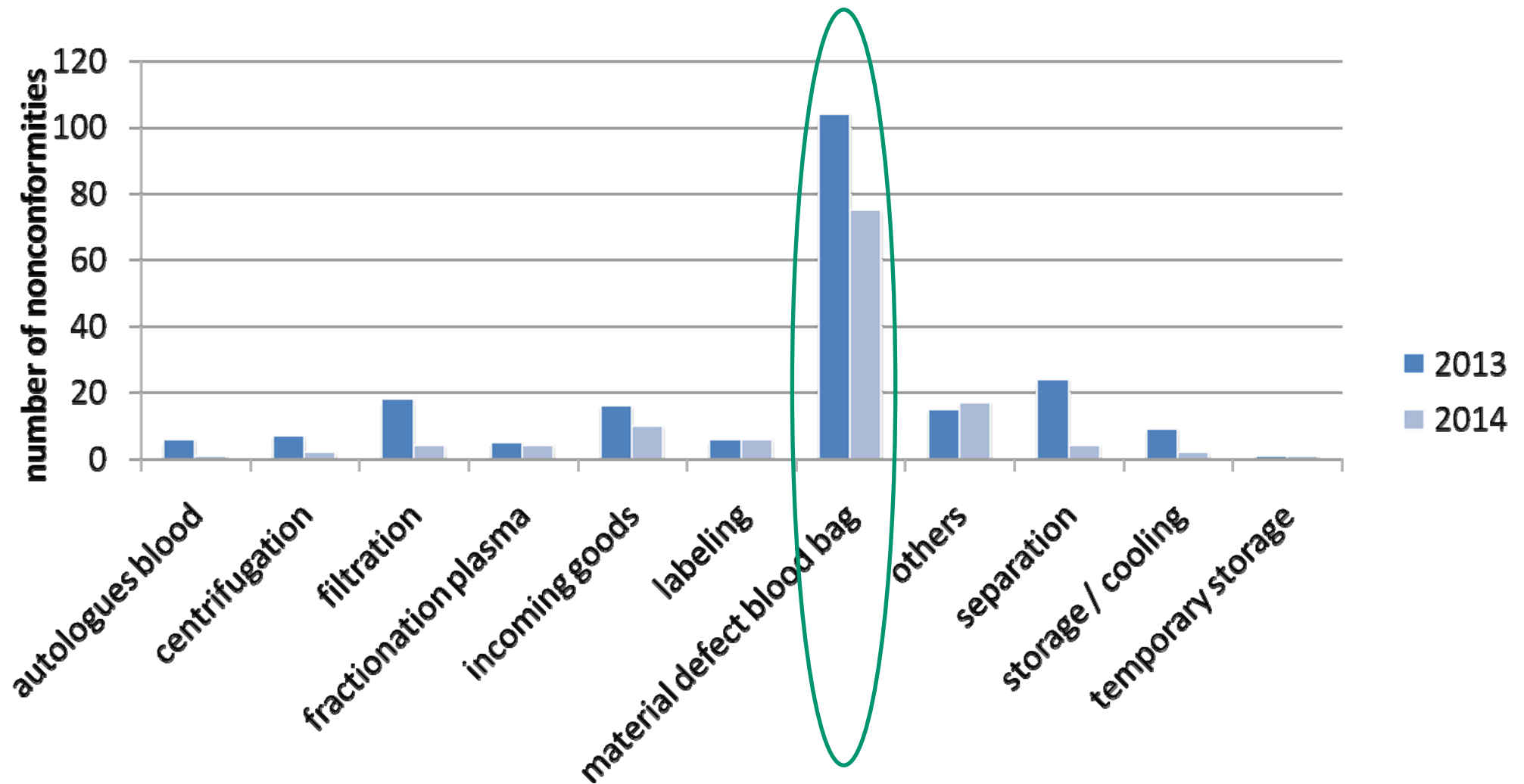
Quality Risk Management

- **Tool for Systematic Risk Assessment on Quality and Safety of SoHO:**
to detect critical steps → “Fishbone-Diagram”
(Ishikawa-Diagram)
- **Specification of Quality Indicators**

Systematic Risk Assessment to detect critical steps → “Fishbone-Diagram

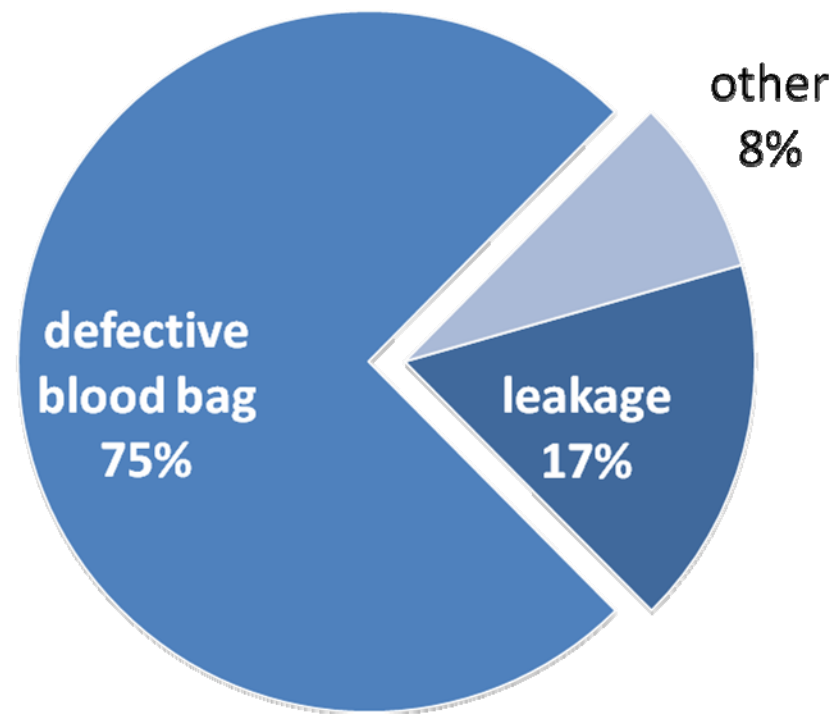


Nonconformities processing 2013 - 2014



Nonconformities materiovigilance 2014

■ leakage ■ defective blood bag ■ other



Quality controls – Tissue and cells

Quality controls related to therapeutic application:

- **Volume** (via weight, Hct corrected)
- **Cells Count:** CD34+ content, T cells content, frequency of MNC
- RBC-content in ml (via Hct and volume), total WBC

SoHO: allogeneic blood stem cells transplantation (aBSCT)

principle: cellular Immune therapy

aBSCT graft

$>2 \times 10^6$ CD34+
kg/BW

HLA-identical

(HLA-A,B,C,DRB1,DQB1- 10/10 Antigens)

GvL – Effect

Conditioning:

High-Dose
Chemotherapy

GvHD-Propylaxe, and - Treatment

Aplasia
11-21 Days

Immunological
Reconstitution:

several years after aBSCT

Immuno-depletion of stem cell grafts

Indications:

- Limiting GvHD in case of non HLA matched donors/grafts
- Intolerance/side-effects to immuno suppression therapeutics

Starting material:

Peripheral blood stem cells (PBSCs) w/apheresis

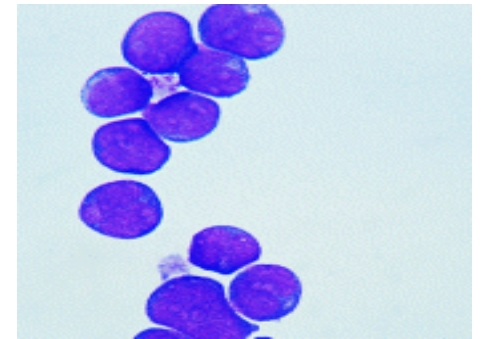
Preparation technique:

Immuno magnetic **stem cell (CD34+) enrichment, T-/B-cell depletion**

Immunomagnetic CD 34+ Selection



CliniMACS
Magnetic Separator

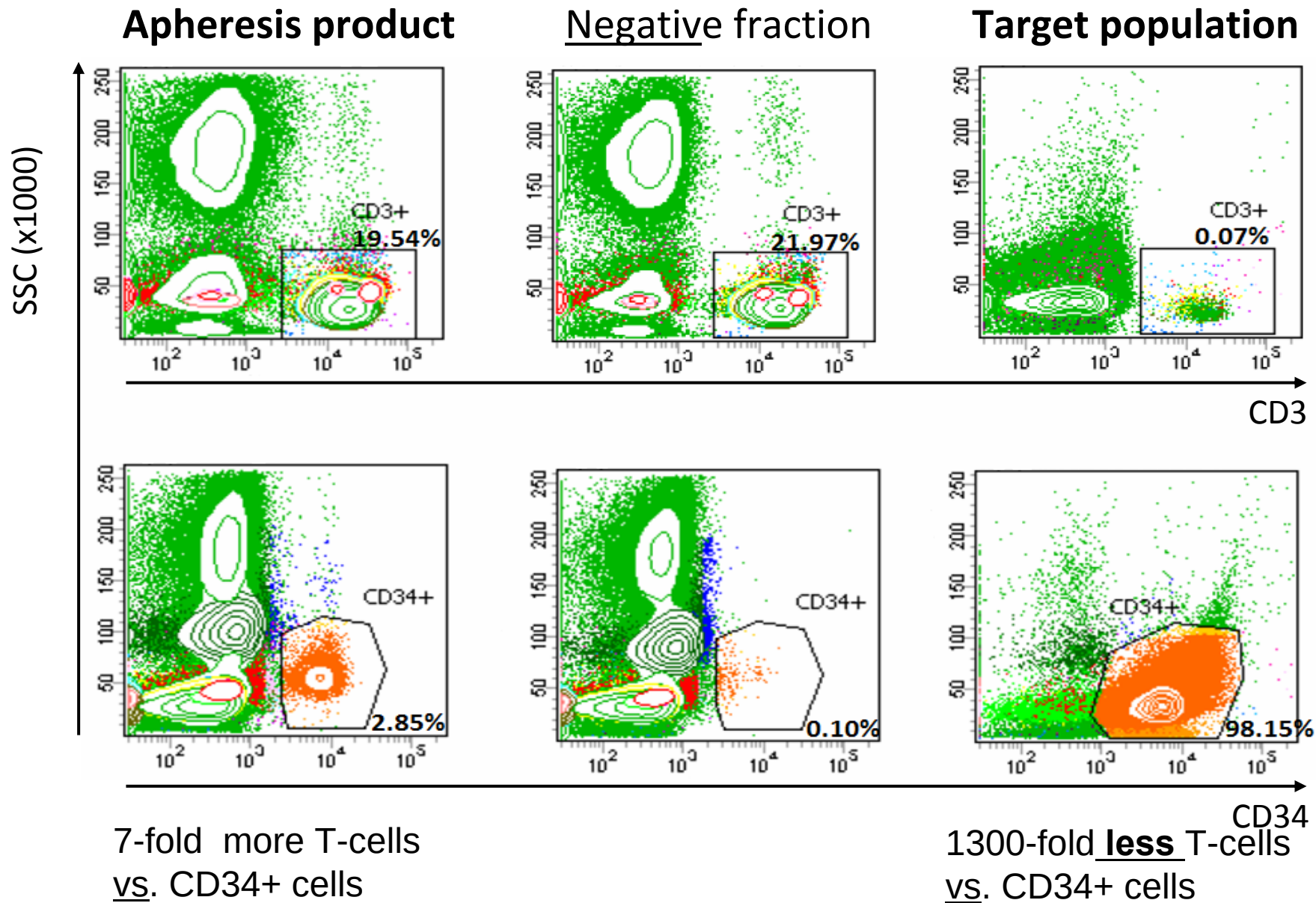


CD34+
positive
cells



MACS Microbeads on the
cells surface

FACS analysis of a selection process



Immuno-depletion of stem cell grafts

Quality control parameters:

- Purity, Stem cell dose, T-cell content,
- no bacterial contamination
- IDM negative following license specification.

Quality parameters - CD34-selected PBSCs:

10-80 ml/Bag , 1-2 bags per therapeutic dose

CD34+ Dose: $>4 \times 10^6/\text{kg}$ in 90% of preparations,

Purity: $>90\%$ in 90% of preparation;

MNC $>50\%$;

CD3+ Dose: $<5 \times 10^4/\text{kg}$ of the recipient (patient) in 90% of preparations

Concentration $<6 \times 10^8/\text{ml}$;

Viability $>95\%$ in 90% of preparations;

Sterility: no bacterial growth, IDM negative

In case of freeze storage: Viability of CD35+ cells after thawing must be $>70\%$ with dye exclusion (mostly 7AAD by FACS)

Assessment of risk / processes

Tissues and cells:

- Quality control required in 100% / all preparations**
- Quality indicators for processes – in particular ,open‘ preparations**
- Clean room often mandatory**
- Results of infectious disease markers (IDMs) extended
(CMV, EBV, Toxoplasma, WNV, HTLV, ...**
- Results of Bacterial Contamination after releases**

EuBIS - Quality Management and Inspection (www.eubis-europe.eu)

more than 530 institutions from 70 countries



The screenshot shows the EuBIS website homepage. On the left is a red sidebar menu with links: HOME, OBJECTIVES, CONTACT, NEWS, PROJECT MANAGEMENT, WORKING GROUPS, PARTICIPANTS, WORK IN PROGRESS, DOCUMENTS, PUBLICATIONS, LINKS, BLOOD MANUAL (with sub-links: EuBIS Manual, EuBIS Training, EU-Q-Blood-SOP Manual, Ordering Information), and MEMBERS AREA. The main content area has a header with the EuBIS logo and the text 'Quality Management and Inspection of Blood Establishments'. Below this is a section titled 'European Project addressing the safety of blood transfusion' with a sub-header 'EuBIS Common Criteria for the Inspection of Blood Establishments (Manual)'. It features an image of the manual cover and a 'View manual as eBook' button. To the right, there is a section for 'Manuals for Circulation', 'News Publications', and 'Meetings and Courses'. At the bottom, there is a list of countries under the heading 'Europe'.

Free copies as PDF

- Eu-Blood-SOP
- EuBIS Manual
- EuBIS Inspection guide

Europe

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Latvia
Lithuania
Luxembourg
Poland
Portugal
Romania
Slovak Republic
Spain
United Kingdom
• England
• Scotland

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Acknowledgment

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Thank you for your attention

on behalf of all members of the ISBT Working Party on QM

