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

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Pilars - Levels of quality management

External - Third party collection center

Blood
Cells
Tissue

Donor

Patient

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

Therapeutic Interventions
- Surgery
- Intensive care
- Traumatology and emergency care
- Hematology and Oncology
- Transplantation medicine
- Pediatrics
- Gynaecology
- Urology
The 5C 'Pilars' of Quality Management

- Competence
- Complexity
- Continuity
- Components
- Competition
Competence in Transfusion Medicine

Blood Establishment

Customer
- Patient
- Blood Collection (Donor)
- Laboratory
  - Clinical Diagnostics / BC Quality Control
- Special Components
  - Therapeutic Intervention
- Blood Component Production and Testing

Customer
- Hospital (Physician / Patient)
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

Bar chart showing percentages of GMP, ISO standards, CoE, GLP, national standards/guidelines, and WHO standards and guidelines used by blood establishments. ISO certification or accreditation is in process for CoE. ISO certified or accredited for GMP and ISO standards, GMP ISO certified or accredited for GLP, and national standards/guidelines are in process.
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:

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular (erythrocyte and/or platelet concentrates)</td>
<td>100%</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>100%</td>
</tr>
</tbody>
</table>

#### Related preparations:

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>25%</td>
</tr>
<tr>
<td>Blood stem cells</td>
<td>44%</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>48%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>36%</td>
</tr>
</tbody>
</table>

#### Source plasma for fractionation

<table>
<thead>
<tr>
<th>Source Plasma</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source plasma</td>
<td>57%</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>60%</td>
</tr>
</tbody>
</table>

#### Autologous blood components

<table>
<thead>
<tr>
<th>Components</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous blood</td>
<td>84%</td>
</tr>
</tbody>
</table>
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 effectiveness 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
EU legislation – substances of human origin


  - 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

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.


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

with kind permission from Th. Bregeon, DG Sanco, European Commission
Legal Framework – Blood and Pharma legislation

Expected and experienced interactions

Directive 2002/98/EC
Directive 2004/23/EC
Directive 2001/83/EC

modified with kind permission from DG Santo, European Commission
COMMISSION DIRECTIVE 2005/62/EC
of 30 September 2005

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

Risk Assessment
- Risk identification
- Risk analysis
- Risk evaluation

Risk Control
- Risk reduction
- Risk acceptance

Output / Result of the Quality Risk Management Process

Risk Review
- Review events

Risk Management Tools

Communication
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
• Continuous training of SOPs (documents)

Level 1 Self-Inspection / Continuous Improvements

Non-Conformance / Risk-Management
• Deviations
• Complains
• Recall
• Corrective and preventive action
Level 2

**Identified Areas/Activities for improvements (I)**

**ISBT-WP-QM survey/database**

**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

Donor selection

Storage / Transport

Donor Testing

Labelling

Secondary Processing, Re-Labelling, Release

Processing

Release

Storage and Distribution

Collection / Procurement

Donor Reception

Blood Component

Examples for Statistical Quality Control and quality Indicators

Reference to EuBIS Manuals: Chapter ... or Criterion No. ...
Nonconformities materiovigilance 2014

- Defective blood bag: 75%
- Leakage: 17%
- Other: 8%
Quality controls – Tissue and cells

Quality controls related to therapeutic application:

• **Volume** (via weight, Hct corrected)

• **Cells Count:** CD34+ content, T cells content, frequence 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 x 10^6 CD34+ kg/BW

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

GvL – Effect

Conditioning:
High-Dose Chemotherapy

GvHD-Prophylaxe, 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

MACS Microbeads on the cells surface

CD34+ positive cells
FACS analysis of a selection process

Apheresis product | Negative fraction | Target population

7-fold more T-cells vs. CD34+ cells

1300-fold less T-cells vs. CD34+ cells

Spohn et al. 2015
Immuno-depletion of stem cell grafts

Quality control parameters:
• Puritiy, Stem cell dosis, 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+ Dosis: >4x10e6/kg in 90% of preparations,
Purity: >90% in 90% of preparation;
MNC >50%;
CD3+ Dosis: <5x10e4/kg of the recipient (patient) in 90% of preparations
Concentration <6x10e8/ml;
Viabilität >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

Free copies as PDF
• Eu-Blood-SOP
• EuBIS Manual
• EuBIS Inspection guide

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• Scotland

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Algeria
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Armenia
Brazil
Bosnia
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Croatia
Columbia
Cuba
Egypt
Georgia
Guatemala
Hong Kong
India
Israel
Indonesia
Korea
Montenegro
Nigeria

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Turkey
Sri Lanka
USA
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Survey – ISBT –WP-QM participants

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www.equal-blood.eu / eubis-europe.eu / catie-europe.eu

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