Session (Monday): Quality Management

Self-Inspection and Audits based on GMP and GPG preparing for regulatory Inspections – The EuBIS experience.

Prof. Dr Christian Seidl
Red Cross Blood Donor Service Baden-Wurttemberg - Hessen (Germany)
Structure of a quality management system

- Regulations / Laws
- Quality Manual (Site Master File)
- General/Operating Procedures (GP / OP)
  - Guidelines on Document Change Control (GP/OP)
  - Guidelines on Personnel Training (GP/OP)
- Standard Operating Procedures (SOP)
- Records (RP)

Regulations / Law - Legal Requirements and Guidelines

- **National Legal Frame** (e.g. Directives, regulations, laws) plus national guidelines and standards

- Eudralex, *EU-GMP Good Manufacturing Practice*
- EDQM (European Directorate for the Quality of Medicines & HealthCare) *Good Practice Guidelines for Elements of the Quality System – (GPG)*
- CoE (Council of Europe) *Guide to Preparation, Use and Quality Assurance of Blood Components*

- WHO GMP standards and technical reports
- PIC/S (Pharmaceutical Inspection Co-operation Scheme) *Guide for Blood Establishments*
- ISO (International Standards Organisation) *ISO 9001 standards*
Legal Framework – Substances of Human Origin (SoHO) Blood components, tissues and cells

• Designation, authorisation, accreditation or licensing of blood/tissue establishments

• Supervision of SoHO components collection/procurement, testing, processing, storage and distribution

• Quality management systems

• Inspection and control measures

• Traceability

• Notification of Serious Adverse Events and Reactions (SAE/SAR)
Inspection and control measures

**Regulatory Inspection - by competent authority (CA)**

- Accreditation Body
- Third Party Manufacturer

**Self-Inspection ( = Audit/Self-Assessment )**

Monitor your Quality Management System if it is in-line with the quality policy and legal requirements and standards (preparing for the regulatory inspection or 'other')
Legal Framework – Blood and Pharma legislation
Expected and experienced interactions

Directive 2002/98/EC

Directive 2001/83/EC

modified with kind permission from DG Sanco, European Commission
Common standards and practices for inspection of blood establishments

Reference: EuBIS Manual

Self-Inspection – Chapter 5

Regulatory Inspection - Chapter 6

Inspection Guide w/cross references to GMP, GPG, PIC/S and EU directives
The EuBIS manual

**Manual content**

- **Common standards and criteria for performing inspections**
  (e.g. inspection team, qualification of inspectors, type of inspection, classification of non-compliances (NCs))

- **Frame-work documents:**
  - Site-Master-File for blood establishments
  - Inspection report
The EuBIS guide

Guide content

- Quality management criteria following critical process steps with cross references to
  - Blood Directives, D2016/1214 -GPG (Good Practice Guideline)
  - Common standards: GMP, PIC/S, EDQM (CoE) guide

- Inspection criterion description
- Example evidence to be given during inspection
- Self-Inspection Record / Audit Trail
SIII-Q11-1: Please indicate by whom has your blood establishment been inspected and/or audited:

Non-Government Authority (Audit)

- ISO (32%)
- AABB (US), EFI, JACIE
### Levels for quality improvements in blood transfusion services

**ISBT - Working Party on Quality Management - Survey on quality management and inspections**

<table>
<thead>
<tr>
<th>Quality area/sector</th>
<th>Minor (%)</th>
<th>Medium/Major (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel and organisation</td>
<td>33,3</td>
<td>53,3</td>
</tr>
<tr>
<td>Quality policy</td>
<td>24,1</td>
<td>44,8</td>
</tr>
<tr>
<td>Organigrams and responsibility of staff</td>
<td>41,4</td>
<td>34,5</td>
</tr>
<tr>
<td>Job description (qualification/re-qualification)</td>
<td>34,5</td>
<td>31,1</td>
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<tr>
<td><strong>Documentation</strong></td>
<td></td>
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</tr>
<tr>
<td>SOP system / Change control of documents</td>
<td>37,9</td>
<td>41,4</td>
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<tr>
<td>Continuous training of SOPs (documents)</td>
<td>50,0</td>
<td>36,7</td>
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<tr>
<td><strong>Self-Inspection / Continuous Improvements</strong></td>
<td>26,7</td>
<td>46,7</td>
</tr>
<tr>
<td><strong>Non-Conformance:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deviations</td>
<td>39,3</td>
<td>39,3</td>
</tr>
<tr>
<td>Complains</td>
<td>35,7</td>
<td>39,3</td>
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<tr>
<td>Recall</td>
<td>32,1</td>
<td>35,7</td>
</tr>
<tr>
<td>Corrective and preventive action</td>
<td>35,7</td>
<td>46,4</td>
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<tr>
<td><strong>Premises</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor area, collection area,</td>
<td>46,4</td>
<td>25,0</td>
</tr>
<tr>
<td>Processing and testing,</td>
<td>32,1</td>
<td>39,3</td>
</tr>
<tr>
<td>Storage</td>
<td>40,7</td>
<td>33,3</td>
</tr>
<tr>
<td><strong>Storage and distribution</strong></td>
<td>50,0</td>
<td>25,0</td>
</tr>
<tr>
<td><strong>Processing and validation</strong></td>
<td>33,3</td>
<td>33,3</td>
</tr>
<tr>
<td><strong>Laboratory testing</strong></td>
<td>40,0</td>
<td>20,0</td>
</tr>
</tbody>
</table>

Vuk T et al, submitted, Vox Sanguinis Science, 2017
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**

**Premises**
- Donor area, collection area
- Processing and testing, storage

- *(Infrastructure) – Third Developing Countries*
  e.g. electricity

**Storage and distribution**

**Processing and validation**

**Laboratory testing**
Assessment of Areas/Activities for improvements

covering all activities and processes of a BE (Chapter 3 – EuBIS guide)

3.1 Licensing requirements and General Principles QS/QA
3.2 Personnel and Organisation
3.3 Premises
3.3.1 Collection
3.3.2 Testing and processing
3.3.3 Storage,
3.3.4 Waste disposal
3.4 Equipment and Materials
3.5 Blood collection, testing and processing
3.5.1 Donor eligibility
3.5.2 Collection of blood and blood components
3.5.3 Laboratory testing
3.5.4 Processing and validation
3.5.5 Labelling
3.5.6 Release of blood and blood components
3.6 Storage and distribution (Cold chain)
3.7 Contract Management
3.8 Non-Conformance
3.8.1 Deviations
3.8.2 Complains
3.8.3 Recall
3.8.4 Corrective and preventive actions (CAPA)
3.9 Self-inspection, audits and improvements
3.10 Traceability and SAE / SAR
3.11 Information Technology (IT)
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, GPG
  – International: GMP, EDQM (CoE), PIC/S
• Document templates
  – Self inspection record / audit trail.
  – Self inspection summary report
Inspection classification

- Routine Inspection
- System-Inspection
- Product/process related inspection
- Event related inspection
Self-Inspection Plan covering all activities*

- Donor Recruitment
- Testing
- Processing
- Storage
- Distribution
- Including Staff qualification/requalification,
- Equipment, Facilities,
- Material and Supply
- Subcontractors (Audits)

*Annually – every 12 month or based on risk analysis every 24 month
Inspections of blood establishments

**Inspection Team** - for setting up an inspection

- **Lead Inspector**
- **Technical expert**
- **Trained inspectors**
- **Trainee inspector**
Inspections of blood establishments

Qualification and experience of inspector

Inspectors should have an academic background in the field of biological science or medicine and should have work experience in a blood establishment or hospital blood bank.

The education and training of inspectors requires a documented training programme for these personnel.
Inspections of blood establishments

Training of inspectors

The training of self-inspectors should include detailed knowledge of the quality management system in place and the organisational requirements of the inspection system.

- e.g. report forms, inspection checklists
Qualification and experience of inspectors

This will include knowledge of:
• national and international regulations and standards including the blood legislation.
• structure and organisation of the blood service including differences and commonalities if different locations are used.
• processes of collecting, manufacturing, testing, storage and distribution of blood and blood components.
• principles of issuing and therapeutic use of blood and blood components.
• principles of good laboratory procedures (GLP),
• principles of good manufacturing procedures (GMP), and
• principles of good practice guideline (GPG).
Planning for an inspection

Before the inspection

During the inspection

After the inspection
Before the inspection

QM shall inform in advance the Department about:

- the objectives and scope of the inspection
- the date and time of the inspection
- the inspection team members and their respective roles
- the blood establishment staff whose presence is required during the inspection
- the expected time and duration for each major inspection activity (premises, processes, etc.)
- the time table for the opening and final meetings, and
- the approximate time frame for the transmission of the written inspection report.

During the inspection

General system evaluation

Technical and process evaluation

Both types of inspections include the identification of critical elements giving proof for the overall quality of the blood establishment.
During the inspection

The inspection process can be divided into two phases:

**System related inspection**
- job descriptions and the role of the Responsible Person
- training of staff
- maintenance (e.g. change control) of standard operating procedures (SOPs)
- validation (processes)
- qualification (equipment, facilities)
- purchases
- subcontractor or third party contracting (if applicable)
- internal auditing system / self-inspection procedure
- quality control (e.g. results of random sampling analysis)
- donor selection criteria
- testing
- management of complaints, non-conformities, recalls, etc.

**Process/product related inspection**
- the donor management system (e.g. donor registration)
- traceability of each individual unit of blood or blood component from the donor to its final destination (e.g. donor identification, labelling)
- specific standard operating procedures (SOPs) related to the particular process being inspected
- documentation including relevant records, print-outs or electronic data handling
- hygiene and cleaning procedures
- environmental monitoring (e.g. waste, particular measurements for classified production rooms)
- equipment maintenance (e.g. log-book)
- quality control data, starting materials, intermediates and finished components
- relevant quality control measurements to safeguard the product specifications
- release procedures
- storage and distribution.

### 3.1 Licensing requirements

<table>
<thead>
<tr>
<th>Scope:</th>
<th>Licensing requirements</th>
<th>EuBIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LR 001</strong>&lt;br&gt;2002/98/EC Article 5 – Licensing and authorisation&lt;br&gt;Article 11. Quality system for blood</td>
<td>Licensing requirements</td>
<td>GMP Annex 14&lt;br&gt;PIC/S Chap. 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Inspection criterion description</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Blood Establishment has submitted the information listed in Annex I (2002/98/EC) to the Competent Authority.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Competent Authority has verified that the blood establishment complies with the requirements of Directive 2002/98/EC and indicated which activities it may undertake and which conditions apply.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Example evidence</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Manufacturers license and whole sale distribution license as appropriate to the activity profile assigned by the Competent Authority</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• N.B. For those blood establishments that follow the requirements defined by 2001/83/EC, individual product licenses are required.</td>
</tr>
</tbody>
</table>
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

Communication

Risk Management Tools

Unacceptable
**Classification of non-compliances (NCs)**

- **Critical NCs**
- **Major NCs**
- **Minor NCs**
- **Observation**

**An inadequacy in a system or process that is not a failure to comply with standard.**

**A serious NCs in a process or a written procedure which directly affects the safety of the donor or patient.**

**A NCs in a system or process or there is insufficient information to classify it as a major or critical.**

*Note: several observations can lead to a minor/major NC*
Inspection completion

After the inspection

- Official inspection report
- Auditee response to inspection report
- QMs response to Auditee
  - Corrective /preventive actions or measures
  - Follow up of corrective action
  - Scheduling new inspection
The Structure of Official Inspection Report

• The inspection scope and objectives of the audit.
• Details of the audit plan.
• Identification of the audit criteria against which the audit was conducted.
• Results (findings, NCs, observations).
• Evaluation of systematic aspects of the QMS.
• Proposals recommended for corrective actions and timeline for corrective action
• Responses made to these proposals and a follow-up time frame (if applicable).
• The dates of submission for any corrective actions
• Conclusions
ISBT Developing Country Award, Seminar and Training, NIHBT, ISBT WP-QM and EuBiS Academy, Hanoi, March 2017
• more than 530 institutions from 70 countries (www.eubis-europe.eu)

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

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Slovak Republic
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• Scotland

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10th EuBIS Seminar and Training
‘Good practices in blood components and medicinal products referring to GPG and GMP’
Quality management and inspection criteria for blood establishments and pharmaceutical products

24th – 26th of October 2018, Palermo, Italy

Final Programme
organised by the EuBIS Academy
in cooperation with the Centro Nazionale Sangue (CNS)
Acknowledgment

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- International Plasma Fractionation Association (IPFA)
- Western Province (WP) Blood Transfusion Service (South Africa)
- Belgian Red Cross (BRC)-Flanders (Belgium)
- IWK Health Centre, Halifax (Canada)
- Beijing Blood Center (China)
- National Institute of Transfusion Medicine - CITM (Croatia)
- National Blood Transfusion Services, Ministry of Health (MOH) (Egypt)
- National Blood Transfusion Services - EFS (France)
- German Red Cross Blood Transfusion Services - GRCBDS (Germany)
- National Blood Transfusion Service (Hungary)
- Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute (India)
- Indonesian Red Cross Blood Transfusion Services (Indonesia)
- Sanquin Blood Supply Foundation (The Netherlands)
- Regional Blood Centre (Romania)
- General Directorate of Health Services - GDHS (Turkey)
- Blood Transfusion Services BTS (United Arabic Emirates, UAE)
- American Red Cross - ARC (United States of America, USA)
- National Institute of Health - NIH (United States of America, USA)

Cooperating partners:
- EDQM - Council of Europe
- EBA - European Blood Alliance
- EuBIS - Academy
Acknowledgement EuBIS Academy members and collaborating organisations

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EU Commission / CHAFEA  
European Blood Alliance (EBA)  
Turkish Red Crescent and Ministry of Health  
Saudi Society for Transfusion Medicine (SASTM)
Thank you for your attention

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