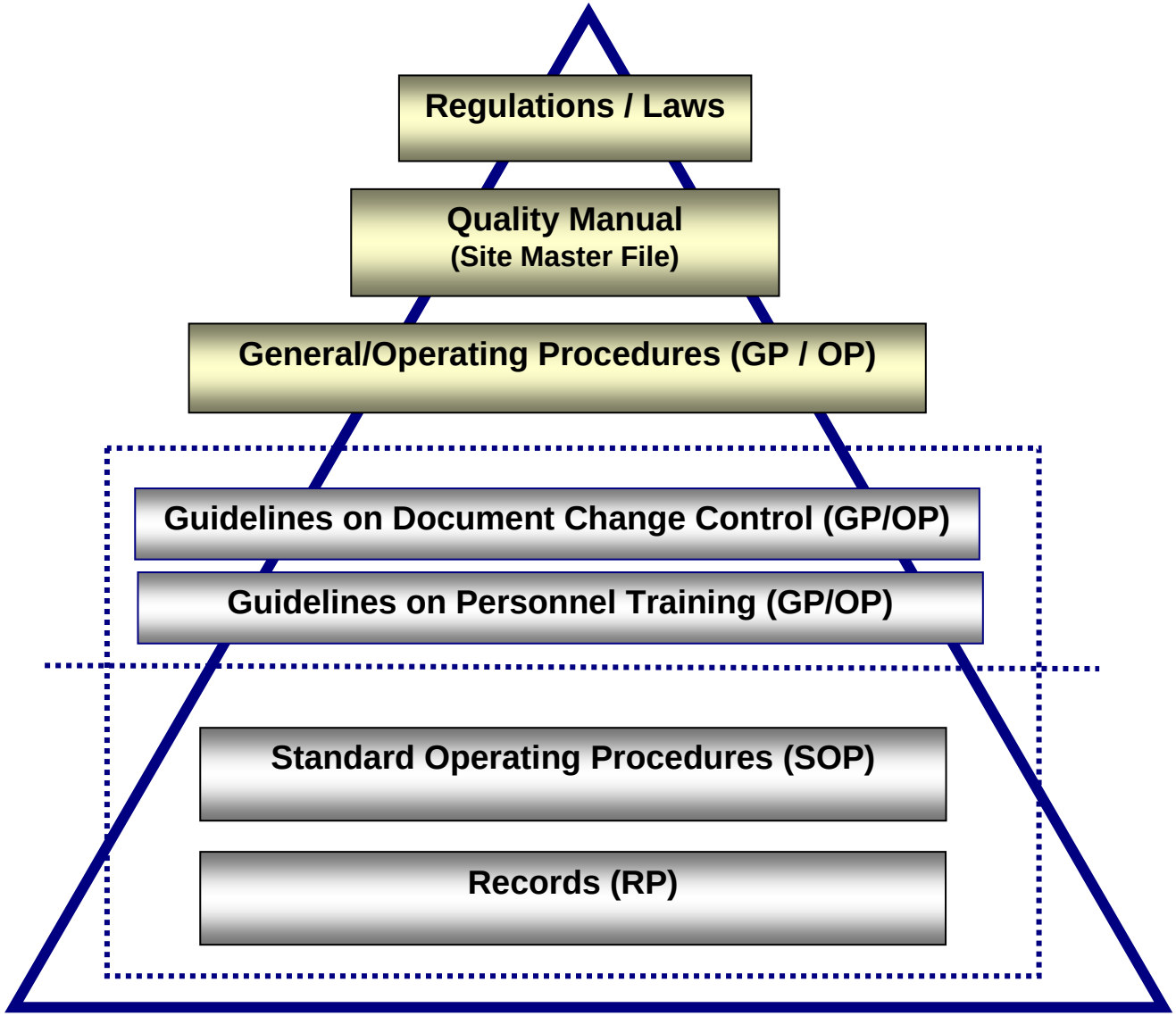
Session (Monday): Quality Management

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)

ISBT International Society of Blood Transfusion Working Party on Quality Management

Structure of a quality management system



Manual, EU-Blood-SOP project, www.eubis-europe.eu

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*

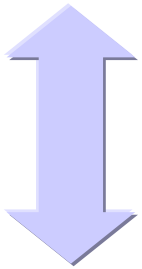
- WHO *GMP standards and technical reports*
- PIC/S (Pharmaceutical Inspection Co-operation Scheme) *Guide for Blood Establishments*
- ISO (International Standards Organisation) *ISO 9001 standards*

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)



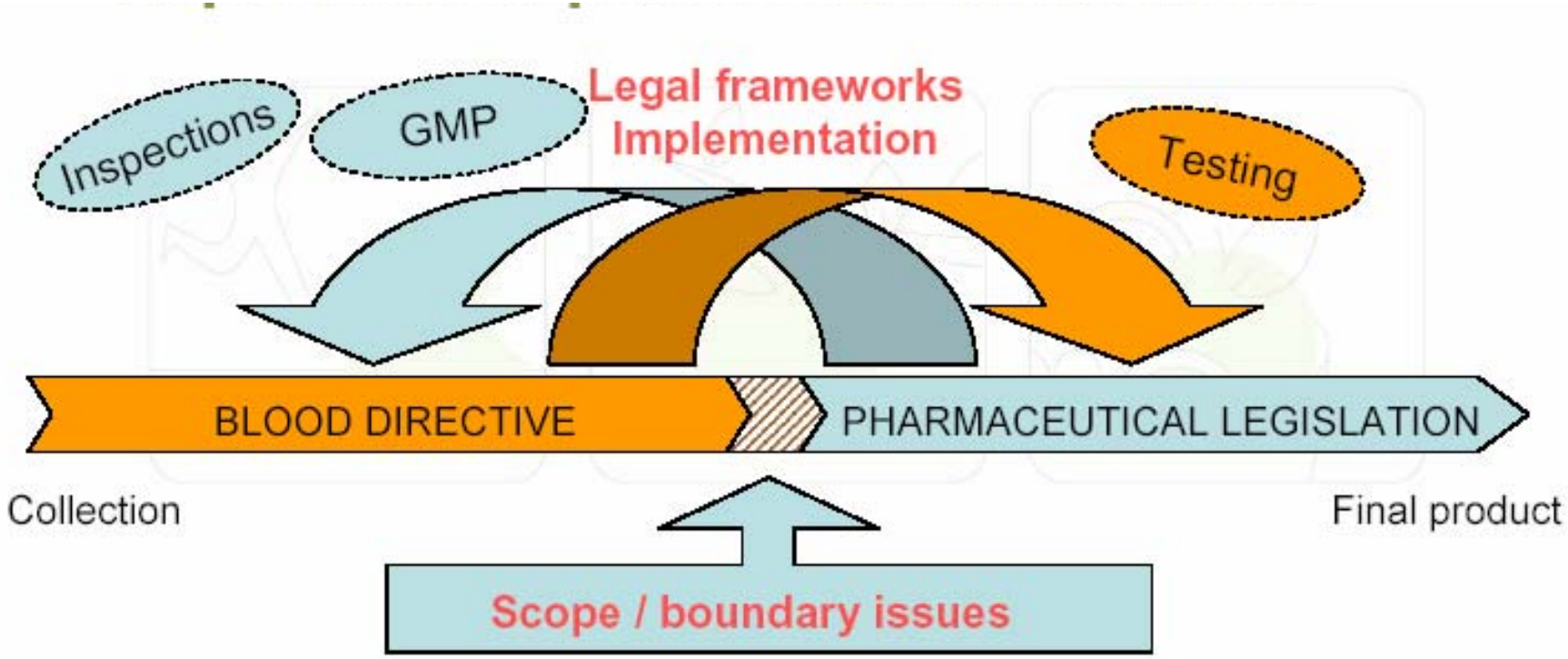
or ‚other'

- Accreditation Body
- Third Party Manufacturer

Self-Inspection (= Audit/Self-Assessment)

Monitore 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

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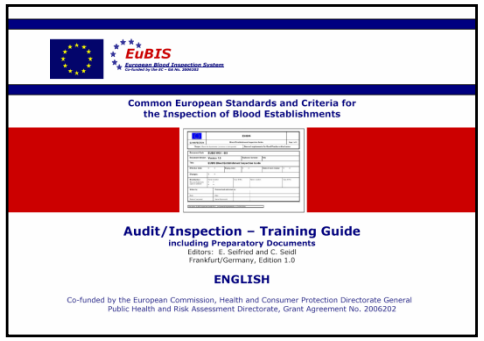
Common standards and practices for inspection of blood establishments

Reference: EuBIS Manual

Self-Inspection – Chapter 5

Regulatory Inspection - Chapter 6

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



EuBIS
European Blood Inspection System
Co-funded by the EC – GA No. 2006202

Inspections of blood establishments

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

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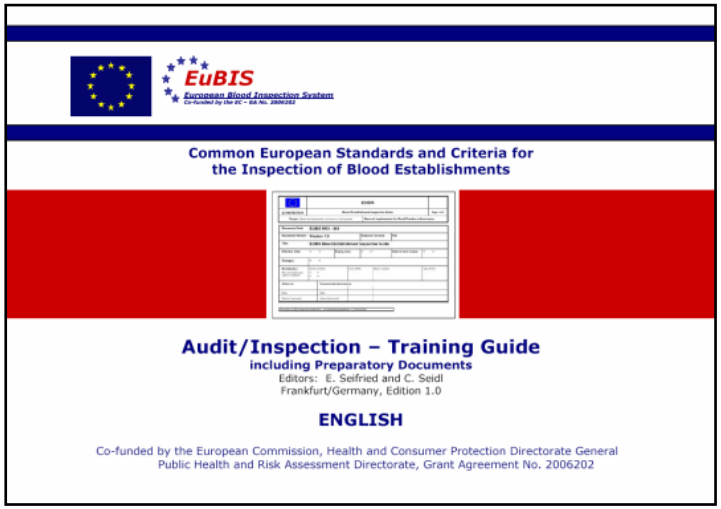
Inspections of blood establishments

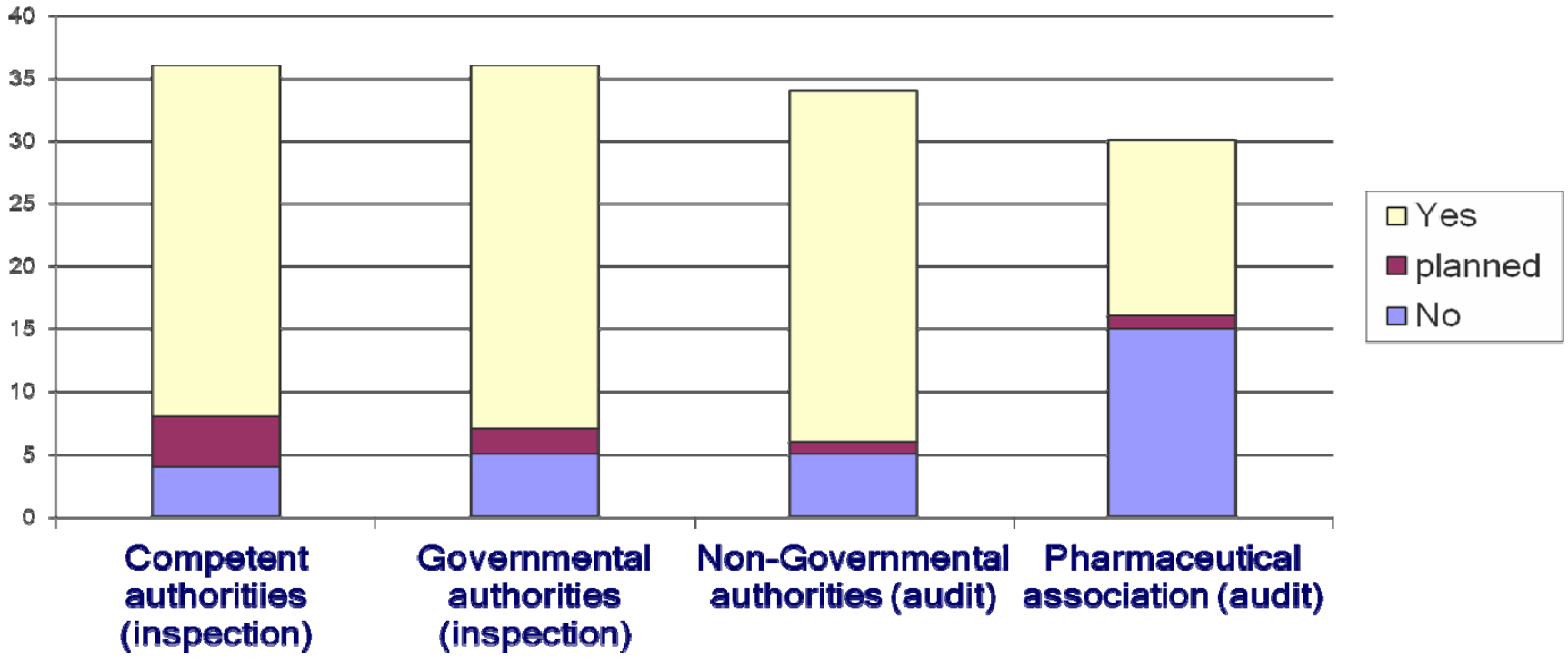
The **EuBIS guide**



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

Quality area/sector	Minor (%)	Medium/Major (%)
Personnel and organisation	**33,3**	**53,3**
Quality policy	24,1	44,8
Organigrams and responsibility of staff	41,4	34,5
Job description (qualification/re-qualification)	34,5	31,1
Documentation	**46,7**	**33,3**
SOP system / Change control of documents	37,9	41,4
Continuous training of SOPs (documents)	50,0	36,7
Self-Inspection / Continuous Improvements	**26,7**	**46,7**
Non-Conformance:		
Deviations	39,3	39,3
Complains	35,7	39,3
Recall	32,1	35,7
Corrective and preventive action	35,7	46,4
Premises*	**27,6**	**37,9**
Donor area, collection area,	46,4	25,0
Processing and testing,	32,1	39,3
Storage	40,7	33,3
Storage and distribution	**50,0**	**25,0**
Processing and validation	**33,3**	**33,3**
Laboratory testing	**40,0**	**20,0**

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
- 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 (II)

ISBT-WP-QM survey/database

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

Inspections of blood establishments

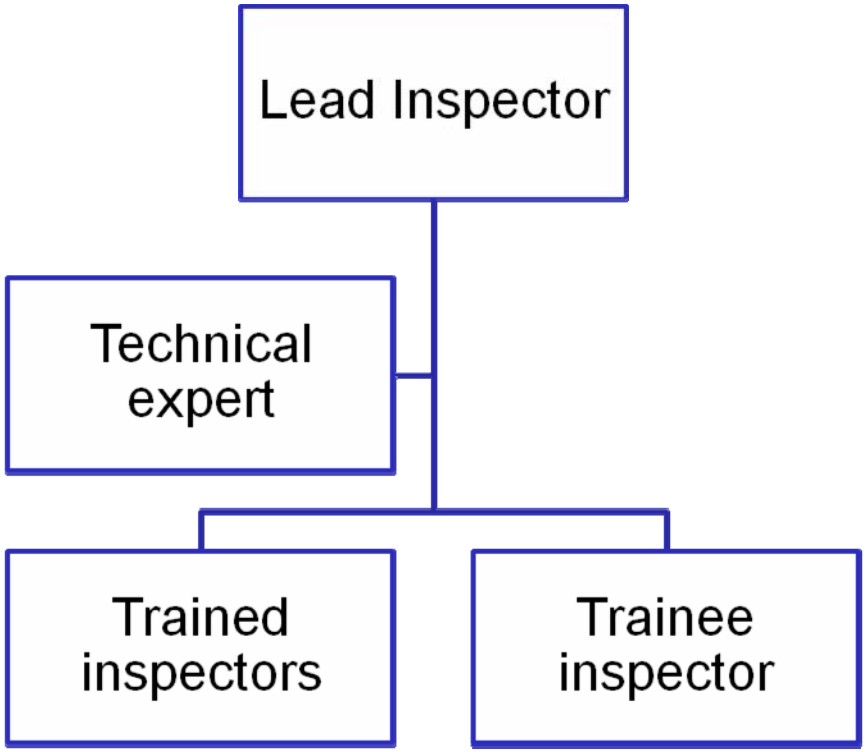
Self-Inspection Plan covering all activities*

- Donor Recriutement
- 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



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.

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

Inspections of blood establishments

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

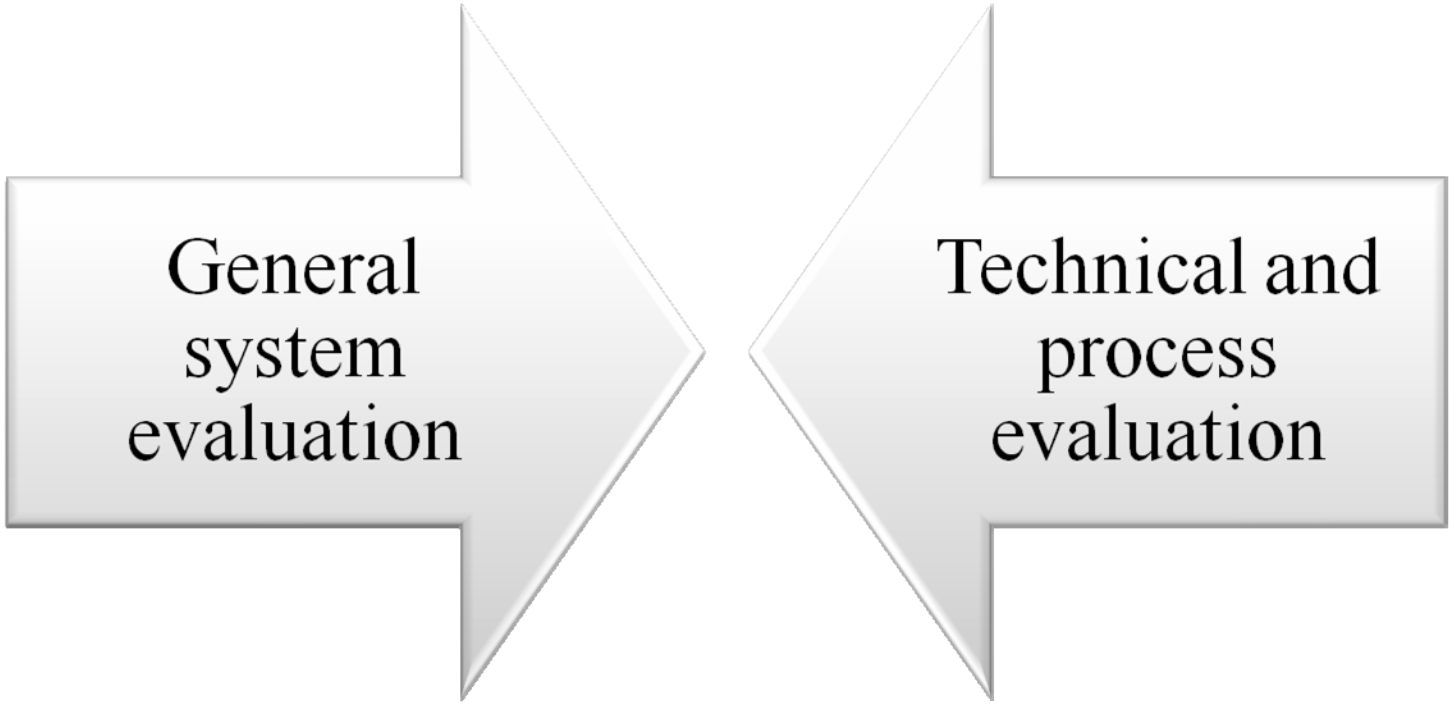
QM shall inform in advance the Department about:

Inspection schedule

- 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.

Reference: EuBIS Manual, www.eubis-europe.eu

During the inspection



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

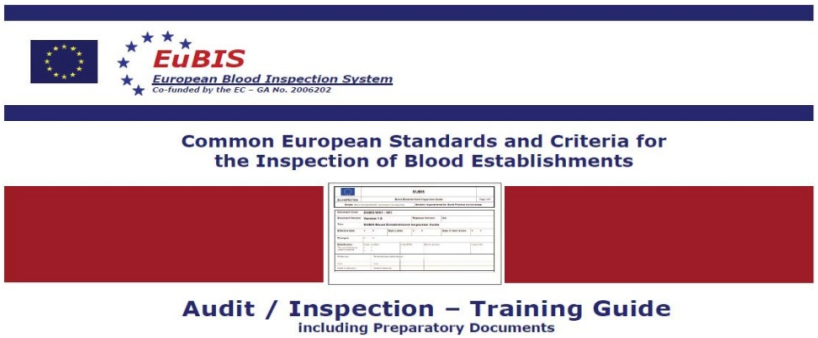
- job descriptions and the role of the Responsible Person
- training of staff
- maintenance (e.g. change control) of standard operating procedures (SOPs)
- validation (processes)
- qualification (equipment, facilities)
- purchases
- subcontractor or third party contracting (if applicable)
- internal auditing system / self-inspection procedure [33]
- 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[34] (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.

Reference: EuBIS Manual, www.eubis-europe.eu

Inspection tool



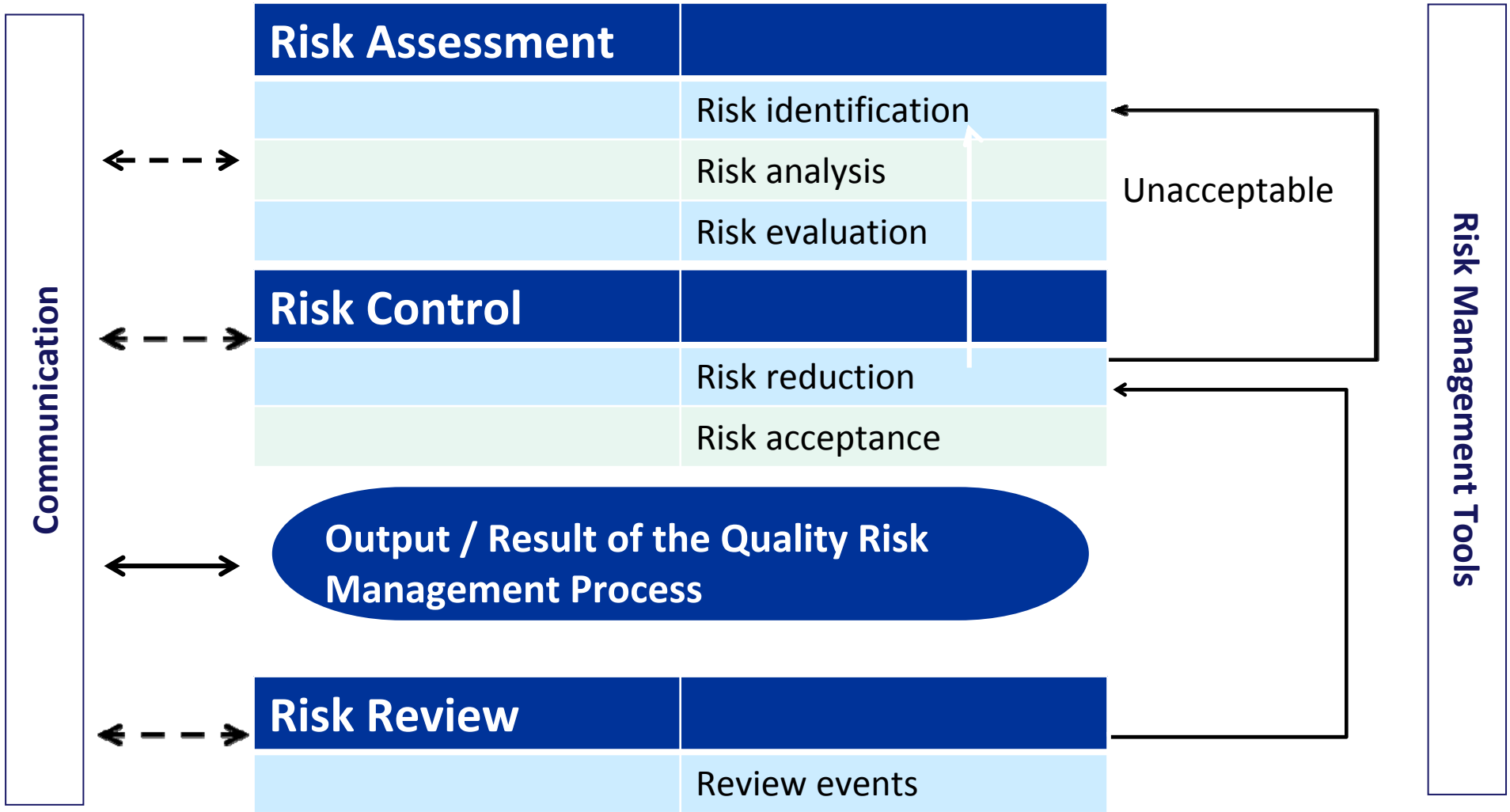
3 Inspection Guide

3.1 Licensing requirements

	Blood Establishment Inspection Guide	EuBIS

Scope:	Licensing requirements			
Criterion No. and Primary Ref. (EU Dir.)	**Sub-process/ control point**	**Cross-Ref. source**	**Inspection criterion description**	**Example evidence**
LR 001 2002/98/EC Article 5 – Licensing and authorisation Article 11. Quality system for blood	Licensing requirements	GMP Annex 14 PIC/S Chap. 2	The Blood Establishment has submitted the information listed in Annex I (2002/98/EC) to the Competent Authority. 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.	• Manufacturers license and whole sale distribution license as appropriate to the activity profile assigned by the Competent Authority • N.B. For those blood establishments that follow the requirements defined by 2001/83/EC, individual product licenses are required.

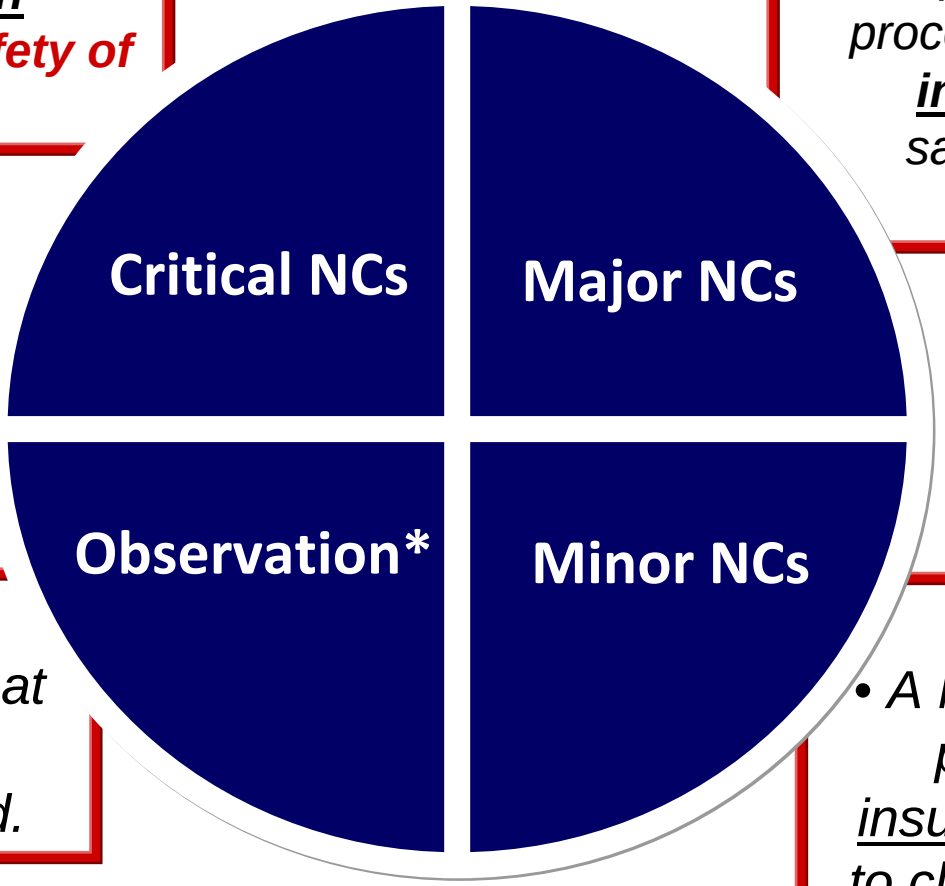
Quality Risk Management Process



Classification of non-compliances (NCs)

• *Any NCs in a process or a written procedure **which directly affects** the **safety of the donor or patient***

• *A **serious NCs** in a process or a written procedure but **does not in its own affect** the safety of the donor or patient.*



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

• *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

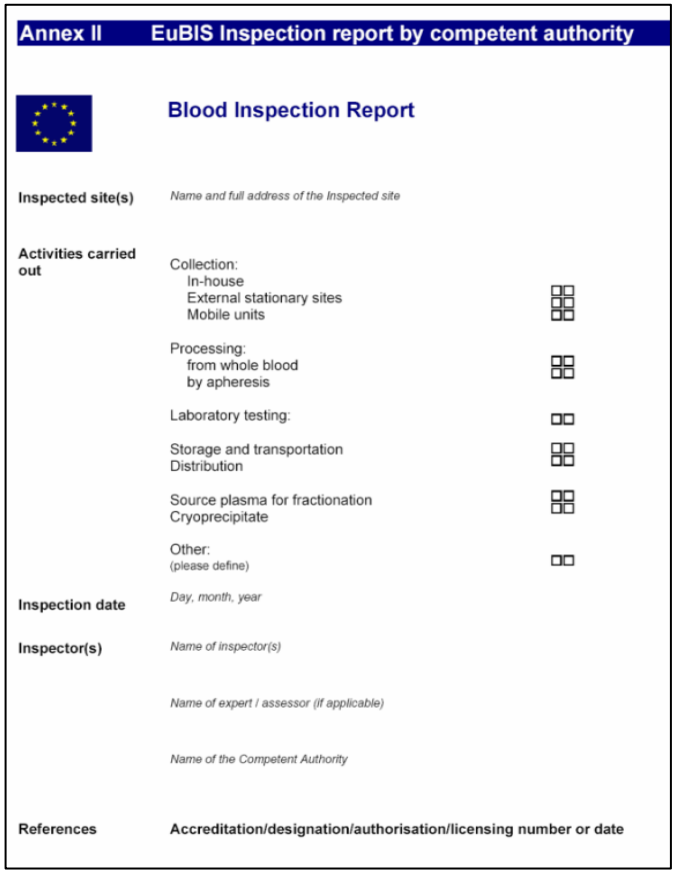
Inspection completion

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



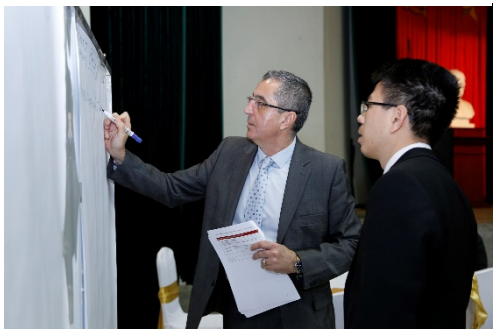
Annex II EuBIS Inspection report by competent authority

Blood Inspection Report

Inspected site(s)	*Name and full address of the Inspected site*
Activities carried out	Collection: In-house External stationary sites Mobile units Processing: from whole blood by apheresis Laboratory testing: Storage and transportation Distribution Source plasma for fractionation Cryoprecipitate Other: (please define)
Inspection date	*Day, month, year*
Inspector(s)	*Name of inspector(s)* *Name of expert / assessor (if applicable)* *Name of the Competent Authority*
References	**Accreditation/designation/authorisation/licensing number or date**

EuBIS, www.eubis-europe.eu

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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- England
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EuBIS
European Blood Inspection System
Initiated under the Public Health Programme of the European Commission, DG Sanco, EC – GA No. 2006202

Funded by

Istituto Superiore di Sanità

Centro Nazionale Sangue

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)
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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

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

International Society of Blood Transfusion

Thank you for your attention

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