EuBIS

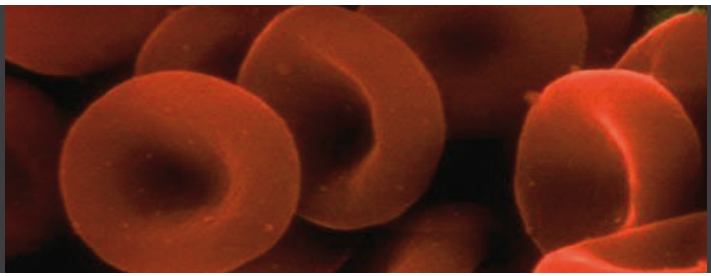
European Blood Inspection System

Co-funded by the EC – GA No. 2006202

Co-funded by the European Commission
Health and Consumer Protection Directorate General
Public Health and Risk Assessment Directorate
Grant Agreement No. 2006202

Common European Standards and Criteria for the Inspection of Blood Establishments

Reflecting European good practice within the area addressing the quality and safety of blood



Editors: E. Seifried and C. Seidl
Frankfurt/Germany, Edition 1.0

ENGLISH

Publication notice:

This manual has been developed by the participants of the EuBIS Project co-funded by the European Commission, Health and Consumer Protection Directorate General, Public Health and Risk Assessment Directorate, DG Sanco Grant Agreement No. 2006202. (2003-2008)

The manual gives valuable information and guidance on common criteria and standards for the inspection of blood establishments based on the requirements set-out in the blood legislation of the European Commission.

Further information on this manual including updated versions, national training courses or seminars organised by the project participants is available from the project Website of **EUBIS (European blood inspection system)** (www.eubis-europe.eu).

Supported by the European Blood Alliance (EBA)

Disclaimer:

Red Cross Blood Donor Service Baden-Württemberg – Hessen, University Hospital Frankfurt am Main, Germany

Editors: Erhard Seifried and Christian Seidl

Edited in cooperation with the Project Participants and Collaborating Partners

Project Participants and Collaborating Partners:

AFSSAPS – France	Agence française de sécurité sanitaire des produits de santé (France)
BSDBH – Germany *(Project Coordinator)*	Deutsches Rotes Kreuz Blutspendedienst, Baden-Württemberg, Hessen *(German Red Cross Blood Donation Service)*
BTS – Iceland	Blóðbankinn, Landspítali (The Blood Bank, Landspítali University Hospital)
CNS, ISS – Italy	Centro Nazionale Sangue, Istituto Superiore di Sanita
DHCSS - Malta	Directorate of Health Care Services Standards, Government of Malta
EBS – Estonia	Põhja-Eesti Reginaalhaigla Verekeskus *(North-Estonian Regional Hospital Blood Centre)*
EFS – France	Etablissement Français du Sang (*French Blood Establishment*)
FMP – Romania	Universitatea de Medicina si Farmacie "Victor Babes" Timisoara (*University of Medicine and Pharmacy "Victor Babes" Timisoara)*
FOK – Czech Republic	Fakultni nemocnici Ostrava Krevni centrum *(Blood center)*
BRCF – Belgium	Rode Kruis Vlaanderen (Belgian Red Cross-Flanders)
HNBT – Hungary	Országos Vérellátó Szolgálat *(Hungarian National Blood Transfusion Service)*
IBT – Malta	Centru Nazzjonali ta't-Trafuzjoni tad-Demm (*National Blood Transfusion Service*)
IBTS – Ireland	Irish Blood Transfusion Service
IHT – Poland	Instytut Hematologii I Transfuzjologii *(Institute of Haematology and Blood Transfusion)*
IMB – Ireland	Irish Medicines Board - Blood & Tissue Section
JAZM – Slovenia	Javna agencija RS za zdravila in medicinske pripomočke *(Agency for medicinal products and medical devices)*

MSC – Spain	DG Salud Pública. Ministerio de Sanidad y Consumo (Madrid) represented by Centro Vasco de Transfusion (San Sebastian)
MSP – Romania	Ministerul Sanatatii Publice (*Ministry of Public Health*)
MOH – Cyprus	Υπουργείο Υγείας της Κυπριακής Δημοκρατίας - Ιατρικές Υπηρεσίες κσι Υπηρεσίες Δημόσιας Υγείας *(Ministry of Health of the Republic of Cyprus - Medical and Public Health Services)*
NHS-BT – United Kingdom	National Blood Authority, National Health Service Blood and Transplant (England and North Wales)
NBT – Bulgaria	НАЦИОНАЛЕН ЦЕНТЪР ПО ХЕМАТОЛОГИЯ И ТРАНСФУЗИОЛОГИЯ *(National Centre of Hematology and Transfusiology)*
PEI – Germany	Paul-Ehrlich-Institut *(Federal Government Institution)*
RPDA – Germany	Regierungspräsidium Darmstadt *(State Governmental Institution)*
SAM - Estonia	State Agency of Medicines, Department of Biologicals
Sanquin – The Netherlands	Stiching Sanquin Bloedvoorziening (*Sanquin Blood Supply Foundation*)
SUKL – Czech Republic	Vedoucí oddělení klinických praxí a dohledu nad zpracováním biologických materiálů. Státní ústav pro kontrolu léčiv *(State Institute for Drug Control)*
TILAK – Austria	Zentralinstitut für Bluttransfusion und Immunologische Abteilung, Universitätsklinikum

Supported by the European Blood Alliance (EBA)

COOPERATIVE WORKING PARTNERSHIPS

CoE – EDQM	Council of Europe - Blood Transfusion & Organ Transplantation activities. European Directorate for the Quality of Medicines and Health Care (EDQM – CD-P-TS), Strasbourg, France
EBA	European Blood Alliance (Executive office in Amsterdam*),* The Netherlands
JACIE	JACIE Accreditation Office - EBMT Secretariat, Spain
KMF	Koch-Metschnikow Forum (KMF), МЄЧНИКОВ-КОХ-ФОРУМ (МКФ).an initiative of the Petersburg Dialogue. (Germany and Russia)
WHO	World Health Organisation (WHO) Regional Office for Europe (Copenhagen), Denmark
DOMAINE Project	DOMAINE Project, Nijmegen and Amsterdam, The Netherlands
EUSTITE Project	EUSTITE – Project, Italy
Optimal Blood Use Project	EU Optimal Use of Blood Project, United Kingdom

AFFILIATED PARTNERS FOR THE INSPECTION SURVEY

AFSSAPS - France	Agence française de sécurité sanitaire des produits de santé (France)
FAGG - Belgium	Federal Agentschap voor Geneesmiddelen en Gezondheidsproducten (Belgium)
ASST - Portugal	Autoridade para os Serviços de Sangue e da Transplantação, (Portugal)
BDA - Bulgaria	Bulgarian Drug Agency (Bulgaria)
DMA - Denmark	Danish Medicines Agency (Denmark)
ITM – Rep. Macedonia	Institute of Transfusion Medicine (Republic of Macedonia)
MoH - Latvia	Ministry of Health, Health Statistics and Medical Technologies State Agency (Latvia)
MoH - Liechtenstein	Amt für Gesundheit (Health Ministry) (Liechtenstein)
SIDC - Slovakia	State Institute for Drug Control (SIDC), Bratislava (Slovakia)
Socialstyrelsen - Sweden	The National Board of Health and Welfare, Socialstyrelsen (Sweden)
Swissmedic - Switzerland	Swiss Agency for Therapeutic Products (Swissmedic), Bern (Switzerland)
Uni-Graz - Austria	Universitätsklinik für Blutgruppenserologie und Transfusionsmedizin (Austria)

Abbreviations

BE	Blood Establishment
CA	Competent Authority
CAPA	Corrective and preventive actions
CoE	Council of Europe
EDQM	European Directorate for the Quality of Medicines and Health Care of the Council of Europe
EMEA	European Medicines Agency
EQSTB	European Quality System for Tissue Banking
EU	European Union
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISO	International Standards Organisation
MS	European Union Member State
PIC/S	Pharmaceutical Inspection Convention / Pharmaceutical Inspection Co-operation Scheme
QA	Quality Assurance
RP	Responsible Person
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMF	Site Master File
SOP	Standard Operating Procedure

Preface

Ensuring that '*patients who receive blood transfusion in the European Union are given safe blood' is a* major objective within the framework of public health on the national and European level.

The objective of EuBIS is to set out a methodology for inspecting blood establishments based on the European Commission's directive requirements related to ensuring the quality and safety of blood.

It is the result of a collaborative effort of representatives from 27 governmental institutions, blood establishments and competent authorities participating in the EuBIS project co-funded by the European Commission.[1] In this context, the EuBIS project is the first project that has brought together regulators and manufacturers to jointly develop criteria and standards.

Initiated and coordinated by the Red Cross Blood Donor Service Baden-Württemberg – Hessen in Frankfurt am Main, Germany, this project aimed to develop a manual to assist

- *blood establishments in need to optimise their quality system and self-inspection process related to the EU blood directive.*
- *blood establishments to prepare for regulatory inspections by competent authorities, and*
- *competent authorities, which wish to use the manual and training guide as a reference for the implementation process of the European blood legislation related to regulatory inspections.*

The manual is accompanied by an audit / inspection training guide to assist the inspection process. It also contains master templates of key documents used during the inspection. These documents give examples for the implementation of good practice (GP) as defined by the EU blood directives.

Using commonalities between Member States and the requirements and definitions given by the EU blood legislation, the manual summarises good practice standards. The implementation of these standards will improve the safety of blood. This will reduce the incidence of harm to patients that

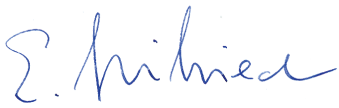
[1] Grant Agreement N°2006202) within the framework of its Public Health Programme (Decision N°1786/2002/EC)

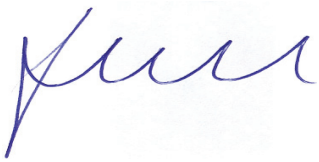
would otherwise arise from citizens travelling around the enlarged EU; and from the movement of blood components within the EU, either through the open-border policy or through crisis-management measures.

The project coordinators herewith express their sincere appreciation to the participating institutions and their representatives, as well as to the team of advisors, in particular to Dr. Jeroen deWit, Ms. Frances Delaney, Dr. Margarethe Heiden, Dr. Helga Marie Huber, Mrs. Wiebke Siegel and Mr. Angus Macmillan Douglas (OBE) for their continued cooperation, collaboration and support throughout the life of this undertaking. The project coordinators also acknowledge the effort and spirit of Dr. Fewzi Teskrat, Mr. Boudewijn Hinloopen, Dr. Jan Peter Jansen van Galen, Mr. Jan Ceulemans, Dr. Alex Aquilina and Mr. Mark Nightingale in developing educational material for training purposes. Their willingness to share their expertise and experience at the national level on the use of the manual is gratefully appreciated.

The project participants also express their gratitude for the constructive cooperation with the representatives of the European Commission – Mr. Tapani Piha, Mrs. Patricia Brunko and Mr. Thomas Bregeon. Finally, the project participants acknowledge the support given by the European Blood Alliance at present and in sustaining the future dissemination of the Project's deliverables and the continual development of its ideas.

This 1st Edition of the manual is presented on behalf of the project participants and collaborating partners. An electronic form can be ordered via the Project Website (www.eubis-europe.eu).





Prof. Dr. med. Erhard Seifried

Prof. Dr. med. Christian Seidl

On behalf of the Project Participants

TABLE OF CONTENTS

1 Introduction

1.1 The EuBIS project

EuBIS, the European Blood Inspection System, is a project funded by the European Commission under its 2006 Call for Proposals and within the framework of its Public Health Programme (2003-2008) addressing the quality and safety of blood. The Project aims to develop pan-European standards and criteria for the inspection of blood establishments. These requirements are intended for use not only by those responsible for the operation of blood establishments but by those in charge of inspecting them, in compliance with relevant European Union (EU) legislation. (www.eubis-europe.eu).

EuBIS is coordinated by the German Red Cross Blood Donation Service with the participation of 27 collaborating partners from 20 Member States, cooperative working partnerships with five organisations and three projects, affiliations with twelve partners involved in conducting its inspection survey, and is supported by the European Blood Alliance. Launched in August 2007, the project has a three-year duration.

1.1.1 Background

The entry into force of European Union legislation on blood, based on Directive 2002/98/EC[2] and its technical requirements, has been accompanied by noteworthy progress towards ensuring the provision of consistently safe blood and blood components across Europe. The significant expansion of the European Union, however, focused attention on the need to have common pan-European standards and criteria for the inspection of blood

[2] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003. Official Journal of the European Union. L33, 8.2.2003. p.30

establishments - a key element in the implementation of good practice[3].

Currently such inspections are conducted according to national criteria and standards which differ between Member States. A 1994 report by the European Commission noted that 'divergent national regulations concerning collection and treatment of blood has contributed to reluctance, if not a refusal, to accept blood and plasma coming from different Member States and even different centres'[4]. This can lead to risks with respect to consistently safe blood across Europe which, by itself, the Directive cannot help to guarantee.

The 2006 Work Plan of the Public Health Programme (Area 2.2.4) gave impetus to the need for equivalent recognition of inspections of blood establishments among Member States through the development and implementation of commonly accepted criteria and standards. Without them, the levels of risk from having a blood transfusion in the Member States could continue to differ.

1.1.2 Project Objectives

The overall objective of the Project is to develop and implement commonly accepted criteria and standards to ensure equivalent recognition of inspection of blood establishments among Member States.

It aims to do this through the development of a manual that will set out:

- common criteria and standards for the inspection of blood establishments
- requirements for the implementation or expansion of quality management systems to be inspected

[3] 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. Official Journal of the European Union. L256, 1.10.2005. p.41. (Article 2.2)
[4] Communication on Blood Safety & Self-sufficiency (Com(94) 652 final. 21.12.1994)

- inspection checklists which closely follow Directive 2002/98/EC and its technical requirements, and
- evaluation criteria for inspections and a benchmark system for deviations and improvements.

It will also serve as the basis of a training programme for inspectors of blood establishments. This will help to ensure common acceptance of the standards and criteria.

1.1.3 Methodology

EuBIS activities got underway in September 2007 with the establishment of an internet platform for communication with the project's participants. This was followed in October with the development and distribution of a questionnaire to the project's participants to collect information on current practices related to the inspection of blood establishments in the European Union. It was divided into six sections - the first five were specifically related to blood establishments and addressed: processes covered; Member State establishments; quality systems; inspections and audits; and the inspection process. The sixth section summarised the objectives and deliverables of the EuBIS project itself. The responses were compiled and an EU Inspection survey report prepared.

The first meeting of the Project's participants was convened in November at which time the results of a comparative analysis of the survey were presented. These results, in combination with Directive 2002/98/EC and its technical requirements, were used to establish the basic structure for the quality systems and pan-European blood inspection standards.

In order to develop the basic structure, the project's participants were divided into four working groups each with responsibility for a specific subject area. These were: quality management system evaluation; donor recruitment and blood collection; processing and testing; and blood component issuing, storage and logistics. In

continuous work and in individual working group meetings, draft inspection checklists and criteria for the evaluation of inspection results (acceptance or rejection) in the assigned areas were developed.

Recognising that several inspection criteria and programmes in the health care area had already been established, the EuBIS project from the outset consulted these sources and conferred with the responsible authors. These included:

- the Joint Accreditation Committee of the International Society of Cellular Therapy (ISCT) and the European Group for Blood and Marrow Transplantation (EBMT) (jointly referred to as JACIE)
- the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation scheme (jointly referred to as PIC/S)
- the European Medicines Agency (EMEA)

Moreover, EuBIS has collaborated and exchanged ideas with the EUSTITE (European Union Standards and Training for the Inspection of Tissues Establishments[5]) project, co-financed under the 2005 Work Plan of the EU's Public Health Programme. EuBIS has drawn extensively from EUSTITE's 'Guidelines for the Inspection of Tissue and Cell Procurement and Tissue Establishments' and this manual is complementary to it. It has also been in contact with the national competent authorities in the Member States and the International Plasma Fractionation Association (IPFA).

1.1.4 Background Summary

A major aim of the European Commission is to give practical assistance to competent authorities (CA) and blood establishments (BE) in implementing the Directives' requirements.

[5] www.eustite.org

However, in a recent Commission survey[6] it was noted that at least five Member States that have transposed the Directive into National law do not perform inspections of BEs. It is hoped that the EuBIS manual will assist them in carrying out this responsibility.

2 Aim and Scope of the Manual

The EuBIS manual aims to provide assistance to EU Member States in their implementation of regulatory requirements set out in Directives 2002/98/EC, 2004/33/EC[7], 2005/61/EC[8] and 2005/62/EC[9]. These include *inter alia*:

- designation, authorisation, accreditation or licensing of blood establishments (BEs)
- authorisation of the activities which can be undertaken and the applicable conditions for blood collection
- provisions for ensuring the quality and safety of blood and blood components, and
- requirements for imported blood and blood components.

The developed inspection standards and criteria will assist in the independent assessment of quality system structures established

[6] European Commission, Health & Consumer Protection Directorate-General, Directorate C - Public Health and Risk Assessment, C6 - Health measures. Compilation of Responses from Competent Authorities: Questionnaire on the transposition and implementation of the European Blood and Blood Components regulatory framework, SANCO C6 TB/ci D(2008)/360028

[7] Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. Official Journal of the European Union, L91, 30/03/2004, p.25

[8] Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events. Official Journal of the European Union, L256, 1/10/2005, p.32

[9] 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. Official Journal of the European Union, L256, 1/10/2005, p.41

by individual blood establishments in compliance with the EU's legislation.

The manual will assist blood establishments in preparing for inspections. The standards and checklists used for external inspections could be used for internal audits by blood establishments. With respect to the different standards and guidelines that are currently in place, the inspection guide summarizes the most critical aspects to be addressed in order to achieve good practice. For each of these critical points, the Guide provides references to commonly used standards for the inspection of BEs. Common criteria and standards for external inspection of BEs following Article 8 of Directive 2002/98/EC are summarized in the 'Aide Memoire' for competent authorities. The 'Aide Memoire' gives practical guidance for those, who are less experienced or new in the area of blood and blood components.

Defined principles for the structure of quality systems will assist in implementing or expanding the currently used quality management systems in blood establishments. Moreover, the manual will help to ensure the incorporation of standard operating procedures (SOPs) in a site master file or a quality management handbook reflecting GMP standards.

The manual's scope reflects that set out in Directive 2002/98/EC, i.e. 'the collection and testing of human blood and blood components, whatever their intended purpose, and to their processing, storage and distribution when intended for transfusion[10]'.

The work plan of the EuBIS project includes the preparation of a draft of the manual and subsequently a final edition. The draft text, after being circulated to the project participants for their initial comments and contributions, will be discussed at meetings of each of the working groups. Taking into account all relevant

[10] Directive 2002/98/EC. Article 2.1

remarks and observations, the draft will be revised and a validation process undertaken. The draft will be given to competent authorities or blood establishments that are planning to modify or to set up their inspection system. Potential Member State candidates for the evaluation are Malta, Romania and Slovenia (Malta and Romania would need a start-up, while Slovenia would need to modify their system). Evaluation of the draft manual in a blood establishment could also be undertaken in Romania where their facilities need to introduce quality systems. The draft will be provided to all evaluators in electronic from. It may also be printed for each of the participants and/or collaborating partners depending on financial considerations.

Upon receipt of the evaluations and incorporation of amendments, a final edition of the EuBIS manual will be prepared.

In drafting the manual, EuBIS drew upon the procedures and recommendations that had already been issued in existing documents and guidelines related to inspections. It made a concerted effort to harmonise its guidance and procedures with those of the EUSTITE project as inspectors of the competent authorities frequently have responsibility for inspection of both blood establishments and tissues and cell facilities. The documents consulted are included in **Annex III.**

The project participants are aware that national legal requirements as indicated by Article 152, Paragraph 4, of the Treaty of Amsterdam will require the use of established standards, i.e. GMP-Eudralex or the ISO-series.

Comments or suggestions from individuals responsible for blood establishments or the Member State competent authorities on the use of the draft manual are welcome. They will be taken into account in the finalisation of the Manual. Comments and suggestions should be sent to: eubis@blutspende.de.

3 EU legislative requirements for quality systems of blood establishments

3.1 Directive 2005/62/EC[11]

Commission Directive 2005/62/EC sets out the technical requirements for blood establishments related to the implementation and maintenance of standards and specifications relating to a quality system. It covers general principles, personnel and organisation, premises, equipment and materials, documentation, blood collection, testing and processing, storage and distribution, contract management, non-compliance and self-inspection, audits and improvements.

As per the EU blood legislation[12] 'q*uality shall be recognised as being the responsibility of all persons involved in the processes of the blood establishment with management ensuring a systematic approach towards quality and the implementation and maintenance of a quality system. The quality system encompasses quality management, quality assurance, continuous quality improvement, personnel, premises and equipment, documentation, collection, testing and processing, storage, distribution, quality control, blood component recall, and external and internal auditing, contract management, non-compliance and self-inspection. The quality system shall ensure that all critical processes are specified in appropriate instructions and are carried out in accordance with the standards and specifications set out in this Annex. Management shall review the system at regular intervals to verify its effectiveness and introduce corrective measures if deemed necessary.*

[11] 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. Official Journal of the European Union, L256, 1/10/2005, p.41.

All blood establishments and hospital blood banks shall be supported by a quality assurance function, whether internal or related, in fulfilling quality assurance. That function shall be involved in all quality-related matters and review and approve all appropriate quality related documents. All procedures, premises, and equipment that have an influence on the quality and safety of blood and blood components shall be validated prior to introduction and be re-validated at regular intervals determined as a result of these activities.'

3.2 Related blood legislation

The primary piece of EU legislation related to blood is Directive 2002/98/EC. It lays down the general framework for ensuring quality and safety for the collection, testing, processing storage and distribution of blood and blood components. Complementary to it are three European Commission Directives which set out the technical requirements. In addition to Directive 2005/62/EC, Commission Directive 2004/33/EC specifies certain technical requirements for blood and blood components including definitions, information to be provided to and obtained from potential donors, donor eligibility criteria, including temporary and permanent deferral, quality and safety requirements and storage, transport and distribution conditions for blood and blood components. Commission Directive 2005/61/EC deals with requirements for the traceability of blood and blood components and the notification of serious adverse reactions and events. Although adopted prior to Directive 2002/98/EC, elements of the Council's Recommendation[13] of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Union are still applicable unless superseded by the

[13] Council Recommendation of 29 June 1998 on the Suitability of blood and plasma donors and the screening of donated blood in the European Community. Official Journal of the European Communities, L203, 21.07.1998, p.14

Directives. Directive 2001/83/EC[14] on the Community code relating to medicinal products for human use sets out *inter alia* requirements for blood and plasma used for this purpose. However, Commission Directive 2003/63/EC[15] amends its Article 109 so that determination of the suitability of human blood donors and the testing of donations of starting materials for plasma-derived medicinal products must comply with the requirements of Directive 2002/98/EC.

4 Common standards and criteria for the inspection of blood establishments

4.1 Introduction

The 'vein' to 'vein' activities linked to blood transfusion involve a large variety of processes carried out by blood establishments including the collection, preparation, distribution and issuance of blood and blood components. Regulatory requirements at the European Union level are given by Directives, which differentiate between requirements for plasma-derived medicinal products and blood and blood components. Directive 2001/83/EC applies to all medicinal products, defined as 'any substance or combination of substances presented for treating or preventing disease in human beings'. By contrast, Directive 2002/98/EC and its current technical annexes - Directive 2004/33/EC, 2005/61/EC and 2005/62/EC - set the legal framework for blood and blood components. For those Member States that classify blood as a medicinal product as defined by the pharmaceutical legislation, requirements related to collection and testing of blood and plasma

[14] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Union L311, 28/11/2001, p.67.

[15] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. Official Journal L159, 27.6.2003. p.46

still apply[16]. Similar quality and safety requirements have been introduced for tissues and cells [17,18,19].

4.2 Activity profiles of blood establishments

In order to assess the currently used standards and criteria for quality management systems in Europe, an extended survey among the participants of the EU co-funded EUBIS Project was performed (Survey report available on http//www.eubis-europe.eu). Processes were subdivided in section 1 of the survey as follows:

- Blood collection
- Blood component preparation
- Apheresis component preparation
- Related preparations
- Source plasma for fractionation
- Cryoprecipitate
- Autologous blood components
- Blood component testing
- Blood component storage and distribution

[16] '*This Directive shall apply to the collection and testing of human blood and blood components, whatever their intended purpose, and to their processing, storage, and distribution when intended for transfusion*'. Article 2, Para 1, Directive 2002/98/E

[17] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, *Official Journal L 102, 7.4.2004, p. 48.*

[18] 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. Text with EEA relevance. *Official Journal L 038, 09/02/2006, p. 40.*

[19] Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. *Official Journal L 294, 25/10/2006, p. 32.*

The activity profile obtained from this survey demonstrated that, besides standard blood component preparation, the majority of participating blood establishments are involved in manufacturing processes covered by pharmaceutical regulations; 60% perform the preparation of cryoprecipitate while 80% are involved in the collection of source plasma for fractionation. Autologous blood components are prepared by 88% of blood establishments. In addition, the activities of several blood establishments cover the area of tissues and cells. More than half the participating blood establishments are involved in the preparation of blood component related preparations, such as cord blood, granulocytes and lymphocytes for therapeutic use.

Table 1: EU Directives and activity profile of blood establishments

Area and activity	percentage (%)
Blood and blood component Directives	
Whole blood preparation	
Cellular (erythrocyte or platelet concentrates)	100
Fresh frozen plasma	94
Apheresis	
Cellular (erythrocyte or platelet concentrates)	100
Fresh frozen plasma	75
Autologous blood components	88
Tissue and cells Directives	
Stem cells	75
Cord blood	31
Granulocytes	69
Lymphocytes	50
Pharmaceutical Directive related preparations	
Source plasma for fractionation	75
Cryoprecipitate	56

The results of the survey revealed that several standards and guidelines are commonly used by:

- blood establishments for their quality management systems including internal inspections, and
- competent authorities performing external inspections of those blood establishments

in European Member States (**Table 2**). These are the European Good Manufacturing Practice (GMP) standard, the European Good Laboratory Practice (GLP) standard, the technical report series developed by the World Health Organisation (WHO), the Council of Europe (CoE) 'Guide to the preparation, use and quality assurance of blood components' and also the International Standard Organisation (ISO) 9000 series of standards and norms.

With respect to the commonly used European or international standards, the EU GMP and CoE standards are the most commonly implemented for routine processes. EU GMP is very often used in combination with EU GLP (Good Laboratory Practice) by blood establishments performing blood component related processes that fall under pharmaceutical legislation. The survey also revealed that the ISO 9000 series standards are widely recognised by blood establishments. One third of blood establishments have already implemented these standards in their quality management systems, being ISO certified and/or accredited. One tenth are in the process of preparing for ISO certification.

Table 2: Commonly used standards and guidelines in Europe

Standard/guideline	percentage (%) *[1]
Quality management systems and inspections (internal) by blood establishments:	
Good Manufacturing Practice (GMP)	88
Good Laboratory Practice (GLP)	35
International Standard Organisation (ISO)	47 *[2]
Council of Europe (CD-P-TS)	82
World Health Organisation (WHO)	12
National (based on individual Member State)	29
External inspection (audits) by competent authorities:	
Good Manufacturing Practice (Eudralex, EU-GMP)	50
PIC/S guide for blood establishments	50
WHO GMP standards	25
International Standard Organisation (ISO)	10
CoE (EDQM)	65
National guidelines and standards	40

[1] based on the EuBIS survey including blood establishments and competent authorities from 20 EU Member States

[2] including 12% of blood establishments with ISO accreditation in progress

4.3 Council of Europe (CD-P-TS)

The Council of Europe, which has been involved in issues related to blood transfusion since the early 1950s, has long advocated the principle of voluntary non-remunerated blood donation and promoted mutual assistance, optimal use, and protection of the donor and recipient. Complementary to the GMP guidelines, the

Council of Europe has developed a 'Guide to the preparation, use and quality assurance of blood components' [Recommendation No. R (95) 15]. The CoE Guide is commonly used among blood establishments throughout the EU Member States. Only in some Member States, e.g. United Kingdom or Germany, do national recommendations surpass the CoE guide in its application for routine work.

The consultancy process on Recommendation No. (95) 15 started in 1986 leading in 1995 to the adoption of this document as a technical annex by the Committee of Ministers. Recommendation No. R (95) 15 is updated annually by the members of the Committee of Experts on quality assurance in blood transfusion services keeping it in line with scientific progress and EU legislation. The CoE Guide is divided into two Parts: Part A – Principles and Part B – Standards. *Principles* are regarded as essential requirements that 'must' be complied with, while *standards* are requirements that 'should be' considered.

Similar to GMP or ISO standards (see below), the CoE Recommendation explains the contents and background of quality systems for blood establishments, including the activities to be included in these systems and the subjects to be addressed. The proposed quality system of the CoE guide is based on the principles of good practice and quality management, as described in the EU GMP guidelines and the ISO 9000-series standards. Its 2009 version contains recommendations on blood collection, blood components, technical procedures, transfusion practices and quality systems for blood establishments. As of 2009, this appendix – 'Guide to the preparation, use and quality assurance of blood components'[20] - is in its 15th edition.

[20] Guide to the preparation, use and quality assurance of blood components. Council of Europe. Strasbourg

4.4 PIC/S

PIC/S is the acronym for the Pharmaceutical Inspection Convention / Pharmaceutical Inspection Co-operation Scheme. These are 'instruments' between countries and pharmaceutical inspection authorities, which together provide active and constructive co-operation in the field of Good Manufacturing Practice (GMP). PIC/S has as its mission 'to lead the international development, implementation and maintenance of harmonised (GMP) standards and quality systems of inspectorates in the field of medicinal products.' It aims to do this 'by developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations.' There are currently 31 participating authorities from around the world in PIC/S. Its expert circle on blood and tissue was founded by the Paul-Ehrlich-Institute (PEI) in 1994 recognizing the need for specialized knowledge on these special issues related to blood and transmissible diseases.

In response to the need for a modification of EU-GMP standards, the expert circle on blood and tissues developed a GMP 'Guide for blood establishments'. This PIC/S GMP Guide intends to facilitate the introduction of GMP standards for blood and apheresis establishments and is used by PIC/S inspectors in assessing the quality management systems of those establishments. Although the Guide follows the structure of the EU GMP standard, it addresses specific processes to be covered in the collection, preparation and distribution of blood and apheresis components, such as blood donor areas, mobile donor sessions, irradiation of blood components or whole blood collection and component preparation. The PIC/S expert circle on blood and tissues has also developed an 'aide memoire' for the inspection of blood establishments, a PIC/S guide to the inspection of source plasma establishments and plasma warehouses, site master files for

source plasma establishments and plasma warehouses and training guidelines for the qualification of inspectors.

4.5 EU-GMP (Eudralex)

The EU-GMP standard (Eudralex) gives detailed and very specific standards for the production of pharmaceutical components. In particular blood establishments that perform cryoprecipitation or the collection of source plasma for fractionation have established quality management systems that relate to these standards. In some Member States, e.g. Germany, where pharmaceutical legislation applies for all blood components, the EU-GMP standard is mandatory. Chapters 1 – 9 of the EU-GMP standard give detailed specifications for quality management, personnel, premise and equipment, documentation, production, quality control, contract manufacturers and analysis, complaints and recall and self inspections. In addition, Annex 2 (biological products) and Annex 14 (blood components) of the EU-GMP standard are used as specifications for plasma fractionation. Both EU-GMP annexes contain requirements and specifications that can be adapted to the production of standard blood components and are used *inter-alia* by blood establishments. In contrast, several standards defined by EU-GMP are derived from specific production, storage and distribution characteristics of pharmaceutical production processes, such as process monitoring of intermediate and bulk products, batch processing records or ongoing stability programme to monitor the product over its shelf life. These EU-GMP standard requirements are more suited to the manufacturing facilities and production processes for medicinal products by the pharmaceutical industry and are difficult to adapt to standard blood component collection, preparation and distribution as covered by Directive 2002/98/EC.

4.6 ISO Standards

In addition to EU-GMP and the Council of Europe (CD-P-TS) guide, the International Standard Organisation (ISO) 9000 standards are commonly accepted by blood establishments. ISO 9001:2000 specifies requirements for a quality management system where an organisation:

- Needs to demonstrate its ability to consistently provide products that meet customer and applicable regulatory requirements, and
- Aims to enhance customer satisfaction through the effective application of the system, including processes for continual improvement of the system and the assurance of conformity to customer and applicable regulatory requirements.

Blood establishments using ISO 9001:2000 are required to address the effectiveness of their quality management system. In the context of ISO 9001, effectiveness means the extent to which planned activities are realized and planned results achieved. Further requirements specify the need for continual improvements to the quality management system and not for sporadic or irregular evaluations or campaigns. Following ISO 9001, the organisation shall continually improve the effectiveness of the quality management system through the use of

- quality policy
- quality objectives
- audit results
- analysis of data
- corrective and preventive actions, and
- management review.

ISO standards require that the suitability and effectiveness of the quality management system shall be determined. The standards given by ISO 9001 specify requirements for quality management systems that can be used for internal application by organisations,

or for certification, or for contractual purposes. In this context, ISO 9001 focuses on the effectiveness of the quality management system in meeting customer requirements.

4.7 Inspection guide and cross references

The increasing diversity of processes covered by blood establishments, from blood components, pharmaceutical products, to tissue and cells, requires that quality systems need to be flexible in order to adapt to national and European quality requirements. Harmonisation of standards, therefore, would be useful. However, this has to take into account the different legal requirements of the European Union for pharmaceutical products, blood components and tissues and cells. In addition, despite transposition of EU Directives to the Member State level, national laws may require additional modifications for quality management systems. The EuBIS expert group has discussed the importance of those European and national standards in place and has developed a cross-reference guideline for quality management systems of blood establishments based on Directive 2005/62/EC. This cross-reference guideline includes the EU-GMP standards, the PIC/S GMP for blood establishments, the CoE Guide and the ISO 9000 series. By cross-referencing the relevant quality requirements to Directive 2005/62/EC, commonalities between these standards can be identified.

Cross reference guidance to 'good practice' following the EU Directives

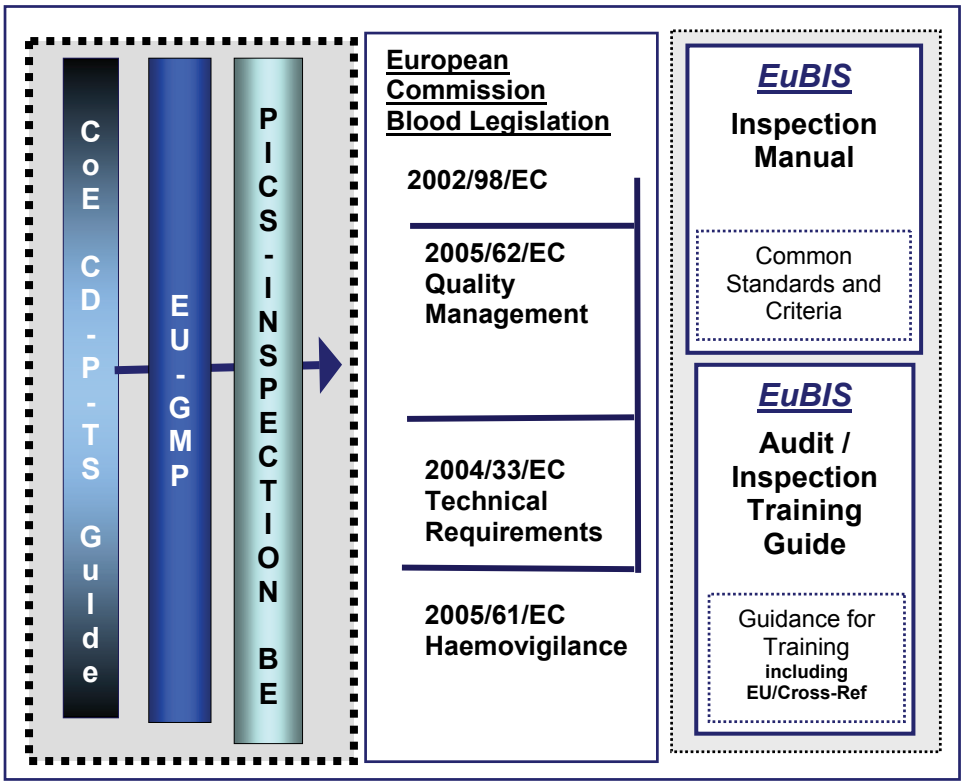


Figure 1: The EuBIS Project expert circle developing a manual for common European standards and criteria for the inspection of blood establishments for good practice (GP) following the EC blood legislation. The manual is supplemented by an audit / inspection – training guide on the relevant aspects to be addressed during the inspection process including cross-references for common European standards and criteria for quality management systems of blood establishments.

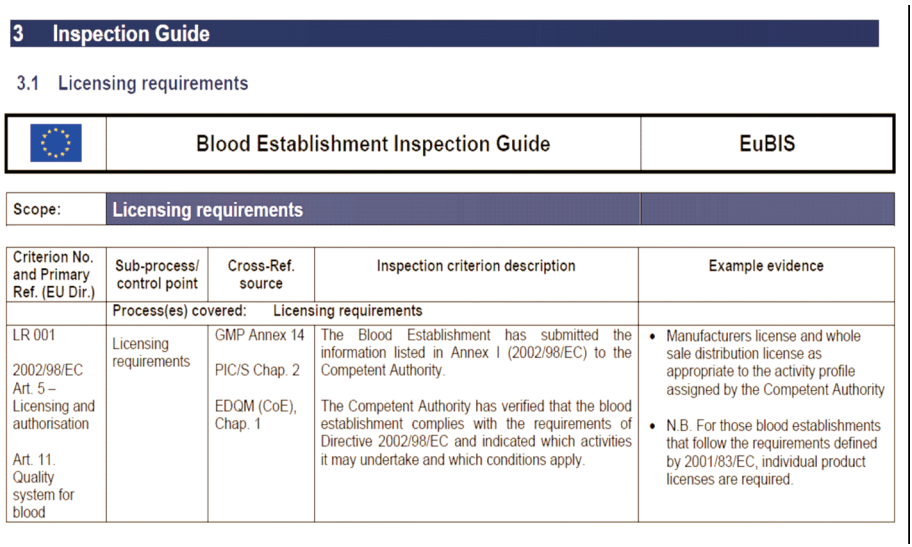
The inspection guide is a manual comprising common European standards and criteria used for the process of inspection and self-inspection of blood establishments. There are separate sections on these topics (Chapter 5 'Self-inspection' and Chapter 6 'Inspection by competent authority') including chapters on the conduct of an inspection (Chapter 7), the inspection procedures after the inspection (Chapter 8) and the evaluation of the inspection system (Chapter 9).

The guide is complemented by documents (Annex I and Annex II) that are commonly used during inspections [e.g. modified site-master-file for blood establishments (SMF-BE), inspection summary report]. These documents facilitate the harmonisation of inspection processes and should assist in the documentation of observed deviations. Complementary to this guide, inspection criteria that cover the regulatory standards that apply within the EU based on the EU blood directives have been developed. These include cross-references to commonly used standards. It is anticipated that these criteria will prove useful for trainees involved in regulatory and self-inspections. The criteria, however, are not exhaustive and authorities and blood establishments may wish to supplement this material with additional requirements.

Each section of the guide contains a description of the inspection criterion and example evidence that should be obtained during the inspection to demonstrate compliance. Each criterion is identified by an individual number (criterion no.), a reference to the applicable standard(s) and identifies the sub-process or control point.

The criteria listed in the guide can be used to assist the inspector in preparing the inspection record. For the less experienced inspector it may be suitable to transfer these directly to the inspection record (with any additional criteria identified). Depending on experience, others may prefer to record only the clause and a short description of the area inspected. The guide

may be also used as a reference by inspectors of competent authorities who wish to get assistance in the implementation of inspection criteria and standards based on the EU blood legislation.



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
	Process(es) covered: Licensing requirements			
LR 001 2002/98/EC Art. 5 – Licensing and authorisation Art. 11. Quality system for blood	Licensing requirements	GMP Annex 14 PIC/S Chap. 2 EDQM (CoE), Chap. 1	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.

Figure 2: Inspection Cross reference guide for good practice following the EU blood legislation developed by the EuBIS experts. The cross-reference guide will assist blood establishments in implementing quality system requirements based on EU legislation.

5 Self-inspections of blood establishments

Inspection of blood establishments integrated in quality management (quality assurance) is addressed in Directive 2002/98/EC, Article 8 and Directive 2005/62/EC, Annex, Section 10.

5.1 General requirements for self-inspections

There are several equivalent definitions for the expression 'self-inspection'. Although it is very often used interchangeably with the terms 'audit' or 'internal-audit', for the purpose of this Manual only the term self-inspection is used.

Self-inspections are an essential part of any quality management system. Section 10 of the Annex to Directive 2005/61/EC clearly defines the need to perform regular self-inspections by blood establishments and to use them for improvements.

'Self-inspection or audit systems shall be in place for all parts of the operations to verify compliance with the standards set out in this Annex. They shall be carried out regularly by trained and competent persons in an independent way according to approved procedures. All results shall be documented and appropriate corrective and preventive actions shall be taken in a timely and effective manner'. (Directive 2005/62/EC, Annex. Section 10, Para 1 and 2).

A self-inspection should be conducted by trained and competent persons managerially independent of the department concerned. Its purpose is primarily to assess, in practice, if regulations, standards and guidelines defined in the overall quality management system are correctly implemented. These inspections will also offer the chance for personnel at all levels to

discuss processes and quality relevant steps. Self-inspections should include data from trend analysis of non-compliance, deviations and errors to focus on processes in need of improvement. If performed properly and effectively, self-inspections are an ideal tool for optimising processes, implementing preventive measurements and thus supporting continuous improvement of blood safety and component quality. Furthermore, self-inspection will prepare the blood establishment for regulatory inspections carried out by the competent authority or accreditation body.

Regulatory inspections, on the other hand, are formal and objective controls according to adopted standards to assess compliance with European and other relevant blood legislation and to identify problems. It has to be noted, however, that regulatory inspectors cannot examine all areas and documentation during an inspection. They are not responsible if, due to limited time, scope or inability to conduct certain processes, they do not observe a particular non-compliance.

In contrast to the national regulatory or competent bodies, the blood establishment is fully responsible for any blood and blood components manufactured and distributed. It is of vital interest, therefore, for blood establishments to establish solid self-inspection procedures.

Depending on the size of the blood establishment, self-inspections may be organised differently. Large blood establishments or services comprising several blood establishments tend to implement a peer-inspection system. This is carried out by inspectors from different facilities within the same blood establishment. Often, the ‘peer’ inspection is based in a blood service which is comprised of different institutions at different locations that provide experts with equivalent skills and knowledge. Alternatively, ‘peer’ inspections can be organised through cooperation between national or regional blood services.

A self-inspection is carried out by a team comprising several individuals. Very often the team consists of only two inspectors. One will inspect the quality system and in the case of peer inspections a technical specialist may also be involved. The lead inspector is responsible for coordinating the activity of the team and presenting its findings and outcomes. In smaller blood establishments, the self-inspections are frequently carried out by one individual.

5.2 Requirements for integrated self-inspections

The following section gives a general description of an integrated self-inspection system. Blood establishments interested in modifying or adapting their self-inspection system are advised to perform a '*stage*' / rotation in a service with extensive experience in order to assist in the development of their own implementation plan.[21]

Definitions[22]

Critical non-compliance: Any non-compliance in a process or a written procedure which directly affects the safety of the donor or patient.

Major non-compliance: A serious non-compliance in a process or a written procedure but does not on its own affect the safety of the donor or patient.

[21] Contacts and references of services willing to assist in these '*stages*' / rotations are available through the EuBIS Office. (www.eubis-europe.eu)

[22] There are similar terms in use for describing deficiencies. In this manual deficiencies and /or non-conformances are defined as non-compliances (see also SMF-BE in Annex) II of this manual.

Other significant non-compliance: A non-compliance in a system or process or there is insufficient information to classify it as a major or critical.

Observation - an inadequacy in a system or process that is not a failure to comply with a standard.

There could be a combination of several 'other' significant non-compliances, none of which, on their own, may be major or critical, but may together represent a major or critical non-compliance. These should be clearly explained and reported as such.

Responsible Person - person(s) named on the Blood Establishment licence

Inspection Master Plan - This defines the self-inspection frequency for each department / institution including the period (dates), the inspection duration (e.g. half-day or two-day inspection), the scope, and identifies the inspector (or lead inspector, when more than one inspector is involved). The inspection master plan should also include the criteria adopted to formulate the plan (e.g. a plan could envisage one comprehensive inspection and two specific inspections in particular sectors of the blood establishment; the criteria for this choice should be clearly expressed).

5.2.1 Responsibilities

Quality assurance

The quality assurance will be responsible for preparing a draft annual self-inspection calendar, circulating this calendar to the inspected (e.g. department, etc) and publishing the approved self-inspection calendar. Subsequently, the quality assurance department will allocate the lead inspector and organise self-

inspection teams depending on the scope of the inspection to be performed. In a 'Peer' inspection system this will also include organising respective technical experts. Approval of the annual self-inspection calendar is given by the self-inspection stakeholders. In general, these are senior staff members responsible for particular areas of the service (e.g. executive management, institutional director, department heads).

Within blood services comprising several blood establishments, quality management (QM) can comprise local QA departments. These will assist in the co-ordination of the corrective action plan by monitoring its progress, and verifying if appropriate actions are completed and implemented. The local quality assurance office notifies the head of QM when all non-compliances are addressed.

Final approval of the corrective action plan is the responsibility of the head of quality assurance. The QA head will also decide about discussing structural deficiencies or non-compliances (e.g. GMP facility renovations) with the management. In addition, regular briefing sessions (e.g. management review) should be organised with management (e.g. Chief Executive Officer (CEO), Director) at least annually, in order to summarise non-compliance, errors, preventive measurements implemented including trend analysis of component quality and tests performance. This QA management meeting would also define potential steps for continual quality improvement in-line with the design planning for management decision taking for the future (e.g. implementation of new products or test procedures).

Lead self-inspector

The lead self-inspector agrees on the date of the inspection with the establishment to be inspected, plans it, and issues inspection documentation. He/she will also manage the inspection team and chair the opening and closing meetings during the self-inspection. The lead self-inspector defines the number and type of non-compliances observed and prepares the inspection report

including a plan for corrective actions. The lead self-inspector will subsequently monitor the transposition (realisation) of this plan, arrange review meetings if appropriate and finally approve the corrective action plan.

Self-inspector

The self-inspector performs the inspection and documents non-compliance details.

The Inspected

The inspected provides guidance to the inspector and in co-operation with him/her proposes and agrees on corrective actions and timescales. The inspected is responsible for implementing the corrective actions within the agreed timescales and informing quality assurance when the corrective actions are completed.

5.2.2 Education and training of inspectors

The education and training of inspectors requires a documented training programme for these personnel. The European blood legislation does not give any restrictions. However, it is generally accepted that regulatory 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. This will include knowledge of:

- national and international regulations and standards including the European 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, and
- principles of good manufacturing procedures.

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). The inspector should also be trained in inspection techniques (e.g. risk-based approach, top down or bottom-up system inspections), communication skills ('open questions'), objectivity (including ethical behaviour) and accurate record keeping for the purpose of documentation. Training of self-inspectors in large blood services will rely on experienced personnel. In contrast, small blood establishments may decide to organise training programmes together with other blood services in their region.

5.2.3 Evaluation criteria for deviations, non-compliances and corrective action

Deviations and non-compliances observed during self-inspections should be classified in order to assess the importance and time scale for correction. There are several schemes used to classify them. Deviations identified during external inspection can be classified as critical, major and other significant non-compliances. The classification of non-compliances interacts with the type of corrective action needed.

5.2.4 Associated documents

5.2.4.1 Self-inspection record Trail

The self-inspection record trail is used to document the different steps performed during an inspection. An inspection trail gives information on the following:

- Date of self-inspection
- Inspection reference (e.g. inspection number)
- Organisation / department involved (this will extend to section and activities)
- Scope of the self-inspection
- Attendance list (those involved in the inspection). These individuals should be referred to in the final inspection report.
- Inspectors (their role, name and signature). With respect to a self-inspection report it should only be signed by the lead inspector on behalf of the team.
- List of clauses / areas examined including notes on details observed during the inspection. This can also include the names of staff present during the self-inspection and / or those with whom there has been an interaction.
- List of non-compliances and/or deviations observed. These non-compliances should give a precise indication as to the topic and the measures for correction.

A template based on the EU-SOP format[23] can be found in Audit / Inspection - Training guide complementing the EuBIS manual. The self-inspection record trail can serve as or be accompanied by an '*inspection checklis*t'.

[23] The EU-SOP format has been developed by the EU-Q-Blood-SOP Project based on the requirements of the European Union blood legislation (www.eu-q-blood-sop.de)

5.2.4.2 Self-Inspection Guide

The self-inspection guide details those requirements that should be inspected. Although restrictive, it enables the inspector to cover the essential areas. Several aspects are similar to those required by the inspection trail.

- Date of inspection
- Inspection reference (e.g. inspection number)
- Organisation / department involved (this will extend to section and activities)
- Scope of the inspection
- Attendance list (Complete list of all individuals present during the opening and closing meetings as well as those involved in the inspection). These individuals should be referred to in the final inspection report.
  Remark: Staff interviewed during the inspection are not required to sign. These individuals can be mentioned in the inspection (finding) report.
- Personnel that are essential during the opening and / or closing meetings are:
  - Inspection guide (the person from the organisation responsible for coordination during the self-inspection)
  - Staff involved in the inspection [e.g. Institutional director, department manager, lead technician(s)]

  The names and signatures of these personnel should be recorded.

The self-inspection guide will be based on relevant standards for a particular section / activities to be inspected (e.g. blood component testing). This list will use cross-references to existing applicable standards. Several common standards are presented in the EuBIS inspection guide. It would be advisable, therefore, to refer to these standards as a platform for designing a checklist.

The minimum elements for inclusion in the inspection record trail format would consist of the following:

- Criterion Number (e.g. 1,2,3, etc,)
- Description of criterion
- Findings / evidence
- Conclusion / outcome (classifications)

An example of such a self-inspection record trail is given in the Audit / Inspection Training guide complementing the EuBIS manual

5.2.4.3 Self-inspection summary report

The self-inspection summary report can be free-form, completely narrative or follow a set template. However, whichever format used, the following elements must be included:

- Date of inspection
- Inspection reference (e.g. inspection number)
- Organisation / department involved (this will extend to section and activities)
- Scope of the inspection
- Attendance list (names should be listed, however reference should be made to the self-inspection trail and / or self-inspection checklist for their signatures).
- The inspector and his / her role (i.e. lead inspector, expert, etc.). In general the self-inspection report, sections of which may be drafted by different individuals, will be only signed by the lead inspector on behalf of the inspection team.
- Number of non-compliances
- Description of non-compliances including classification
- Corrective action request
- Corrective and preventive action (CAPA) to be completed by:
    - Department
    - Person

    - Date
- Corrective action
    - Taken
    - Not taken
- Corrective action verified by (name and date)

5.2.4.4 Site-Master-File for blood establishments (SMF-BE)

The site-master-file modified for blood establishments (SMF-BE) comprises information on the activity profile of the blood establishment, including the names of key personnel, facilities, equipment, documentation, contracts / agreements, complaints and product recalls and the quality system.

Information given by the SMF-BE will be used by the competent authorities in preparing and conducting the inspection. It would be advisable for the blood establishment to regularly verify the information in the SMF-BE during self-inspection in order to be prepared for any regulatory / external inspection. Further details are presented in **Annex I.**

5.3 The integration of quality risk management into self-inspection

Quality risk management, as set out in Volume 4, Annex 20 of the 'Rules Governing Medicinal Products in the European Union'[24] is a 'systematic process for the assessment, control, communication and review of risks to the quality of a product across its lifecycle. It can be applied both proactively and retrospectively.'

[24] EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 20. Quality Risk Management.

With respect to self-inspection, integration of a quality risk management system in the process can help to ensure that any assessment of the risk to quality is based on scientific knowledge, experience with the process, and is linked to patient protection.

Annex 20 provides a schematic of a quality risk management process.

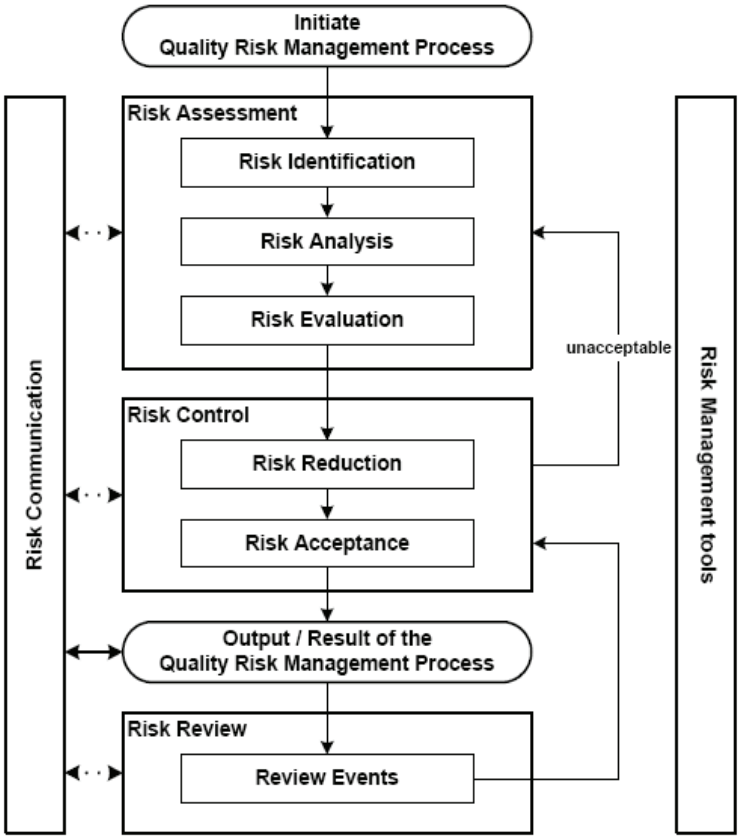


Figure 3: Overview of a quality risk-management process

Effective quality risk management can help blood establishment administrators to reach better and more informed decisions as well as increase the confidence of regulators in its ability to deal with potential risks. To be effective, however, both blood establishment and regulatory personnel require training in decision-making processes and quality risk management outcomes.

Note: Additional information on the Quality Risk Management process is elaborated in Volume 4, Annex 20.

5.4 The self-inspection process

This section summarises a detailed step-wise description of a self-inspection. In general, it will be essential to set-up a central documentation system in the quality management department. The quality management / assurance together with the key responsible persons will set-up an inspection master plan. It will define the self-inspection frequency for each department / institution including the period (dates), the inspection duration (e.g. half-day or two-day inspection), the scope and the inspector. Based on this inspection master plan the following steps will be pursued.

Before the self-inspection

- **Prepare self-inspection plan and assign inspection team** (5.4.1)
  - Ensure that up-to-date information is available on the processes carried out in the department to be inspected.
  - Identify significant changes made within the department since the last self-inspection, and any changes to the inspection standards.
  - Review the previous self-inspection and external inspection report for the department.

- Define the detailed scope and assign the inspection team and responsibilities.

- **Agree inspection date and verify inspection details** (5.4.2)
  - Based on the scope, define the inspection agenda (time scale), the staff (inspected) required to be present and inspection date.
  - Inform the inspected department / staff and agree on a date and time scale for the inspection.

- **Prepare the inspection trail based on the self-inspection guide**
  In order to prepare the trail, refer to the EuBIS template given in Annex I of the *Audit / Inspection - Training Guide* complementing the EuBIS manual.

During the self-inspection

- **Perform the inspection and prepare draft report** (5.4.3)
  - Open a self-inspection meeting ('opening meeting'), confirm the audit scope, agenda and audit process.
  - Conduct the inspection following the checklist and agenda. During the inspection, use an inspection trail (refer to the EUBIS self-inspection record / trail template).
  - At the end of the inspection, draft a report of the findings / outcomes including proposed target dates for corrective action (this should be done by the lead inspector, may be hand-written or using the inspection report format based on the EuBIS template).
  - Close the meeting (agree on the findings / outcomes including classification of the findings observed during the inspection). Agree who will respond to the inspection and confirm the target date(s).

After the self-inspection

- **Final inspection report and corrective action plan** (5.4.4)
- **Monitor progress against corrective action plan** (5.4.5)
  - Evaluate and confirm the acceptability of the received response (including action-plan) from the inspected department.
  - Follow-up the action-plan and if necessary plan a follow-up inspection.
- **Close inspection** (5.4.6)

The following sections describe in more detail the step-wise organisation of the self-inspection process.

5.4.1 Prepare inspection plan and assign inspection team

Step	Responsibility		Description
	Quality assurance (QA)		
1	Prepare draft audit calendar (inspection master plan).	1.1 1.2	Prepare draft annual inspection calendar based on previous years inspection performance Define scope of individual inspections (Scope should be officially approved by the BE's responsible person)
	Inspection Stakeholders Group		
2	Approve inspection calendar.	2.1 2.2 2.3 2.4	Review draft annual inspection calendar. If required amend annual calendar. Approve annual inspection calendar. Document approval in minutes of meeting. Target: 4 weeks before the start of the inspection calendar
	Quality assurance (QA)		
3	Approve inspection calendar (QA-Head)	3.1 3.2	If required by the inspection Stakeholders Group amend annual inspection calendar. 'Approve' amended inspection calendar

4	Allocate Lead Assessors. (in small BE the lead assessor, auditor, head of QA may be the same person)	4.1 4.2	Allocate Lead inspector to each inspection and document the audit scope. Inform Lead inspectors of the inspections allocated to them (e.g. by e-mail) Target: 4 weeks before the start of the inspection calendar
5	Establish inspection team	5.1 5.2	Allocate inspectors to the inspection and document the role. Decide on technical experts needed, either In-House or external. Inform inspectors and/or technical experts of inspection allocated to them.

5.4.2 Agree inspection date and verify inspection details

	Lead Inspector		
6	Agree date of inspection.	6.1 6.2	Contact the site Target: 4 weeks before the month the inspection is scheduled. Agree a date for the inspection during the scheduled month. Liaise with site via quality assurance (QA)

7	Prepare inspection plan.	7.1 7.2 7.3 7.4	Review audit scope and confirm details with QA*. If required amend audit scope*. Review last inspection report for site. Prepare inspection plan. May include pre-audit site visit. * Major changes of the scope will require the approval of the BE's responsible person (see step 1)
8	Verify inspection details via quality management department	8.1	Verify details to Site confirming: • Date and time of inspection • Who the inspectors will be • Inspection scope and plan • Need for a guide(s) • Other requirements (e.g. meeting room, IT facilities) Target: 4 weeks before the month the inspection is scheduled.
9	Contact audit team.	9.1 9.2	Verify details with inspection team and send the following documents: • Inspection scope • Inspection plan • Inspection worksheets Verify arrangements for accommodation etc.

5.4.3 Perform the inspection and prepare draft report

	Inspection Team chaired by lead inspector		
10	Convene opening meeting.	10.1	Convene opening meeting with inspected to: • Perform introductions • Explain purpose of inspection • Confirm scope of inspection • Explain that the inspection will be conducted against guidelines, policies and procedures • Explain how the inspection will be conducted • Agree the timetable
11	Perform inspection. Inspection tools & techniques available: • Inspection worksheets • Ask questions • Observe activities • Check documents and records	11.1 11.2 11.3 11.4 11.5	Perform inspection. Ask inspected to confirm information that may indicate a non-conformity. Document findings clearly. Decide if findings are: • Critical non-conformity • Major non-conformity • Other non-conformity • Observation Inform Lead inspector of findings

12	Prepare draft report.	12.1 12.2	Prepare draft inspection report. Co-ordinated by Lead inspector Document the following using Inspection Report Template: • Inspection details • NC details • Applicable clause (Guideline, policy, procedure) • Severity of NC • Cause / Reason • Any observations • Exclusions to inspection scope (e.g. processes not inspected)
13	Convene closing meeting. Chaired by Lead Inspector Attended by local staff members, responsible persons and quality assurance	13.1	Convene closing meeting to: • Thank audited and staff • Review findings • Correct inaccuracies • Explain reporting arrangements • Highlight findings which require immediate attention • Mention any activities which were impressive • Invite questions or comments

5.4.4 Prepare final inspection report and agree on corrective action plan

	Lead inspector		
14	Prepare final inspection report.	14.1 14.2	Prepare final inspection report using inspection report template. Post and/or E-mail final report to: QA at inspected site Target: within 10 working days of closing meeting
15	Document inspection and non-compliance details	15.1 15.2 15.3 15.4	Document inspection date and performance in annual inspection plan. Document inspection and non-compliance details in 'central' inspection system. Attach an electronic copy of the inspection report to the inspection record in your quality system. Inform 'centre' QA that the inspection report has been documented.
	QA at Inspected Site		
16	Receive inspection report.	16.1 16.2	Receive inspection report from Lead inspector. Send inspection report to inspected. (e.g. via e-mail)

17	Convene meeting(s).	17.1	Convene meeting(s) with inspected to review inspection report and prepare corrective action plan.
18	Prepare corrective action plan. Realistic and based on risk and complexity of corrective action	18.1 18.2 18.3	Review inspection report. Agree the following with QA at audit site: • Underlying problem • Corrective action(s) • Target completion date • Person responsible for corrective action • Cause / reason If required refer non-compliance to a National Officer / Strategic Head if issue cannot be resolved locally.
	QA at Inspected Site		
19	Document corrective actions	19.1 19.2	Document corrective actions by preparing • required documents • Changes in procedures (e.g. validation data) Define individual 'Supporting Actions' if corrective action is required by more than one department.
	Lead Inspector, Head of QA and Site QA		
20	Review corrective action plan.	20.1 20.2 20.3	Schedule meeting to review corrective action plan. Review corrective action plan

			Are proposed corrective actions and target dates acceptable? • List number of acceptable and not-acceptable items • Sent summary of these items to inspected • Agree on revised corrective action plan Target: within 30 working days of the closing meeting
21	Approve corrective action plan.	21.1	Approve corrective action plan and document agreed corrective action plan in the QA-system.
22	Perform corrective actions.	22.1 22.2 22.3	Perform corrective actions as agreed in corrective action plan. Inform QA at inspected site when individual corrective actions have been completed. Inform QA at inspected site if the corrective action cannot be completed by the target date and the reason why.

5.4.5 Monitor progress against corrective action plan

	QA at Inspected Site		
23	Monitor progress against corrective action plan.	23.1	Monitor completion of corrective actions against

		23.2	corrective action plan.
		23.3	Receive notification that corrective action has been completed.
		23.4	Verify that corrective action has been completed and is
		23.5	effective.
		23.6	If required amend target corrective action date and note reason why. Reason
		23.7	for change must be justified
			Communicate amended audit plan and time scale to inspected.
			Document the actual corrective / supporting action details.
			Close the individual non-compliance list.
24	Notify Head of QA.	24.1	Notify Head of QA that all Corrective Actions have been completed.

5.4.6 Close inspection

Step	Responsibility		Description
28	Close inspection.	28.1	Receive notification from QA at inspected site that all
		28.2	corrective actions have been
		28.3	completed.
			Review corrective actions.
			Document that inspection is closed.

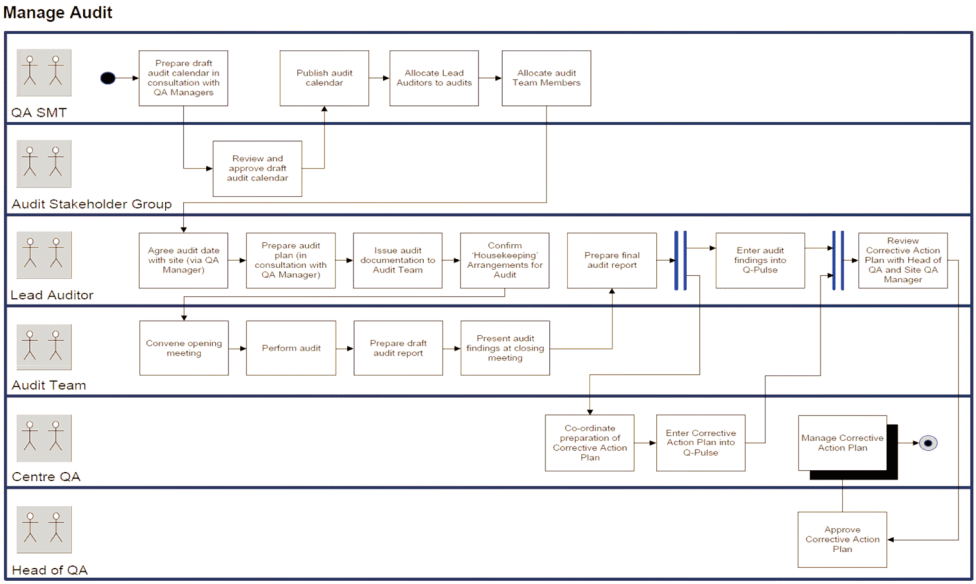


Figure 4A: Example flow-chart for an integrated self-inspection / audit system (NHS-BT)[25]

[25] The flow-chart represents the self-inspection process used by the National Health Service Blood and Transplant (UK) in performing peer-audits (© NHS-BT).

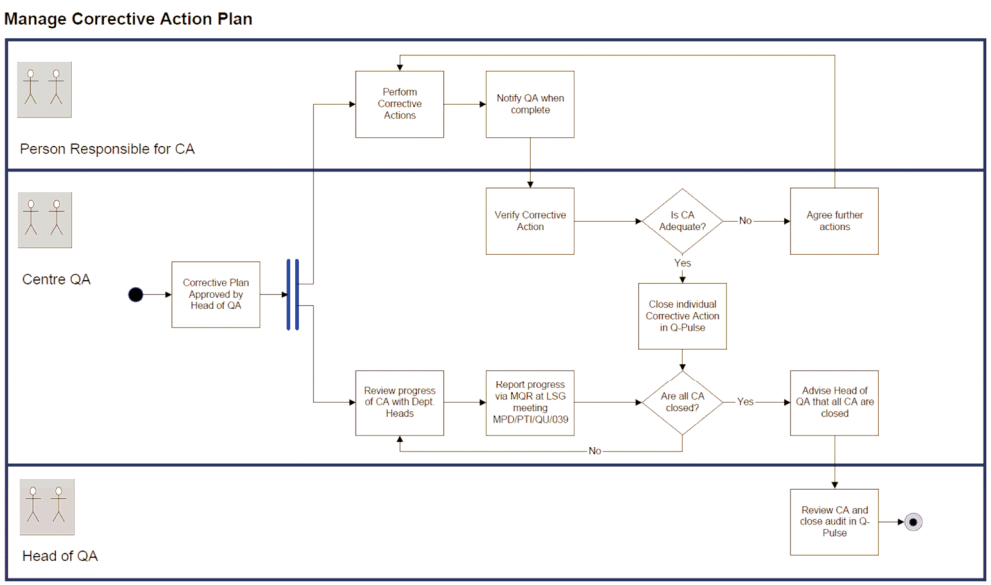


Figure 4B: Example flow-chart for an integrated self-inspection / audit system (NHS-BT)[26]

[26] The flow-chart represents the self-inspection process used by the National Health Service Blood and Transplant (UK) in performing peer-audits (© NHS-BT).

6 Inspections of blood establishments by competent authorities

Specific requirements exist for the inspection of blood establishments by national regulators [competent authorities (CA)]. Directive 2002/98/EC (Article 8 para. 1) requires that Member States organise inspection and control measures to ensure that blood establishments comply with its provisions. These procedures, which are conducted by officials representing the CA, involve blood establishments and facilities of third parties entrusted to carry out evaluation and testing procedures. They include the collection of samples for examination and analysis, and require the examination of documents relating to the inspection (para. 3)

The regulatory inspection process serves as a formal and objective method, according to adopted standards, for assessing a blood establishment's compliance with the European Union's blood legislation and other relevant requirements and identifying problems and deficiencies or non-compliances. For a better understanding of this process, the following chapters provide background on several aspects related to the implementation of this legislative requirement. Although it focuses on the EU blood legislation, it has taken into account the inspection criteria and standards developed by the EUSTITE project consortium for tissues and cells.

General requirements

6.1 Qualifications of Inspectors

6.1.1 Education

Although no specific requirements related to the education and experience of inspectors of blood establishments are set out in the European Union's legislation, it is generally accepted that they possess a diploma, certificate or other evidence of formal qualification in the field of medicine, pharmacy or other life-science disciplines.

These requirements reflect to a large extent those required by Directive 2002/98/EC (Article 9, para. 2a) for the 'responsible person' (RP) of a blood establishment.[27]

6.1.2 Experience

Practical experience in operational areas of blood or tissue and cell establishments has been of significant benefit for someone interested in becoming an inspector. Knowledge of hospital procedures, manufacturing aspects in the pharmaceutical industry, or regulatory requirements has also proven to be 'beneficial'. A valuable trait is the ability to communicate effectively and with discretion and tact. Once recruited, inspectors are usually given basic / induction training (e.g. quality systems) before receiving specialised training in selected areas (e.g. blood components). Their competence is assessed periodically.

[27] NOTE: The EUSTITE guidelines for the inspection of tissue and cell procurement and tissue establishments
suggests, that '*at least one member of the inspector team should have the same level of qualification as the responsible person of the institute to be inspected or have the necessary education and experience to inspect such a site*'.

6.1.3 Training

In general, there are no specific requirements given by the EU legislation for an inspectorate training programme.

However, Member State inspectors have qualifications and experience that are needed to carry out the functions of this position. Nevertheless, however well-qualified and experienced the individual may be, basic training and orientation may have been required due to the specialised nature and responsibilities of the job. This is normally provided by the national inspectorate.

Basic training covers general topics essential for the inspector, including principles of inspection techniques (e.g. risk-based approach). It also includes;

- a number of site inspections with a certified inspector initially as an observer,
- at least two site inspections as a trainee,
- followed by two site-inspections as an inspector supervised by an experienced (lead) inspector.

Qualification of an inspector by the competent authority, which includes the evaluation of the individual's performance, enables the trainee to become a lead inspector.

Depending on the education and experience of the candidate inspector, the basic training programme may be omitted and *specialised training* initiated directly. It focuses on topics essential for the optimal qualification of the inspector. This specialised training includes a familiarisation visit to a blood establishment in order for the candidate to become acquainted with its overall processes, functions and operations. These visits are preferably arranged with a BE, that is not audited by the same CA.

In order to keep the inspectors up to date, the specialised training programme is normally repeated at regular intervals. In addition on-going training is normally organised.

The following topics are normally covered by the training programmes.

Basic training programme

- European blood legislation (Directives)
- European legislation for medicinal products
- European and International Quality management standards in place for blood establishments [e.g. GxP regulations (GMP, GDP, GLP), Council of Europe (CD-P-TS), PIC/S, WHO]
- Accreditation, designation, authorisation or licensing systems in the Member State
- National legislation in place in the Member State
- National health systems and organizational structures for human blood and blood components in the Member State
- Organisation of national / international regulatory authorities and inspectorates
- Organisation of the national blood supply.
- Inspection techniques (e.g. risk-based approach, top-down or bottom-up system inspection)
- Communication skills (including 'open questions')
- Objectivity including ethical behaviour
- Accurate record keeping for the purpose of documented evidence

Specialised training programme

- Principles of quality management (e.g. risk and error management, change control)
- Knowledge of the processes and equipment to be audited by theoretical and practical training (collection, testing, processing, storage and distribution). The practical training may comprise familiarisation visits to blood establishments
- Data processing and protection systems
- Diseases transmissible by blood

- Laboratory techniques / In-vitro diagnostic tests (screening tests)
- General hygiene
- Detailed design, validation and maintenance of environments
- Haemovigilance (including look-back procedures)
- Risk and error management

On-going training

- Standards, guidelines and legislation
- New techniques
- State-of-the-art related to blood and blood components

6.1.4 Responsibilities

The inspector's responsibility is to verify that the information provided by the blood establishment is accurate and that all procedures in place are in compliance with the European blood legislation.

As a representative of the competent authority he / she has a written mandate to carry out inspections and control measures[28]. This includes the compilation of a detailed report about the blood establishment, enabling the competent authority to accredit, designate, authorise, or license it. The inspector also assesses the suitability of the processes in use for the preparation of blood and blood components.

Inspectors, however, cannot examine all areas and documentation during an inspection. Consequently, they are not responsible if, due to limited time, scope or inability to conduct certain processes, they do not observe a particular non-compliance.[29]

[28] Directive 2002/98/EC, Art 8.
[29] Eustite inspection guidelines, Chapter 2

In carrying out the inspection, an inspector, as a rule, is aware of the particular situation (e.g. nervous tension?) created by external audits. The inspection style attempts to create a positive and open atmosphere with indications that the inspection will not be limited to the disclosure of deficiencies or non-compliances. With respect to the category of deviation observed, the inspector gives clear causative explanations (refer to Chapter 7.2.9 - Inspection completion). If, however, he / she have the impression that the inspected does not consider or respect his / her observations, the inspector provides clear indications on the regulatory and legal background and the respective clause.

6.1.5 Confidential information

Confidentiality is an essential aspect of the inspection process. Therefore, the national inspectorate and inspectors advice the blood establishment to be inspected that confidential information obtained in oral, written or observed form before, during or after the inspection process, will be handled in compliance with legal requirements for the protection of confidentiality and those for disclosure for the protection of public health.

Respecting confidentiality requirements is of particular importance in situations where a blood establishment holds an individual license or patent for a particular test or manufacturing procedure or where a third party has given a licensing agreement for certain procedures.

The inspection of personnel files (dossiers) for evidence of qualifications requires a sensitive approach, in that these data are highly confidential and access for the inspector may be limited by national regulations.

In order to overcome strict confidentiality requirements related to personnel, a summary dossier, which covers the key education

and qualifications of the staff with respect to their functions, may be used. This would include, in particular, the continuing internal or external education of the staff member.

6.2 Inspection planning and capacity assessment

An important and critical first step in attaining a successful inspection is correct planning and documentation at the national level. The competent authority (inspectorate) is responsible for setting up an inspection plan, in order to fulfil the minimum requirements of Directive 2002/98/EC that 'inspections have to be performed at least every two years'.

The planning, therefore, first requires an overview of the exact number and activity profiles of the blood establishment(s) in the Member State, taking into account observations / deviations of previous inspections. This includes reported changes of the activity profile (e.g. registration profile of blood components) or incidents / events (e.g. serious adverse events) reported by the institution or third party.

Depending on the activity profile, the competent authority decides on the qualification and the number of inspector(s) required to conduct the inspection. In general, the relationship between qualified inspectors per blood establishment varies between Member States depending on their size and activity profile (Table 3).

A newly formed inspectorate in a Member State may find it useful to draft an annual inspection master plan. These master plans will require assigning inspection teams and prospective dates for inspections and thus assessing the capacity.

Table 3: Relation between trained inspectors and blood establishments in various Member States (EuBIS survey 1.0, 2008)

Member State	Inspectors (N)	Blood establishments – BE (N)	Population (Mio)	Relation BE / Inspector
1	10	12	8	1
2	4	78	10	12
3	30	159	82	5
4	6	17	62	3
5	3	64	10	21
6	5	5	4	1
7	45	324	58	7
8	6	5	60	1
9	5	4	10	1

6.3 Classification of inspections

Inspections can be classified according to the time frame in which they are carried out.

6.3.1 Authorisation inspection

Authorisation inspections take place in order to assess a particular situation (e.g. prior to the opening of a new blood establishment / a new facility / new activity in order to confer a processing license). Generally, these inspections require a larger time frame to be carried out and therefore extra time has to be included in the

planning process to allow for flexibility. Assessment of the inspection scope and the composition of the inspection team, however, relies on comparable experience from similar profiled inspections.

6.3.2 Routine inspection

Routine inspection implies a visit to the blood establishment at least every two years in accordance with Directive 2002/98/EC, Article 8. The scheduling of these inspections takes into account the risk-assessment findings of the individual blood establishment from previous inspection reports.

6.3.3 Product / process related inspection (Change control of authorisation)

In addition to routine inspections, situations arise when an inspector is required to look at a particular product / process related change. This may be a new or modified process which may affect product specifications. The inspection of limited areas of a particular blood establishment may be appropriate such as in cases where the blood establishment has given notification of process changes affecting the product specifications and / or previously given authorisation of these processes by the competent authority. The scheduling for and complexity of these inspections depends on the risk assessment by the inspectorate and is based on information provided by the blood establishment. In cases where the risk assessment indicates only minor modifications, written evidence based on validation data may be accepted by the inspectorate and the inspection postponed until the next routine re-inspection.

6.3.4 Event-related inspection

This classification of inspections is scheduled at short notice in cases where serious adverse events or reactions have been reported by the blood establishment or third party. Event-related inspections require a specific risk assessment of the process by the competent authority. In cases where product quality is affected by equipment, material or substances provided by suppliers, the inspection process may also include evidence presented by these suppliers.

6.3.5 Non-routine / unannounced inspections

In contrast to the aforementioned, these inspections are conducted at very short notice or are unannounced. An unannounced inspection is usually as a consequence of a suspected 'illegal or fraudulent activity or serious breach of legal requirements which might expose donors or recipients to risk'[30]. Such inspections may also be as a result of a request from a competent authority in another Member State or another official authority in the Member State itself *to* investigate specific issues. In such serious cases, the inspection team may include representatives from the legal authorities (e.g. public prosecutor).

6.3.6 Frequency of inspections

The elaboration of an inspection programme and the scheduling of visits to individual blood establishments are prepared by the competent authority. In order to adhere to a planned inspection schedule, sufficient resources need to be available and allocated so that the inspections can be conducted successfully.

Although the interval between two inspections and control measures must not exceed two years, other types of inspections could be carried out during this period. These could focus on a

[30] EUSTITE manual, chapter 3

specific area or process (e.g. a non-compliance issue or new procedures) or they could be an office-based review of an updated SMF-BE (see Annex I for proposed standard format).

6.4 Planning for and assessment of an inspection

In planning for an inspection, the competent authority carries out a thorough assessment of the blood establishment. With respect to routine inspections, the following criteria may be used:

- Activity profile of the blood establishment
  - number of blood components produced
  - different production areas or facilities
  - CE certified test systems and / or in-house test systems
  - Type of blood collection (on-site or external) using either mobile units or fixed facilities
- Type and specification of blood and blood components prepared by the blood establishment
  - standard blood components alone, or
  - in combination with related components (e.g. granulocytes, lymphocytes)
  - pharmaceutical production (plasma for fractionation, cryoprecipitation)
- Compliance with the SMF-BE
- Number and severity of non-conformities in a previous inspection
- Number of adverse events / reactions or recalls conducted.

6.5 Compliance verification pending (or in absence of) a site visit

Situations may arise when a site inspection cannot be carried out. On such occasions, another course of action may be taken in

order to ensure that the BE's activities comply both with EU legislation and national requirements. Taking fully into account a risk assessment, a review of an updated SMF-BE may provide the CA with an alternative regulatory approach (e.g. Product / process related inspection instead of routine inspection).

In order to implement this approach, first it is necessary for the CA to receive from the blood establishment an updated SMF-BE. This should be accompanied by documentation on any non-compliance issues and how they have been successfully addressed. The responsible person's signature confirming the accuracy of the information in the SMF-BE should also be included. The file then can be evaluated by an inspector to ensure compliance with regulatory requirements. If a specific technical issue arises, the opinion of an expert, not affiliated with the blood establishment, could be sought.

Information on any modification to an existing process in the blood establishment or the introduction of a new one, however, must be incorporated into the SMF-BE and submitted to the competent authority for approval.

6.6 Composition of the inspection team

The right composition of the inspection team is essential for an efficient inspection. As a rule, the team consists of two inspectors, each with specific experience. Inspections by a single inspector are avoided.

Lead inspector

A lead inspector, with responsibility for coordinating the activities of the inspection and presenting its findings and outcomes, is assigned.

Trainee inspectors

A trainee inspector may accompany the inspection team in order to observe the procedures and gain practical experience. In general, there is only one trainee in the inspection team. Trainee inspectors perform their inspection under the supervision of an experienced inspector.

Technical experts[31]

Technical experts may be invited by the lead inspector to take part in the inspection in order to assist the team when a specific area of technical knowledge is required (e.g. GMP clean room facilities). The technical expert has no inspection mandate. His / her role is to advise the inspection team He / she must comply with any confidentiality agreement and avoid any conflict of interest.

6.7 Type of Inspection

Inspections are of three types according to the area to be looked at.

1) **General system evaluation**: This inspection focuses on the quality management system or site-master file including the overall quality policy in place that ensures the quality and safety of the blood and blood components. Inspection of the quality policy can be carried out through documented evidence. This can be, for example, external proficiency testing results, error and risk management, or document change control.
2) **Technical and process evaluation**: This part of the inspection concentrates on assessing practical performance during working hours. The focus is on monitoring the handling procedures and the qualification of the staff involved at different levels during the collection,

[31] EUSTITE manual, chapter 2

testing or processing for blood and blood components. Technical and process evaluation also comprises the verification of process quality results. This type of inspection is highly important where an innovative process or a very significant change to an authorised process has to be evaluated. Inspections may also focus on quality control or donor testing laboratories or third parties.

3) **Subcontractor or third party evaluation**: The inspection of subcontractors on a Member State's own territory[32] depends on the activity profile of the BE.

   In cases were the testing or processing of blood or blood components is subcontracted fully or in-part to an external organisation clear evidence is obtained on compliance with the quality and safety regulations in place. Examples for this procedure are e.g. external NAT testing for viral markers or supply of blood components derived from / processed by another blood establishment.

   This is done through documentation provided by the subcontractor (e.g. 'conformity statements' given by competent authorities on this subcontractor, lot verification and / or CE conformity statement) or by an inspection of this external site.

   It is the responsibility of the BE to verify the compliance of the subcontractor and/or third party supplier for critical goods (e.g. medical devices, IVD) with the appropriate requirements by the EU legislation and/or any other related regulation(s).

[32] Directive 2002/98, Art 8, Para 3, :'…inspect blood establishments as well as facilities of any third parties on its own territory entrusted by the holder of the designation, authorisation, accreditation or licence referred to in Article 5 with the task of carrying out evaluation and testing procedures pursuant to Article 18'.

6.8 Inspection schedule

Preparation of an inspection schedule prior to the visit to a blood establishment greatly facilitates the work to be carried out. It identifies issues that require attention, particularly if they have been identified during a review of the SMF-BE, outlines concerns that may have been identified during a prior inspection, and notes any other matters that may need to be addressed.

The inspection is also facilitated if the blood establishment is made aware in advance of:

- 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.

7 Conduct of Inspection

7.1 Inspection Procedures – before the inspection

Prior to the inspection of a blood establishment, the team familiarises itself with the organisation. They

- examine the contents of the SMF-BE particularly its adherence to the EU Blood Directives and any relevant national regulations
- review what blood components are prepared and the processes applied
- review the reports from previous inspections
- review follow-up actions (if any) arising from previous inspections
- review any blood or blood component recalls initiated since the previous inspection
- take note of any Serious Adverse Events or Reactions (SAE and SAR) notified since the previous inspection, and
- take note of any national standards or guidelines associated with the site to be inspected.

7.1.1 Information provided by blood establishment (Site Master File for Blood Establishment - SMF-BE)

The blood establishment to be inspected provides the following prior to the inspection.

- SMF-BE (refer to Annex I)
- blood establishment registration and licence
- important changes since the last inspection
- examples of SOPs and other types of documents on request.

7.2 Inspection procedures – during inspection

7.2.1 Opening meeting

The inspection starts with an opening meeting comprising the senior management of the blood establishment, the responsible person (RP) and the quality assurance,

The purpose of this meeting is to

- introduce the inspection team and the BE personnel participating in the inspection outlining their responsibilities
- summarize the purpose and scope of the inspection
- discuss the timetable of the inspection agenda.
- review the management structure of the blood establishment
- identify documentation that may be required during the inspection
- reiterate the confidential nature of the visit

In order to have an overview of the blood establishment site to be inspected, the inspection team requests information on:

- its quality management system
- the organisation's quality policy
- significant changes in facilities, equipment, processes and personnel since the last inspection, and
- how non-compliances have been resolved, if this information has not already been forwarded to the CA.

In cases where there is a team conducting the inspection, a separate room is required for debriefing meetings.

When the inspection is the first visit to the BE, the inspection team may make a short site tour for familiarisation following the opening meeting.

7.2.2 Key elements of the inspection

The essentials covered during the inspection of the blood establishment are:

- Quality management
    - quality system and quality assurance
    - risk management system
- Personnel and organisation
    - organizational structure (personnel, training and qualifications)
- Premises (areas for donor selection, blood collection, testing, processing, storage, waste disposal)
    - e.g. SOPs for decontamination cleaning, cross contamination prevention, etc.
- Equipment and materials
    - e.g. reviewing of process change control [installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)]
- Haemovigilance
    - traceability (e.g. coding system used)
    - adverse reactions or events.
- Blood collection, testing and processing
    - donor requirements (e.g. donor records including donor consent)
    - collection procedures (e.g. SOPs, records)
    - mobile units or external collection facilities (if applicable)
    - laboratory procedures (e.g. handling of samples)
    - testing (e.g. validation records)
    - packaging and labelling

  - release of components (verification of product safety and quality)

- Storage and distribution *(e.g. compliance with Good Distribution Practice)*
- Contract management
- Non-Compliance: deviations, complaints, recall, corrective and preventive actions.
- Self-Inspection, audits and improvement
- Quality control
- Questions raised relating to the assessment of licensing application *(e.g.authorization inspections)*
- Other specific issues identified *(e.g. relevant future changes announced by company)*
- Assessment of the SMF-BE (*e.g. all changes are updated*)

The key elements are further addressed in the EuBIS Audit / Inspection –Training Guide including cross-references to common inspection standards used.

7.2.3 Practical implementation

Implementation of the inspection focuses on verifying information included in the SMF-BE through the assessment of documents on-site, the questioning of staff to determine their competence, visiting facilities and observing / surveying the actual performance of collection, testing, processing, storage and distribution of blood and blood components.

In order to implement the inspection process, it can be divided into the following:

- **System-related inspection**
- **Process/Product-related inspection**

The general system evaluation, which is a static process, focuses on the evaluation of documents that are part of quality management.

In contrast, the process evaluation is an active process, which requires the presence of the inspector at any site of the blood establishment while in operation. This also allows the direct contact with different levels of staff.

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

- The **system-related inspection** will include examples of
  - 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.

[33] The system for performing self-inspections in the organisation is examined, although the reports themselves are not normally read by the inspector.

- management of adverse events and reactions
- look-back procedures
- retention of donation samples for re-testing
- data handling, confidentiality

The **process / product - related inspection** is an active process on-site, which may follow part of the 'vein-to-vein' chain from the blood donor to the distribution of the blood components. This inspection includes examples of

- 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.

[34] Directive 2005/61/EC, Art 1: '*Final destination whether this is a recipient, a manufacturer of medicinal products or disposal, and vice versa*'.

7.2.4 Donor selection and blood collection

7.2.4.1 Donor selection requirements

Directive 2004/33/EC (Annex II Part B) requires every blood donor to provide to the blood establishment not only personal data that uniquely distinguishes them but also their medical history. Therefore, every blood establishment must have donor registers that contain the provided information as well as any clinical data emanating from that donation. The donor register contains:

- Identification of the donor (first name, family name, sex, date of birth)
- Contact details (e.g. address)
- Health and medical history of the donor
- Donor questionnaire
- Informed consent
- Self-exclusion form (if applicable by national regulations).

Maintenance of these records must comply with Directive 95/46/EC on the protection of individuals with regard to the processing of personal data as well as the data protection and confidentiality measures set out in Article 24 of Directive 2002/98/EC. These records must be legible and permanent.

It is recommended that the identity of blood donors is verified by a photo-document (e.g. passport, identity card, drivers licence).

In accordance with Directive 2002/98/EC and / or equivalent national requirements, the inspector checks that the donor screening procedures and their records comply with the requirements regarding: donor identity, list of donor selection / deferral criteria, completion of a donor questionnaire, donor consent, medical history, and the identification of behavioural risks that would lead to donor deferral.

He / she checks to ensure that SOPs exist for the donor selection process and that evaluation is assessed by trained personnel and the outcome documented.

Donor register requirements are inspected by examining examples (documents) of the following from at least two donors:

- Completed donor questionnaires
- Self-exclusion form (if applicable by national regulations)
- Donor consent form
- Donor history (e.g. donation frequency, health and medical history)

The process-related inspection is carried out while the relevant activities are operational. This includes:

- Donor identification
- Health examination
- Pre-donation testing (e.g. haemoglobin, blood pressure, temperature)
- Donor history review and acceptance / deferral

7.2.4.2 Blood collection requirements

With respect to the actual collection of blood and blood components, the inspector verifies that it is carried out under conditions that protect the health of the donor and the safety of the donations, is performed by trained personnel, and is in accordance with SOPs.

The process-related inspection is carried out while the relevant activities are operational. This includes verification of:

- donor identity
- use of sterile single-use needles and collection bags / apheresis sets

- unique labelling of collection bags / apheresis sets and any sampling tubes for testing
- appropriate skin disinfection
- donation time and volume
- storage and transport of blood components

7.2.4.3 Traceability requirements

For each blood or component collected, there must be sufficient data to ensure traceability. This includes:

- identification of the blood establishment
- identification of the donor
- identification / description of collected blood and blood components

In addition, the inspection covers

- reports of any serious adverse event or reaction and the associated corrective action(s).
- Product recall procedures
- Look-back procedures

7.2.5 Inspection of premises and equipment

Inspection includes an intensive visit to all premises of the blood establishment relevant for the collection, testing, processing, storage and distribution of blood and blood components. This includes

- Blood collection and processing areas
- Mobile units or external facilities (if applicable)
- Blood testing area
- Blood and blood component storage areas (released and non-released)
- Relevant equipment for transportation of blood components (including mobile units and/or external facilities)

- Relevant equipment for transportation of issued blood components
- Storage area for disposable materials (e.g. blood bags, test kits, labels)
- Waste disposal areas
- Engineering support (e.g. temperature control system, air conditioning / heating systems)

The inspection also includes equipment such as balances, apheresis machines, cell counters, centrifuges, separators, sterile connecting devices, tubing sealers, freezers, irradiators and the specialised equipment for blood group and infectious-marker testing.

The inspection effort may concentrate in one department (area) of the blood establishment if there are special problems or requirements.

Observations by the inspector are announced immediately to the relevant blood establishment personnel during the premises tour.

7.2.6 Laboratory Testing

Prior to the inspection, the inspector reviews the SMF-BE to determine if the testing is carried out only internally or if there are tests that are subcontracted.

The inspector verifies compliance with the testing requirements of Directive 2002/98/EC (Annex IV) by:

- Following a number of donations through the testing procedure
- Confirming the certification / accreditation for each test used.
- Checking that tests are used according to the manufacturers instructions. In the event, tests are

modified, sufficient validation must be available by the laboratory to prove its performance.
- Checking pre-acceptance procedures prior to the use of new batches of kits.
- Examining the records to prove verification of the test kit performance by internal quality control using
    - reference standards for accuracy of equipment (calibration)
    - working standards (or reference material) tested at intervals for determination of drift occurring during testing.
- Examining equipment log-books and maintenance records
- Checking the results of external proficiency testing

If the blood establishment has subcontracted an external laboratory to perform the testing, the inspector verifies that;

- the blood establishment has a contract with the external laboratory,
- the external laboratory is authorised by the competent authority for the contracted activities,
- the external laboratory is regularly audited either by the BE or an appropriate third party,
- the BE checks its compliance with testing requirements and its regular and successful participation in external proficiency testing.

7.2.7 Processing and storage

The inspector verifies compliance with the legislative requirements by:

- following a donation through the processing steps for standard blood component preparation including the relevant process records.

- reviewing the documentation for special manufacture steps (e.g. washing, splitting, volume-reduction, leukocyte filtration, irradiation)
- examining quality assurance results based on statistical process control in order to monitor blood component specifications (including microbiology testing)
- reviewing the reception procedure for supplies used by the blood establishment (e.g. blood bags including stabilising and additive solutions, solutions for washing cellular components)
- examining equipment log-books and maintenance records
- examining the release process of blood components from the production area
- reviewing non-conformities during processing recorded and the corrective and preventive actions taken)

With respect to storage, the inspector visits storage areas and examines:

- Temperature records and if applicable humidity records
- Separate storage of quarantined blood or blood components and those 'released for distribution'
- Procedures for authorising and transferring blood or blood components from quarantine to 'released for distribution'
- One maintenance and calibration record of a critical piece of storage equipment selected by the inspection team.
- Procedures to ensure restricted access and prevent cross-contamination
- Requirements for storing and disposing of biohazard waste

7.2.8 Transport and distribution

With respect to the transportation of blood and blood components, the inspector verifies that there are written procedures to check that transport and distribution conditions are met. Several packaging containers and their labels are examined and a determination made as to their suitability for the distribution of the released blood and blood components so that their sterility and integrity are maintained. The inspector also reviews procedures in place to ensure traceability.

7.2.9 Inspection completion

Upon completion of the inspection, the lead inspector convenes a meeting with representatives of the blood establishment to summarize the team's findings. Meeting participants include the responsible person, quality manager, any other personnel invited by the responsible person as well as members of the inspection team. Discussions focus on issues related to non-compliance that were observed during the inspection with supportive facts and observations presented. The seriousness of any non-compliance, which may be classified as critical, major or other, is emphasised by the inspector. All relevant observations are discussed so that the blood establishment can undertake corrective actions as soon as possible. In the event of any non-compliance that may put at risk the quality and safety of the blood or blood components, the inspector may request the quarantine and / or cessation of supply of specific components.

A provisional summary statement can be prepared that reflects the inspection's findings. All non-compliances would be listed and reference to the EU Directives and other relevant EU Guidelines and national regulations and standards mentioned. All non-compliances found are listed even if corrective actions have taken place straight away.

Non-compliances or deficiencies can be classified as:

Critical non-compliance: Any non-compliance in a process or a written procedure which directly affects the safety of the donor or patient.

Major non-compliance: A serious non-compliance in a process or a written procedure but does not on its own affect the safety of the donor or patient.

Other significant non-compliance: A non-compliance in a system or process or there is insufficient information to classify it as a major or critical.

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

It is to be noted that there could be a combination of several "other" significant non-compliances, none of which on their own may be major or critical, but may together represent a major or critical non-compliance. These should be clearly explained and reported as such.

Observations (suggestions) obtained during the inspection, where action can be taken by the blood establishment, are listed.

8 Inspection procedures – after the inspection

8.1 Official written inspection report

Following the inspection, the lead inspector prepares an official inspection report within a fixed time frame – ideally no later than four weeks post inspection. A sample template for this report is given in **Annex II**. It covers *inter alia* the scope of the inspection and its findings.

The conclusions clearly identify non-compliances, classified as critical, major or other according to the preceding definitions. The inspector provides a clear statement about the outcome of the inspection and whether the BE is in compliance with EU legislation and national requirements on blood.

The report includes a date by which the BE must submit proposals and a time schedule for rectifying the non-compliances (an action plan).

8.2 Conformity statement

Upon request, the CA can prepare a conformity statement related to the activities of the SMF-BE. This statement indicates that the BE complies with the EU legislation and relevant national regulations.

8.3 Blood establishment's response to inspection report

The inspected blood establishment must notify the competent authority in writing and within certain time limits, in accordance with the classified non-compliances, of the actions proposed.

In case of critical non-compliances corrective actions must be taken by the BE without delay. It is generally accepted that for major non-compliances the BE must respond within 14 days; in case of 'other' significant non-compliances within 30 days of receipt of the inspection report. The response includes the specific steps (action plan) which have been or will be taken to correct the failures mentioned above and to prevent their recurrence.

If corrective actions cannot be completed within 30 days, the inspected blood establishment should state the reason for the delay and the time within which the corrections will be completed (the authority will decide upon the acceptability of the given time period). After this the blood establishment has to report about the final corrections.

The inspector evaluates the proposed action plan submitted by the BE. Based on the evaluation, the inspector recommends to the CA that *i)* it accredits / designates / authorises / licenses the BE, *ii*) that it authorises a second site visit by the inspection team, or *iii*) that it requests additional information regarding corrective actions from the BE before an authorisation recommendation can be made.

8.4 Scheduling re-inspection of the blood establishment

Depending on the overall performance, the type of non-compliances observed during the previous inspection and the blood establishment's response to the inspection report (CA), a re-inspection may be scheduled.

9 Evaluation of the inspection system

In order to ensure that a national inspection system is functioning efficiently and effectively, the CA undertakes periodical reviews of its procedures and practices related to blood establishments. Performance indicators, such as presented below, are used in this review.

- number and type of inspections conducted per year
- number of blood establishments certified/authorised/licensed per year

Performance of inspectors is reviewed periodically. Their training needs are addressed and they are provided with updated training possibilities by the CA.

Whenever possible, the composition of the inspection team varies. This is beneficial for the inspectors who gain knowledge from the experience of others.

Annex I Site master file modified for blood establishments (SMF-BE)

Following the requirements given by Directive 2002/98/EC, the following information must be provided by the blood establishment to the competent authority for the purpose of designation, authorisation, accreditation or licensing in accordance with Article (29)[35]

General information:

- identification of the blood establishment
- name, qualification and contact details of responsible persons
- activity profile
- a list of blood components manufactured.

A description of the quality system, to include:

- documentation, such as an organisation chart, including responsibilities of responsible persons and reporting relationships
- documentation such as site master file or quality manual describing the quality system in accordance with Article 11(1)
- number and qualifications of personnel
- hygiene provisions
- premises and equipment
- list of standard operating procedures for recruitment, retention and assessment of donors, for processing and testing, distribution and recall of blood and blood components and for the reporting and recording of serious adverse reactions and events.

[35] Directive 2002/98/EC

Report of the blood establishment's preceding year's activity. This annual report will include:

- total number of donors who give blood and blood components
- total number of donations
- an updated list of the hospital blood banks which it supplies
- total number of whole donations not used
- number of each component produced and distributed
- incidence and prevalence of transfusion transmissible infectious markers in donors of blood and blood components
- number of product recalls
- number of serious adverse events and reactions reported.

Site-Master-File for Blood Establishments (SMF-BE)

Section A. General Information

Full name of the establishment
Establishment postal address and street address if different
Telephone number
Fax Number
Email address
Contact telephone Number

Activity summary

Please tick the relevant boxes or indicate the activities carried out on site

Activity		Blood and Cells		Processes	
Collection	☐	Whole blood	☐	Whole blood donation	☐
Testing	☐	Erythrocytes	☐	Apheresis	☐
Processing	☐	Thrombocytes	☐	Washing	☐
Storage	☐	Fresh Frozen Plasma	☐	Splitting	☐
Distribution	☐	Plasma for fractionation	☐	Cryo preservation	☐
Importation	☐	Cryoprecipitates	☐	Cell selection	☐

Exportation	☐	Granulocytes	☐	Leukocyte depletion	☐
		Others (please specify)	☐	Freezing	☐
				Irradiation	☐
				Others (please specify)	☐

Section B. Activity–Details

Does the establishment conduct donor testing? Yes ☐ No ☐
(If no, indicate which organization conducts testing

Types of Blood* collected by the establishment:

* Whole blood, autologous or allogeneic
* Blood components, received by apheresis

Types of blood components, processed by the BE

Processing methods
(please add here the room numbers)

Number of donors in the previous year

Number of produced blood components in the previous year

Quality control testing methods

Section C. Personnel

Name of the Responsible person as defined in Directive

(Please attach a brief curriculum vitae)

Name of Establishment Director

Name of Medical Director

Name of the head of quality control

Name of the quality Manager

Name(s) of other relevant key personnel

Total number of the staff

Section C - This should include the following:

- Qualification, experience and responsibilities of key personnel
- Outline of arrangements for basic and in-service training and how records are maintained
- Personnel hygiene requirements, including clothing
- Functional organization chart which identifies roles and reporting relationships
- Organization chart indicating how many people are working in collection, processing, quality control, quality assurance, administration, storage and transport.

Section D. Facilities

- Short description of the site (size, location and adjacent environment)
- Number of outside collection sites, number of mobile sites (busses)
- Description of the processing and storage facilities indicating the number of rooms, their dimensions and

environmental classification, where relevant. Simple floor plan of collection, production and laboratory areas.
- Description of preventive maintenance programs and recording system

Section E. Equipment

- Brief description of major production and control laboratory equipment,
- Qualification and calibration including recording system,
- Arrangements for computerized systems validation.

Section F. Documentation

- Arrangements for the preparation, revision and distribution of necessary documentation for collection of blood and manufacture of blood products
- Standard operation procedures (SOP)
- Donor questionnaire
- Manufacturing records
- Analytical methods
- Product specifications
- Release procedures including the release for sale of finished products.

Section G. Contracts / Agreements with other organizations

Are there any activities carried out by a third party (e.g. testing, cleaning, storage, transport)?

Yes ☐ No ☐

If yes, indicate which steps and name the organization that acts as the third party. Add a copy of the contract, if available.

Section H. Haemovigilance system

SAE / SAR investigation and reporting system and management of look-back procedures.

Section I. Complaints and product recall

Describe the arrangements for the handling of complaints and product recalls.

Section J. Risk management system

Section K. Quality System

Give a short description of the quality system applied at the blood establishment including the self inspection program.

Has the BE been certified by any external body e.g. ISO? Yes ☐ No ☐

If yes, add the certification number and institution

_____

Section L. Signature and Date

Date (DD/MM/YYYY):

_____

Signature of the Responsible Person

_____

Section M. Instructions for the submission of form

The form should be submitted as an initial application for accreditation/ designation/ authorization/ licensing by the Competent Authority for blood. It should be re-submitted prior to any following re-inspection or whenever significant changes in activity, staffing or processes applied have taken place.

Each CA to insert relevant instructions:

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**
1. Introduction	**1.1 Short description of the blood establishment and the activities performed** **1.2 Issuing Date / Version of Site-Master-File or Quality Manual** **1.3 Date of previous inspection** **1.4 Names of Inspector(s) involved in the previous inspection** **1.5 Major changes since the previous inspection**

2. Brief report of the inspection activities undertaken

2.1 Scope of Inspection
Short description of the inspection: Classification (e.g. Authorisation or routine -inspection) and the type of inspection (e.g. system related. , product / process-related)

2.2 Inspected area(s)
(Each inspected area should be specified)

2.3 Activities not inspected
(Where necessary attention should be drawn to areas or activities not subject to inspection on this occasion)

2.4 Personnel met during the inspection
(The names and titles of key personnel met, should be specified < listed in annex >)

3. Inspection Team's findings and observations relevant to the inspection

Relevant headings from Directive 2005/62/EC and 2005/61/EC. (Standards & specifications of quality systems, traceability & notification of SAE and SER)

3.1 General requirements
(quality system and quality assurance; assessment of the SMF-BE or quality manual)

3.2 Personnel and organisation

3.3 Premises including mobile sites

3.4 Equipment and materials

3.5 Documentation

3.6 Blood collection, testing and processing

3.6.1 Donor eligibility

3.6.2 Collection of blood and blood components

3.6.3 Laboratory testing

3.6.4 Processing and validation

3.6.5 Labelling

3.6.6 Release of blood and blood components

3.7 Storage and distribution

3.8 Contract management

3.9 Non-compliance Management of deviations, complaints, recalls, corrective and preventive actions

3.10 Self-Inspections, audits and improvements

3.11 Traceability and notification of serious adverse reactions (SAR) and events (SAE)

3.12 Information technology (IT)

3.13 Other specific issues identified *(e. g. relevant future changes announced by company)*

4. Miscellaneous

4.1 Distribution of Report

4.2 Other

(List attached)

5. Annexes

-
-
-

Section 6: All non-compliances should be listed and the relevant reference to the EU Directives and other relevant EU Guidelines and relevant national regulations and standards should be mentioned. All non-compliances found should be listed even if corrective actions have taken place straight away. If the non-compliances are related to the assessment of the marketing application it should be clearly stated.

Definition of significant non-compliances

Critical non-compliances: *Any non-compliance in a process or a written procedure which directly affects the safety of the donor or patient.*

Major non-compliances: *A serious non-compliance in a process or a written procedure but does not on its own affect the safety of the donor or patient.*

Other significant non-compliances: *A non-compliance in a system or process or there is insufficient information to classify it as a major or critical.*

Note: There could be a combination of several "other" significant ***non-compliances****, none of which on their own may be major or critical, but may together represent a major or critical* ***non-compliance.*** *These should be clearly explained and reported as such.*

6. List of non-compliances classified into critical, major and other significant

6.1 Critical non-compliances

6.1.1

6.1.2

6.2 Major non-compliances

6.2.1

6.2.2

6.3 Other significant non-compliances

6.3.1

6.3.2

	Section 7: List non-compliances type observations obtained during the inspection, where action to be taken by the blood establishment is suggested
7. Suggestions(observations)	*The company should be asked to inform the Inspectorate about the progress of the corrected actions and a proposed time schedule for corrections.*
8. Summary and conclusions	*8.1* *8.2* *This should include a time line for response by the BE (see chapter 7.3 response from BE)*
Final statement	*Compliance or non-compliance with GP/GMP standards, EU or national laws* *The Inspection Report should be signed and dated by the Inspector(s) / Assessors who participated in the inspection*
Name(s) and signature(s)	1. Competent authority or regulatory Institution that has performed the inspection 2. If applicable national regulatory office
Organisations	
Date	

Annex III Documents consulted in Manual's development

EU Legislation

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Union L311, 28/11/2001, p.67.

Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. Official Journal of the European Union, L33, 8/02/2003, p.30.

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. Official Journal L159, 27.6.2003. p.46.

Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. Official Journal of the European Union, L91, 30/03/2004, p.25.

Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events. Official Journal of the European Union, L256, 1/10/2005, p.32.

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. Official Journal of the European Union, L256, 1/10/2005, p.41.

Council Recommendation of 29 June 1998 on the Suitability of blood and plasma donors and the screening of donated blood in the European

Community. (98/463/EC). Official Journal of the European Communities, L203, 21.07.1998, p.14.

European Commission Documents

European Commission, Health & Consumer Protection Directorate-General, Directorate C - Public Health and Risk Assessment, C6 - Health measures. Compilation of Responses from Competent Authorities: Questionnaire on the transposition and implementation of the European Blood and Blood Components regulatory framework, SANCO C6 TB/ci D(2008)/360028.

European or International Regulators

EMEA GMP inspection guidance documents: CoCP (Compilation of Community Procedures) Inspection Conduct (EMEA/INS/GMP/313513/2006) and report writing. EMEA/INS/GMP/313539/2006.

EudraLex, The rules governing medicinal products in the European Union, Volume 4 – EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and veterinary Use, Chapter 1-9., European Commission, Enterprise and industry Directorate-General, 2005.

EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 20. Quality Risk Management.

EudraLex, The rules governing medicinal products in the European Union, Annex 2 – Manufacture of biological medicinal products for human use, European Commission, Enterprise and industry Directorate-General, 2005.

EudraLex, The rules governing medicinal products in the European Union, Annex 14 – Manufacture of medicinal products derived from

human blood or plasma, European Commission, Enterprise Directorate-General, Working Party on Control of Medicines and Inspections, 2000.

ISO Guidelines for quality and/or environmental management systems auditing (ISO 19011).

Council of Europe

Recommendation No. R(95) 15 of the Committee of Ministers to Member States on the Preparation, Use and Quality Assurance of Blood Components.

European Directorate for the Quality of Medicines & HealthCare (EDQM), European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS), (Ed. Council of Europe). Guide to the preparation, use and quality assurance of blood components. 15th Edition, 2009.

World Health Organisation

World Health Organisation, The Clinical Use of Blood – Aide Memoire, Part 1: Principles, products and procedures, Part 2: Transfusion in clinical practice, Part 3: The appropriate use of blood, 2005

World Health Organisation, Quality Management Training for Blood Transfusion Services, Facilitator's Toolkit, WHO/EHT/04.13, 2004

Professional Societies or Projects in the field of blood, tissue and cells

European Union Standards and Training in the Inspection of Tissue Establishments (EUSTITE) – European Public Health Programme co-funded Project, Grant Agreement No 2005204. Guidelines for the Inspection of Tissue and Cell Procurement and Tissue Establishments, 1st Edition, 2007

Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Co-operation Scheme (PIC/PICS) PIC/S GMP Guide for blood establishments, PE-005-3, 25. September 2007

PIC/S Standard Operating Procedure (pi 026-1 October 2006) Qualification and training of inspectors in the field of human blood, tissues and cells.

Joint Accreditation Committee of the ISCT and EBMT (JACIE). Accreditation Manual: Haematopoetic Progenitor Cell Collection, Processing and Transplantation. Version 2.0, 2005

Annex IV Additional references and Project publications

Minimum Requirements for Blood Bank Compliance with Article 14 (Traceability) and Article 15 (Notification of Serious Adverse Reactions and Events) of EU Directive 2002/98/EC. Published by the Irish Medicines Board and the Irish National Accreditation Board. Edited by IMB/INAB Expert Group on Blood and Blood Components and should be used in conjunction with the ISO15189 Standard (available via the IMB homepage)

Guide of Recommendations for Tissue Banking. Edited by SANCO-EQSTB Project participants. Recommendations have been developed as a result of a European project entitled *European Quality System for Tissue Banking* (EQSTB) co-funded by DG Sanco.http://sanco-eqstb.hospitalclinic.org/sanco/index.html

Guidelines for the inspection of cell and tissue procurement and tissue establishments (Eustite). These Guidelines have been produced as part of an EU funded project entitled 'European Union Standards and Training for the Inspection of Tissue Establishments' (see www.eustite.org)

Seidl C, Schellenberg E, Sobaga L, O'Connell M, van Kimpers P, McMillan Douglas A, Gorham M, Letowska M, de Wit J, Seifried E on behalf of the Project's participants. EU-Q-Blood-SOP: Development of European Quality Management in Transfusion Medicine. Transfusion Today 2006; 69:8-10.

Seifried E, Seidl C (ed.) European standard operating procedure (SOP) methodology reflecting European best practice within the area addressing the quality and safety of blood. Manual, Edition 1.0, 2007 published by the EU-Blood-SOP project co-funded by the European Commission, DG Sanco, Public Health and Risk Assessment Directorate (available under www.equal-blood.eu or www.eubis-europe.eu).

Seidl C, O'Connell M, Delaney F, McMillan Douglas A, Gorham M, van Krimpen P, Letowska M, Sobaga L, de Wit J, Erhard Seifried E. European best practice in blood transfusion: Improvement of quality related processes in blood establishments. ISBT Science Series, Vox Sanguinis, Volume 2 (1), 2007; 143-9.

Seidl C, Cermakova Z, Costello P, Delanay F, McMillan Douglas A, Siegel W, Slopecki A, Sobaga L, De Wit J, Seifried E. Development of Pan-European Standards and criteria for the inspection of blood establishments (Eu-Blood-Inspection) – EuBIS. ISBT Congress Macao, Vox Sanguinis Vol 95(Supp 1): P525, 249, 2008.

Seidl C, Nightingale M, Brixner V, Müller-Kuller T, Costello P, van Galen JP, Sireis W, Sobaga L, deWit J, McMillan Douglas A, Delaney F, Siegel W, Cermakova Z, Seifried E. Blood transfusion in Europe: Differences and communalities leading to pan-European standards and criteria for the inspection of blood establishments. The EuBIS Project. Transfus Med Hemother, 2008

Annex V Terminology (Glossary)

Term	Definition	Source
Audit	Documented review of procedures, records, personnel functions, equipment, materials, facilities, and/or vendors in order to evaluate adherence to written SOPs, standards, or government laws and regulations, conducted by professional peers, internal quality system auditors or certification body auditors.	Adapted from the Council of Europe Guide for Safety and Quality Assurance for Organs, Tissue and Cells for Transplantation, 3rd Edition, 2007
Audit programme	A systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.	Council of Europe: EDQM, Guide. 14th edition, 2008
Audit Trail	see **Self-Inspection Record**	
Blood	Whole blood collected from a donor and processed either for transfusion or for further manufacturing	Directive 2002/98/EC
Blood component	A therapeutic constituent of blood (red cells, white cells, platelets, plasma) that can be prepared by various methods	Directive 2002/98/EC
Blood establishment	Any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks.	Directive 2002/98/EC

Term	Definition	Source
Calibration	The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.	EudraLex
Clean area	An area with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area. Note The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products.	EudraLex
Clean / contained area	An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.	EudraLex
Deficiencies, critical	See non-compliance	EMEA
Deficiencies, major	See non-compliance	EMEA
Deficiencies, other significant	see non-compliance	EMEA

Term	Definition	Source
Distribution	The act of delivery of blood and blood components to other blood establishments, hospital blood banks and manufacturers of blood and plasma derived products. It does not include the issuing of blood or blood components for transfusion.	Directive 2002/98/EC
Donation	Blood and blood components collected from an individual and intended for transfusion to another individual (allogeneic) or to the same (autologous).	EuBIS
Donor	A person in normal health with good medical history who voluntarily gives blood or plasma for therapeutic use.	Council Recommendation 98/463/EC
Donor, first time	Someone who has never donated either blood or plasma	Council of Europe: EDQM, Guide.
Donor, regular	Someone who routinely donates their blood or plasma (i.e. within the last two years), in accordance with minimum time intervals, in the same donation centre.	Council of Europe: EDQM, Guide. PIC/S GMP Guide
Donor, repeat	Someone who has donated before but not within the last two years in the same donation centre.	Council of Europe: EDQM, Guide. PIC/S GMP Guide
Expert	Individual with appropriate qualifications and experience to provide technical advice to a CA inspector	EUSTITE Guidelines

Term	Definition	Source
Familiarisation visit	An activity, that includes a visit to a blood establishment in order for a candidate inspector to become familiar with its overall processes, functions and operations.	EuBIS
Good practice	All elements in established practice that collectively will lead to final blood or blood components that consistently meet predefined specifications and compliance with defined regulations	Directive 2005/62/EC
Good Manufacturing Practice	All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with national and international regulations.	PIC/S GMP for blood establishments, PE 005-3, 25 September 2007
Inspection	Formal and objective control according to adopted standards to assess compliance with this Directive and other relevant legislation and to identify problems	Directive 2002/98/EC
Inspection schedule	A schedule prepared by the competent authority for an specific inspection. The schedule comprises the inspection content (based on the scope) and the time frame	EuBIS
Inspection team	A team comprising several individuals that perform an inspection. Very often an inspection team consists of two inspectors. One inspector will inspect the quality system and in the case of 'peer' inspections a technical specialist inspector may also be available.	EuBIS

Term	Definition	Source
Inspection, external (regulatory)	An inspection carried out by the Competent Authority or accreditation body. Formal and objective control according to adopted standards to assess compliance with the European blood legislation and other relevant legislation and to identify problems. (This definition expands on the definitions given by the Directive 2002/98/EC and the CoE Guide).	EuBIS
Inspection, peer	A 'peer' inspection is carried out by inspectors from different facilities within the same blood establishment. The 'peer' inspection will require a multi-centre structure of the same blood establishment that provides experts with equivalent skills and knowledge based at different locations. Alternatively, 'peer' inspections can be organised through the cooperation between national or regional blood services.	EuBIS
Inspection, self-	An inspection conducted by trained and competent representatives of the organisation but managerially independent of the department concerned *Note:* There are several equivalent definitions for this term. The word self-inspection is very often used inter-alia with the terms 'audit' or 'internal-audit'.	EuBIS
Inspector, lead	The lead inspector is responsible for coordinating the activity of the inspection 'team' and presenting the findings and outcomes of the self-inspection. In smaller BE very often the	EuBIS

Term	Definition	Source
	inspections are carried out by a single inspector.	
Inspectorate training programme	An inspectorate training programme covers general topics essential for the inspector, including principles of inspection techniques as well as specific and on-going training.	EuBIS
Non-Compliance	Deficiency observed during an inspection. This term is used similar to the term non-conformance defined by EMEA	GMP
Critical non-compliance	*Any non-compliance in a process or a written procedure which directly affects the safety of the donor or patient.*	GMP
Major non-compliance	*A serious non-compliance in a process or a written procedure but does not on its own affect the safety of the donor or patient.*	GMP
Other significant non-compliance	*A non-compliance in a system or process or there is insufficient information to classify it as a major or critical.* *Note: There could be a combination of several "other" significant non-compliances, none of which on their own may be major or critical, but may together represent a major or critical non-compliance. These should be clearly explained and reported as such.*	GMP
Observation (suggestion)	An inadequacy in a system or process that is not a failure to comply with a standard. Observations obtained during the inspection, are 'non-compliances' where action to be taken by the blood establishment is suggested	GMP

Term	Definition	Source
Pathogen Reduction Technologies (PRT)	Procedures that alter pathogen surface structures and/or penetrate into pathogens irreversibly impeding proliferation of pathogens	Council of Europe: EDQM, Guide.
Processing	Any step in the preparation of a blood component that is carried out between the collection of blood and the issuing of a blood component.	Directive 2005/62/EC
Qualification	As part of validation means the action of verifying that any personnel, premises, equipment or material works correctly and delivers expected results	Council of Europe: EDQM, Guide.
Quality system	The organisational structure, responsibilities, procedures, processes, and resources for implementing quality management.	Directive 2005/62/EC
Quarantine	The physical isolation of blood components or incoming materials/reagents over a variable period of time while awaiting acceptance, issuance or rejection of the blood components or incoming materials/reagents.	Directive 2005/62/EC
Responsible person	A person responsible for - ensuring that every unit of blood or blood components has been collected and tested, whatever its intended purpose, and processed, stored, and distributed, when intended for transfusion, in compliance with the laws in force in the Member State,	Directive 2002/98/EC Article 9

Term	Definition	Source
	- providing information to the competent authority in the designation, authorisation, accreditation or licensing procedures — the implementation of the requirements of [specified Articles] in the blood establishment.	
Risk assessment	Method to assess and characterise the critical parameters in the functionality of an equipment, system or process.	Council of Europe: EDQM, Guide.
Self-Inspection Record	see also audit trail	
Serious adverse event	Any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity.	Directive 2002/98/EC
Serious adverse reaction	An unintended response in donor or in patient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity.	Directive 2002/98/EC
Specification	A description of the criteria that must be fulfilled in order to achieve the required quality standard.	2005/62/EC

Term	Definition	Source
Standard	The requirements that serve as the basis for comparison.	Directive 2005/62/EC
Standard operating procedures	A document describing a regularly recurring operation that affects the quality of the process. Its purpose is to ensure that the operations are carried out correctly and in a consistent way.	EU-Blood-SOP Manual
Statistical process control	Method of quality control of a product or a process that relies on a system of analysis of an adequate sample size without the need to measure every product of the process.	Council of Europe: EDQM, Guide.
Third country	Any country that is not a Member State of the European Union.	European Commission ec.europa.eu
Third party / Subcontractor	Any organisation that provides a service to a procurement organisation or a BE on the basis of a contract or written agreement. Includes donor or blood testing laboratories, contract sterilisers and user hospitals which store blood components pending human application.	European Quality System for Tissue Banking (EQSTB), Guide for auditing tissue establishments,
Traceability	The ability to trace each individual unit of blood or blood component derived thereof from the donor to its final destination, whether this is a recipient, a manufacturer of medicinal products or disposal, and vice versa;	Directive 2005/61/EC
Validation	The establishment of documented and objective evidence that the pre-defined requirements for a specific procedure or	Directive 2005/62/EC

Term	Definition	Source
	process can be consistently fulfilled.	
Validation Plan	A description of the validation activities, responsibilities and procedures. It describes specifically how a certain validation is to be done.	Council of Europe: EDQM, Guide.

Annex VI Participating and collaborating institutions institutions and individuals

Country	Participants		Working Group members
AT **AUSTRIA**	Zentralinstitut für Bluttransfusion und Immunologische Abteilung *(Central Institute for Blood Transfusion and Department of Immunology)* University Clinics Innsbruck Anichstrasse 35 A - 6020 INNSBRUCK		Prof. Dr. Harald Schennach Director
BE **BELGIQUE / BELGIË**	Het Belgische Rode Kruis Dienst voor het Bloed, Rode Krius-Vlaanderen Vieurgatsesteenweg 98 1050 BRUSSEL Mailing address: Motstraat 40, 2800 MECHELEN	Prof. Dr. Philippe Vandekerckhove CEO, Director	Jan Ceulemans QA Manager Dr. Matine Baeten, Medical Director
BG **BULGARIA**	НАЦИОНАЛЕН ЦЕНТЪР ПО ХЕМАТОЛОГИЯ И ТРАНСФУЗИОЛОГИЯ *National Center of Hematology and Transfusiology* Plovdivsko Pole Str. 6 1756 SOFIA	Prof. Andrey Andreev, MD, PhD, Director	Svetla Bakalova, MD, PhD Quality Assurance Department

Country	Participants		Working Group members
CZ ČESKÁ REPUBLIKA	Fakultni nemocnici Ostrava *(Faculty Hospital Ostrava)* Krevni centrum (Blood center) 17. Listopadu 1790 CZ 708 52 OSTRAVA	Prim. MuDr. Zuzana Cermáková Director Member of the Project Advisory Board	Ing. Roman Nemec Quality Assurance Manager
	*Vedoucí oddělení klinických praxí a dohledu nad zpracováním biologických mat*eriálů Státní ústav pro kontrolu léčiv *(State Institute for Drug Control*) Státní ústav pro kontrolu léčiv-State Šrobárova 48 CZ-10041 Praha 10		MUDr. Renata Zimová
CY KYPROS	Υπουργείο Υγείας της Κυπριακής Δημοκρατίας - Ιατρικές Υπηρεσίες κσι Υπηρεσίες Δημόσιας Υγείας (*Ministry of Health of the Republic of Cyprus - Medical and Public Health Services*) Medical Services and Public Health Services 10 Marcou Drakou, Pallouriotissa 1449 LEFKOSIA (Nicosia)	Dr. Stala Kioupi Dr. Androulla Agrotou, Acting Director	Zoe Sideras

Country	Participants		Working Group members
DE DEUTSCHLAND	*Red Cross Blood Donation Service Baden-Württemberg-Hessen* Institut für Transfusionsmedizin und Immunhämatologie Sandhofstrasse 1 60528 FRANKFURT AM MAIN	Prof. Dr. med. Dr. h.c. Erhard Seifried Medical Director and CEO Project Leader and Member of the Project Advisory Board Roger Fleck Head Administration and Finances – Frankfurt Dr. Thea Müller-Kuller Project Management Dr. Petra Skrablin Project Management	Prof. Dr. med. Christian Seidl Vice Medical Director, GRCBDS Frankfurt Project Coordinator Working Group 1 Leader MUDr. Walid Sireis Division Director – Quality Management Project Management
	Regierungspräsidium Darmstadt *State Governmental Institution* - Hessia Dezernat VI 65.2 - Pharmazie Louisenplatz 2 (Kollegiengebäude) DE - 64283 DARMSTADT	Wiebke Siegel Member of the Project Advisory Board	

Country	Participants		Working Group members
	Paul-Ehrlich-Institut eine Einrichtung im Geschäftsbereich des Bundesministeriums für Gesundheit Paul-Ehrlich Straße 51-59 DE - 63225 LANGEN	Prof. Dr. Rainer Seitz, Director Division Hematology and Transfusion Medicine Dr. Magarethe Heiden	Dr. Helga Marie Huber
EE **EESTI**	Põhja-Eesti Regionaalhaigla Verekeskus Blood Centre North Estonia Regional Hospital J. Sütiste tee 19 13419 TALLINN	Dr. Riin Kullaste, MD, Director	Dr. Tatjana Plahhova, MD Quality Manager
	State Agency of Medicines Department of Biologicals 1, Nooruse str, 50411Tartu, Estonia		Svetlana Orlova, Specialist
ES **SPAIN**	Centro Vasco de Transfusion Av. Zuatzu, 4 ES - 20018 SAN SEBASTIAN		Dr. Jose Manuel Cardenas Technical Director
	DG Salud Pública, Ministerio de Sanidad y Consumo Pº del Prado 18-20. ES - MADRID 28047	Dr. Elena Moro	

Country	Participants		Working Group members
FR FRANCE	Etablissement Français du Sang (EFS) 20 avenue du stade de France 93218 LA PLAINE SAINT-DENIS Cedex	Prof. Dr. Jacques Hardy Director Dr. Alain Beauplet Direction Qualité Nationale	Leslie Sobaga Direction des Affaires Internationales Direction Qualité Nationale, Gestion des Inspections - Analyse de Risque Working Group 4 Leader
	Agence française de sécurité sanitaire des produits de sante (AFSSAPS) Inspectorate and Companies Department 143, 147 boulevard Anatole 93285 SAINT-DENIS Cedex France	Dr. Chantal Guiol, Ph.D.	Dr. Fewzi Teskrat, PhD Conseiller Spécial pour les produits issus du corps humain Affaires européennes et internationales Direction de l'inspection et des Etablissements
HU MAGYARORSZÁG	Orszàgos Vèrellàtò Szolgàlat Hungarian National Blood Transfusion Service Karonlina str. 19 – 21 1113 BUDAPEST	Dr. Eszter Miskovits, MD Director	Dr. Klára Baróti-Tóth, Ph.D. Director QA-QC

Country	Participants		Working Group members
IE IRELAND	The Irish Blood Transfusion Service Board (IMB) Irish Blood Transfusion Service National Blood Centre James´s Street IE - DUBLIN 8	Dr. William Murphy National Medical Director	Dr. Marie O`Connell QA Director
	Irish Medicines Board Blood & Tissue Section Earlsfort Centre Earlsfort Terrace IE - DUBLIN 2I	Dr. Patrick Costello Blood & Tissues Manager, Compliance Department	Dr. Grace Cunningham
IS ICELAND	Blóðbankinn, Landspítali (The Blood Bank, Landspítali University Hospital), Snorrabraut 60 IS-105 Reykjavík	Dr. Sveinn Guðmundsson, MD. Director and CEO	Ína Björg Hjálmarsdóttir, Cand.Scient, Quality Manager
IT ITALIA	Centro Nazionale Sangue (CNS) (Italian National Blood Centre) Istituto Superiore di Sanità National Institute of Health Via Giano della Bella, 27 00162 Rome	Prof. Dr. Giuliano Grazzini General Director - CNS	Dr. Simonetta Pupella

Country	Participants		Working Group members
LU **LUXEMBOURG**	11 rue Batty Weber L-7259 Bereldange Luxembourg	Frances Delaney Project Consultant Member of the Project Advisory Board	
MT **MALTA**	Centru Nazzjonali ta't-Trafuzjoni tad-Demm *National Blood Transfusion Service* St. Luke`s Square MSD 07 G´MANGIA		Dr. Alex Aquilina Director
	Government of Malta Directorate of Health Care Services Standards Palazzo Castellania 15 Merchants' Str. VALETTA VLT 2000	Dr. Richard Zammit	Dr. Miriam C. Vella
NL **NEDERLAND**	Stiching Sanquin Bloedvoorziening Sanquin Blood Supply Foundation Plesmanlaan 125 1066 CX AMSTERDAM	Dr. Jeroen De Wit CEO Member of the Project Advisory Board President European Blood Alliance (EBA) former chairperson CD-P-TS (CoE) on Blood Transfusion	Dr. Jan Peter Jansen van Galen Division Director Sanquin North Working Group 2 Leader Boudewijn Hinloopen, BEd, BSc. Head Production Department Sanquin Region Northeast

Country	Participants		Working Group members
PL POLSKA	Instytut Hematologii i Transfuzjologii (Institute of Haematology and Transfusion Medicine) I. Gandhi St.14 02-776 Warszawa	Prof. Dr. Krzysztof Warzocha, Director	PhD MSc. Elzbieta Lachert
		MD PhD Magdalena Letowska, Deputy Director	PhD MSc. Jolanta Antoiewicz-Papis
RO ROMANIA	Universitatea de Medicina si Farmacie "Victor Babes" Timisoara Physiology and Immunology Uta loan Colonel Martir No.2 300041 TIMISOARA	Prof. Dr. Virgil Paunescu Director	Dr. Carmen Tatu, Ph.D. Blood Transfusion Center Timisoara
	Ministerul Sanatatii Publice *(Ministry of Public Health)* 1-3 Cristian Popisteanu Street 010024 BUCHAREST		Dr. Antoaneta Dragoescu Dr. Gabriela Uifalean
	Transfusion Department Universitary Emergency Hospital Bucharest, Bucharest,		Dr. Corina Posea, MD Ministry of Health Medical Expert
SO SLOVENIA	Zavod Republike Slovenije za transfuzijsko medicino (*Blood Transfusion Centre of Slovenia)* Slajmerjeva 6 SI-1000 LJUBLIJANA	Dr. Dragoslav Domanovic, Director	Dr. Irena Razborsek, MD

Country	Participants		Working Group members
	Javna agencija RS za zdravila in medicinske pripomočke *(Agency for medicinal products and medical devices)* Ptujska ulica 21 SI-1000 LJUBLJANA		Dr. Andrijana Tivadar, mag. farm. farmacevtska nadzornica *Pharmaceutical inspector (GCP)*
UK ENGLAND	The National Blood Authority -Blood and Transplant (NHS-BT) (England and North Wales) Oak House Reeds Crescent WD24 4QN WATFORD, HERTS	Dr. Lorna Williams Medical Director NHSBT Dr. Alan Slopecki Head of Quality Assurance Crescent Drive Brentwood Essex, CM15 8DP Steve Morgan NHSBT International 2440 The Quadrant Aztec West Bristol BS32 4AQ	Mark Nightingale Quality Officer Southampton Facilities Working Group 3 Leader Sarah Raymond Quality Officer
UK SCOTLAND	The Martin Gorham Douglas Gorham Partnership Consulting Brigton Douglastown, Forfar SCOTLAND, DD8 1TP	Angus Macmillan Douglas, OBE Project Consultant Member of the Project Advisory Board	

Annex VII Associated or observing institutions and participants

Country	Collaborating Partners	Collaborating members
AT **Austria**	Universitätsklinik für Blutgruppenserologie und Transfusionsmedizin Auenbruggerplatz 3 8036 Graz	Prof. Dr. Gerhard Lanzer
	Abteilung III/4 - Strategische Angelegenheiten, Blut, Gewebe und Transplantationswesen Bundesministerium für Gesundheit Radetzkystraße 2 1031 Wien	Min.-Rat. Dr. Johann Kurz
BE **Belgique /** **België**	Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten Eurostation Bloc 2 Place Victor Horta 40 bte 40 Brussels	Walter Bontez
BK **Bulgaria**	Bulgarian Drug Agency, Sofia 26, Yanko Sakazov Blvd. 1504 Sofia	Lyubina Gaydarova
DK **Denmark**	Danish Medicines Agency Axel Heides Gade 1 DK-2300 København S	Christina Palvad, MSc Pharm
FYROM **Macedonia**	Institute Of Transfusion Medicine Vodnjanska 17, Skopje Republic of Macedonia	Dr. Risto Dukovski Dr. Olga Todorovsca

Country	Collaborating Partners	Collaborating members
LV **Latvia**	Health statistics and medical Technologies State Agency Duntes 12/22, Riga, LV-1005	Anita Daugavvanaga Head of System of Standards for Biomedicine Health Statistics and Medical Technologies
PT **Portugal**	Autoridade para os Serviços de Sangue e da Transplantação Ministério da Saúde, Av. João Crisostomo, 9 1000 Lisboa	Alice Lopes Cordeiro
SE **Sweden**	The National Board of Health and Welfare (Socialstyrelsen) Socialstyrelsen 106 30 Stockholm	Monica Axelsson and Torsten Mossberg
SK **Slovakia**	State Institute for Drug Control (SIDC) Kvetná 11 825 08 Btaislava 26a	Renáta Ovádeková, Ph.D.
UK **United Kingdom**	Medicines and Healthcare products Regulatory Agency (MHRA) 18-105 Market Towers 1 Nine Elms Lane London SW8 5NQ	Ian Rees
Liechtenstein	Amt für Gesundheit (Health Ministry) Amt für Gesundheit Äulestrasse 512, 9490 Vaduz	Brigitte Batliner
Switzerland	Swissmedic, Swiss Agency for Therapeutic Products Hallerstr.7 CH-3000 Bern 9	Dorit Schmidkunz-Eggler

MANUAL
Common European Standards and Criteria
for the Inspection of Blood Establishments
Edition 1.0, 2010