Guidelines for the Blood Transfusion Services

Chapter 2: Quality in blood and tissue establishments and hospital blood banks

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Chapter 2:

Quality in blood and tissue establishments and hospital blood banks

2.1: Introduction

The key requirements for Blood Establishments and for hospital blood banks are defined in the Blood Safety and Quality Regulations (Statutory Instrument 2005 No. 50) as amended,[1] and are enforced by the Medicines and Healthcare products Regulatory Agency (MHRA). Those for tissues and cells are defined in the Human Tissue (Quality and Safety for Human Application) Regulations, 2007 (Statutory Instrument 2007 No. 1523),[2] and are enforced by the Human Tissue Authority (HTA).

These regulations require that Blood and Tissue Establishments are licensed and subject to regular inspection for compliance. Hospital blood banks are not formally licensed but must submit annual compliance reports to the MHRA. Based on these compliance reports, the MHRA select a number of hospital blood banks for inspection every year and can also decide to do ‘for cause’ inspections when there is evidence of non-compliance.

The MHRA and HTA have powers to remove licences from Blood and Tissue Establishments, respectively, and the MHRA can issue cease and desist orders to prevent blood banks from continuing in operation. These powers derive from the relevant UK legislation, which is designed to ensure that appropriate standards of performance are achieved and maintained. This inspection process is designed to generate a climate of continual quality improvement, and this chapter will look at the key issues which have to be addressed in achieving an effective quality management system.

2.2: Key initiatives

2.2.1: European Union Blood Safety and Quality Directives

- Commission 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.[3]
- Commission Directive 2004/33/EC of the European Parliament and the Council 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.[4]

- 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.[5]
- 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.[6]

The first two Directives came into force in UK law on 8 February 2005 as the Blood Safety and Quality Regulations 2005 (BSQR),[1] with their requirements becoming effective in November 2005. They set standards of quality and safety for the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion. The regulations also cover the collection and testing of blood and blood components for autologous use. In effect, therefore, they cover the whole process from donor to patient – from 'vein to vein'.

The latter two Directives came into force in August 2006 and relate specifically to traceability requirements and notification of adverse reactions and events, and introduce EC standards and specifications relating to a quality system for Blood Establishments. They also added provisions relating to record keeping and traceability of blood and blood components to a new category of facility, defined as a hospital, another facility or service owned or managed by a health service body, a care home, an independent clinic, a manufacturer or a biomedical research institute.

The Directives define certain activities which can only be undertaken by Blood Establishments, namely:

- the collection and testing of blood or blood components, whatever their intended purpose
- the processing, storage and distribution of blood and blood components when they are intended to be used for transfusion.

Hospital blood banks are not permitted to undertake these activities unless licensed as Blood Establishments, but are able to store, distribute and perform compatibility tests on blood and blood components for use within hospital facilities.

2.2.2: Medical devices legislation

Blood and Tissue Establishments and Hospital Blood Banks are key users of medical devices such as blood bags and in vitro diagnostic medical devices such as test kits for blood grouping. Some establishments also manufacture CE or UKCA marked in vitro diagnostic medical devices (guidelines for reagent manufacture are included in Chapter 11). The Good Practice Guidelines for Blood Establishments and the HTA Guide Quality and Safety Assurance for Human Tissue and Cells for Patient Treatment mandate the use of CE or UKCA marked medical devices wherever possible. Knowledge of medical devices legislation is therefore important for Blood and Tissue Establishments and Hospital Blood Banks.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the designated authority that administers and enforces the law on medical devices in the UK. It has a range of investigatory and enforcement powers to ensure the safety and quality of medical devices placed on the UK market. Different regulatory requirements apply to Great Britain (England, Wales and Scotland) and Northern Ireland and these are set out below.

2.2.2.1: Regulation of medical devices in Great Britain

Medical devices are regulated under theMedical Devices Regulations 2002(SI 2002 No 618, as amended) (UK MDR 2002) which is based on requirements derived from the following EU Directives:

- Directive 90/385/EEC on active implantable medical devices (EU AIMDD)
- Directive 93/42/EEC on medical devices (EU MDD)

- Directive 98/79/EC on *in vitro* diagnostic medical devices (EU IVDD)

The UKCA (UK Conformity Assessed) marking is a UK product marking used for certain goods, including medical devices, being placed on the Great Britain market. UKCA marking is not recognised in the Northern Ireland or the EU. UKCA marking requirements are based on the requirements of the relevant Annexes to the EU Directives listed above, which have been modified by Schedule 2A to the UK MDR 2002.

Under the UK MDR 2002, a CE marked device with a valid declaration of conformity or EC certificate is viewed as meeting the UKCA marking requirements whilst CE marking continues to be recognised in Great Britain - until 30 June 2023. This applies to devices that have been CE marked under and fully conform with the following applicable EU legislation:

- Directive 90/385/EEC on active implantable medical devices (EU AIMDD) (for devices that have been CE marked prior to 26 May 2021)
- Directive 93/42/EEC on medical devices (EU MDD) (for devices that have been CE marked prior to 26 May 2021)
- Directive 98/79/EC on *in vitro* diagnostic medical devices (EU IVDD) (for devices that have been CE marked prior to 26 May 2022)
- Regulation (EU) 2017/745 on medical devices (EU MDR)
- Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (EU IVDR)

From 1 July 2023, devices that are placed on the Great Britain market will need to conform with UKCA marking requirements.

2.2.2.2: Regulation of medical devices in Northern Ireland

Under the terms of the Northern Ireland Protocol, the rules for placing medical devices on the Northern Ireland market differ from those applicable to Great Britain. CE marking is needed for medical devices placed on the Northern Ireland market and the following EU Regulations apply:

- Regulation (EU) 2017/745 on medical devices (EU MDR)
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices (EU IVDR)

In addition, the UKNI indication is required if a UK Notified Body undertakes mandatory third-party conformity assessment.

2.2.2.3: In-house manufacture of medical devices by Health Institutions

Health Institutions are exempt from the provisions of the UK MDR 2002 for products manufactured and used within the same Health Institution and either on the premises of their manufacture or on premises in the immediate vicinity without having been transferred to another legal entity. Additional requirements apply to Health Institutions in Northern Ireland and the requirements for Health Institution Exemption (HIE) set out in Article 5 of the EU MDR and IVDR must be complied with.

2.2.2.4: Off-label use and exceptional use of non-complying medical devices

Medical devices should be used as described by the manufacturer in the instructions for use. If a device is used in any other way, it is considered ‘off-label’ use. Without the manufacturer’s approval this will be at your own risk and you or your employer could become liable for civil claims for damages from injured patients or their families if something goes wrong with the device. Modification of a device where this is not described in the manufacturer’s instructions for use is also considered to be off-label use. Use of a non-CE or UKCA marked product for a medical purpose also carries risk and should be avoided; this includes use of products labelled as ‘Research Use Only’. Although rare, there may be occasions where there is no option but to use a device off-label; the MHRA may authorise the use of a non-complying device on humanitarian grounds if they are satisfied that such use would be in the best interests of the patient and the protection of

health. Further information on off-label use and exceptional use of non-complying medical devices is available on the MHRA web site.

2.2.2.5: Future regulation of medical devices in the UK

The MHRA are planning significant changes to how medical devices will be regulated in the UK. This will be implemented through amendments to the UK MDR 2002, and it is anticipated that these will enter in to force on 1st July 2023. Furthermore, changes to how the Northern Ireland Protocol will apply may have an impact on how medical devices are regulated. Readers are advised to check the MHRA website for up-to-date guidance on regulation of medical devices in Great Britain and Northern Ireland.

2.2.3: Human Tissue Act 2004[11]

The Human Tissue Act 2004 replaced the Human Tissue Act 1961, the Anatomy Act 1984 and the Human Organ Transplants Act 1989 as they relate to England and Wales, and the corresponding Orders in Northern Ireland.

The Human Tissue Act 2004 covers England, Wales and Northern Ireland. It established the Human Tissue Authority (HTA) to regulate activities concerning the removal, storage, use and disposal of human tissue. Consent is the fundamental principle of the legislation and underpins the lawful removal, storage and use of body parts, organs and tissue. Different consent requirements apply when dealing with tissue from the deceased and the living. The Human Tissue Act 2004 lists the purposes for which consent is required (these are called Scheduled Purposes).

There is separate legislation in Scotland – the Human Tissue (Scotland) Act 2006.

While provisions of the Human Tissue (Scotland) Act 2006 are based on authorisation rather than consent, these are essentially both expressions of the same principle.

2.2.4: The European Union Tissues and Cells Directives

- 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.[12]
- 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.[13]
- 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.[14]
- Commission Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells.[15]

These Directives establish a harmonised approach to the regulation of tissues and cells across Europe. They set a benchmark for the standards that must be met when carrying out any activity involving tissues and cells for human application (patient treatment). The Directives also require that systems are put in place to ensure that all tissues and cells used in human application are traceable from donor to recipient.

The HTA, as one of the Competent Authorities in the UK under the EU Tissues and Cells Directives, has responsibility for regulating tissues and cells (other than gametes and embryos) for human application.

2.2.5: Human Tissue (Quality and Safety for Human Application) Regulations 2007[2]

The Directives were fully implemented into UK law on 5 July 2007, via the Human Tissue (Quality and Safety for Human Application) Regulations 2007. The HTA's remit includes the regulation of:

- procurement
- testing
- processing
- storage
- distribution
- import/export

of tissues and cells for human application.

Establishments where these activities are carried out will normally need a licence. To obtain this, establishments carrying out the above activities are required to meet the standards which are detailed in the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment[14] as implemented by HTA Directions 001/2021.

The HTA also publishes Codes of Practice, which provide guidance and lay down expected standards for each of the sectors it regulates (see www.hta.gov.uk).

2.3: Other standards

There are a number of other standards that help define how a quality management system should be designed to meet the needs of a particular aspect of a Service's work. Table 2.1 provides information on some key standards inspection, licensing, accreditation and certification.

They are all applicable within England. Some apply directly to the whole of the UK (e.g. the International Standards), others to England and Wales (e.g. the NHS Litigation Authority Risk management assessment programme). Where there is not a direct cross-reference the reader should investigate further to determine how the standards might apply.

All the primary sources cited here are places where sound advice on management systems to address the various requirements of a modern Blood Service can be found. These will support the design and establishment of a system that can be confidently subjected to an external inspection process. The list is not intended to be exhaustive and by the nature of change is only current at the time of publication. It is for this reason version numbering has not been applied to the available standards; they will be constantly updated.

Table 2.1 List of some key inspection/licensing/accreditation/certification standards

Key standards	Applicable to	Responsible body	Website
Caldicott Report 1997, implementation 1998	Confidentiality of patient data	Department of Health	www.dh.gov.uk
Care Quality Commission Fundamental Standards 2014	Health and social care services in England	Care Quality Commission	www.cqc.org.uk

Health and Care Standards 2015	Healthcare in Wales	Healthcare Inspectorate Wales	www.hiw.org.uk
Health and Social Care Standards 2017	Care and treatment delivered by NHS Scotland	NHS Quality Improvement Scotland	www.nes.scot.nhs.uk
Quality standards for health and social care 2006	The availability and quality of health and social care services in Northern Ireland	The Regulation and Quality Improvement Authority, Department of Health, Northern Ireland	www.rqia.org.uk
European Foundation for Quality Management (EFQM) Self-Assessment	Measurement of the effectiveness and, over time, the improvement in a Blood Service's management system. Helping understand where they are on the path to excellence	British Quality Foundation	www.bqf.org.uk www.efqm.org
European Blood Inspection System (EuBIS)	The safety of blood transfusion in Europe	Institut für Transfusionsmedizin und Immunhämatologie	www.eubis-europe.eu
Standards for Histocompatibility & Immunogenetics Testing	Histocompatibility and Immunology (H&I) – reference and tissue typing	European Federation for Immunogenetics (EFI)	www.efiweb.eu
The Data Protection Act UK General Data Protection	Protection regarding processing of personal data of UK residents	Information Commissioner's Office	www.ico.org.uk
General Data Protection Regulation	Protection regarding processing of personal data of EU residents	EU Commission	www.eugdpr.org
Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture	Validation of computer systems	International Society for Pharmaceutical Engineering	www.ispe.org

Good Manufacturing Practice (GMP) guidelines	Pharmaceutical environments	The European Commission publishes this online as EudraLex Volume 4	https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
HTA Directions 011/2021 – the standards required under the Human Tissue (Quality and Safety of Tissues and Cells for Human Application) Regulations 2007 HTA Codes of Practice	Quality and Safety Assurance for Human Tissue and Cells for Patient Treatment	Human Tissue Authority	www.hta.gov.uk
International standards for unrelated haematopoietic stem cell donor registries WMDA Accreditation Programme	Stem cell and donor registries	World Marrow Donor Association (WMDA)	www.worldmarrow.org
ISO 15189 Medical Laboratories - requirements for quality and competence	Medical laboratories	UKAS	www.ukas.com
ISO 17799 Information Security Management	Information security	BSI British Standards	www.bsigroup.com
ISO 9000 2000 and ISO 9001 2008 Quality management system requirements	Quality management system	BSI British Standards	www.bsigroup.com
ISO 20000 IT Service Management Standard	Service management	BSI British Standards	www.bsigroup.com
ISO 13485 Medical devices - Quality management systems - Requirements for regulatory purposes	Management of medical devices	BSI British Standards	www.bsigroup.com
Joint Accreditation ICT Europe and EBMT (JACIE) assessment standard	Stem Cell Immunology – Human Progenitor Cells (SCI – HPC) collection, processing and storage	The Joint Accreditation Committee ISCT & EBMT (JACIE)	www.ebmt.org

NHSLA risk management assessment programme for NHS Trusts	Management of claims and litigation	National Health Service Litigation Authority	www.nhsla.com
PRINCE2	Project control	Cabinet Office	www.gov.uk/government/publications/best-management-practice-portfolio/

2.4: Systems

2.4.1: Quality management system

Within a Blood/Tissue Establishment an effective quality management system (QMS) is a well-designed, structured and organised method of quality assuring the provision of consistent, safe and efficacious products. It also covers all diagnostic activities, reagent production, clinical trials and R&D. It provides both a means to confirm to regulatory bodies, management and customers that the establishment's service is in compliance with relevant standards, and also a basis whereby improvement in quality may be demonstrated.

The European Blood and Safety Quality Directives require that a quality system is to be applied for any blood and blood components circulating in the EC and that member states therefore should ensure that for all blood and blood components including those coming from third countries there is a quality system in place for Blood Establishments equivalent to the quality system provided under these Directives.

The EU Tissues and Cells Directives have equivalent requirements for the provision of a quality management system. These are defined as follows: 'an efficient QMS comprises a series of inter-related elements and a quality system for Blood/Tissue Establishments should embrace the principles of quality management, quality assurance, and continuous quality improvement, and should include personnel, premises and equipment, documentation, collection, testing and processing, storage and distribution, contract management, non-conformance and self-inspection, quality control, blood component recall, and external and internal auditing'.

2.4.2: Good manufacturing practice

The application of GMP is the cornerstone of an effective QMS and provides the structure upon which the elements of the quality system can be built. The objective of GMP is formally stated as being 'to assure the quality of the medicinal product for the safety, well-being and protection of the patient'.[17] The BSQR requires that Blood Establishments and hospital blood banks meet the requirements of good practice. This is taken by the MHRA to mean that Blood Establishments and hospital blood banks should comply with all relevant sections of the EC Guidelines to GMP.[18] This applies to hospital blood banks, even though they are not manufacturing anything, but are part of the distribution chain which is defined as part of the overall manufacturing process.

The EC Guidelines to GMP are described more fully in section 2.6 using the quality system format provided by Directive 2005/62/EC.[6] Elements are presented under separate headings, and in practical terms all of these must be considered for each and every procedure or process to conform to the principles of good manufacturing practice.

2.5: Application of a quality management system

2.5.1: Blood Establishments

Blood Establishments are required under Directive 2005/62/EC[7] to implement EC standards and specifications relating to a quality system for Blood Establishments, taking fully into account the principles of GMP. Commission Directive (EU) 2016/1214 of 25 July 2016 amended Directive 2005/62/EC as regards quality system standards and specifications for blood establishments.[19] This replaced article 2 with the requirement that systems should be developed taking into account the Good Practice Guidelines jointly developed by the Commission and the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe and published by the Council of Europe.[20]

The approach we have taken in this chapter is to outline the requirements of a quality management system in the context of the collection, processing, testing, storage and distribution of blood and blood components and tissues.

In addition, Blood Establishments should ensure they are compliant with the specific standards identified within the Blood Safety and Quality Regulations 2005[1] and other relevant standards and guidelines. These elements of the quality management system can be adapted to support other activities that a Blood Establishment may undertake, such as diagnostic testing and reagent production.

Blood Establishments are required to obtain a Blood Establishment Authorisation from MHRA before operating and to ensure that it is maintained through inspections scheduled every 2 years.

2.5.2: Hospital blood banks

Hospital blood banks are required to comply with the elements of the quality system outlined below relevant to their activities (see section 2.6). In addition, they must:

- Maintain donor to recipient traceability. Specifically BSQR (SI 2005 No.50) Regulation 9 (1)(e) requires hospital transfusion laboratories to ‘maintain, for not less than 30 years, the data needed to ensure full traceability of blood and blood components, from the point of receipt of the blood or blood component by the hospital blood bank’.

- Undertake mandatory reporting of serious adverse events and serious adverse reactions related to transfusion to the Competent Authority. Specifically BSQR (SI 2005 No. 50) Regulation (1)(f) and Regulation 12B, Directive 2005/62 Annex, section 9.2 requires that ‘there are procedures in place for quality assurance within the transfusion laboratory – Reporting Serious Adverse Events (SAE) and Serious Adverse Reactions (SAR)’.

- Complete an annual form, the Blood Compliance Report, developed by the MHRA, in which the laboratory indicates its compliance with the regulations. The form is reviewed by the Inspectorate division of the MHRA and those laboratories where there is deemed non-compliance are inspected as ‘for cause’ inspections. There may also be some control inspections undertaken to verify the use of the Blood Compliance Report and its completion.

- Establish their bona fides with the supplying Blood Establishment and sign a service level agreement between both parties to outline how compliance will be achieved. This must be done before a hospital blood bank can operate.

2.5.3: Tissue and cell establishments

These establishments should also operate a quality system that reflects the requirements below (section 2.6). The Tissues and Cells Directives are not as explicit on the requirements of a quality management system as the Blood Safety and Quality Directives and a quality system in the context of the Tissues and Cells Directives consists of the following elements: the organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management, and includes all activities which contribute to quality, directly or indirectly. Experience has shown that the elements below are effective in maintaining quality and safety in the procurement and supply of tissues and cells.

2.6: Quality management system

Note that where key advice is given elsewhere in the guidelines, the relevant sections have been cross-referenced. Where there is not a direct cross-reference, the reader should investigate further the relevant chapters of these guidelines and the standards in Table 2.1.

2.6.1: Personnel and organisation

The Blood Service must ensure that adequate resources are provided to implement and operate the quality management system, to continually improve its effectiveness and to satisfy customer requirements. The physical resources to undertake the work must be suitable to attain the required standards; this will include equipment, consumables, work areas, utilities etc. (see section 4.2 on staffing and training principles for donation sessions).

All personnel shall have up-to-date job descriptions that clearly set out their tasks and responsibilities. Organisations shall assign the responsibility for processing management and quality assurance to different individuals who function independently.

All personnel shall receive initial and continued training appropriate to their specific tasks. Training records shall be maintained. Training programmes shall be in place and shall include good practice.

The contents of training programmes shall be periodically assessed and the competence of personnel evaluated regularly.

There shall be written safety and hygiene instructions in place adapted to the activities to be carried out and in compliance with requirements.

2.6.2: Premises

2.6.2.1: General

Premises including mobile sites shall be adapted and maintained to suit the activities to be carried out. They shall enable the work to proceed in a logical sequence so as to minimise the risk of errors, and shall allow for effective cleaning and maintenance in order to minimise the risk of contamination (see section 6.4 on component processing).

2.6.2.2: Donation area

There shall be an area for confidential personal interviews and assessment of individuals to determine their eligibility to donate. This area shall be separated from all processing areas (see section 4.1 on premises at blood donor sessions).

2.6.2.3: Collection area

Collection shall be carried out in an area intended for safe donation, appropriately equipped for the initial treatment of donors experiencing adverse reactions or injuries from events associated with donation, and organised in such a way as to ensure the safety of both donors and personnel as well as to avoid errors in the collection procedure (see section 4.1 on premises at blood donor sessions).

2.6.2.4: Testing and processing areas

There shall be a dedicated laboratory area for testing that is separate from the processing area with access restricted to authorised personnel.

2.6.2.5: Storage areas

Storage areas shall provide for properly secure and segregated storage of different categories of blood, blood components, tissues and materials including quarantine and released materials and donations collected under special criteria (e.g. autologous donation).

Provisions shall be in place in the event of equipment or power failure in the main storage facility (see section 6.7.1 on the specifications for component storage areas).

2.6.2.6: Waste disposal area

An area shall be designated for the safe disposal of waste, disposable items used during the collection, testing and processing, and for rejected blood or blood components.

2.6.3: Equipment and materials

2.6.3.1: Equipment checks and record keeping

All equipment shall be validated, calibrated and maintained to suit its intended purpose. Operating instructions shall be available and appropriate records kept.

2.6.3.2: Selection of equipment

Equipment shall be selected to minimise any hazard to donors, personnel or blood components.

2.6.3.3: Selection of materials

Only reagents and materials from approved suppliers that meet the documented requirements and specifications shall be used. Critical materials shall be released by a person qualified to perform this task. Where relevant, materials, reagents and equipment shall meet the requirements of Directive 93/42/EEC[9] for medical devices and Directive 98/79/EC[8] for *in vitro* diagnostic medical devices or comply with equivalent standards in the case of collection in third countries (see section 4.7 on the control of purchased material and services).

2.6.3.4: Inventory records

Inventory records shall be retained for a period acceptable to and agreed with the Competent Authority.

2.6.3.5: Computerised systems

When computerised systems are used, software, hardware and back-up procedures must be checked regularly to ensure reliability, be validated before use, and be maintained in a validated state. Hardware and software shall be protected against unauthorised use or unauthorised changes. The back-up procedure shall prevent loss of or damage to data at expected and unexpected downtimes or function failures.

2.6.4: Change control

There shall be a system of change control in process. The system's aims shall be to ensure that changes are evaluated and made only if they provide tangible benefits to the organisation as judged by, for example, benefit to patients through risk reduction. It may also be driven by efficiency savings to ensure that maximum resources are devoted to patient care.

The system shall then ensure that the change is planned and implemented in a controlled way, incorporating training for staff in new procedures, and demonstration that the expected outcome has been delivered. Supporting documentation, including for example standard operating procedures (SOPs), shall ensure there is a record of the processes operated before and after the change, that the date of the change is known, and that material processes through the changed system can be identified.

There shall also be a system to ensure that the effectiveness of the newly implemented process is monitored and opportunities for further improvement are investigated and, where relevant, implemented. It shall support the organisation in trying to learn from incidents, complaints and other event information, as analysis of this will help identify potential beneficial changes.

2.6.5: Validation

Validation is a pre-defined exercise to ensure that equipment or a procedure (either current or proposed) is fit for its intended purpose and meets its pre-defined specification. The benefits of validation include assurance that critical aspects of a process are in control, increased probability of uniform product quality, reduced product waste and reduced customer complaints. New equipment, blood packs and manufacturing processes are examples where validation is essential before they are introduced into routine application.

2.6.6: Documentation

Effective documentation, whether in written or electronic format, must be accurate, authorised, controlled at issue and reviewed on a regular basis to ensure that it remains relevant. It provides clear instructions on what to do and prevents errors that may result from spoken communication. Records must be legible and made at the time actions are completed using indelible ink; corrections shall be signed and dated and made so that the original entry can be seen. This ensures consistency of manufacture and service provision, provides objective evidence that tasks have been correctly performed, permits investigation if problems arise and facilitates traceability from donor to patient and vice versa.

Records can be transferred to other media following procedures which meet applicable British or international standards.

Comprehensive documentation includes a hierarchy of documentation starting with:

- a quality manual
- policies
- specifications
- SOPs
- forms and worksheets, batch processing records, labels, equipment logbooks and investigation /validation records.

Effective document control must be practised to ensure that documents being used are current and an archive of superseded documents shall be established to provide an historical record.

2.6.7: Collection

2.6.7.1: Donor eligibility

- Procedures for safe donor identification, suitability interview and eligibility assessment shall be implemented and maintained. They shall take place before each donation and comply with legislative requirements (see section 3.2 on blood donation, and section 20.1 on tissue donation).
- The interview shall be conducted in such a way as to ensure confidentiality (see section 3.4 on informed consent for blood donation, and section 20.2 for tissue donation).
- The donor suitability records and final assessment shall be signed by a qualified health professional (see section 3.4 on informed consent for blood donation, and section 20.3 for tissue donation).

2.6.7.2: Collection of donated blood, blood components and tissues

- The collection procedure shall be designed to ensure that the identity of the donor is verified and securely recorded and that the link between the donor and the blood, blood components and blood samples is clearly established (see Chapter 5 on the collection of a blood component).
- The sterile systems used for the collection of donations and their processing shall be CE marked or comply with equivalent standards if the donations are collected in developing countries. The batch number of the key consumables shall be traceable for each blood component (see section 4.7 on the control of purchased material and services).
- Collection procedures shall minimise the risk of microbial contamination.
- Laboratory samples shall be taken at the time of donation and appropriately stored prior to testing.
- The procedure used for the labelling of records, donations and laboratory samples with donation numbers shall be designed to avoid any risk of identification error and mix-up.
- After collection, the donations shall be handled in a way that maintains their quality at a storage and transport temperature appropriate to further processing requirements.
- There shall be a system in place to ensure that each donation can be linked to the collection and processing system into which it was collected and/or processed.

2.6.8: Manufacture

2.6.8.1: Procedures and controls

Manufacturing processes must follow clearly defined procedures in order to obtain products or services of the requisite quality. The inputs to any process must be controlled: for example the use of approved suppliers to agreed specifications. Goods requiring incoming inspection must be held in quarantine until the inspection has been performed. During manufacture any in-process controls shall be carried out and recorded (see Chapter 7 on specifications for blood components). Statistical techniques may be used to provide confidence that processes remain in control.

2.6.8.2: Calibration

Calibration is a procedure that confirms, under defined conditions, the relationship between values obtained from an instrument or system and those obtained using an appropriate certified standard. Examples include any equipment from which physical measurements are obtained, for example weights, scales, temperature loggers, thermometers, light sources etc.

2.6.8.3: Quality control and quality monitoring

These provide confirmation either during or at completion of a process that manufacturing materials, processes and products meet their pre-defined specification. They may be release requirements (quality control tests), such as a non-reactive microbiological test results or demonstration of the effectiveness of a new batch of reagents (see Chapter 9 on microbiology tests for donors and donations, and section 20.5 on tissue donor testing). They may provide evidence that systems are operating as expected (quality monitoring), such as meeting a stated leucodepletion requirement by random sampling of finished product, or testing white cell content and then subjecting the result to statistical analysis perhaps by the use of control charts (see section 6.3 on component and process monitoring tests). These latter tests would not normally prevent the issue of material.

2.6.8.4: Proficiency testing

Proficiency testing monitors the capability to perform procedures within defined limits of accuracy by analysis of unknown samples. Successful outcomes are dependent on the combined outputs of operators, equipment and process. Proficiency testing exercises are applied to a wide spectrum of laboratory procedures and may be managed on a local or national basis. National External Quality Assurance Schemes (NEQAS) are widely used in the UK.

2.6.8.5: Contract manufacture

When contract manufacture/testing are undertaken the company supplying the goods or service shall have been employed following a formal contracting process. This shall include supplier audit, if the goods or service had been deemed critical, on the basis of a GMP risk assessment, by the organisation letting the contract. The goods and services provided shall be subject to regular monitoring to ensure they comply with the service specified in the original contract and may be subject to ongoing audit depending on the quality of the service/goods provided and their criticality to the organisation letting the contract.

2.6.9: Labelling

At all stages, all containers shall be labelled with relevant information of their identity. In the absence of a validated computerised system for status control, the labelling shall clearly distinguish released from non-released units of blood and blood components (see section 6.6 for labelling of blood components).

The labelling system for the collected donations, intermediate and finished blood components, tissues and samples must unmistakably identify the type of content, and comply with the labelling and traceability requirements.

For autologous blood and blood components, the label also shall comply with requirements.

2.6.10: Release of blood and tissue components

There shall be a safe and secure system to prevent release until all mandatory requirements have been fulfilled (see Chapter 9 on microbiology tests for donors and donations for blood, and section 20.11 on release criteria for tissues). Each establishment shall be able to demonstrate that each blood, blood component, tissue, reagent or diagnostic test result has been formally released by an authorised person. Records shall demonstrate that before a blood component or tissue is released, all current declaration forms, relevant medical records and test results meet all acceptance criteria.

Before release, blood and blood components, tissues and reagents shall be kept administratively and physically segregated from released items. In the absence of a validated computerised system for status control a labelling system shall identify the release status.

In the event that an item fails release due to a confirmed positive infection test result, a check shall be made to ensure that other components from the same donation and components prepared from previous donations given by the donor are identified. There shall be an immediate update of the donor record.

2.6.11: Storage and distribution

Procedures for storage and distribution shall be validated to ensure blood and blood component quality during the entire storage period and to exclude mix-ups of blood components (see section 6.7 on component storage).

Autologous blood, blood components and tissues as well as blood components and tissues collected and prepared for specific purposes shall be stored separately.

Appropriate records of inventory and distribution shall be kept.

Packaging shall maintain the integrity and storage temperature of blood or blood components during distribution and transportation (see section 6.11 on transportation of blood components).

Return of blood, blood components and tissues into inventory for subsequent reissue shall only be accepted when all quality requirements and procedures laid down by the Blood Establishment to ensure tissue and blood component integrity are fulfilled.

2.6.12: Traceability

There must be a system to ensure that material can be traced through the procurement, testing, and production and issue systems to a patient (for blood, see sections 5.2.1 on donor identification, and 5.5.3 on labels). If the material is donated then traceability must be maintained from the donor to the patient. Any products must be uniquely identified to help support traceability. For example, for reagents this can be to batch level. Where appropriate this should be to individual units, for example apheresis donations split into multiple doses. Any material obtained from outside the EU must maintain a standard of traceability to its origin equivalent to that expected within a Blood Establishment. Under the terms of the BSQR, traceability records of blood components must be maintained for a minimum of 30 years. A similar requirement is in place for tissues and cells under the terms of the Tissues and Cells Directive.[12]

2.6.13: Continuous improvement

It is important to take a holistic view using all available information, including information derived from analysis of incidents, errors, near misses and complaints as well as from audit processes, litigation and peer organisations. This approach will help prioritise those improvements that will be most beneficial to patients, donors and staff. As root cause analysis places a significant drain on expert resources it should be targeted on activities that on the balance of risk are most critical to the organisation. This process should be linked to the Blood Establishment’s planning process so that improvements that require significant resources can be given sufficient consideration and support in their implementation.

2.6.14: Non-conformance

2.6.14.1: Deviations

Blood components or tissues deviating from required standards shall be released for transfusion only in exceptional circumstances and with the recorded agreement of the prescribing physician and the Blood Establishment physician.

2.6.14.2: Complaints

All complaints and other information, including serious adverse reactions and serious adverse events, which may suggest that defective blood components or tissues have been issued, shall be documented, carefully investigated for causative factors of the defect and, where necessary, followed by recall and the implementation of corrective actions to prevent recurrence. Procedures shall be in place to ensure that the Competent Authorities are notified as appropriate of serious adverse reactions or serious adverse events in accordance with regulatory requirements.

2.6.14.3: Recall

A system (usually, but not necessarily, computer software) shall be in place to allow full traceability of products. This will ensure that efficient recall of products can be effected and that look-back studies can be undertaken. The recall operation shall be capable of being initiated promptly and at any time. It is essential that all recalled products are stored separately and securely until a decision is made on the fate of the product. Records of recall must be maintained. A review of the recall procedures for effectiveness needs to be carried out periodically (for blood, see section 6.12 on component recall and traceability).

2.6.14.4: Serious adverse events and reactions

Serious adverse events (SAEs) and serious adverse reactions (SARs) (as defined in the EU Directives) must be reported to the relevant Competent Authority through the relevant website reporting tool:

- For blood and blood components, these are reported to the MHRA as serious adverse blood reactions and events
- For tissues, these are reported to the HTA as serious adverse events and reactions.

2.6.15: Audit (self-inspection)

Quality audit is a planned process of inspection conducted in an independent and detailed way by competent, trained individuals to ensure that procedures and associated quality assurance comply with the principles of GMP. The results of such inspections shall be recorded and non-compliances reported in writing to a designated individual whose responsibility it is to ensure corrective and preventive actions are applied in an effective and timely manner.

There will also be an opportunity to learn from the problems identified through audit, to identify underlying root cause and possibly to support conclusions on areas to improve, identified through incidents and error reporting. As noted above this process should also be linked to the Blood Service’s planning process so that improvements that require significant resources can be given sufficient consideration and support in their implementation.

For Blood and Tissue Establishments, audits shall extend to suppliers of goods and services. The frequency or appropriateness of audit shall be decided on the basis of risk. This can be incorporated into the procurement system.

2.7: Reporting of incidents to external bodies

2.7.1: Serious Hazards of Transfusion (www.shotuk.org)

For blood components, serious adverse reactions and events must be reported to the MHRA (see section 2.6.14.4). However, in addition, blood banks and Blood Establishments are encouraged to report to the Serious Hazards of Transfusion (SHOT) scheme. SHOT collects data on serious sequelae of transfusion of blood components. Through the participating bodies, the information obtained contributes to improving the safety of the transfusion process, informing policy within the transfusion services, improving standards of hospital transfusion practice and aiding production of clinical guidelines for the use of blood components.

Participation in the scheme is voluntary, and covers both NHS and private hospitals in the UK and Ireland. Reports are made via SABRE (see www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Blood/index.htm).

Near misses should also be reported to SHOT. These are incidents where an action has placed a patient at risk. This could include, for example, the placing in stock of incorrectly labelled blood components where the discrepancy in blood group, genotype or test status would have placed a patient at risk of an adverse outcome if the component had been transfused.

It is assumed that if transfusion of products in this ‘near miss’ category occurs resulting in adverse outcome the incident would be reported back to the supplying service, so that they can investigate, identify root cause and prevent further occurrence. In this case it is important that it is understood that in these situations capturing data about events is not about assigning blame or liability but is about improving systems and reducing risk. Such incidents should also be reported to SHOT.

2.7.2: Devices (www.mhra.gov.uk)

The remit of the Medicines and Healthcare products Regulatory Agency (MHRA) is to enhance and safeguard the health of the public by ensuring that medicines work and are acceptably safe.

Blood Services, blood and tissue banks shall have a mechanism to report problems with medicines, medical devices or *in vitro* diagnostic devices to the MHRA. This will provide an opportunity for problems with medicines and devices to be viewed on a UK or European-wide level.

There may be additional local requirements which also must be met. For example, in Northern Ireland there has been a recent Directive that all critical adverse incidents be reported directly to the Northern Ireland Department of Health, Social Services and Public Safety.

Adverse incidents involving medical devices in England and Wales should be reporting using the Yellow Card scheme or via the Yellow Card app. Such incidents should be reported to the Northern Ireland Adverse Incident Centre in Northern Ireland and to Health Facilities Scotland online incident reporting system in Scotland.

2.7.3: Serious untoward incidents

Serious untoward incidents can be defined as ‘something out of the ordinary, or unexpected, with the potential to cause serious harm, and/or likely to attract public and media interest that occurs on NHS premises or in the provision of an NHS or a commissioned service’ (NHS London, 2007).[21] Blood Services may choose to refine this definition further.

Many of these incidents will be captured and investigated using a Blood Service’s quality management system processes. Investigations shall be undertaken promptly, be coordinated by a board director and shall be considered for reporting externally.

Reports may be referred to:

- Department of Health or equivalent
- National Patient Safety Agency (NPSA), although the lead report should be from the Trust or facility where the patient involvement occurred. If this is not a Blood Service then the final report should contain the blood service's contribution
- National Health Service Litigation Authority (NHSLA) if litigation may result
- NHS Information Authority (NHSIA) for IT-related events
- Police in the case of criminal activity
- Health and Safety Executive (HSE) – RIDDOR
- Department of Health Estates and Facilities for fires
- Local Counter-Fraud Specialist (LCFS) for fraud
- Department of Health Estates and Facilities for defect and failure reporting in plant or facility or associated services
- Other stakeholders identified as relevant during the investigation of the serious untoward incident.

2.8: References

1. Statutory Instrument 2005 No. 50. The Blood Safety and Quality Regulations 2005. Available at www.legislation.gov.uk
2. Statutory Instrument 2007 No. 1523. The Human Tissue (Quality and Safety for Human Application) Regulations 2007. Available at www.legislation.gov.uk
3. Commission Directive 2002/98/EC 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. OJ, L 33, 08.02.2003, p. 30.
4. Commission Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. OJ, L 91, 30.03.2004, p. 25.
5. Commission Directive 2005/61/EC 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. OJ, L 256, 01.10.05, p. 32.
6. Commission Directive 2005/62/EC 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. OJ, L 256, 01.10.05, p. 41.
7. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices'. OJ, L 331, 07.12.1998, p. 1.
8. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. OJ, L 169, 12.7.1993, p. 1–43.
9. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 201/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223 /2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. OJ, L 117, 05.05.2017, p.1-175
10. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227 /EU. OJ, L 117, 05.05.2017, p.175-332.
11. Human Tissue Act 2004. Available at www.legislation.gov.uk/ukpga/2004/30/pdfs /ukpga_20040030_en.pdf
12. 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. OJ, L 102, 07.04.2004, p. 48.

13. 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. OJ, L 038, 09.02.2006, p. 40.
14. 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. OJ, L 294, 25.10.2006, p. 32.
15. Commission Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells. OJ, L 327, 27.11.12, p. 24-25.
16. Human Tissue Authority, Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment. Available at www.hta.gov.uk
17. Medicines and Healthcare products Regulatory Agency (2007). Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007. London: Pharmaceutical Press.
18. EC Guidelines to Good Manufacturing Practice. Available at http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
19. Commission Directive (EU) 2016/1214 of July 2016 amending Directive 2005/62/EC as regards quality system standards and specifications for blood establishments. OJ, L 199, 26.7.16, p. 14-15.
20. Council of Europe (2013). Guide to the Preparation, Use and Quality Assurance of Blood Components, 17th edition, Appendix 1.
21. NHS London (2007). Serious Untoward Incident Guidance. www.london.nhs.uk/webfiles/tools%20and%20resources/NHSL_SUI_Guidance.pdf