

Hospital Blood Banks:

Compliance, Inspections and the Future - MHRA Perspective

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My background

- Studied chemistry at university
- Healthcare industry for 15 years with companies such as SmithKline Beecham, Bausch & Lomb, GlaxoSmithKline, Avecia Biotechnology and Johnson & Johnson
- Mainly in Quality Assurance but some commercial roles
- Manufacture of Active Pharmaceutical Ingredients and Medical Devices
- Joined MHRA in January 2006
- Trained as Blood Inspector and inspect Blood Establishments and Blood Banks

Agenda

- Legislation – a brief overview
- Blood Compliance Report Process
- Requirements for Blood Banks - MHRA Expectations
- Update on inspection process
 - Common inspection findings
- MHRA Experiences
- The Future of Blood Bank Compliance

Legislation

European Legislation

Directive 2002/98/EC (setting standards)

- Technical Directives:
 - Directive 2004/33/EC (technical requirements)
 - Directive 2005/61/EC (haemovigilance / traceability)
 - Directive 2005/62/EC (quality systems)

United Kingdom Legislation

- SI 2005/50 (Principal Regulations) {8 Nov 2005}
- SI 2005/1098 (Amending Regulations 2005) {8 April 2005}
- SI 2005/2898 (Amending Regulations 2005 (No. 2)) {8 Nov 2005}
- SI 2006/2013 (Amending Regulations 2006); Implementing Technical Directives 2005/61/EC & 2005/62/EC {31 August 2006}
- SI 2007/604 (Amending Regulations 2007); Fees changes and typos

The Problem.....



- Directive 2002/98/EC exempts hospital blood banks from routine inspection.
- The Competent Authority is required to ensure hospital blood banks comply with requirements for personnel, quality system, storage, transport, distribution, traceability, reporting serious adverse events and reactions *etc.*
- MHRA are the interim Competent Authority – continue as is until 2010
- RATE take over (shadow form) in April 2008 with full responsibility in April 2009

The solution.....



Regulation 10 of SI 2005/50 - Annual Compliance Report

- Substitute for inspection.
- Specific information required from all Transfusion Labs to demonstrate compliance with the Regulations.
- Report any changes which may affect compliance.
- Provide grounds for a 'for cause' inspection where there is apparent non-compliance.
- *Reporting year 1st April 2006 to 31st March 2007, reported by 30th April 2007*



Blood Compliance Report Process

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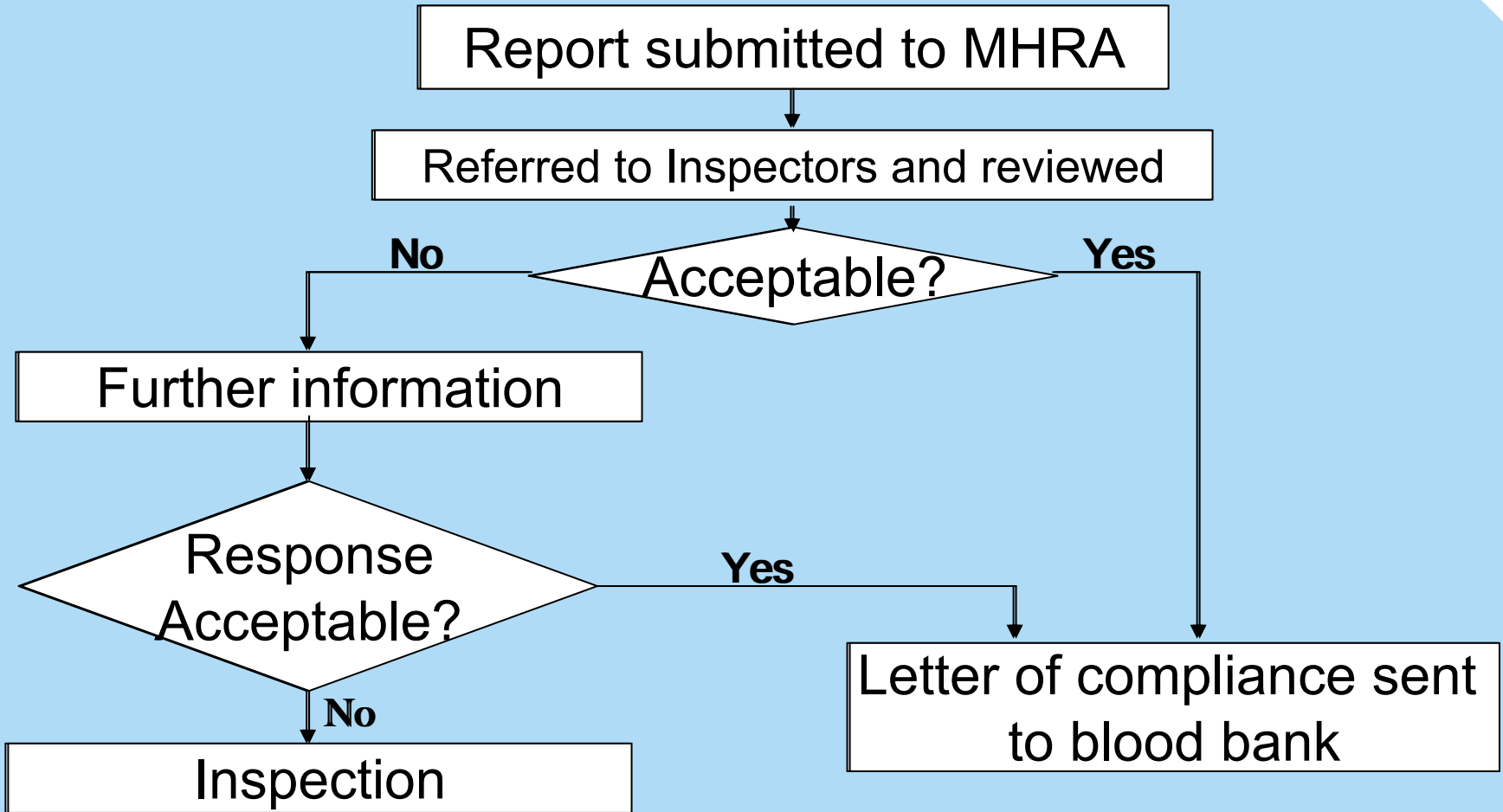
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BCR template review process

- The BCR template was reviewed by Blood Inspectors in light of experiences from the first round of assessments, and inspection findings.
- Changes were made to version 2 of the BCR, to:
 - Improve guidance to sites
 - Provide improved structure and detail to questions
 - Address areas of weakness identified during inspections, to assist sites in achieving compliance with BSQR.
 - References are provided to BSQR 2005, EU Directives and EU GMP, to assist sites in understanding the requirements, enabling them to best demonstrate their compliance.
 - References to applicable site SOPs required.
- The review was assisted by stakeholders and MHRA colleagues in Devices Division and Policy Unit.

The Compliance Report assessment process



Compliance Report Inspection Triggers

- Poorly defined or inadequately resourced Quality System
 - Missing or incomplete key systems, e.g.
 - Recall, complaints, incidents, CAPA, training, documentation, validation, technical agreements, equipment calibration or maintenance failings, self inspection.
- No (or unsuccessful) external accreditation
- Cold chain compliance issues
- Apparent failings in the traceability system
- Significant numbers of internally initiated recalls or repeat SAEs
- Apparent lack of SABRE reporting systems
- Poorly completed forms. Too much information missing to assess remotely.

The aim of the process is to assess compliance. This can only be done with adequate information.

Requirements for Blood Banks - MHRA Expectations

Key areas of scope for assessment – Hospital Blood Banks

- Qualification and training of personnel
- Quality Systems
- Documentation (SOPs, guidelines, records)
- Traceability systems (retention period 30 years)
- Haemovigilance/Notification of SAE and SAR
- Validation
- Acceptable storage and transport of components
(BSQR Regulation 9(1) a-h)
- Accreditation status
- Sites for onward supply

Good Practice Guidelines

- Blood Directives make reference to ‘Good Practices’
- EU Commission intends to publish specific ‘Good Practice Guidelines’ in the future (blood and tissues)
- In the interim, guidance is obtained from:
 - Annex to Directive 2005/62 (Quality Systems)
 - Referenced in Regulations 4 & 6 of SI 2006/2013
 - EU Good Manufacturing Practice Guidelines
 - Chapters 1-9, Annexes 11 and 15
 - <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm>

Training & Records (1)

A typical training record may include:

- A brief CV
- A job description
- Records of induction training
(less of an issue for staff in post for many years)
- Records of regular refresher Good Practice/GMP training
(typically done annually)

Training & Records (2)

- Records of staff awareness of specific regulations
 - a signed/dated attendance sheet would suffice with presentation/training material available for review if requested
- Records of technical training specific to the role demonstrating competency
- Records of training in SOPs
- Copies of relevant professional qualifications/exams taken

Quality Systems (1)

- Change Control
 - Formal system for recording change proposals should include:
 - Justification *i.e.* why is the change necessary
 - Approvals by relevant staff
 - Actions required to implement the change
 - Information relating to implementation effectiveness and closure
 - Change controls should be raised to record significant facility and equipment changes
 - Change controls should consider and indicate whether validation or qualification is/is not required

Quality Systems (2)

- Incident reporting
 - Hospital systems should link closely to Blood Bank system...and there should be a feedback loop
 - Records should include details of the incident/deviation, root cause, corrective actions, preventative actions and closure
 - Not only for SAE/SAR but should include laboratory incidents
 - Should link to SAE/SAR procedures to ensure clarity of how and when to report to SABRE
 - Should link to recall procedures

Quality Systems (3)

- Recalls
 - Must consider internal and externally notified recalls
 - Should link to incident procedures
 - Should be challenged regularly by means of a mock recall (if no live recalls in previous year)
 - Should record details of notification and actions taken to complete the recall
 - Should record the final disposition *i.e.* recalled and discarded, transfused *etc.*
 - (Should ensure medical staff are aware when recalled blood components have been transfused)

Quality Systems (4)

- Self-inspection (internal audit)
 - Should be performed regularly
 - Audits can be performed by trained laboratory staff or other trained personnel with knowledge of blood bank activities
 - Should include review of the following areas:
 - The use of work instructions/procedures
 - Staff training records
 - Traceability system
 - Recall system
 - Incident reporting system and status (including SARs and SAEs)
 - Service level agreements, if applicable
 - Status and effectiveness of significant change projects
 - Equipment calibration and maintenance records
 - Review of temperature monitoring of blood components
 - *Etc.*

Documentation



- Documentation *e.g.* SOPs, work instructions, record sheets *etc.* should be formally controlled and approved before implementing
- Responsibility for document control should be stated
- Access to master copies of SOPs should be limited to the responsible person(s)
- It is acceptable to have SOPs *etc.* on a computer network, although only current versions should be available to staff
- A system should be in place to remove previous versions from circulation
- Appropriate review and retention periods should be stated

Traceability Systems

SI 2006/2013 Section 6 states:

“A blood establishment shall ensure, when it issues a unit of blood or blood components for transfusion, that the facility to which the unit of blood is issued has in place a procedure to verify that each unit of blood issued has been transfused to the intended recipient or, if not transfused, to verify its subsequent disposition.”

i.e. Blood banks must ensure traceability from receipt to final fate.

Systems observed during inspection and BCR review include fully paper based through to electronically controlled systems for traceability.

Neither is considered to be better than the other, so long as compliance with BSQRs is demonstrated.

Records must be held for at least 30 years.

Haemovigilance/Notification of SAE and SAR



- System for haemovigilance should link to incident and recall procedures
- Responsibility for notification to SABRE should be clearly stated
- Notification of SAEs/SARs for hospitals (outside of the Trust) supplied by the blood bank should be documented in a service level agreement
- For hospitals within the same Trust it is acceptable to use shared procedures to define responsibilities
- Records must be held for at least 15 years

Validation

The BSQR definition of Validation:

“...the establishment of documented and objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.”

Blood Banks are required to:

“ensure that all processes referred to in Part 4 of the Schedule which are applicable to activities carried out by the hospital blood bank, are validated”

Part 4: Storage, Transport & Distribution and Autologous Donations

Validation

- The need to validate should be assessed through the change control system
- A validation policy or master plan should define the approach to validation
- Requires Blood Banks to document (e.g. for new test equipment, new transport containers, computer systems, interfaces *etc.*) the following:
 - Requirements (user requirements specification)
 - How to install (IQ – protocol and report)
 - How it operates (OQ – protocol and report)
 - How it performs using samples/standards (PQ – protocol and report)
 - Validation report summarising the above and confirming if equipment is suitable to use (prior to use)

Note: OQ and PQ can be combined

Storage of Blood Components



Component	Temperature	Time
Red cells	2°C to 6°C	28-42 days Dependant on anticoagulant
Platelets	20°C to 24°C	5 days
FFP/Cryo	-30°C or below	24 months 12 months if MB treated
Granulocytes	20°C to 24°C	24 hours

Cold Chain Compliance

- Air temperature alarms set at 2°C and 8°C
 - **ALERT ALARM** to warn of possible problems
 - This can have a reasonable time delay built in (e.g. 10 minutes)
- A buffered load alarm is required to work on the core temperature of the blood.
 - This alarm must have trigger points of 2°C and 6°C
 - Acceptable probe calibration tolerance of +/- 0.5°C
 - This is an **ACTION ALARM** and must not have a time delay.
- The thermal mass and position of this probe should be at a position defined by suitable temperature mapping and scientific considerations, as defined in BS 4376*
 - The time between sampling should be ≤ 5 minutes

Temperature Mapping

- All blood storage equipment should be temperature mapped regularly
- The mapping exercise should be risk based and:
 - Have duration of at least 24 hours
 - Include a minimum of 3 points - normally top, middle and bottom
 - Use a sufficient number of probes to comprehensively cover the area being mapped
- Correlation between the routine probe readings and the mapping probes should be demonstrated
- The cabinet can be used during the test. The amount and type of product in the cabinet during the test must be recorded with the test results
- The minimum mapping probe calibration tolerance is $\pm 0.5^{\circ}\text{C}$ and the frequency of temperature logging should be ≤ 5 minutes

Cold Chain Calibration and Maintenance

- All probes used to record and maintain the cold chain should be calibrated at least over the operating range
- Probe calibration should be done regularly *i.e.* annually is expected unless otherwise justified
- Fridges, freezers, platelet incubators should be on maintenance contracts with regular service visits
- Maintenance frequency should be based on risk assessment, although annual is expected
- Maintenance, repair and calibration records should be reviewed and signed by relevant Blood Bank staff

Transport and Distribution – Cold Chain Validation



- Validation is not required if controls are in place to ensure that blood is not kept out of the fridge for more than 30 minutes
- If > 30 minutes then blood must not be returned to stock
- If blood is transported to remote locations the system for validating cold chain should include:
 - The type of containers to be used and (max/min) number of blood units per load
 - The number and position of any cool packs used
 - Use of probes and dataloggers to confirm temperature for the duration of the transportation period
 - Should consider risks associated with transporting during summer and winter months
- Data from the study should be reported and used to confirm the maximum acceptable time for transportation.

Update on inspection progress

Transfusion Laboratory Inspections – Non-compliant sites

- The 2005-2006 BCR review process identified 60 sites requiring inspection for apparent non-compliance with BSQR
- These sites were scheduled for inspection by 31st March 2007
- All inspections have been completed
- Two sites have been referred for possible Regulatory Action following Critical findings
- The outcomes from these inspections demonstrated the effectiveness of the first BCR in identifying non-compliant sites

Transfusion Laboratory Inspections – Compliant sites

- Six sites which were assessed as ‘compliant’ were selected at random for inspection, to verify the effectiveness of the BCR process.
- All six inspections have been completed.
- One site has been referred for possible Regulatory Action due to a Critical finding.
 - The assessment of ‘compliance’ was based on the BCR submitted by a laboratory which had subsequently closed, and relocated to a new site.
 - The relocation project was found to have been poorly controlled.
- Findings from the ‘compliant’ sites were generally favourable towards the BCR process.

2007/2008 Blood Bank Inspections

- All (398) Blood Compliance Report reviews are now complete
- Inspections required will be identified on 22nd June 2007
- The plan is to notify sites of outcome by letter at end of June
- Inspection program will begin shortly thereafter and should be completed by end March 2008
- Two sites have already been inspected due to apparent issues highlighted during review of Blood Compliance Reports

MHRA Inspection Format

Opening meeting with senior staff

- Opportunity for questions and outline of activities on site
- Quality System review
- Facilities inspection
 - Review of lab processes and equipment
 - May include visit to satellite locations
 - Documentation (SOPs and records)
- Collation of (any) findings
- Closing meeting
 - Presentation of findings (& site acceptance of accuracy)
 - Classification of deficiencies

Post Inspection Process

- Deficiency letter sent to site within 14 days
- Response from site required within 28 days
- The Inspector may ask for clarification or amended responses, if necessary.
- On receipt of a satisfactory response, a close-out letter will be sent, indicating compliance with BSQR.
- There will be no re-inspection of a Blood Bank, unless:
 - Further concerns are raised through future Compliance Reports or SABRE.
 - The site is identified as 'high risk' during the inspection
 - The site is referred for Regulatory Action

Common inspection findings

Common inspection findings (1)

- Quality Systems
 - Ineffective / missing reporting and investigative systems for incidents, deviations, recalls or complaints
 - CAPA poorly defined
 - Self inspection incomplete or missing
 - Disjointed procedures
 - Inadequate resource to manage and operate the system
 - Non-compliance with established systems
 - Lack of technical agreements & description of responsibilities
 - Deficiencies in SABRE reporting arrangements

Common inspection findings (2)

- Validation and Change Control systems missing or incomplete
- Traceability
 - Assumed transfusion
 - Missing records
 - 'Vein to vein' not confirmed
- Documentation scope and control
 - Missing SOPs
 - Uncontrolled / multi-versions
- Temperature monitoring

Common inspection findings (3)

- Laboratory practices
 - Process controls and actions in the event of failure
 - Incomplete description of systems
 - Insufficient prevention of mix-up in records, samples or labelling
 - Lack of contemporaneous records
- Maintenance and Calibration
 - Incomplete records
 - Lack of knowledge of maintenance requirements
 - Untraceable calibration



MHRA Experiences

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MHRA Experiences

- Positive interaction with transfusion staff, and willingness to comply with BSQR
- Sites experience inadequate resource in some cases
- Lack of full awareness of regulatory requirements at inspected sites
- Transfusion staff have expressed a 'step change' from previously applied voluntary accreditation schemes
- Opportunities to work with stakeholders to improve compliance

The Future of Blood Bank Compliance

- Possible further improvements to BCR template
 - Changes will be based on this years experience and feedback from stakeholders
 - Further feedback from inspection process
- Better understanding of BSQRs by Blood Banks...more compliant sites
- Fewer 'for cause' Blood Bank inspections
- **Reduced risks to transfusion patients**



References

Statutory Instruments : www.opsi.gov.uk/

MHRA : www.mhra.gov.uk

EMA : www.emea.eu.int

EU GMP Guide:

<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/home/ev4.htm>

Thank you

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