Good Manufacturing Practice (GMP) —*What it means to you!*

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Aims and Objectives

- Brief overview of GMP Laws & Principles of GMP
- Discuss the implications of GMP on Blood Establishments and Hospital Blood Banks.
- Look at the links between GMP & the BSQR
- Discuss what we need to do to comply with GMP
Introduction

- Good Manufacturing Practice (GMP) ensures that quality is built into the organisation and processes involved in manufacture.
- GMP covers all aspects of “manufacture” including collection, transportation, processing, storage, quality control and delivery of the finished product.
Laws...... the why

- 1937 ......USA ...... Sulphanilamide tragedy ......107 children die.
- 1965 ......Europe ...... Thalidomide ......foetal abnormalities
- 1986 ....USA ....Conneticut Blood Bank
  - Poor computer controls
  - Blood rejected by the laboratory ...(due to HIV)
  - Computer failed to stop dispatch /use of rejected blood

- Despite increasing public demand for “no risk” products ....errors continue!
GMP is…...

.... that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their use. GMP is an integral part of Quality Assurance
Basic Requirements of GMP

- All manufacturing processes are clearly defined, systematically reviewed, and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with specifications.

- Critical steps of the process and significant changes to the process are validated.

- In November 2005 changes in law came into force, that give powers to control Blood Establishments and Blood Banks.
- These controls are based on a long established method for controlling medicines manufacture.
What GMP means to us …

- BSQR Standards 2005 mean that we are now audited as a Blood Establishment.
- Blood Establishments must implement:
  - Effective quality systems, and….
  - A systematic approach to compliance
    - Good manufacturing Practice – GMP
What GMP means to us.....

- Common standards for such a system will be.....
  - Implemented by the blood establishments
  - Enforced by the competent authority –

**Medicines Healthcare & Regulatory Agency**
Regulatory Expectations

- Requirements are now defined in statute
  - Blood Establishments are inspectable
  - Non-compliance is subject to legal sanction
  - Strict product liability applies
- Key to regulatory expectations are
  - Arrangements made for quality assurance
  - Operation of defensible GMP
  - Clearly –defined individual responsibilities
MHRA Inspection Observations

- **Critical**: has produced a product harmful to a person, leads to a significant risk of harming a person.

- **Major**: has produced or may produce a product which does not comply with GMP, indicates a major deviation from GMP.

- **Other**: a combination of several “other” deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such. A departure from GMP.
EU Directive 2002/98/EC states that….

“blood establishments should establish and maintain quality systems involving all activities that determine the quality policy objectives & responsibilities ………. taking into account the principles of good manufacturing practice”
Article 6 of 2002/98/EC Directive

- .....states that Blood Banks must comply with the following Articles of the Directive: Article 7, 10, 11(1), 12(1), 14, 15, 22 & 24.
- Article 11(1) states “member states shall take all necessary measures to ensure that each blood establishment establishes & maintains a quality system based on the principles of good practice”
GMP Orange Guide

- Quality Management
- Personnel
- Premises and Equipment
- Documentation
- Production/Processes
- Quality Control
- Contract Manufacture
- Complaints & Product Recall
- Self Inspection

…Annexes on:
Computer systems
Validation and qualification
GMP & BSQR

- BSQR Article 10 – Qualified personnel with appropriate training
- GMP Guide– Chapter 2: Personnel- Qualified personnel with appropriate training
- BSQR Article 11(1) – Quality Management System
- GMP Guide – Chapter 1: Quality Management – comprehensive QA system incorporating GMP & QC
GMP & BSQR

- BSQR Article 12(1) – Full documentation including operating procedures, guidelines, training reporting forms etc.
- Article 14 – Traceability – involving all documentation
- GMP Guide – Chapter 4: Documentation - full documentation and written procedures for all activities performed which may directly or indirectly affect the product
• BSQR Article 15: Adverse Incident Reporting – all serious adverse events and reactions are reportable to SABRE

• GMP Guide - Chapter 8: Complaints and Product Recall – written instructions for the recall of all defective products & Chapter 9: Self Inspection-provision of internal audits to achieve quality improvements
BSQR Article 22: Storage, transport and distribution – all blood and blood products are stored appropriately and storage conditions monitored

GMP Guide - Chapter 3: Premises and Equipment – ensure premises and equipment is designed and constructed to ensure products are safe for use.
1. Quality Management System

- Satisfy regulatory/accreditation requirements
- “owned” and understood by the workforce
- Is an integral part of how everyone works
- GMP focused
- Ensures the delivery of high quality products and/or services
- Commitment from everyone is vital
# Quality Management System for BSQR

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Quality Management System for BSQR

- Quality manual incorporating specifications agreed with MHRA
- Access to Quality Manager with designated responsibility
- Staff are provided with timely, relevant and regularly updated training
- Document control system
- Traceability requirements are met
- Regular performance reviews of QMS

Chapter 1 - GMP
Chapter 2 - GMP
Chapter 4 - GMP
Quality Management System for BSQR

- Sops for the storage, distribution & transport of blood/blood components within & outside hospital
- SOPs covering temperature controlled storage, its monitoring and management of the “cold chain”
- Standard procedures for the validation & calibration of processes & equipment
- SOPs for the notification of serious adverse events & reactions
- SOPs that allow the accurate, efficient & verifiable withdrawal of blood/blood components if notified of a quality issue
2. Personnel - GMP

- There are competent and appropriately qualified personnel in sufficient numbers to ensure service provision.
- The responsibilities of all staff should be clearly understood and recorded.
- All personnel receive initial and continuing training relevant to their needs.
- Only staff who have appropriate training are authorised to carry out that procedure.
2. Personnel - GMP

- Training should be structured and continuous. Training records based on SOPs are a good means of evidencing that staff are able to perform tasks.
- Competency Assessments can also be used to assess procedural training.
National Occupational Standards – HCS BT1: Determine major blood groups

- **KSF Dimension & Level**: Health and wellbeing HWB8: Biomedical investigation and intervention
  Level 2: Undertake and report on routine biomedical investigations and/or interventions.

- **Performance criteria**
  a) Select the correct techniques and reagents and controls.
  b) Prepare the blood grouping system for use.
  c) Avoid cross contamination through application of correct procedures.
  d) Determine ABO & Rh and other major blood groups by use of selected techniques.
  e) Accurately document and record results.
  f) Recognise instrument or system errors in data.
  g) Interpret results with reference to controls.
  h) Identify anomalous results and investigate.
  i) Identify samples requiring further or additional testing.
  j) Validate current grouping results with reference to previous test results.
  k) Place sample and associated records in the location and storage conditions appropriate for next stage of processing.
  l) Minimise clinical impact of process delays by analysing with suitable degree of urgency for clinical need.

- **Knowledge & Understanding**
  1. The effects of anticoagulants and other substances present in blood samples.
  2. The range of tests, equipment, techniques and procedures used for blood grouping including:
     a. Routine ABO grouping.
     b. Routine Rh grouping.
     c. Other routine phenotyping.
  3. Significance of controls and procedures to adopt in the event of test/control failure.
  4. Antigens of major blood group systems.
  5. Special testing of blood samples i.e., neonatal use.
  6. The clinical need for ABO and RhD typing in patients and donors.
  9. Principles and purpose of routine antenatal sample testing.
  10. Sample handling procedures and management of high risk samples.
3. Premises & Equipment - GMP

- The premises and equipment must be located, designed, constructed, validated and maintained to suit the intended operations.
- Lay out, design and operation must be designed so as to minimise the risk of errors and permit effective cleaning and maintenance.
- There is adequate and safe provision of lighting, heating, ventilation, power gases water and drainage.
3. Premises and Equipment - GMP

- There should be defined storage areas for quarantine, released, rejected and recalled materials.
- Where specific storage conditions are required these should be provided, checked and monitored for compliance.
- Storage areas should be secure, restricted to authorised person access.
3. Premises and Equipment - GMP

- Adequately specified prior to purchase
- Validated correctly before being put into use and when in use (IQ; OQ; PQ)
- All equipment should have an original identifier. E.g. serial number.
- All equipment should be calibrated, cleaned and maintained according to written instructions
3. Premises and Equipment - GMP

- There should be a procedure for revalidation at regular intervals.
- Maintenance, cleaning and fault logs should be maintained for each piece of equipment.
- There should be corrective action procedures for out of specification equipment. Defective equipment should ideally be removed from the area or if not labelled clearly as defective and signed by a senior member of staff.
4. Documentation – Why?

● To be clear about what we are going to do i.e. the documentation should define the quality system. It prevents errors and is the basis for control.

● To confirm that we have followed correct procedures and that we are consistent.

● To enable us to investigate problems, errors, defects, complaints etc. thereby determining the best corrective and preventative actions to take.
4. Documentation - GMP

- There should be documentation available for all aspects of the activities performed. These will include, procedures, instructions, specifications, records.
- Documents should be clear, concise and unambiguous.
- Documents should be regularly reviewed and controlled.
4. Documentation - GMP

- Only official copies should be used.
- Records should be completed in ink.
- Any alteration to a record should be signed and dated with the original entry still visible.
- Changes to official documents should be avoided, where absolutely necessary they must be signed by an authorised person.
5. Production/Procedures - GMP

- Must follow clearly defined procedures and only be performed by staff who are trained and competent.
- Significant amendments to the production process, including any change in equipment or materials which may affect the quality of the product or reproducibility of the process should be validated.
Written procedures should be in place to describe actions if a change or deviation occurs.

All changes and/or deviations that affect product quality or reproducibility of the process should be formally requested, documented and accepted.
5. Production/Procedures - GMP

- Validation studies should be conducted to show that the process, equipment and/or activity leads to the expected results, this includes laboratory equipment and computer systems.
- There should be a formal documented system for change control.
- All changes that affect product quality or reproducibility of the process should be formally requested, documented and accepted.
6. Quality Control - GMP

- Laboratory Sampling & Testing requires:
  - Defined written procedures
  - Validated methods
  - Qualified, calibrated & maintained equipment
  - Approved reagents and/or test kits
  - Validated procedures for data transfer
  - Documented acceptance and rejection criteria
7. Contract Manufacture

- For GMP critical activities only:

- Defined contract giving explicit details for both the contract giver and contract acceptor.

- Examples of this would be SLAs with WBS, agreements for testing with other trusts etc.
8. Complaints & Product Recall

- All complaints concerning potentially defective products must be reviewed according to written procedures.
- There should be written recall procedures that are checked and updated as necessary.
- Recall operations must be able to be initiated promptly and at any time.
8. Complaints & Product Recall

- Full traceability of all products
- Systems to ensure recording of:
  - Product defects
  - Adverse reactions
  - General complaints
- System to ensure rapid recall of any product subsequently found to be defective
9. Self Inspection - Audit

“A planned, independent investigation of selected elements of a quality assurance system to collect objective evidence that the system has been implemented, is effective and is being complied with.”
9. Self Inspection

- Internal audits are conducted to monitor the implementation and compliance with GMP.

- Internal audits should be conducted in an independent and detailed way by designated competent people.
Validation and Qualification

- It is a requirement of GMP that manufacturers identify what validation is needed to prove control of critical aspects of production.
- Significant changes to the facilities, equipment and processes which may affect the quality of the product should be validated.
“all action proving, in accordance with the principles of GMP that any procedure, process, equipment, material, activity or system actually leads to the expected result.”
Validation Master Plan

- Describes “what” to validate … not “how” to validate – defined in SOPs
- Defines the validation lifecycle
- Roles and responsibilities
- Documentation
- Change control
- Review & Revalidation
**Installation Qualification (IQ)** should be performed on new, modified facilities, systems & equipment.
- IQ confirms that the equipment has been installed correctly

**Operational Qualification (OQ)** - the OQ establishes that the equipment is “fit for purpose”
- Completion of successful OQ should allow formal “release” of the facilities, system or equipment.

**Performance Qualification (PQ)** – should follow on from OQ.
- PQ demonstrates that the equipment, system or process can consistently produce the quality that is required.
Thank you for listening

Any questions?