Medicines & Healthcare products Regulatory Agency

Strategic approach to resolving issues found at inspection



CPRD NIBSC MHRA

Findings at Inspection

For the 2018/19 inspection cycle there were 3 HBBs referred to CMT, 1 that remained at IAG and 3 that remained at CMT from the previous year.

- Senior management not fulfilling their responsibilities
- Self-inspection
- Non-conformances/incidents/events and CAPA implementation
- Document Control
- QMS Failures - Change control management, Validation and Risk Management
- Resourcing and training
- Failure to complete previous commitments
- Data integrity failures
- Capacity – (Separate presentation)
- Traceability

One approach to self inspection

1.2.2. 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-conformance and self-inspection (Directive 2005/62/EC/Annex 1.1.2).

9.4.8. As part of periodic Quality System reviews, an assessment should be made of whether corrective and preventive actions or any re-validation should be undertaken. The reasons for such corrective actions should be documented. Agreed CAPAs should be completed in a timely and effective manner. There should be procedures for the on-going management and review of these actions and the effectiveness of these procedures should be verified during self-inspection.

10.1. Self-inspection or audit systems must be in place for all elements of operations to verify compliance with the standards set out in the Annex to Directive 2005/62/EC. They must be carried out regularly by trained and competent persons, in an independent way, and according to approved procedures (Directive 2005/62/EC/Annex 10.1).

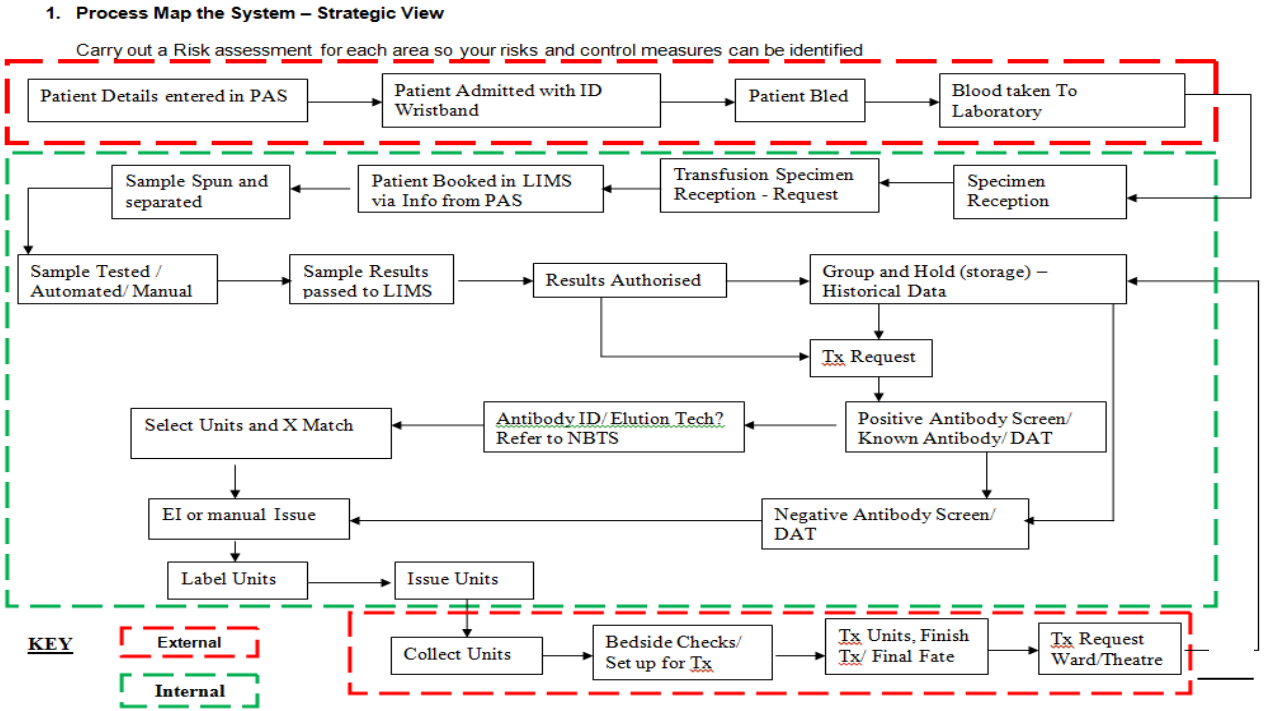
10.2. All results must be documented and appropriate corrective and preventive actions must be taken in a timely and effective manner (Directive 2005/62/EC/Annex 10.2).

- Identify your audit areas to create an audit calendar – Critical (often), Major (quarterly), Other (as a result of a practice change)
- How? – Process Map your business processes to identify the component parts.
- Examples:

    - Adverse Incidents – Track and trend. To make sure mitigation has workedTrack and trend. To make sure mitigation has worked and have effective signal detection.
    - Training – Is it effective
    - IQC/EQA – Performance, failures
    - Traceability – Regulatory requirement

THIS LIST IS NOT EXHAUSTIVE

The overall Strategic Process - BT



If you know your processes you know where to audit it i.e. when an error occurs

Influences – Internal and External

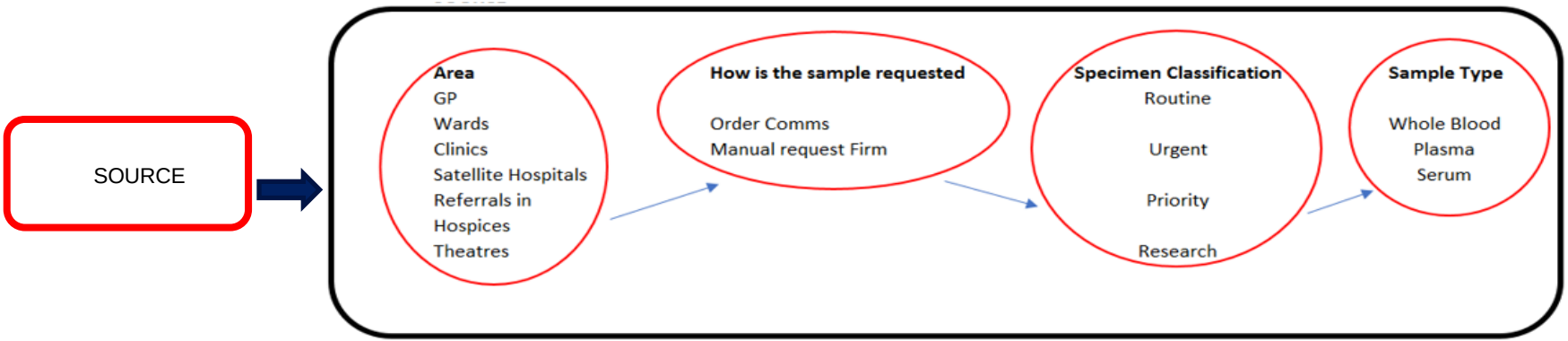
The individual elements as a sum of and all of the parts of the business process

The Component parts

Take one area of the process
Split it into its component parts
Think about everything
Risk assess everything
Think about what you do and how you do it – Business Process

Their will be some repetition i.e. LIMS influences all of the strategic and the individual parts BUT in different ways so account for them i.e. Personnel are trained but trained in different aspects of the process as the process moves thorough the system

Component Parts - Source



Questions

- How does this fit together
- What technology is involved
- What is the TAT – Area to Lab (Effect on Testing)
- What are the special requirements if any
- Do the interfaces, i.e. PAS, work and how are they maintained/backed up
- Sample rejection/acceptance policy/SOP
- Personnel – Training/ competency/ SOP
- capacity planning
- BCP – Have you tested it against failure in ALL parts of the process (LIMS Outage – how do you recover/reconcile orders)
- Manual/ technology interactions where what and how
- Look Back requests – Phone requests for results
- Errors – Track and Trend (categorise)

Adverse Incidents

When to do a full RCA

When a CAPA is needed.

The closing of incidents and trending incidents.

The Good Practice Guide (GPG)

1.2.13. A formal system for the handling of deviations and non-conformances must be in place. An appropriate level of root-cause analysis should be applied during the investigation of deviations, suspected product defects, and other problems. This strategy can be determined using Quality Risk Management principles. If the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing them. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system-based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed in accordance with Quality Risk Management principles.

9.1.6. Deviations from established procedures should be avoided as much as possible and should be documented and explained. Any errors, accidents or significant deviations that may affect the quality or safety of blood and blood components should be fully recorded and investigated in order to identify systematic problems that require corrective action. Appropriate corrective and preventive actions should be defined and implemented.

9.1.7. Investigations relating to serious deficiencies, significant deviations and serious component defects should include an assessment of component impact, including a review and evaluation of relevant operational documentation and an assessment of deviations from specified procedures.

Level of RCA and CAPA evaluation via a Severity Index Score (one method)

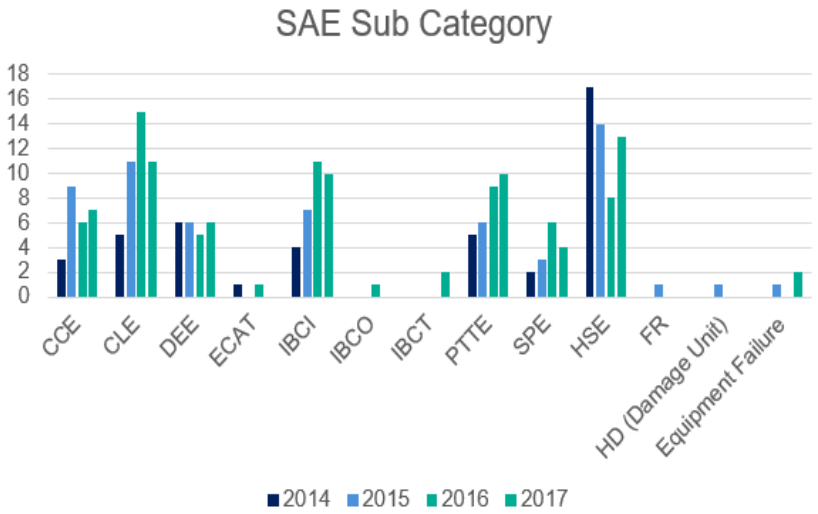
The time periods stated in the table below are only an example and NOT a definitive figure mandated by the MHRA. Base your timescales on your Quality Management Policies

SEVERITY INDEX	RCA Type	Immediate Action	Target Period for Completion of RCA by type	Comment
MAJOR/CRITICAL • Serious Harm to Patient/Donor • Failure of service provision which indicates a breakdown in supply chain • Significant loss of product in one event • An event that has a significant effect on laboratory operations	**Full RCA**	Assess the ACTUAL and POTENTIAL risk using Quality Risk Management Principles immediately. Introduce immediate mitigation based on the initial investigation so further risk is reduced	Optimum of 30 days but with a maximum of 8 weeks. Extension, with justification may be required i.e. when several departments are involved.	Justify and evidence all extensions if required i.e. Police involvement and ONLY when the immediate risks have been reduced.
MINIMAL • Noncritical event caused by a significant failure in the QMS • Recurrent failure	**RCA** Full or minimal dependant on actual and potential risks. Can be upgraded.	Assess the ACTUAL and POTENTIAL risk using Quality Risk Management Principles immediately. Introduce mitigation based on the initial investigation	2-4 weeks	If necessary, upgrade to Major based on initial findings
OBSERVATION • All other events not covered by the above • Any failure on the QMS that has no direct effect on function but requires action	**Minimal RCA** May upgrade to a more detailed RCA based on findings	Assess the ACTUAL and POTENTIAL risk using Quality Risk Management Principles. Introduce mitigation based on the initial investigation	1-2 Weeks	A one-off failure i.e. IQC/EQA failure (upgrade where required

Carried out by the most appropriate individuals with enough knowledge of the issues and keeping the investigation who can be Independent and objective.

Tracking and Trending – Function of Audit

SAE Other Sub Category's				
	2014	2015	2016	2017
CCE	3	9	6	7
CLE	5	11	15	11
DEE	6	6	5	6
ECAT	1	0	1	0
IBCI	4	7	11	10
IBCO	0	0	1	0
IBCT	0	0	0	2
PTTE	5	6	9	10
SPE	2	3	6	4
HSE	17	14	8	13
FR	0	1	0	0
HD (Damage Unit)	0	1	0	0
Equipment Failure	0	1	0	2



Essential in identifying errors, by type, to allow for mitigation

You must know your processes to ID the component parts

Monitoring system – Self Inspection audits (process map)

Expected as part of your quality risk management principles

CAPA Management

Set realistic targets – You must have a reason for a target being set

Extending target dates - Give a reason as to why a target has been extended (Resource issue is NOT valid)

Ensure you close the loop – Change Control, Training and competency

Evaluate the impact/risk and mitigate– the NOW and the WHEN

Closure – RCA complete, risk and impact assessed and mitigated, change control/management/training and competency cycle complete

Has it worked – Audit (Independent and objective) – don’t just leave it and hope it does not happen again

Document Control Overview – GPG

5.1.3. There are two primary types of documentation used to manage and record Good Practice compliance: instructions (directions, requirements) and records/reports. Appropriate practices should be applied with respect to the type of document. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded or documented on media from which data may be rendered in a readable form for humans.

See also Section

5.2. Required good practice documentation (by type)

Overview – Documents

Records where alterations made to the entries on the documents are not signed and dated

The alterations do not ensure that the original information may be read and they lack explanations for the alterations

Obliteration (including Tippex tape (or stickers) and overwriting) had been used to amend original entries

Historically procedures had been made Active without using the approvals process – Have you got one?

The active dates on Policies and Procedures can differ – Document differs from the electronic system

Overview – Documents

Evidence of forged documents relating to staff training records

Deletion of key analytical data from hard drives and audit data

Data generated lacked reliability and accuracy

Laboratory records are not in compliance with established standards – GPG section 5.2

Data Integrity - GPG

4.2. Data processing systems

4.2.1. If 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 must be protected against unauthorised use or unauthorised changes. The back-up procedure must prevent loss of or damage to data at expected and unexpected down-times or function failures (Directive/2005/62/EC/Annex 4.5).

4.2.2. Systems must be properly maintained at all times. Documented maintenance plans must be developed and implemented. This strategy must include audits of quality assurance systems.

4.2.3. Changes in computerised systems must be validated; applicable documentation must be revised and relevant personnel trained appropriately before any change is introduced into routine use. Computerised systems must be maintained in a validated state. This must include
user-testing to demonstrate that the system is correctly performing all specified functions both at initial installation and after any system modifications.

4.2.4. There must be a hierarchy of permitted user access to enter, amend, read or print data. Methods of preventing unauthorised entry must be in place, such as personal identity codes or passwords that are changed regularly.

4.2.5. All necessary measures must be taken to ensure protection of data. These measures must ensure that safeguards against unauthorised additions, deletions or modifications of data and transfer of information are in place to resolve data discrepancies, and to prevent unauthorised
disclosure of such information.

4.2.6. Computer systems designed to control decisions related to inventories and release of blood components should prevent the release of all blood or blood components considered not acceptable for release. Preventing release of any components from a future donation from a deferred donor should be possible.

MHRA Data Integrity guide https://mhrainspectorate.blog.gov.uk/2018/03/09/mhras-gxp-data-integrity-guide-published/

Data Integrity - GPG

- Data Integrity - maintaining and assuring the accuracy and consistency of data over the entire life cycle
  - Back up cycle
  - Accurate retrieval
  - Adequate Archive process
  - Validated and tested (Leeds)

The QMS Engine Room

Change control

Validation/URS

Risk assessments

Why/When/Example common failures/good practice

Change Control - GPG

1.2.12. A formal change control system must be in place to plan, evaluate and document all changes that may affect the quality, traceability, availability or effect of components, or the safety of components, donors or patients. The potential impact of the proposed change must be evaluated, and the degree of re-validation or additional testing, qualification and validation needed must be determined.

Encompasses everything – Personnel, training, communication, analysers, SOP etc.

Change Triggers – Best practice, audit findings, quality incidents, complaints, changes within a process (Projects)

Responsibility – Everybody, influenced by external (manufacturers) and internal (BCP) pressures

Change planning – Strategic plan (Policy), tactical (a local process)

Change evidence – What it is (Process Map), Impact of, associated risks and mitigation, Who, why, what and When, training and competency

Change review – Audit both internal and external - independent and objective

NB: Minor amendments to written procedures may not need to be subject to Change Control, but must be managed through the document control process.

Validation - GPG

1.2.11. A general policy regarding qualification of facilities and equipment as well as validation of processes, automated systems and laboratory tests must be in place. The formal objective of validation is to ensure compliance with the intended use and regulatory requirements.

4.3.1.2 The principles of qualification and validation are applicable to the collection, preparation, testing, distribution and issuance of blood components. It is a requirement of Good Practice that blood establishments and hospital blood banks control the critical aspects of their operations through the life cycle of the blood components and the associated processes. Any planned changes to the facilities, equipment, utilities and processes should be formally documented and the impact on the quality on blood components should be validated.

Initial Validation starts with a change control process

Adhere to a Validation Policy – Define Strategy

Validation Master Plan (VMP) – List all critical processes with evidence of pre and post qualification data (Fit for purpose)

- Validation Plan – Project Plan (members, targets)
- Validation Protocol – How Why, Who and When
- Validation Summary Report – Qualification data (IP, OP, QP – Acceptance Criteria)

Validation includes Training and Competency of internal and if appropriate external staff

DOCUMENT EVERYTHING FOR EVIDENCE

User Requirement Specifications - GPG

4.3.4.2. User requirements specification (URS): the specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any Good Practice risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.

Part of the validation process

Process map your processes (see previous slide)

Include Documents such as specification ,User Manuals, Tender documents, Project Plans

Describes Essential and Desirable Requirements and functions from password control to final reports

Defines the operating environment/ parameters

Time and cost implications

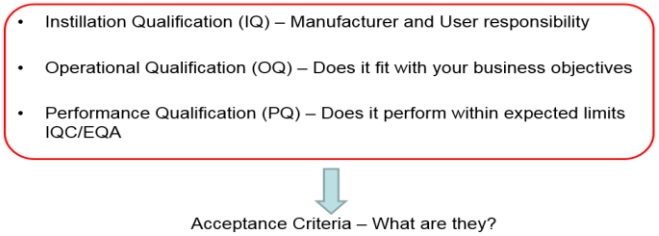
User Requirement Specifications

Functional Requirements – The functions it will perform, Facilities required to meet URS, System acceptance test (confirms Instillation data - Written by the supplier in conjunction with the URS)

Non Functional Requirements – Covers the behaviour in respect of compliance to Legislation, best and Good Practice)

Not a design solution it's a requirement

Each requirement must be tested or verifiable



Each requirement must be prioritised (Essential and Desirable)

The URS should have a review, approval and authorisation section (reviewed and authorised by the appropriate people)

Changes must be put through the change control process.

Training

Training requirements (Lab and Collection staff)

- Why/When
- Common failures
- Good practice

Training - GPG

4.7.2.5. The training programme should be re-assessed for any critical change in environment, equipment or processes. Training records (including plans and protocols of training status) must ensure that training needs are identified, planned, delivered and documented appropriately for maintenance of validated systems and equipment.

2.7 All personnel must receive initial and continued training appropriate to their specific tasks. Training records must be maintained. Training programmes must be in place and must include Good Practice (Directive/2005/62/EC/Annex 2.3).

2.8. Training should be provided for all personnel whose duties take them into preparation areas or into laboratories (including the technical, maintenance and cleaning personnel)

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2.9. There should be written policies and procedures to describe the approach to training, including a record of training that has taken place, its contents, and its effectiveness.

2.10. The contents of training programmes must be periodically assessed and the competence of personnel evaluated regularly (Directive/2005/62/EC/Annex 2.4).

Training

- **What are you trying to achieve? – Training Policy must**
  - Know your processes – SOPs/ Policies (Something to train against)
  - Know your staff – Abilities, Skill Mix and staff selection
  - Limit Risk – Risk Assessments (controls) / Reduce Error
  - Resource – Dedicated Staff and Time
  - Know your limitations
  - Review/ Audit/ Revise – KPIs (targets), Fit for task

Training Cycle

- **Complexity of task (how many steps are involved)**
- **Continuity of staff carrying out the task (staff turnover)**
- **How many times the task is carried out (familiarity of the process)**
- **Error rates associated with the process and staff members i.e.**
    - **Errors associated with one staff member**
    - **Errors associated with the process.**

Capacity Issues

Available resource – Workload to resource not resource to workload

- Why cant an MLA electronic issue?
- Recording extra time – are you only working 37.5 hours a week

Availability of experienced and qualified staff – Are you making best use of your resource?

- Do you need a fully qualified BMS to do everything?
- Can you use an appropriate training and competency plan to utilize non BMS qualified staff?

Support from Executive Management – Evidence based concerns (Error rates. Audit findings, sickness levels)

- Evidence based approach – Cost it out
- Record everything and avoid anecdotal evidence

Technology – Fit for task

- LIMS – Downtime, does it fit with your business processes
- Analysers – Downtime IQC/EQA, are they truly walk away

The Good Practice Guide

1.2.2. 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-conformance and self-inspection (Directive 2005/62/EC/Annex 1.1.2).

1.2.5. **Executive management has the ultimate responsibility** to ensure that an effective Quality System is in place and resourced adequately, and that roles and responsibilities, are defined, communicated and implemented throughout the organisation. Executive management's leadership and active participation in the Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Quality System.

2.2. The organisation should have an **adequate number of personnel with the necessary qualifications and experience**. Management has the ultimate responsibility to determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Quality Management System and continually improve its suitability and effectiveness through participation in management review. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

This underpins the fact that personnel are a central cog in the management of EVERY Quality Management System and as such the management has the ultimate responsibility for providing this resource that is fit for task to ensure business continuity through an adequate capacity plan.

To ensure adequate resource, relevant evidence needs to be provided so sufficient capacity is available to suit all situations so business continuity can be preserved..

A Detailed View – Risk Status and Impact

Severity and Risk stauts against KPI								
QMS Support	KPI	Required Capacity WTE	Current Capacity WTE	Associated/ Curret Risks	itigation in pla	Detail of Mitigation	Current Score Vs Compliance	Impact
	Training and Competency	0.3	0.1	Currently only achieving 70% compliance and thjerefore unable to meet 100% KPI as staff cannot be released to train junior members. Senior BMS staff unable to be released for conferences, TADG	No	No mitigation in place as workload and staffing levels only allow for routine workload targets to be met		Unable to meet regulation 2.2 of the GPG as only 70% of staff are adequately trained and competency assessed at current staffing levels. Continuing at this level is increasing our SABRE reportable events, 2% increase in the last quarter all associated with ineffective and inadequate training of junior, new and locum staff. 2.2. The organisation should have an adequate number of personnel with the necessary qualifications and experience. Management has the ultimate responsibility to determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Quality Management System and continually improve its suitability and effectiveness through participation in management review. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

Raise this issue as a major non compliance to the BSQR's at your hospital risk committee meeting

A true evidenced reflection of the current situation

Use the regulations to support your case

Record not just the issue but the actions and time frame for implementation and keep track

Add to your hospital risk register

Strategic KPIs have component parts i.e.

Severity and Risk stauts against KPI			
QMS Support	KPI	Required Capacity WTE	Current Capacity WTE
	Training and Competency	0.3	0.1
	SOP Review	0.1	0.1
	IQC	0.1	0.1
	EQA	0.2	0.1
	Attendance at TADG, HTT, etc	o.3	0.1
	Internal Management Meetings	0.3	0.1
	Adverse Incident reporting	0.1	0.1
	Adverse Incident AUDIT	0.1	0.1
	Traceability	0.5	0.1
	IT Support	0.1	0.1
	Automation	0.1	0.1
	Staffing Levels including Holiday and Sickness		-0.3
	Change Control and Validation Projects	0.1	0.1
	Stock Management	0.1	0.1
	Overall Total and Score	**2.1**	**1**
		based on 37.5 hour week	**working at -1. WTE**

Extrinsic Factors

Internal Meetings – are these factored in, how many, are they needed

External Meetings/Conferences – Essential for networking for best practice sharing and communication of ideas

Internal and External Projects – What are they, how do they impact

CPD – It's an obligation of the Employee and Employer – investors in people, what is the Trusts/ professional body Policy? What do the clinician and nursing staff do (setting precedence) – STUDY DAYS

Double Hatted – How many balls can you juggle

Breaking down barriers – Them and us, knowing both sides

Telephone communicates – Are they necessary, can they be filtered

Interruptions – Outside Staff, Alarms, Induction, Mandatory Training

Locums – Cost them out BOTH in employment costs but also with training and competency requirements

Traceability - GPG

1.2.12. A formal change control system must be in place to plan, evaluate and document all changes that may affect the quality, traceability, availability or effect of components, or the safety of components, donors or patients. The potential impact of the proposed change must be evaluated, and the degree of re-validation or additional testing, qualification and validation needed must be determined.

5.5.2.2. Traceability data (that allow tracing from donor to recipient and vice versa) should be retained for a minimum of 30 years (Directive 2002/98 Article 14.3).

5.8.2 Preparation record: each unit is considered to be a unique batch, but preparation records should provide sufficient information to build the history and traceability of a prepared component. Usually this information is captured in the computerised systems of the blood establishment. In general, the blood establishment should have access to the following processing records for each unit.

6.8.3. There should be a defined procedure for exceptional release of non-standard blood and blood components under a planned non-conformance system. The decision to allow such release should be documented clearly and traceability should be ensured.

Traceability – Evidence

Expected

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- 100% traced from manufacture to final fate - investigate your failures (98% traced what constitutes the 2%? – assumed Tx is NOT a final fate)
- Manual/ Electronic or a mixture – Validated is it fit for purpose?
- If a mix of methods are used make sure you use a reference system that links it all together.
- Records must be contemporaneous
- Track and trend the failures – common issues, person/process, offender rates
- Investigate ALL deviations – base this on actual and potential risk factors.

Summary

Adequate Policy – Covers all aspects (routine on call, initial, refresher)

Dedicated Resource – identify what you need to do and how to do it and allocate the appropriate time and people

KPI’s – make them realistic

What are your Core needs (100% trained)

Esoteric functions train only those that need it – i.e. Flow

Training Cycles – Multi factual (Error rates, Staff turnover, changes to processes, complexity of task)

Know your people – Capabilities and selection

Training and competency programs based on your processes (SOPs/ Policies)

Include the core TQM System – Everybody's responsibility not just the managers