Developing, validating and monitoring blood components in the UK

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Outline

- Overview of the United Kingdom
- UK Transfusion Services
- NHSBT operations
- Component evaluation in the UK
- Quality monitoring in NHSBT
Governments of the UK

UK Government

- Scottish Government
- Northern Ireland Executive
- Welsh Assembly Government
- No devolved equivalent for England

- Each with its own Department of Health
- Decision makers
Government advice

Safety of Blood, Tissues and Organs (SaBTO)

- Advisory Committee
- makes recommendations to UK governments

- Departments of Health
  - Make the decisions, may need ministerial approval
  - Instruct Blood Services to implement

- Risks related to blood components considered:
  - vCJD
  - Bacterial contamination of platelets
  - CMV, Hepatitis E
Regulations

• Blood Safety & Quality Regulations
  • EU Directive, transcribed to UK law in 2005
  • www.transfusionguidelines.org.uk/regulations

• Council of Europe Blood Components
  • 2013, 17th Ed. (Print copy required to access on-line)
  • www.edqm.eu/en/blood-transfusion-guides-1608.html

• Red Book
  • Guidelines for the UK BTS, 2013, 8th Ed.
  • www.transfusionguidelines.org.uk/red-book
UK Regulator

- Medicines and Healthcare products Regulatory Agency (MHRA)
- UK Competent Authority for safety and quality of blood and blood components.
UK Blood Services

- SNBTS
- NIBTS
- NHSBT
- WBS
## Number of units - 2013/14

<table>
<thead>
<tr>
<th></th>
<th>NHSBT 86%</th>
<th>SNBTS 8%</th>
<th>WBS 4%</th>
<th>NIBTS 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC</td>
<td>1,700,000</td>
<td>180,000</td>
<td>80,000</td>
<td>50,000</td>
</tr>
<tr>
<td>Apheresis PC</td>
<td>220,000</td>
<td>21,000</td>
<td>6,600</td>
<td>7,000</td>
</tr>
<tr>
<td>Buffy Coat PC</td>
<td>51,000</td>
<td>4,000</td>
<td>2,900</td>
<td>1,000</td>
</tr>
<tr>
<td>FFP</td>
<td>231,000</td>
<td>21,000</td>
<td>10,000</td>
<td>5,000</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>158,000</td>
<td>3,600</td>
<td>1,400</td>
<td>1,000</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>1,700</td>
<td>80</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BC</td>
<td>300</td>
<td>0</td>
<td>700</td>
<td>0</td>
</tr>
</tbody>
</table>
NHS Blood and Transplant is a Special Health Authority responsible for:

• Encouraging people to donate organs, blood, stem cells and tissues

• Optimising the safety and supply of blood, organs, stem cells and tissues and matching them to patients

• Helping to raise the quality, effectiveness and clinical outcomes of blood and transplant services

• Providing expert advice to other NHS organisations, and to the health departments of the four UK countries

• Commissioning and conducting research and development to improve outcomes for patients

• Implementing relevant EU statutory frameworks and guidance
Blood donation

90 donation teams
• Made up of 65 mobile donation teams and 25 static donor centre sites.
• 23,000 sessions per year

West
- Bath
- Birmingham DC
- Bristol DC
- Bristol North
- Bristol South
- Cornwall
- Dorchester
- Exeter
- Gloucester
- Gloucester DC
- Kings Norton
- Oxford
- Oxford DC
- Plymouth
- Plymouth DC
- Poole DC
- Portsmouth
- Reading
- Slough
- Southampton
- Southampton DC
- Solent BM
- Sutton Coldfield
- Solihull
- Swindon
- Taunton
- Telford
- Worcester

East
- Ashford
- Ashford BM
- Brentwood
- Brighton
- Cambridge
- Cambridge DC
- Central London
- Coventry
- Edgware DC
- Epsom
- Harlow
- Hertfordshire
- Hither Green
- Horsham
- Huntingdon
- Ipswich
- London Middlesex
- Luton
- Luton DC
- Maidstone
- Milton Keynes
- Mitcham
- Northampton
- Norwich
- South Anglia
- Thetford
- Tooting DC
- Tunbridge Wells
- West End DC

North
- Bradford
- Bradford DC
- Caernarfon
- Cumbria
- Hull
- Lancaster
- Lancaster DC
- Leeds City DC
- Leeds DC
- Leeds East
- Leeds West
- Leicester
- Leicester DC
- Lincoln
- Liverpool
- Liverpool DC
- Manchester East
- Manchester NH DC
- Manchester PG DC
- Manchester West
- Newcastle
- Newcastle DC
- Nottingham
- Nottingham DC
- Sheffield DC
- Sheffield North
- Sheffield South
- Stoke
- Stoke DC
- Teeside
- Wrexham
- York
The whole blood business plan has decreased year-on-year since 2011/12.

This is due to a reduction in hospital demand for blood.

Around ~935k active whole blood donors donating on average 1.88 times/year help us achieve this plan.
Platelet Donation Activity

- Following an initial increase in platelet donation, our platelet business plan has also decreased over recent years.
- This is primarily due to a removal of the requirement to issue at least 80% of apheresis collected platelets.
- Around ~13.3k active platelet donors donating on average 8.5 times/year help us achieve this plan.
Blood Supply Operations and Distribution Structure

Key

Testing and Manufacturing and SHU Centres
- Manchester
- Filton

Manufacturing and SHU Centres
- Newcastle
- Sheffield
- Colindale

Stock Holding Units (SHU)
- Lancaster
- Leeds
- Liverpool
- Birmingham
- Oxford
- Southampton
- Plymouth
- Tooting
- Brentwood
- Cambridge.
Principal Blood Components

- Red Cells
- CD Platelets
- Pooled Platelets
- Cryo
- FFP

Locations:
- Colindale
- Filton
- Manchester
- New castle
- Sheffield
Joint Professional Advisory Committee (JPAC)

- UK wide collaboration
  - UKBTS
  - National Institute for Biological Standards and Control
  - Regulators (MHRA, HTA)
- Specialist professional advice to medical directors
- Standing Advisory Committees
- “The Red Book”
  - Conforms with EU directive, enshrined in UK law by the BSQR 2005; and CE Guide
Evaluating new components

- The Red Book
  - Chapter 8 – Evaluation of novel components
  - Chapter 7 – Specifications for components
  - Chapter 6 – Evaluation and Manufacture of components
Evaluating new components

Component Strategy Group

Component Development Laboratory

Manufacturing Development Team

Operational Teams

Operational Teams

Phase 0

Phase 1

Phase 2

Local PQ

Live

National Operations Leadership Team
8.6.3: Phase 0: Evaluation

• After an initial familiarisation with novel bag/filters (pre-Phase 0) the purpose of Phase 0 studies is to:

• assess suitability to progress to Phase 1

• determine suitable quality monitoring parameters

• disclose any quality problems that might prevent components collected or prepared in these packs from being used for transfusion.

• Processing conditions used in the Phase 0 evaluation should be the same as those applied to Phase 1 and 2 evaluations.

• \( n = 10 \) to 16 components

• in depth study throughout shelf life (Chapter 8)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Leuco-depletion</th>
<th>Pathogen reduction</th>
<th>Extended storage</th>
<th>Sterile connection</th>
<th>New bag, additive or anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (d1)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Platelet content</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Leucocyte content (d1)</td>
<td>✔</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Leucocyte subsets (%)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Morphology, e.g. Swirl test</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Activation, e.g. beta thromboglobulin</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Lysis, e.g. lactate dehydrogenase</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Metabolic activity, e.g. ATP, pH</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Function e.g. Aggregation</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Cytokines/chemokines</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>FXIIa</td>
<td>?</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterility</td>
<td>if dock on</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>PrP&lt;sup&gt;α&lt;/sup&gt; and microvesicles</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathogen reduction*</td>
<td>?</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: ✔ = recommended; ? = optional; other tests are not excluded. * = normally undertaken by the manufacturer. Planned studies may fall into more than one category in which case all indicated assays should be performed. d1 = Day 1.
Phase 0 Evaluation

- Example of a recent evaluation

Pathogen inactivation of platelets using ultraviolet C light: effect on in vitro function and recovery and survival of platelets


TRANSFUSION Volume 53, May 2013
THERAFLEX UV PLATELETS System

THERAFLEX Dual Bag Kit

MACOTRONIC UV Illuminator

- Orbital agitation of platelets
- Double sided UVC illumination
- 259 nm, 0.3 J/cm²
- <1 minute
Metabolism

PC from pooled BC

**HSR**

% Recovery

Days

PC from single BC

**HSR**

% Recovery

Days

**HSR 20% lower in treated PC from day 1 through 7**
No significant difference

Trend towards lower levels of glucose and higher levels of lactate in treated units
8.6.4: Phase 1: Validation

- The purpose of this phase is to allow:
  - staff to familiarise themselves with the packs and any associated equipment
  - the generation of quality monitoring data
  - the development of an appreciation of the suitability of the packs for routine use, i.e. progression to Phase 2 trial.

- Phase 1 of the validation process normally will require not less than 125 packs to be tested at the centre undertaking the trial.

- It is expected that a smaller number of packs will be used for familiarisation in other centres.

- This phase will include the finalisation of standard operating procedures (SOPs) for use in Phase 2.
8.6.4: Phase 1: Validation

8.6.4.1: Component quality monitoring

• Starting donations and all final components will be tested for compliance with relevant parameters listed in the component specifications in these guidelines.

8.6.4

• Blood components produced during Phase 1 may be used therapeutically where they comply with appropriate release criteria.
Phase 1 Validation

• Following a SaBTO recommendation, platelets are to be suspended in additive solution

• vCJD risk reduction, in place of apheresis quota

• Evaluations of candidate PAS underway
  – Pooling
  – Apheresis…
<table>
<thead>
<tr>
<th>Leucodepleted Platelet Component</th>
<th>Volume (ml)</th>
<th>Swirling (Present macroscopically)</th>
<th>Aggregates (Absent macroscopically)</th>
<th>Platelet Count (x 10⁹/unit)</th>
<th>WBC Count (x 10⁶/unit)</th>
<th>pH tested after expiry (specify day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count = 128</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n= 128</td>
<td>n= 128</td>
<td>Not done, as Phase 0 data were acceptable.</td>
</tr>
<tr>
<td>Mean: 304.2</td>
<td>YES</td>
<td>NO</td>
<td></td>
<td>296.6</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>SD: 16.7</td>
<td>-</td>
<td>-</td>
<td></td>
<td>48.8</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Min: 232</td>
<td>-</td>
<td>-</td>
<td></td>
<td>185</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Max: 337</td>
<td>-</td>
<td>-</td>
<td></td>
<td>472</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Cpk: 1.91</td>
<td>-</td>
<td>-</td>
<td></td>
<td>0.39</td>
<td>5.76</td>
<td></td>
</tr>
<tr>
<td>Specified Limit: 150-400</td>
<td>Present</td>
<td>Absent</td>
<td></td>
<td>&gt;240</td>
<td>&lt;1.00</td>
<td></td>
</tr>
<tr>
<td>Specification: 75%</td>
<td>100%</td>
<td>99%</td>
<td></td>
<td>75%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>% meeting specified limit: 100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td>86.7%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
8.6.5: Phase 2: Evaluation

- A minimum of 2000 packs from each of two batches for whole blood collection processes or
- 300 sets for apheresis collection will be used in this phase to allow data on consistency of manufacture to be collected.
- Relevant SOPs will be available before commencing Phase 2. Customer communication and any associated training will also have been done by this date.
- Blood components produced during Phase 2 may be used therapeutically where they comply with the normal release criteria.
8.6.5: Phase 2: Evaluation

- 8.6.5.5

- A minimum of 1% of components (or as determined by statistical process monitoring) produced for whole blood collection processes or

- 300 of each component (one of each relevant component per procedure) for apheresis collection

- will be subjected to routine quality monitoring for parameters specified in this book.

- *Data used in assessment of bids from suppliers*
## Candidate PAS#1

<table>
<thead>
<tr>
<th>Leucodepleted Pooled Platelet Component</th>
<th>PRE BACTERIAL SCREENING</th>
<th>POST BACTERIAL SCREENING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume (ml)</td>
<td>Platelet Count x 10^9/unit</td>
</tr>
<tr>
<td>Count N = :</td>
<td>126</td>
<td>126</td>
</tr>
<tr>
<td>Mean:</td>
<td>301.6</td>
<td>306.6</td>
</tr>
<tr>
<td>SD:</td>
<td>15.3</td>
<td>40.9</td>
</tr>
<tr>
<td>Min:</td>
<td>232</td>
<td>168</td>
</tr>
<tr>
<td>Max:</td>
<td>334</td>
<td>438</td>
</tr>
<tr>
<td>Cpk:</td>
<td>2.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Specified Limit:</td>
<td>150-400</td>
<td>&gt;240</td>
</tr>
<tr>
<td>Specification:</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>% meeting spec.</td>
<td>100%</td>
<td>96%</td>
</tr>
</tbody>
</table>
Local process qualification

- Defined by NHSBT, to ensure equal operation at each of our five sites
- Whole blood process $n = 125$
- Apheresis process $n = 10$
- 100% QM testing
Local process qualification

- Defined by NHSBT, to ensure equal operation at each of our five sites
- Whole blood process $n = 125$
- Apheresis process $n = 10$
- 100 % QM testing
Component Validation - summary

<table>
<thead>
<tr>
<th>Process</th>
<th>Testing</th>
<th>Phase 0</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Local process qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td>Component evaluation</td>
<td>n = 10 to 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tables 8.2 to 8.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality monitoring</td>
<td>n = 10 to 16 100% tested</td>
<td></td>
<td>n = 125 100% tested</td>
<td>2000 from each of two batches Minimum 1% tested</td>
<td>n = 125 100% tested</td>
</tr>
<tr>
<td>Apheresis collection</td>
<td>Component evaluation</td>
<td>n = 10 to 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tables 8.2 to 8.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality monitoring</td>
<td>n = 10 to 16 100% tested</td>
<td></td>
<td>n = 125 100% tested</td>
<td>n = 300 100% tested</td>
<td>n = 10 (each machine) 100% tested</td>
</tr>
</tbody>
</table>

Red Book, Table 8.6
Quality Monitoring Activities

1. Component validation
2. Component routine testing
3. Full Blood Counts
4. Calibration Support
5. Environmental Monitoring
6. Bacterial Arm Monitoring
7. Stem Cells Monitoring
Routine Quality Monitoring

• The aim is to have a controlled process

• Same result every time…
QM Regulations

• BSQR v Red Book v CoE

  • Regulations require conformance to defined specifications and statistical process control

  • Revisions are not contemporaneous across all

  • BSQR is mandatory legislation but includes fewest components and specifications
QM Regulations

• BSQR v Red Book v CoE

• Has led to inconsistencies that need interpretation

  • Leucodepletion (rWBC)
    - BSQR states <1x10^6/unit
    - CoE states 90% <1x10^6/unit
    - Red Book states 90% <1x10^6/unit and 99%
      <5x10^6/unit both with 95% confidence

  • Factor VIII concentration FFP
    - Red Book: 75% of components >0.7IU/mL
    - CoE/BSQR: Post freeze/thaw: average of
      >70% of freshly collected plasma unit
Component Routine QM

- Monitor all routine component production processes and workstreams
- Confirmation of compliance with specifications
- Sampling frequency is based on process capability
- Intervention dependent on potential impact of controlled changes to a process
## Component Routine QM

<table>
<thead>
<tr>
<th>Component</th>
<th>Routine</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>TAT &amp; BAT</td>
<td>Volume, Hb, rWBC, (Haemolysis)</td>
</tr>
<tr>
<td></td>
<td>Exchange &amp; IUT</td>
<td>Volume, Hb, Hct</td>
</tr>
<tr>
<td>FFP</td>
<td></td>
<td>Volume, FVIII, Protein, rPlt, rRBC, [rWBC if BAT]</td>
</tr>
<tr>
<td>Cryo</td>
<td></td>
<td>Volume, FVIII, Fibrinogen</td>
</tr>
<tr>
<td>Platelets</td>
<td>Apheresis &amp; Pooled</td>
<td>Volume, Platelets, rWBC, (pH)</td>
</tr>
<tr>
<td>Granulocytes</td>
<td></td>
<td>Volume, WBC Diff</td>
</tr>
<tr>
<td>Secondary processing</td>
<td>Only the changed parameters</td>
<td>E.g. RBC Splits measure volume &amp; Hb but not rWBC</td>
</tr>
</tbody>
</table>
QM Equipment

• QM labs participate in relevant EQAS schemes

<table>
<thead>
<tr>
<th>Analyser</th>
<th>QM Labs</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckman Coulter LH780</td>
<td>All</td>
<td>Donor FBC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Component Hb, Plts, Hct, rWBC</td>
</tr>
<tr>
<td>IL ACL TOP 500</td>
<td>Filton</td>
<td>Factor VIII</td>
</tr>
<tr>
<td></td>
<td>Manchester</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Becton Dickinson FACSCalibur</td>
<td>Colindale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Filton</td>
<td>rWBC</td>
</tr>
<tr>
<td>Beckman Coulter Navios</td>
<td>Manchester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Newcastle</td>
<td>rWBC</td>
</tr>
<tr>
<td></td>
<td>Sheffield</td>
<td></td>
</tr>
<tr>
<td>Thermo Multiskan FC</td>
<td>Filton</td>
<td>Protein, rRBC</td>
</tr>
<tr>
<td></td>
<td>Manchester</td>
<td></td>
</tr>
</tbody>
</table>
Component sampling

Lean working
• Standardised cell
• Single piece flow
• Barcode replicators to maintain positive sample identification
QM Testing

• Barcode positive sample identification is maintained until analyser test result

• Post analyser reports rely on manual data entry to worksheets and NWA. Risk of transcription errors
QM Data Entry to NWA

- Standardised fields and calculations
- Field value limits for acceptable entries to reduce data entry errors
Component Release Limits

• Discard / Concessionary Release Limits for QM tested components
  – rWBC >5 x 10^6/Unit
  – RBC <30g Hb per Unit
  – Platelets <160 x 10^9/Unit
  – More have been proposed

• As QM is usually not 100% testing there is a risk of issuing out of specification components
Statistical Process Monitoring (SPM)

- Defined QM sampling frequency
  - Red Book baseline was 1% or
  - Minimum numbers for destructive testing
    - 4 cryoprecipitate pools per month
- Defined conformance rate
  - Red Book ≥75% per month except rWBC
- Demonstrate specification compliance but no trending or improvement drivers
Generate monthly QC Report

Is confidence at 95% 'TRUE'

Exclude values >30 and recalculate

Are >90% of components <1

What is the maximum count (all data)

<5

>5 but <30

>30

What is the maximum count (all data)

<5

>5 but <30

>30

GREEN
5 per 500

YELLOW
10 per 500

ORANGE
15 per 500

RED
100% or STOP
Statistical Process Control (SPC)

- QM sampling frequency is defined by process capability
  - Demonstrate process control and/or
  - Sufficient data collection rate to allow timely intervention
- SPC charts analyse each data point/set to identify out of specification events and monitor for trends
Process Capability (Cpk)

• The Cpk index is the lower of the two values where an USL and LSL are both defined
  – Cpk = (USL – Mean) / 3 x SD [1]
  – Cpk = (Mean – LSL) / 3 x SD [2]
• The Cpk index indicates how well the process is centred about the target value. It predicts non-conformity.
  – If LSL and USL are defined and Cpk = 1 then the process Mean +/-3SD is exactly centred within the specification
  – A widget factory would expect Cpk >1.3. Normal biological variation in components means our Cpk are often lower.
Component Criticality Algorithm

1. **Start**
   - Can low Cpk cause immediate patient harm?
     - Yes: High, Within 24 hours
     - No: Can low Cpk reduce benefit to patient?
2. **Can low Cpk reduce benefit to patient?**
   - Yes: Medium, Within 1 week
   - No: Can low Cpk be used to improve production process?
3. **Can low Cpk be used to improve production process?**
   - Yes: Low, Within 1 month
   - No: OUT OF CONTROL DETECTION TIME

**Examples**
- Leucodepletion
- Plasma protein washing
- IUT/Exchange Hct

- Sub-optimal platelet yield or low Hb in RBC
- Sub-optimal total protein in single FFP
SPC Charts

• LSL: Lower Specification Limit
• USL: Upper Specification Limit
• CL: Central Line (Mean)
• LCL: Lower Control Limit (Mean – 3SD)
• UCL: Upper Control Limit (Mean + 3SD)
• Range: Max – Min (for sample subgroup)
SPC Trends – in control

- Data points can be expected to fall outside control limits
SPC Trends - Consecutive Out of Specification (OOS) event

Filton Platelet Pools
Log White Blood Cell count
DATE From 01/04/14 To 01/06/14

X-bar: 5.46736  ucl: 5.89  lcl: None
Range: cl: 0.1276  ud: 0.99  lcl: 0
USL: 6.69  LSL: None

BD Leucocount kit sensitivity limit 1 WBC/μL
SPC Trends – Rule of 7

- Up, Down or either side of CL
  - Data from production cells with different male/female ratios
SPC Trends - Change in trend

- LCL breaches are from a different centrifuge workstream
QM SPM/SPC Summary

- Assign the component specification a “criticality level”
- Use Red Book algorithm to identify appropriate SPC monitoring method
  - Use Cpk, SPC control charts or conformance monitoring as appropriate
- QM sampling frequency based on monitoring specification non-compliance
  - when necessary adjust the sampling rate to capture non-compliance events within the appropriate timeframe
- Problem?
  - Defined roles, responsibilities and escalation procedures within Management Quality Review process
Current QM Process Issues

- FVIII in FFP from Day 1 Processing of WB
  <75% compliance at Red Book 0.7IU/mL

- Apheresis Platelet Counts
  <75% compliance at 240x10⁹/unit post bacterial screening sample volume losses
  - Sufficiency vs collection cost vs compliance
Pooled vs Apheresis
ATD3 Platelet Counts

National Platelet Pools
Post Bacti Platelet count
DATE From 01/06/14, DATE From 01/01/14 To 31/08/14

Samples: 2799  Cpk: .451  3sp Lim: (167.63, 431.26)
Mean: 299.447  Cp: .9862  Spec Lim: (240, 500)
Std Dev: 43.939  Act % out: (8.1458, .0000)
Min, Max: (123, 470)

Bristol Apheresis
Post- BACTI Platelet count (10E9/unit)
ATD = 3, DATE From 01/06/14, DATE From 01/01/14 To 31/08/14

Samples: 2983  Cpk: .3343  3sp Lim: (182.39, 355.47)
Mean: 268.93  Cp: 1.56  Spec Lim: (240, 510)
Std Dev: 28.848  Act % out: (14.18, .0000)
Min, Max: (147.03, 439.09)
QM Future Developments

• Automation of results handling

• SAC-BC Reviews
  – Further Concessionary Release Limits
  – Revised specifications

• QM Measurements and Methods
  – More appropriate assays (PAS)

• Component Developments
  – PAS / PI Platelets (plasma content?)
Summary

- Overview of the United Kingdom
- UK Transfusion Services
- NHSBT operations
- Component evaluation in the UK
- Quality monitoring in NHSBT
Tack för att lyssna

Acknowledgements

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon Procter</td>
<td>Lead Specialist for Testing</td>
</tr>
<tr>
<td>Rebecca Cardigan</td>
<td>Head of Component Development</td>
</tr>
<tr>
<td>Jane Pearson</td>
<td>Assistant Director, Blood Donation Operations and Nursing</td>
</tr>
<tr>
<td>Stuart Penny</td>
<td>Assistant Director, National Operations</td>
</tr>
</tbody>
</table>
Back up slides
Process Capability (Cpk)

- There are limits to Cpk
  - Data needs to conform to normal distribution
    - Red cells and platelets in FFP data are not normally distributed so conformance monitoring is maintained.
  - Processes need to be stable and under statistical control
    - Appropriate specifications
    - Change Control process qualification acceptance criteria met
  - Special causes of variation identified and eliminated
    - Abnormal data values will skew Cpk value
  - Minimum of 100 data points measured
    - Provides 95% confidence interval for Cpk of 0.85 – 1.15
# QM Process Capability Table

<table>
<thead>
<tr>
<th>Specification Type</th>
<th>Cpk Value</th>
<th>Non-Conformity</th>
<th>Parameter Criticality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Two Sided</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[LCL &amp; UCL]</td>
<td>&gt;1.47</td>
<td>1.30 – 1.46</td>
<td>Capable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.10 – 1.29</td>
<td>Borderline</td>
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<tr>
<td></td>
<td></td>
<td>0.86 – 1.09</td>
<td>Incapable</td>
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<tr>
<td></td>
<td></td>
<td>0.54 – 0.85</td>
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<tr>
<td></td>
<td></td>
<td>0.39 – 0.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.39</td>
<td></td>
</tr>
<tr>
<td><strong>One Sided</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>[LCL or UCL]</td>
<td>&gt;1.40</td>
<td>1.23 – 1.39</td>
<td>Capable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.03 – 1.22</td>
<td>Borderline</td>
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<tr>
<td></td>
<td></td>
<td>0.77 – 1.02</td>
<td>Incapable</td>
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<tr>
<td></td>
<td></td>
<td>0.43 – 0.76</td>
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<td></td>
<td></td>
<td>0.21 – 0.42</td>
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<tr>
<td></td>
<td></td>
<td>&lt;0.21</td>
<td></td>
</tr>
<tr>
<td><strong>% Non-Conformity</strong></td>
<td>&lt;0.001</td>
<td>0.001 – 0.01</td>
<td>Capable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01 – 0.1</td>
<td>Borderline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 – 10</td>
<td>Incapable</td>
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<tr>
<td></td>
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<td>10 – 25</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;25</td>
<td></td>
</tr>
<tr>
<td><strong>Cpk Banding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Per workstream monitored]</td>
<td></td>
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</tr>
</tbody>
</table>

- **High**
  - Capable: 1% daily
  - Borderline: 10% each work period
  - Incapable: 100% daily

- **Medium**
  - Capable: 0.1% daily
  - Borderline: 1% daily
  - Incapable: 10% each work period

- **Low**
  - Capable: 0.01% monthly
  - Borderline: 0.1% daily
  - Incapable: 1% daily
Full Blood Counts

- Routine Apheresis Donor FBCs
  - Collection algorithms: Plt / Height / Weight
- Potential Apheresis Donor FBCs
  - Collected at WB sessions
- Stem Cell Donor FBCs
Calibration Support

• Temperature Mapping (COL, FIL, NEW)
  — Temperature Loggers & Software
    • NHSBT Comark contract
    • -80°C, -40°C and RT loggers
  — Prepare loggers for use, send to users, download data to software on return and send reports to users

• Component transportation container temperature mapping (NEW)

• Weights (FIL)
  • PULSE balances etc
Environmental Monitoring

- Manufacturing sterile docking devices
- Bacterial Screening Laminar Flow Cabinets
- Other labs also send plates from their clean processing environments i.e. SCI
Bacterial Arm Monitoring

• Monitor arm cleaning performance of every donor attendant who takes blood

• Three contact plates from three different donors (every six months)

• Plates returned to Filton (SW), Manchester (North), NBL (SE)

• Plates read and colonies counted

• Donor attendants re-assessed and retrained if high counts observed
Stem Cells Monitoring

- All SCI products tested for bacterial/ fungal growth
- SCI inoculate all their own agar plates
- Returned to QM for incubation at 35°C and 22°C
- Results reported and returned to SCI
- Any positive results plates are sent to NBL for organism identification