Validation

Processes, Procedures, Support

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Objectives

• Review the regulatory requirements and association standards for validation and qualification

• Review the concepts of process validation used in support of apheresis collections including document validation and BECS software validation.
Definitions

• Process Validation – Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

• Qualification – part of process validation that establishes confidence that a manufacturing device is capable of operating consistently (equipment installation qualification) and can be performed effectively and reproducibly (process performance qualification), and that the finished product meets all of the release requirements for functionality and safety (product performance qualification).
Definitions

- Installation Qualification - Installation qualification demonstrates that the instrument is properly installed in environmental conditions that meet the manufacturer’s specifications.

- Operational Qualification - Operational qualification demonstrates that the installed equipment operates as intended. It focuses on the capability of the instrument to operate within the established limits and specifications supplied by the manufacturer.

- Performance Qualification - Performance qualification demonstrates that the equipment performs as expected for its intended use in the facility and that the output meets specifications. Criteria must be defined which indicates acceptable performance. This may include such items as Product QC specifications and In-process monitor parameters.
Blood Establishment Computer System

Blood Establishment Computer System (BECS) - Software that facilitates manufacturing operations and ancillary functions
Medical Device Data Systems (MDDS)

- MDDS - A device that is intended to provide one or more of the following uses, without controlling or altering the functions or parameters of any connected medical devices:
  - The electronic transfer of medical device data
  - The electronic storage of medical device data
  - The electronic conversion of medical device data from one format to another format in accordance with a preset specification
  - The electronic display of medical device data

- An MDDS may include software, electronic or electrical hardware such as a physical communications medium (including wireless hardware), modems, interfaces, and a communications protocol. Additional criteria for an MDDS are located on the FDA website.
Guidance Documents

• FDA
  – Automated Red Cell, January 2001
  – Platelets by Automated Methods, December 2007
  – Industry Blood Establishment Computer System Validation in the User’s Facility, April 2013
Change Management

cGMP requires a structured approach for change management; including identifying appropriate specifications and verifying that the specifications have been met.

• New or significantly changed production processes must be validated.

• New materials used in current processes may require validation (e.g., new collection set configuration).

• All equipment new to the system must be qualified before placing into operation or using in a pilot.

• Software program upgrades to production equipment (e.g., moving to a newer version for an apheresis machine) require a process validation.

• A pilot or operational trial may be required to assess new equipment or production processes at an operational level.
Process Validation

• Donor Intake and Eligibility
• Donor Collection
• Data Management
• Supporting Materials
• Documentation
Instruments vs Products

• Instruments
  – Installation Qualification
    • Verification of manufacturers installation of new equipment
  – Operational Qualification
    • End user tests of the operation of the equipment as described by the operators manual or vendor documentation

• Products
  – Performance Qualification
    • Product results compared to defined standards
### FDA Performance Qualification Criteria - Platelets

**Table 1. Product Performance Qualification Criteria for the Platelet Component Collection Process**

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommended Results</th>
<th>Target¹</th>
<th>Allowable Process Failures² to achieve recommended results for a set of N tests³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual platelet yield of transfusable component</td>
<td>≥ $3.0 \times 10^9$</td>
<td>95%/75% **</td>
<td><strong>N=11</strong> <strong>N=18</strong> <strong>N=23</strong></td>
</tr>
<tr>
<td>pH</td>
<td>≥ 6.2</td>
<td>95% / 95% ***</td>
<td><strong>N=60</strong> <strong>N=93</strong> <strong>N=124</strong></td>
</tr>
<tr>
<td>Percent component retention</td>
<td>≥ 85% component retention if performed ****</td>
<td>95%/95%</td>
<td><strong>N=60</strong> <strong>N=93</strong> <strong>N=124</strong></td>
</tr>
<tr>
<td>Residual WBC count</td>
<td>Single collection: &lt; $5.0 \times 10^9$</td>
<td>95% / 95%</td>
<td><strong>N=60</strong> <strong>N=93</strong> <strong>N=124</strong></td>
</tr>
<tr>
<td></td>
<td>Double collection: Collection: &lt; $8.0 \times 10^6$ or Components: &lt; $5.0 \times 10^9$</td>
<td>95%/95%</td>
<td><strong>N=60</strong> <strong>N=93</strong> <strong>N=124</strong></td>
</tr>
<tr>
<td></td>
<td>Triple collection: Collection: &lt; $1.2 \times 10^7$ or Components: &lt; $5.0 \times 10^6$</td>
<td>95%/95%</td>
<td><strong>N=60</strong> <strong>N=93</strong> <strong>N=124</strong></td>
</tr>
</tbody>
</table>

¹²³ Process failures only; non-process failures should be excluded.

² Corrective actions for exceeding allowable process failures:
   - If you select a sample size of 11 and find one failure, 17 additional samples would need to be tested with no additional failures.
   - If you select a sample size of 60 and find one failure, 91 additional samples would need to be tested with no additional failures. If you select a sample size of 93 and find two failures, 157 additional samples should be tested with no failures. If you select a sample size of 124 and find three failures, 127 additional samples should be tested with no failures.

²² The sample size numbers can be used in a sampling plan that should be representative of products collected on each machine type in each facility.

²²² The stratified recommended results should ensure that the individual transfusable units will be < $5.0 \times 10^6$ even with a 25% error in equilibration of the volume for double and triple collections.
## Products

### Platelets

#### Minimum Number of Donations to Test

<table>
<thead>
<tr>
<th>Collection Type</th>
<th># Platelet Yield</th>
<th># WBC Count</th>
<th># pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Platelets</td>
<td>29</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Double Platelets</td>
<td>29 parent + 58 splits</td>
<td>60 parent + 120 splits</td>
<td>120 splits</td>
</tr>
<tr>
<td>Triple Platelets</td>
<td>29 parent + 87 splits</td>
<td>60 parent + 180 splits</td>
<td>180 splits</td>
</tr>
</tbody>
</table>

#### Component Details

<table>
<thead>
<tr>
<th>Component</th>
<th>Day 1 Plt Yield Component</th>
<th>Day Exp Yield Component</th>
<th>Day Distrib Yield Component</th>
<th>Day 1 WBC Components</th>
<th>Day Exp or Dist pH Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>1-29</td>
<td>1-8</td>
<td>9-29</td>
<td>1-60</td>
<td>1-60</td>
</tr>
<tr>
<td>Parent Bag of Double/Triple</td>
<td>1-29</td>
<td>1-60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Split 1</td>
<td>1-29</td>
<td>1-8</td>
<td>9-29</td>
<td>1-60</td>
<td>1-60</td>
</tr>
<tr>
<td>Split 2</td>
<td>1-29</td>
<td>1-8</td>
<td>9-29</td>
<td>1-60</td>
<td>1-60</td>
</tr>
<tr>
<td>Split 3</td>
<td>1-29</td>
<td>1-8</td>
<td>9-29</td>
<td>1-60</td>
<td>1-60</td>
</tr>
</tbody>
</table>
Red Cells

• Test 100 consecutive successful RBC components

• Other language
  – RBC components from every instrument must be tested.
  – RBC components from all protocols must be included. Examples of protocols: single red cells drawn concurrently with platelets/plasma; double red cells.
    • Include a minimum of 25 leukocytes reduced components from both single red cells and double red cell collections
    • Include a minimum of 25 non-leukocytes reduced components from both single red cells and double red cell collections
  – If mobile site collections are performed, include samples from mobile site collections.
Plasma

• Not specifically defined other than volume.
• Plasma may be collected concurrently with platelets or red cells, or may be collected as the sole product.
Manufacturing vs Clinical Care

• Manufacturing
  – Product testing for recipient efficacy

• Clinical Care
  – Effective therapy
Document Validation

• Procedures
  – Accuracy
  – Readability
  – Connections to the next step in the process

• Forms including electronic documentation
  – Support the critical steps in the process?
  – Follow the process flow
Document Validation Considerations

• All required forms and materials are listed in a SOP
• Titles and numbers of forms/reference SOPs are correct
• The document is clear and easy to follow, forms follow the process
• The latest manufacturer instructions/user’s manual is followed as applicable
**Validation Plan (Check Appropriate Action)**

- Minor revision to document. Requires QM approval only.
- Read document.
- Read and perform procedure.
- Other: [ ]

Validation Plan prepared by: [ ] Date: [ ]

Specific Validation Instructions: [ ]

**General Considerations:**
- All required forms and materials are listed.
- Titles/numbers of forms/SOPs are correct.
- Clear and easy to follow.
- Latest manufacturer instructions/user's manual is followed, if applicable.

**Validation Execution (Expert User)**

Mark appropriate conclusion.

- Acceptable [ ]
- Acceptable with minor revision(s) [ ]
- Not Acceptable [ ]

Comments (attach additional pages as necessary): [ ]

Validation performed by: [ ] Date: [ ]

**Validation Conclusion (Author)**

Mark appropriate conclusion.

- Acceptable [ ]
- Acceptable with minor revision(s) [ ]
- Not Acceptable [ ]
- Other [ ]

Comments: [ ]

Author's Name: [ ] Date: [ ]

- Mark here if re-validation is required.

**QM Approval of Validation Plan/Conclusion**

QM Approval Signature: [ ] Date: [ ]

Blood Systems
Computer Hardware

• Infrastructure
• Servers
• User Access Points
• Disaster Recovery
Computer Software

- Validation
- Stress Testing
- Mobile Operations
- Regression Testing
Interfaces and Data Exchange

• BECS
• Data Management Systems
• MDDS vs Interface
  • The electronic conversion of medical device data from one format to another format in accordance with a preset specification
Questions

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References

- Guidance for Industry Blood Establishment Computer System Validation in the User’s Facility, April 2013