The (Continued) Evolution of Statistical Process Control Applied to Blood Product Manufacturing

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Issue: Low Production Volume

- A large blood establishment may produce several hundred components per day by a variety of procedures.

- A small blood establishment that produces 100 components per week by four different procedures may have only 25 components per week available for QC testing.

- A very small registered facility may routinely produce blood components in numbers as low as n=10 per week.

- Low volume production facilities have the least opportunity for statistical QC, but may benefit the most due to infrequent use of procedures.
Evolution of a Conceptual Framework for Statistical Process Control (SPC)

1. “Population testing” (aka 100% Quality Contro)*
   - apheresis platelet counts
   - platelet bacterial contamination - AABB standard
   - leukoreduced products for CMV - susceptible patients (proposed in LR draft guidance January, 2001)
II. “Sample”-based quality control without a statistical framework

e.g evaluate 1% of representative products (or at least n=4/month for facilities producing <400 units per month).

- Historically the most common approach to blood component process control
Sample"- based quality control with a statistical framework

- Pre-defined independent random sample clusters are tested for ability to meet product standard over a pre-defined time period with pre-established conformance levels and probability
  - Permits a definition of product conformance to a standard with a defined level of confidence
  - Facilitates the meaningful and efficient identification of non-conformance limits that trigger a need for action
  - Allows QC testing to be customized to individual products
    - Different baseline levels of non-conformance
    - Different health impacts of product failure
  - May actually provide better information with fewer samples
Binomial approach to SPC

- Exact binomial distribution is based on distribution of dichotomous outcome using samples from an undefined or infinite sampling frame (e.g. flip of coin). Some literature refers to this as “sampling with replacement”
Binomial approach to SPC

- Conformance measures can be “pass/fail” (e.g. exact residual WBC counts not necessary)

- User-defined variables:
  - Statistical parameters of the control strategy (% conformance; confidence level)
  - Minimal acceptable time within which to detect a series of non-random process failures (safety)

- The binomial distribution predicts conformance within statistical parameters for an undefined or infinite population (e.g. applicable to validation or device clinical trial analysis)
  - Valid for QC testing, but may not be most parsimonious approach for small samples.
Binomial approach to SPC

Examples of pre-determined sample size and maximum # of failed tests expected (at 95% confidence) for a conforming process

<table>
<thead>
<tr>
<th>Failure rate allowed</th>
<th>Pre-defined QC sample size</th>
<th>Max # failed tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>93</td>
<td>1</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>124</td>
<td>2</td>
</tr>
</tbody>
</table>

Minimum sample is n=59
Binomial approach to SPC for WBC removal
Leukoreduction draft guidance January, 2001

- Binomial SPC to assure with >95% confidence that >95% of leukocyte reduced products meet the product standard.
  - (60) samples counted per month
  - 95% conformance - safe and pure product
  - 95% CI is accepted scientific norm
    (probability <.05 that non-conformance will exceed 5%)

- Compatible with ISBT Working Group recommendations
Hypergeometric Distribution

- Based on distribution of dichotomous outcome using fixed sampling frame with no replacement (e.g. drawing coins from a box)
Hypergeometric Distribution

- Permits more parsimonious sampling for a small pre-defined QC batch size.

- Hypergeometric distribution approximates binomial at \( n = 4500 \)

- Allows inference to defined population size only (e.g. QC cycle)
New SPC approach: Tests of non-conformance based upon a **hyper-geometric** distribution

- Same user-defined parameters as binomial (% conformance, confidence limits)
- Supports sample sizes of \( n < 60 \) for defined QC cycles sizes of 30 - 4500 units. (Would support most blood establishment production volumes)
- Not applicable to inference for undefined population size (e.g. not valid for process validation or device clinical trials)
Hypergeometric approach to SPC

Examples of pre-determined sample size and maximum # of failed tests expected (at 95% confidence) for a conforming process

<table>
<thead>
<tr>
<th>Failure rate allowed</th>
<th>Cycle size</th>
<th>QC sample size</th>
<th>Max # failed tests</th>
</tr>
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<tbody>
<tr>
<td>5%</td>
<td>30</td>
<td>23</td>
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<tr>
<td>5%</td>
<td>40</td>
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<tr>
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<td>100</td>
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</tr>
<tr>
<td>5%</td>
<td>1000</td>
<td>57/90</td>
<td>0/1</td>
</tr>
<tr>
<td>5%</td>
<td>&gt;4500</td>
<td>59/93</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Note: QC of large cycle sizes trends toward sample of n=60 with zero failures. (e.g. binomial)
Advantages and Disadvantages of Binomial or Hypergeometric Approach

**Advantages**
- Defines parameters of product conformance
- Conceptually feasible (FDA)
- Assures that 95% of products labeled as meeting standard will meet the product standard with 95% confidence.
- Unexpected failure can be overcome by assessing additional samples (with a penalty)

**Disadvantages**
- Occasional products that do not meet the product standard may unknowingly be used - (e.g. WBCs to CMV-susceptible patients).
- “Clusters” of failures at end points may be masked
Identifies “clusters” of events in time and space
- many product failures are non-random
  - bad reagent or soft goods
  - faulty machine or software
  - staff errors
How Does This Work?

- For this example, let’s say you perform 10 tests on any given day.
- Start the rolling sample window of 120 tests.
  - As long as you have < 3 failures, the level of non-conformance for the process is considered to be acceptable.
  - After 120 tests are complete, the window “rolls” forward and the next 120 tests now include the testing of the samples from days 2-12, and a new set of 10 samples; those tested on the 13th day.
## First 120

<table>
<thead>
<tr>
<th>Test day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
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<td>1</td>
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<tr>
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<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<tr>
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<td>80</td>
<td>90</td>
<td>100</td>
<td>110</td>
<td>120</td>
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<tr>
<td>Failures</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
continued

<table>
<thead>
<tr>
<th>Test day</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Tests</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
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<tr>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

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<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
<th>110</th>
<th>120</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failures</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Scan Statistics

**Advantages**

- "Clusters" of failures at end points of sample groupings can be captured - may provide more rigorous QC.
- **Computer Software now available for blood establishments** Sigma Blood Systems – Quality Manager™ (not evaluated by FDA).

**Possible Disadvantages**

- Scan statistics is conceptually and computationally complex.
- Operational feasibility not fully assessed.
References

- Tables based upon Hypergeometric distribution have been prepared by CBER Office of Biostatistics and Epidemiology and are expected to be made publicly available in the future.