CLIA Waiver Statistical Issues for CBC/ADCC Devices

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Outline

- Background & terminology
- Establishing “Accuracy”
- Study conditions
- Allowable error
- Reference ranges
- Performance
- Summary
510(k) vs Waiver

- 510(k) Compare to marketed device
  “Substantial equivalence”
- Waived device (WM): Compare to Comparative Method (CM)
  Establish “accuracy”
- 510(k): Most CBC Assays are in hands of laboratorian
- Waiver: CBC Assay in hands of non-lab health providers
Waiver By Regulation

- Dipstick/tablet reagent urinalysis
- Fecal occult blood
- Ovulation tests
- Urine Pregnancy tests
- ESR
- **Hemoglobin (copper sulfate)**
- Blood glucose devices (FDA home use)
- **Spun microhematocrit**
- **Hemoglobin single analyte instruments**
Imprecision vs Systematic Bias

- **Most lab assays have variability:**
  By running samples in duplicate and averaging you reduce variability

- **Systematic bias implies a new assay yields incorrect values on average:**
  If an assay has systematic bias, it cannot be accurate. Averaging over multiple runs of same assay is not sufficient.

- **Guidance allows for assays that have negligible bias**
Traceable Method

- Method traceable to references of higher order. It can be certified reference materials, a reference measurement procedure, or a network of reference laboratories.

- Guidance allows for traceable method if reference method is unavailable.
Establishing accuracy

Manual Counts: Reference method:
- Erythrocytes (Red Blood Cells)
- Leukocytes (White Blood Cells)
- WBC Differentials:
  - 3 part: Lymphocytes, Monocytes, and Granulocytes
  - 5 part: Granulocytes: Neutrophils, Eosinophils, Basophils
- Platelets
Counting Cells: Comparative Method

- Manual Counts are “noisy” (imprecise)
- Sponsor may:
  a) average over multiple manual counts or
  b) show a well-established CBC device is traceable to manual counts:
     i) Citing literature
     ii) In House study
- Reduce imprecision in CM:
  Easier to pass
One Step Design

- Manual counts in duplicate, triplicate or quadruplicate (but it should be consistent across the samples) is CM
- Compare their own device (WM) result to average manual count for the same specimen.
- Very labor intensive with 360 patient specimens.
Two Step Design: Part I

- Possible Traceable method:
  Lab CBC result: also subject to imprecision.
  A good Lab CBC assay: negligible bias.

- Establish Traceability:
  Can use literature, or do a study

- Need at least 40 samples to span the measurement range of each analyte

- Can average replicate lab CBC results (CM)

- Develop equation: Lab CBC versus Manual
Two Step Design: Part II

- Compare Waiver (WM) result to CM
  WM measured in Waiver Setting
- CM: Avg of Duplicates of Lab CBC Counter
- Split sample goes to lab for analysis
- N=360 patient specimens
Manual Count → Traceable Method → Waiver Method

40 samples → 360 samples

360 samples

Sponsor has more than one option
Demonstrating “Accuracy” - Quantitative Study Design

- Split/paired sample design
  - Fingerstick blood
    - WM
    - Waiver site
  - Venous blood
    - CM
    - Professional Lab

Patient
Waiver study

- Should mimic real clinical conditions
  Device use integrated into normal work
  Study takes 2 to 4 weeks
- Should include 3 or more sites
- Should include 9 or more users with no more than 3 per site
- Users should reflect real world use
  Not trained laboratorians
Study conditions

- User aware of safe handling of blood specimens
- Training:
  - Quick reference instructions
  - Package insert
  - 1-800 line if offered when marketed
- Training: consistent with instructions under real world use
Quality Control During Study

- Should mimic real world conditions
- Consistent with state and local requirements for CM
- QC materials need to be recommended or provided by sponsor
Study

- Specimens need to span measurement interval of device:
  
  Consider types of study sites

- Up to 1/3 contrived, or spiked specimens

- About 120 specimens per site

- At least 360 specimens overall
## Allowable Total Error

Defined for some analytes in Guidance:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>CLIA 88 acceptable limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>± 7%</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>± 6%</td>
</tr>
<tr>
<td>WBC</td>
<td>± 15%</td>
</tr>
<tr>
<td>RBC</td>
<td>± 6%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>± 25%</td>
</tr>
</tbody>
</table>
Recently Reported Ranges

<table>
<thead>
<tr>
<th></th>
<th>CLIA88(%)</th>
<th>(International, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>15</td>
<td>5.4-8.8</td>
</tr>
<tr>
<td>RBC</td>
<td>6</td>
<td>1.5-1.8</td>
</tr>
<tr>
<td>Hgb</td>
<td>7</td>
<td>1.2-1.9</td>
</tr>
<tr>
<td>PLT</td>
<td>25</td>
<td>5.2-9.8</td>
</tr>
</tbody>
</table>

Notes: assumes same ATE over entire range
Limits of Erroneous Results

- Definition: Patient results inside the LER pose a risk to patient safety
- Concept defined in Waiver Guidance: need clinical input
Indications and intended use populations for CBC and differential counts are heterogeneous.

ATE and LER should be specified to meet the most demanding intended use settings.

ATE and LER might vary across the range of reportable values.
Allowable Total Error (ATE), Limits for Erroneous Results

Allowable Total Error: (at least 95% of subjects)

Limits for Erroneous Results: (0% of subjects).
Allowable Total Error

- White Blood Cell (WBC) differentials
- CLIA A88:
  - ±3SD for Proficiency Testing
- Criteria not appropriate for an ATE
"Analytical Goals & State of Art"
Buttarello and Plebani AJ CP 2008 130:104-116

<table>
<thead>
<tr>
<th></th>
<th>Recently Reported Intervals (International, %)</th>
<th>ATE (%) for Waiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>3.1-7.0</td>
<td>??</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>4.0-11.9</td>
<td>??</td>
</tr>
<tr>
<td>Monocytes (MON)</td>
<td>13.4-58.7</td>
<td>??</td>
</tr>
<tr>
<td>Eosinophils (EOS)</td>
<td>16.0-37.3</td>
<td>??</td>
</tr>
<tr>
<td>Basophils (BAS)</td>
<td>35.5-155.5</td>
<td>??</td>
</tr>
</tbody>
</table>

Notes: MON, EOS and BAS rarer in healthy patients: uniform ATE (%) may not be ideal
Reference intervals

- 2.5th to 97.5th percentiles of apparently healthy subjects
  - May differ by age, gender, altitude
- Establishing reference interval\(^1\): 120 subjects
- Verifying reference interval\(^1\): 20 subjects

How likely is establishing or verifying a reference interval in a waived setting?

\(^1\)CLSI document C28-A2
Options for Reference Intervals in Waived Settings

- Use values in 510(k): Cited references/real data
- Use values from large surveys (e.g., NHANES\(^1\), broken down by age & sex) and or literature (e.g., textbooks\(^2\))
- Calculated using a well-established lab CBC counter

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\(^1\) NHANES III: National Health & Nutrition Examination survey, NCHS (CDC)
Performance

- Low, medium and high ranges for each analyte predefined
- Allowable Total Error and Limits of Erroneous Results predefined
- Samples should span measurement interval (include abnormal specimens)
- Sponsor must pass for each analyte
Performance: Part I

- Capture bias:
  - Plot of WM (Y-axis) vs CM (X-axis)
  - Overall
  - By site
  - By low, medium and high ranges
  - Regression analyses
**Demonstrating “Accuracy” - Systematic bias**

Appropriate type of regression:

\[ Y = a \times X + b \]

Evaluation of systematic bias at the medically important concentrations.

Negligible systematic bias
At least 95% of WM values fall in ATE

95% two-sided lower Confidence Bound greater than 92%

Similar percentages in low, medium and high ranges

0% of WM values fall in LER

95% two-sided upper Confidence Bound less than 1%
Summary

FDA would like you to consider the following while addressing our questions:

- What the Allowable Total Error ought to be for WBC Differentials
- What the Limits of Erroneous Results ought to be for all CBC analytes
- How reference intervals should be handled