113 Improve Lab Operations with Six Sigma Metrics

Sten Westgard MS

2011 Annual Meeting – Las Vegas, NV

AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
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Chicago, IL 60603
113 Improve Lab Operations with Six Sigma Metrics

This session will demonstrate the power of Six Sigma techniques to improve laboratory operations, including the objective assessment of test quality and the effectiveness of quality control procedures.

- Calculate the Sigma-metric of an analytical testing process
- Assess method quality graphically with a Method Decision chart
- Optimize QC procedures using an Operating Specifications (OPSpecs) chart

FACULTY:

Sten Westgard MS
Entire Pathology Team
Practice and Quality Management
Practice and Quality Management
2.0 CME/CMLE Credits

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Improve Lab Operations with Six Sigma Metrics, Part 1

October 21st, 2011
ASCP Annual Meeting / WASPaLM XXVI World Congress

Sten Westgard, MS
Westgard QC, Inc.

Disclosure

• I work for Westgard QC, Inc.
• Westgard QC, Inc. is now or has in the past worked with the following companies:
  — Abbott, AVL, Bayer (now Siemens), Beckman Coulter, Boston Biomedica (now Seracare), Covance Laboratories, Dade-Behring & DPC-Cirrus (now Siemens), Geisinger Health System, Instrumentation Laboratory, MAS, Mayo Clinic, Organon Teknika, Ortho-Clinical Diagnostics, Perkin Elmer, Pfizer, Randox, Spectra/Fresenius... and others
  — All data and examples shown will be blinded

Six Sigma – A Way to Think About Errors

• Defects Per Million (DPM)
• Scale of 0 to 6
• 6 is world class (3.4 dpm)
• 3 is minimum for any business or manufacturing process (66,807 dpm)

Outline of the Talk

• Do we need to worry about quality?
• A brief introduction to Six Sigma
• Counting defects: How does healthcare perform?
• Calculating Sigma-metrics
  — Setting Goals for Quality
  — Measuring Performance
  — Examples of Current Performance
• Tools for Sigma-metrics
  — Sigma-metric Equation
  — Method Decision Chart

Outline of the Next Talk

• From Assessment to Optimization
  — What changes can we make in QC?
  — What changes can we make in reporting?
• Tools for Optimization
  — OPSecs chart
  — Reference Change Value (RCV)
  — # Tests Required for Diagnosis
• How do we assure the Quality of Sigma-metrics?
A Little More on Six Sigma
(it’s more than counting)

• Calculate Defects, Reduce them, reap internal savings

• Culture and Training: Green belts, Black belts, Master Black belts, Champions

• Many Quantitative tools beyond DPM
  – DMAIC
  – Root cause analysis

Six Sigma – Key Concept: Defects (DPM)

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Two ways to Determine Sigma

• Count Defects, convert to DPM, look up in Sigma table
  – Short Term Sigma typically used
  – Most common method of calculating Sigma

• Measure Variation
  – Sigma-metric Equation

Sigma metrics of Common Lab Processes, 2000

Nevalainen et al, Arch Pathol Lab Med, 2000;124:516-521
Sigma-metrics of Pre- and Post-Analytical Quality

<table>
<thead>
<tr>
<th>Year</th>
<th>Pre-Analytical</th>
<th>Post-Analytical</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>59 errors 0.0056%</td>
<td>47 0.0074%</td>
</tr>
<tr>
<td>2004</td>
<td>1178 errors 0.0094%</td>
<td>47 0.0074%</td>
</tr>
</tbody>
</table>

Westgard QC

Sample Sigma-metrics:
- Hemolyzed serum sample: 4.1 sigma
- Control exceeds limits: 3.4 Sigma
- Biggest problems: Incorrect name/request (2.9) Report takes too long (2.8)

Current Laboratory Performance

Quality indicators and specifications for key analytical-extralytical processes in the clinical laboratory. Five years’ experience using the Six Sigma concept

Westgard QC

What is Performance at the POC?

HbA1c device: 4.0 Sigma
Blood gas/electrolyte: 4.1

"...it is likely that the quality error rate measured here... represents an underreporting of the true rate."

Westgard QC

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Westgard QC

Quality Requirements: Defining the Size of the target

- What is the quality required by a laboratory test? (Do we know?)
- Isn’t every method on the market a quality method?

"Conclusion 7-1. The 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices with some exceptions. The 510(k) process cannot be transformed into a premarket evaluation of safety and effectiveness as long as the standard for clearance is substantial equivalence to any previously cleared device."

Institute of Medicine 2011: Medical Devices and the Public’s Health: the FDA 510(k) Clearance Process at 35 years, prepublication copy

Westgard QC

Quality requirements: many options

- Analytical benchmarks
- PT and EQA standards
- CLIA PT criteria
- RiliBÄK (Germany)
- RCPA (Royal College of Pathologists of Australasia)
- Clinical Benchmarks (better)
- Biologic Variation database (Ricos et al.)
- ISO 15189, ISO 15197
- Simulation studies with patient data (Karon, Boyd, Klee 2010)
- Clinical Decision Intervals: Evidence-Based Medicine & Clinical Guidelines

How do your Doctors use the Test?
From Tolerance Limits to Total Allowable Error (TEa)

- **TEa in the literature**
  - Bias + 2SD (1974) Westgard, Carey, Wold
  - Bias + 3SD (1991) Laessig and Ehrmeyer
  - Bias + 4SD (1991) Westgard and Burnett
  - Bias + 6SD (2001) “Six Sigma”

**Six Sigma and Total Allowable Error:**

```
- TEa   True Value   + TEa
-6s    -5s    -4s    -3s    -2s    -1s   0s   1s   2s   3s   4s   5s   6s
```

```
-6s should fit into spec
+6s should fit into spec
```

**Sigma-metrics + Quality Requirement**

*Cholesterol Example*

- **CLIA:** +/- 10%
  - \(20/6 = 3.33\)
  - \(3.33/200 = 1.66\% CV\)

**How do we measure Sigma performance for analytical tests?**

**Measure Variation**

- Do we measure imprecision (CV)?
- Do we measure inaccuracy (bias)?

**Example Sigma-metric Calculation**

- 3 POC devices cholesterol, data from 2009 POC journal study
- CLIA PT criterion for acceptability = 10%
- Total Precision (CV): 4.0%
- Bias at 5.17 mmol/L: 7.5%

\[
\text{Sigma} = \frac{10 - 7.5}{4.0} = 2.5 / 4.0 = 0.63
\]

**Tool #1: Sigma metric equation for analytical process performance**

\[
\text{Sigma-metric} = \frac{\text{(TEa} - \text{Bias})}{\text{CV}}
\]
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3 POC cholesterol devices, 2009

<table>
<thead>
<tr>
<th>Device</th>
<th>Total Imprecision</th>
<th>%Bias at 5.71 mmol/L (200 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.0</td>
<td>7.5</td>
</tr>
<tr>
<td>B</td>
<td>4.2</td>
<td>6.0</td>
</tr>
<tr>
<td>C</td>
<td>9.5</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Quality Requirement: 10%
Sigma-metric A = (TEa – Bias) / CV
= (10 – 7.5) / 4.0
= 2.5 / 4.0
= 0.625
### Suboptimal BGM 2011

<table>
<thead>
<tr>
<th>Method</th>
<th>Bias</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8.9</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>13.1</td>
<td>6.7</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>3.4</td>
</tr>
<tr>
<td>D</td>
<td>15.8</td>
<td>8.4</td>
</tr>
<tr>
<td>E</td>
<td>6.4</td>
<td>5.5</td>
</tr>
<tr>
<td>F</td>
<td>6.1</td>
<td>3.2</td>
</tr>
</tbody>
</table>

### Display of Sigma-metrics:
- Normalized Method Decision Chart

### 2011: Suboptimal BGM

- Method validation data poster from 2011 IFCC Berlin conference

### 2010: 6 out of 8 HbA1c Devices

- Method decision chart for 10%
POC CBC device

- Small POC device measuring WBC, LYM, MON, and Hb
- 2009 FDA 510k data submission for substantial equivalence determination
- Precision assessed at 3 levels using one lot controls, 20 working days.
- Bias compared with 130 patient samples against the predicate device
- Consensus quality requirements used

Additional data on the POC CBC device

- 2008 Clinica Chimica Acta paper:
  - “The differential count variability showed greater variation and was not suitable for routine monitoring.”
  - Nevertheless, the study concludes:
    “This onsite instrument is the first point of care analyzer, is easy to use and rapidly provides accurate results for CBC and differentials that can circumvent limitations of laboratory based testing.”
  - HUH?

Mid-volume chemistry analyzer, 2011 (IFCC and AACC abstract)

- Study covers BUN, Chloride, Glucose, Potassium, and Sodium
- Precision study performed according to CLSI EP5
- Comparison study performed according to CLSI EP9, comparing against accepted reference methods
- German Rilibak goals selected as the quality requirements

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Level</th>
<th>Rilibak TEa%</th>
<th>%Bias</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>5.2 mmol/L</td>
<td>26</td>
<td>2.6</td>
<td>1.46</td>
</tr>
<tr>
<td>Chloride</td>
<td>122 mmol/L</td>
<td>8</td>
<td>0.9</td>
<td>0.61</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.72 mmol/L</td>
<td>15</td>
<td>0.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.62 mmol/L</td>
<td>8</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Sodium</td>
<td>141.5 mmol/L</td>
<td>5</td>
<td>0.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Analyte</td>
<td>Level</td>
<td>Rilbak Tlа%</td>
<td>%Bias</td>
<td>%CV</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>-------------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>BUN</td>
<td>5.2 ммоль/л</td>
<td>20</td>
<td>2.6</td>
<td>1.48</td>
</tr>
<tr>
<td>Chloride</td>
<td>132 ммоль/л</td>
<td>0</td>
<td>0.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.7 ммоль/л</td>
<td>15</td>
<td>0.6</td>
<td>0.63</td>
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Mid-volume chemistry analyzer, 2011 (IFCC and AACC abstract)

Summary of Sigma-Metrics for Quality Assessment

- Sigma-metrics (concept of hitting the target)
- Quality Requirements (size of the target)
- Method Performance Data (did we hit it?)
- Now what do we do? THE RIGHT QC!

Questions on Part 1?

- Many more details at http://www.westgard.com
Improve Lab Operations with Six Sigma Metrics, Part 2

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Outline

• Brief Review of Current QC Practices
• From Assessment to Optimization
  – What changes can we make in our QC?
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  – OPSpecs chart
  – Reference Change Value (RCV)
  – # Tests Required for Diagnosis
• How do we assure the Quality of Sigma-metrics?

IQC Audit UK 2011

• A survey of qc practices of 86 labs in the UK
• Multiple answers allowed, since different tests will have different practices in the same lab
• Special thanks to David Housley

IQC Audit UK 2011, rules

• 89.5% use the same QC procedure for all analytes
• 55.3% use single 2 SD rules

IQC Audit UK 2011, limits

• 56% use manufacturer derived ranges to set control limits
• 81.3% use peer group or EQA data to set control limits

IQC Audit UK 2011, trouble-shooting

• 82.6% repeat the control on failed QC flag
• 84.9% run a new control
• 93.7% re-calibrate, then re-run the control
IQC Audit Summary

- We’re doing the right thing wrong
  - Corrupting our QC system
  - Corroding our trust in QC
  - Compromising test results

Implications of Sigma-metric analysis: Quality Control

- Dramatic impact of world class performance
  - Less QC Effort Needed?
  - Fewer, maybe NO, repeated controls
  - Fewer Service Visits or Tech Support Calls
  - Fewer recalibrations, trouble-shooting episodes
  - Better compliance for PT, EQA, etc.

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Operating Specifications (OPSpecs) chart:
Optimizing QC Design

Suboptimal BGM 2011, OPSpecs

OPSpecs chart: 3 POC methods, cholesterol 2009
6 out of 8 HbA1c devices, 2010

POC chemistry Analyzer, 2011

Broader Implications of Sigma-metric analysis and QC Design:

- Improved Quality Assurance for all methods
  - Maximize error detection
  - Minimize false rejection
  - Optimize and Customize QC
  - Know which methods are good and bad

- Sigma rule of thumb for 6-Sigma Methods:
  \[ 1_{3s} \text{ or } 1_{3.5s} \text{ with 2 or 3 controls} \]

Still More Implications of Sigma-metric analysis and QC Design

- Better ability to tolerate small shifts (lot and reagent changes)
- Shrink Targets for performance
  *Opportunity to improve patient care* (inform clinicians of smaller clinically relevant changes)
- That’s what’s next!
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**Callum Fraser: Reference Change Value (RCV)**
Are serial test results clinically different? Or is it just noise?

$$RCV = \sqrt{2 \times z \times CV_a^2 + CV_i^2}$$

• 2 samples
• need estimates of analytical imprecision and within-subject biologic variation
• $z$-value of 1.96 for $P < 0.05$ or 95% probability (use 2.56 for $P < 0.01$ or 99% probability)
• No bias included in the calculation

**What’s the deal with the RCV?**

• When changes are **bigger** than the RCV, it’s a real difference
• When changes are **smaller** than the RCV, it may only be noise (imprecision and/or inaccuracy)
• Callum Fraser suggests the following notation on the report
  * = significant change;
  ** = highly significant change
• High Sigma Methods = smaller RCV

**Systemic Impact on Clinical Diagnosis: Callum Fraser’s Number of tests/samples required**

$$# \text{ Tests} = \left( \frac{z \times CV_a^2 + CV_i^2}{D} \right)^2$$

How many tests required to detect a significant change in a patient?

• $D$ is the % deviation allowed from homeostatic set point
  input the quality requirement here
• value of <1 means only 1 test is needed to detect a significant change in patient status.

**One last Example! Homocysteine**

*Performance Characteristics of Six Homocysteine Assays*

- Sue L. Lahti, M.D., Mindy L. Konine, M.D., Christine M. Wright, M.D., Mindy Dang, M.D., and William L. Roberts, M.D., M.P.H.

- American Journal of Clinical Pathology 2008; 130:969-975
- Comparison of Six Homocysteine methods on 5 instruments

**Homocysteine:**
Determining the Size and Shape of the Target

• Sigma-metrics as an assessment tool
• Find the quality requirement:
  – Non-regulated analyte by CLIA
  – Ricos et al database gives 17.7%
• Pick critical level of performance: 15 umol/L
Homocysteine:
Measuring the Method Performance (arrow)

- CV: total imprecision study performed
  - Method A at mean of 17 umol/L, 2.1% CV

- How to calculate Bias?
  (comparison study with HPLC reference method, Deming Regression used)
  - Use the Regression equation:
    \[
    \text{NewMethod} = (\text{slope} \times \text{OldMethod}) + \text{Y-intercept}
    \]
    \[
    \text{Bias} \text{ (in units)} = (\text{NewMethod} - \text{OldMethod})
    \]
    \[
    \text{Bias\%} = \frac{|\text{Bias}|}{\text{OldMethod}}
    \]

- Bias: comparison study with HPLC reference method, Deming Regression used
  - Method A:
    \[
    \text{slope} = 0.93, \text{Y-intercept} = 0.64
    \]
    \[
    \text{Bias} = \text{NewMethod} - \text{OldMethod}
    \]
    \[
    = ((15 \times 0.93) + 0.64) - 15
    \]
    \[
    = 13.95 + 0.64 - 15
    \]
    \[
    = 4.59
    \]

  - Bias % = abs(4.59)/15 = 0.313

- Sigma-metric: (T Ea – Bias) / CV
  - (17.7 – 2.73) / 2.1
  - 14.97 / 2.1 = 7.1

Homocysteine:
Data table

<table>
<thead>
<tr>
<th>Method</th>
<th>Imprecision</th>
<th>Bias</th>
<th>Sigma-metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.1</td>
<td>2.73</td>
<td>7.1</td>
</tr>
<tr>
<td>B</td>
<td>4.3</td>
<td>11.3</td>
<td>1.5</td>
</tr>
<tr>
<td>C</td>
<td>3.4</td>
<td>4.93</td>
<td>3.8</td>
</tr>
<tr>
<td>D</td>
<td>3.4</td>
<td>5.33</td>
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<td>2.5</td>
<td>11.2</td>
<td>2.6</td>
</tr>
<tr>
<td>F</td>
<td>8.3</td>
<td>9.1</td>
<td>1.0</td>
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How do we assure the quality of a Sigma-metric?

- How reliable is a Sigma-metric?

- What are the Best Practices for
  - Choosing a Quality Requirement
  - Measuring Imprecision (CV)
  - Measuring Inaccuracy (Bias)

Example Quality Goals:
- Chemistry
- Hematology

Hierarchy of Quality Goals and Specifications: Stockholm Consensus 1999

- V. Goals based on the current state of the art
  - A. as demonstrated by data from EQA or Proficiency Testing schemes
  - B. as found in current publications on methodology.

- IV. Performance goals set by
  - A. regulatory bodies
  - B. organisers of External Quality Assessment (EQA) schemes

- III. Published professional recommendations
  - A. from national and international expert bodies
  - B. from expert local groups or individuals

- II. Evaluation of the effect of analytical performance on clinical decisions in general:
  - A. data based on components of biological variation
  - B. data based on analysis of clinicians' opinions

- I. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings


General Observations & recommendations

- Regulatory (PT, EQA) and "State of the Art" quality goals tend to be largest and accept the status quo.

- Biologic goals are most "evidence-based" but can also be more demanding than current instrumentation

- "Use-based" (practice guidelines) are often somewhere in the middle.

- Ideally: choose biologic goals, clinical use, and in the last resort, regulatory quality requirements

Best Practice #2: Get the best estimates for imprecision (CV%)

- How to find imprecision (CV)
  - Within-run study (repeatability)
  - Between-day study (intermediate precision)
  - Total precision study (CLSI EPS)

  - Routine (cumulative) data on performance (BEST)
Best Practice #3: Get the best estimates for bias (trueness)

- How to find Bias
  - PT or EQA, Peer group
  - Comparison of methods study (CLSI EP9)
  - Patient split-sample testing (BEST)

- But, compare against what?
  - Local method
  - The old method
  - Reference method, material (BEST)
  - HOWEVER, your relative comparison may sometimes be more relevant

Summary of Best Practices

- Choose the appropriate Target (quality requirement)
- Get the best estimates for imprecision and bias
- We need more data, more data, and more data
  - More data from the manufacturer
  - More data in our studies
  - Multiple studies to show it’s not a statistical fluke

Summary and Conclusion

- Six Sigma and Sigma-metrics offer one tool to help improve efficiency, reduce costs AND assure quality
- Assessment Tools: Sigma-metric Equation, Method Decision Chart, #Tests Required
- Optimization Tool: OPSspecs chart
- Reporting Tool: RCV
- The Tools are Free, It’s your Time and Effort that aren’t

One Final Note: Is this approach being used in the Real World?

- 2011 Leeds Health system
  - 9 chemistry analyzers
  - 7 immunoassay analyzers
  - 71 analytes
  - 50% reduction in recals
  - 70% of analytes 4-6 Sigma

- Part 2

- 2 hospitals in Netherlands: Implementing 2006 onward
  - 5 tests simulated effect: 2 SD = 270 rejections
  - Redesign = 9 rejections
  - Reduction of 261 “repeats”
  - Reduction in control mtls
  - Est. €21,183.04 savings

- Part 3

- [Large US] Health System, AACC 2011

Integration of a Multisite Enterprise Quality Control Program on a Wide Area Network and Use of Sigma statistics to Standardize Westgard QC Rules