Simplifying ISO 15189: The Real-World Impact to Laboratory Quality Management

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Need for improvements in quality and patient safety

  – A better analytical quality should be achieved by setting and implementing evidence-based analytical quality specifications in everyday practice;
  – If this will be done, rules for internal quality control and external quality assessment procedures would be more appropriate.
  – Moreover, there is a compelling need for standardized programs improving metrological traceability and correcting biases and systematic errors.
  – Finally, more stringent metrics, such as Six Sigma, should be largely introduced in clinical laboratory to further improve current analytical quality.
Need for a “scientifically based quality control process”

  - The implementation of national and international guidelines is beginning to standardize clinical practice.
  - There is an urgent need to ensure that different laboratories obtain the same analytical results on any samples.
  - A scientifically based quality control process will be a prerequisite to provide this level of analytical performance which will support evidence-based guidelines and movement of patients across boundaries while maintaining standardized outcomes.
Purpose and Objectives

• Purpose: Understand ISO 15189 as a Scientific Quality Management System
  – Utilize Deming’s “Plan-Do-Check-Act” (PDCA) methodology as your “process”
  – Recognize that ISO 15189 requirements fit into the PDCA process model
  – Implement a Six Sigma Quality Management System (6σQMS) that provides tools and metrics for scientific quality management
Total Quality Management
Perspective on Medical Lab

Laboratory Testing Process

Pre-analytic Phase

Analytic Phase

Post-analytic Phase

Laboratory Management
ISO 15189 Perspective

Technical Requirements
5.1 Personnel, 5.2 Accommodation & environmental conditions
5.3 Laboratory equipment, reagents, and consumables

Pre-examination Process 5.4
Examination Process 5.5-5.6
Post-examination Process 5.7-5.10

4.1 Organization and management responsibility
4.2 Quality management system
4.3 Document control; 4.4 Service agreements
4.5 Examination by referral laboratories
4.6 External services and supplies
4.7 Advisory services; 4.8 Resolution of complaints
4.9 Identification and control of nonconformities
4.10 Corrective actions; 4.11 Preventive actions
4.12 Continual improvement; 4.13 Control of records
4.14 Evaluation and audits; 4.15 Management review

ISO 15189 Management Requirements
ISO 15189 Requirements for Quality and Competence

• 2012 revision is 3rd edition
• Committee chaired by Dr. David Burnett and Lucia Berte
• Burnett has also updated his book
  – Added information and guidance on Six Sigma, including selection of SQC procedures on basis of sigma quality
Simplifying ISO 15189
Make it a PDCA process, not a list!

• Don’t think of ISO 15189 as a long list of requirements
  – Document isn’t organized and ordered to show the “flow” of requirements into a process
  – Better to understand and organize those requirements for a process and system
    • Think 1\text{st} about process for implementing QMS
    • Think 2\text{nd} about a process for managing quality
  – Use Deming’s Plan-Do-Check-Act (PDCA) cycle
Understanding Quality Management Systems

• W. Edwards Deming described a system as a series of functions or activities within an organization that work together for the aim of the organization.”
  
  – Deming talked about “optimization of the system” as the role of management

• In the 1950s, Deming helped Japan rebuild their industries; In the 1980s-90s, Deming helped American industry implement Total Quality Management (TQM)
Developing a QMS
Deming’s PDCA Cycle

Deming’s PDCA describes the “Scientific Method” which provides the foundation for Quality Management Systems.
Burnett’s “Process Model” for ISO 15189

Organization/Management
4.1 Organization & Management Responsibility
   4.4 Service agreements
   4.15 Management review
4.2 Quality Management System
   4.3 Document control
   4.13 Control of records

Resource Management
5.1 Personnel
5.2 Accommodations, environmental conditions
5.3 Equipment, reagents, consumables
5.9 Laboratory information management
   4.6 External service and supplies

Evaluation & Improvement
4.8 Resolution of complaints
4.9 Identification & control non-conformities
   4.10 Corrective action
   4.12 Continual improvement
4.14 Evaluation and internal audit
   5.6 Ensuring quality of results (in part)

Examination Processes
4.5 Examination by referral laboratories
   4.7 Advisory services
   5.4 Pre-examination processes
5.2 Examination processes
5.6 Ensuring quality of examinations
5.7 Post examination processes
   5.8 Reporting of results
Introduced at 2014 AACC Meeting, Chicago

1<sup>st</sup> half considers Implementation of ISO 15189 Management and Technical Requirements

2<sup>nd</sup> half focuses on Six Sigma QMS for Analytical Quality Management

Introduces 2 new tools “Westgard Sigma Rules” and “Proficiency Assessment Chart”

290 pages
Simplifying ISO 15189 Implementation Strategies

• Select a Quality Manager to guide process
  – Coordinate development and implementation

• Assemble a “Management Planning Team”
  – Focus on management requirements
  – Perform a Gap analysis to prioritize needed changes and improvements

• Appoint a “Technical Planning Team”
  – Focus on technical requirements
  – Develop Six Sigma QMS (6σQMS)
Simplifying ISO 15189
Management Planning Team (MPT)

Develop QMS Plan (PLAN)
1. Commit to QMS
2. Select a quality manager
3. Formulate a quality policy
4. Establish Man. Plan. Team
5. Provide initial training
6. Define Q goals, objectives
7. Review ISO 15189
8. Perform “gap analysis”
9. Prioritize improvements
10. Develop action plan

Implement Plan (DO)
1. Start a quality manual
2. Establish a document control system
3. Assign individual tasks
4. Assign MPT projects
5. Assign project teams
6. Expand quality training
7. Document policies, processes, procedures, forms for records

Monitor Progress (CHECK)
1. Monitor tasks/projects
2. Select quality indicators
3. Monitor non-conformities
4. Formalize internal audit processes, procedures, and reports

Management review (ACT)
1. Review quality manual
2. Select accreditor
3. Review application process
4. Perform pre-assessment
5. Identify/prioritize needs for improvement (go to P10)
Divide up the work!

Simplifying ISO 15189

Action Plan for QMS
Implementation of Management Requirements

**Individual Assignments**
1. Start quality manual
2. Prepare organization chart
3. Describe extent of services
4. ........

**MPT Project Assignments**
1. Establish document control system
2. Formulate management policies
3. Expand quality training
4. Monitor quality & performance
5. ........

**Project Team Assignments**
1. Flowchart processes for pre-examination, examination, and post-examination
2. Implement quality indicators
3. ........
Simplifying ISO 15189
Technical Planning Team (TPT)

Action Plan for QMS
Implementation of Technical Requirements

TPT Assignments
Policies and Processes
1. Identify customers
2. Flowchart total testing process
3. Define policies and processes for determining customer requirements
4. Standardize policies and processes for method verification & validation
5. Select quality indicators
6. Define policies and processes for design of QC procedures, selection of indicators, determination of measurement uncertainty

Project Assignments.
Procedures and Forms
1. Flowchart pre-examination, examination, and post-examinations processes
2. Review/standardize SOPs
3. Implement verification and validation protocols
4. Implement SQC design
5. Implement quality indicators including measurement uncertainty

Westgard QC
Simplifying ISO 15189
Adopt PDCA for Scientific 6σQMS

<table>
<thead>
<tr>
<th>PLAN</th>
<th>DO</th>
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<tbody>
<tr>
<td>1. Define goals for intended use based on reg/accr. requirements and clinical and medical applications&lt;br&gt;2. Select analytic measurement procedure; consider traceability and manufacturer’s reference methods and materials</td>
<td>3. Validate method performance or verify manufacturer’s claims&lt;br&gt;4. Implement method and analytic system and address pre-analytic and post-analytic requirements; 4a. Train analysts and operators in new analytic system</td>
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<thead>
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<th>ACT</th>
<th>CHECK</th>
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Westgard QC
6σQMS

1. Define Goals for Intended Use (TEa, Dint)
2. Select Analytic Measurement Procedure
3. Validate Method Performance (CV,bias)
4. Implement Method and Analytic System
5. Formulate “Total QC Strategy”
6. Select/Design SQC (rules, N)
7. Develop Total QC Plan
8. Implement Analytic TQC Plan
9. Verify Attainment of Intended Quality
10. Measure Quality & Performance (EQA, PT, MU)
11. Monitor Failures FRACAS, Quality Indicators
12. Improve Quality, TQC Plan [CQI, CAPA]

(a) Regulatory & Accred. Requirements
(b) Clinical and Medical Applications
(b) Manufacturer’s Ref Methods & Materials
(a) Manufacturer’s Claims
(a) Manufacturer’s Installation/Training
(a) Sigma [(TEa-Bias)/CV]
(a) Sigma QC Selection Tool
(a) Risk Analysis
(a) QC Tools
6σQMS

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(7a) Risk Analysis
(8a) QC Tools

Westgard QC
6σQMS

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(4b) Pre- and Post-analytic Requirements
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(6a) Sigma QC Selection Tool
(7a) Risk Analysis
(8a) QC Tools

Westgard QC
6σQMS

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(5a) Sigma [(TEa - Bias)/CV]

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Check

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(11) Monitor Failures FRACAS, Quality Indicators

(10) Measure Quality & Performance (EQA, PT, MU)
6σQMS

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(7a) Risk Analysis

(8a) QC Tools

(1b) Clinical and Medical Applications

(2b) Manufacturer’s Ref Methods & Materials

(3b) Manufacturer’s Ref Methods & Materials

(4b) Pre- and Post-analytic Requirements

(5b) TQC Plan [CQI, CAPA]

Do

Check

Act
Simplifying ISO 15189
Define Policies, Processes, Procedures

• The laboratory should define policies, processes, and procedures in a Quality Manual to document the implementation of its Quality Management System
  – Policies: Describes what is to be achieved
  – Processes: Describes activities to implement a policy
  – Procedures: Provides step by step directions for activities
ISO 15189
Intended Use, Intended Quality

• 5.5.1.1 Selection, Validation
  – The laboratory shall select examination procedures which have been validated for their intended use.
  – The specified requirements (performance specifications) for each examination procedure shall relate to the intended use of that examination.

• 5.6.2.1 Quality Control
  – The laboratory shall design quality control procedures that verify the attainment of the intended quality of results.
Example Application

Quality Required for Intended Use

- **Policy** - Quality requirement shall be defined for each test to identify critical performance characteristics that must be achieved to satisfy the intended clinical use of each laboratory test.

- **Process** – Analytical goals shall be established for each test based on an assessment of specific clinical diagnostic and treatment requirements for the test, goals based on biologic variability, criteria for performance in PT and EQA programs, and “state of the art” performance.

- **Procedure** – Select specific analytical goal, or quality requirement, by comparison of different quality requirements using an error grid.
Example – Quality Goals for HbA1c
Comparison of CAP, NGSP, ADA

CAP=NGSP=6%, as demanding as ADA clinical diagnostic and treatment criteria
ISO 15189
Validation of Examination Procedures

• Section 5.5.

  – The laboratory shall select examination procedures which have been validated for their intended use...
  
  – The specified requirements (performance specifications) for each examination shall relate to the intended use of that examination
  
  – The independent verification by the laboratory shall confirm through obtaining objective evidence that the performance characteristics for the examination procedure are met.
Validation of Examination Procedures

• **Policy** - The laboratory shall validate the performance characteristics to ensure the quality required for intended use is achieved.

• **Process** - The laboratory shall employ an evaluation study that includes experiments for analytic range, replication, comparison of methods, confirmation of reference ranges, and when appropriate, detection limit, interference, and recovery. Experimental results should be analyzed graphically and statistically and the sigma-metric determined to judge the acceptability for the intended use.
Validation of Examination Procedures

• **Procedure** - Preparation of a Method Decision Chart to determine quality on the sigma scale and assess the acceptability of precision and accuracy for intended use.

1. Define the quality requirement for the test in the TEa format.
2. Scale the y-axis from 0 to TEa and the x-axis from 0 to TEa/2.
3. Draw “sigma lines” for 2, 3, 4, 5, and 6σ, e.g., 2σ line has y-intercept of TEa and x-intercept of TEa/2; 3σ y-int of Tea, x-int of TEa/3; 4σ y-int = TEa, x-int=TEa/4; 5σ y-int=TEa, x-int=TEa/5; 6σ Y-int=TEa, x-int=TEa/6.
4. Obtain %CV from the replication experiment.
5. Obtain %Bias from the comparison of methods experiment.
6. Plot an “operating point” that has %Bias as the y-coordinate and %CV as the x-coordinate.
7. Assess sigma-quality from location of the operating point.
Simplifying Method Validation

Use a Method Decision Chart

Method Decision Chart \(\text{TEa}=6.0\%\)

- 2-sigma
- 3 sigma
- 4 sigma
- 5 sigma
- 6 sigma

Region of Unacceptable Performance

World Class Quality

Accuracy - observed %Bias

Precision - observed %CV

Westgard QC
Goal is Six Sigma Quality!

- Tolerance Specification  Target  + Tolerance Specification

-6 SDs should fit into spec  
+6 SDs should fit into spec

-6s -5s -4s -3s -2s -1s 0s 1s 2s 3s 4s 5s 6s

Westgard QC
Minimum Acceptable Quality is $3\sigma$!
Simplifying Method Validation

Calculate a sigma-metric

\[ \text{Sigma} = \frac{\text{TEa} - \text{Bias}}{\text{SD}} \]

-6s -5s -4s -3s -2s -1s 0s 1s 2s 3s 4s 5s 6s

Lower Tolerance Limit -TEa

True Value

Bias

Upper Tolerance Limit +TEa

Westgard QC
Simplifying Method Validation

Calculate a Sigma-metric

- $\text{Sigma} = \frac{(\text{TEa} - \text{Bias})}{\text{SD}}$
  - TEa, allowable Total Error
  - Bias, inaccuracy of the method
    - Initially from comparison of methods exp.
    - Ongoing from PT/EQA survey or Peer Comparison program
  - SD or CV, imprecision of the method
    - Initially from replication experiment
    - On-going from routine SQC data
- All terms in either % or concentration units
Example Calculations of Sigma

- **Sigma = (TEa – Bias)/CV**
- **Glucose**, TEa=10%
  - Bias=1.0, CV=1.5%
  - Sigma = (10.0-1.0)/1.5 = 6.0
- **HbA1c**, TEa=6.0%
  - Bias=1.0%, CV=1.5%
  - Sigma = (6.0-1.0%)/1.5% = 3.33
ISO 15189
Quality Control

• 5.6.2.1

– The laboratory shall design quality control procedures that verify the attainment of the intended quality of results.

• Must have defined “intended quality”
• Must have QC selection/design process that relates the quality required with the precision and accuracy of the examination procedure and the rejection characteristics of different control rules and different numbers of control measurements
Simplifying QC Design

Use quality-planning tools

• Select SQC procedures on basis of observed sigma quality of examination procedures
  – Sigma QC Selection tool
    • Described in CLSI C24A3
  – Charts of Operating Specifications
    • Available from Westgard QC publications, website
  – “Westgard Sigma Rules” graphic tool
    • Available from Thermo Fisher Scientific
      – http://thermoscientific.com/westgard-poster
Westgard Sigma Rules™
2 Levels of Controls

Data QC

Report Results

Take Corrective Action

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<th>R</th>
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<td>1</td>
</tr>
<tr>
<td>$2_{2s}$</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>$R_{4s}$</td>
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<td>$4_{1s}$</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>$8_x$</td>
<td>2</td>
<td>4</td>
</tr>
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</table>

Sigma Scale = ($\%TEa - \%Bias$)/$\%CV$

Westgard QC
Westgard Sigma Rules™

2 Levels of Controls

Data QC

Report Results

Take Corrective Action

Sigma Scale = (%TEa-%Bias)/%CV

Westgard QC
HbA1c: TEa=6.0%, Bias=1.0%, CV=1.0%, Sigma=(6-1)/1=5

**Data QC**

1. **Report Results**
2. **Take Corrective Action**

**Sigma Scale = (%TEa-%Bias)/%CV**

Westgard QC
HbA1c: TEa=6.0%, Bias=1.0%, CV=1.0%, Sigma=(6-1)/1=5

Sigma Scale = (%TEa-9*Bias)/%CV

Westgard QC
HbA1c: TEa = 6.0%, Bias = 1.0%, CV = 1.0%, Sigma = (6 - 1)/1 = 5

Sigma Scale = (%TEa - %Bias)/%CV
Glucose: TEa = 10.0%, Bias = 1.0%, CV = 1.5%, Sigma = (10-1)/1.5 = 6

Sigma Scale = (%TEa-%Bias)/%CV
Glucose: TEa=10.0%, Bias=1.0%, CV=1.5%, Sigma=(10-1)/1.5=6

Sigma Scale = (%TEa-%Bias)/%CV
Why a low sigma is bad!
Sigma-metric = 3.0

Data QC

Report Results

Take Corrective Action

Sigma Scale = (%TEa-%Bias)/%CV

Westgard QC

Why a low sigma is bad!
Sigma-metric = 3.0

Data QC

Report Results

Take Corrective Action

Sigma Scale = (%TEa-%Bias)/%CV

Westgard QC
ISO 15189
Measurement Uncertainty (MU)

• 5.5.1.4

– The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty.

– The laboratory shall consider measurement uncertainty when interpreting measured quantity values.

– Upon request, the laboratory shall make its estimates... available to laboratory users.
Simplifying MU

Use “Intermediate” QC data

• 5.5.1.4 Note 2
  – Measurement uncertainties may be calculated using quantity values obtained by the measurement of quality control materials under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure, e.g., changes of reagent and calibrator batches, different operators, scheduled instrument maintenance.
Intermediate Precision Conditions

• Should be long enough time period to include changes of calibration, calibrator lots, reagent lots, different operators, instrument maintenance

• Recommend at least 100 data points
  – Confidence interval for SD is about ± 10%
  – Approximately 3 to 4 months data would be the minimum time period
Simplifying Measurement Uncertainty

• **Policy** - The laboratory shall evaluate the uncertainty of measurement for each examination procedure where precision data are available from stable control materials.

• **Process** - The laboratory shall determine standard measurement uncertainty from SQC data obtained under intermediate precision conditions.
5.5.1.4 The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty.

Process - The laboratory shall compare estimates of standard measurement uncertainty to the performance required for intended use of the examination procedure by determination of sigma-metrics.
Simplifying MU
Calculate Sigma-metric

• **Procedure** - Define TEa, estimate SD from intermediate QC data

• Sigma = (%TEa) / %CV
  – Where %TEa is PT or EQA requirement for acceptable performance
  – %CV is determined from laboratory’s intermediate term SQC data
ISO 15189
External Quality Assessment

• 5.6.3.1 Interlaboratory comparison
  – The laboratory shall participate in an intralaboratory comparison programme [PT, EQA] appropriate to the examination and interpretations of examination results.
  – The laboratory shall monitor the results... and participate in the implementation of corrective actions when predetermined performance criteria are not fulfilled.
CAP 2014 HbA1c 6.97 %Hb
Sigma Proficiency Assessment

CAP 2014 GH2-02 6.97%Hb

Observed Inaccuracy (%Bias)

Observed Imprecision (%CV)

Westgard QC
Summary: Simplifying ISO 15189 Development/Implementation

• Select Quality Manager

• Assemble Management Planning Team
  – Adopt PDCA for management requirements
  – Define policies, processes, procedures

• Appoint Technical Planning Team
  – Adopt PDCA for scientific technical requirements
  – Integrate Six Sigma concepts and tools
    • Method Decision Chart, calculation of sigma-metrics
    • QC Planning tools, such as “Westgard Sigma Rules”
Summary: Simplifying ISO 15189 Plan and DO Stages of 6σQMS

- Define quality requirements in form of TEa
- Select examination procedures with attention to traceability
- Validate examination performance by
  - Use Method Decision Chart
  - Calculate sigma-metric
- Implement examination procedures
  - Training for use of SOPs
Summary: Simplifying ISO 15189 Check and Act Stages of 6σQMS

• Select/design SQC procedures for the sigma quality achieved by the method
• Estimate Measurement Uncertainty from intermediate QC data
• Assess acceptability of MU by calculation of sigma-metric
• Assess acceptability of bias from PT/EQA by calculation of sigma-metric
Thank you for your kind attention!
Any Questions?

MUCH, MUCH MORE
Can be found online
At www.westgard.com