The value-assignment protocol for commercial calibrators:

*How to Ensure Suitable Quality of Clinical Measurements*

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*Director, R&D Quality Engineering, Statistics and Data Analytics*
Presenter Biography
Tony Orzechowski (Orz - e - kow - ski)

Tony has over 30 years of experience in the development and application of data analytics, statistics and quality improvement methods in manufacturing and product development.

He received a mechanical engineering undergraduate and a manufacturing systems engineering master’s degree from the University of Wisconsin - Madison. He is also a certified Lean Six Sigma Master Black Belt.

He is currently the Director of R&D Quality Engineering, Statistics and Data Analytics at Abbott Diagnostics where he has been responsible for managing the reliability, predictive maintenance, specification development, statistical analysis, advanced data analytics and quality engineering activities for the launch and support of new products and systems worldwide. He also currently serves as an adjunct professor at Northwestern University where he teaches the use of statistical quality improvement methods in new product development for the Master of Product Design and Development Management program.
The Essential Question ...

“What amount of medical harm due to analytical error is it OK to let go undetected?”

Dr. Frederick A. Smith
Children’s Hospital - Chicago

My personal translation as a manufacturer and a father…

“What amount of medical harm due to analytical error is acceptable for me to let go undetected when testing is done on my girls?”
Agenda
Ensure Suitable Quality of Clinical Measurements

Guiding Principles
Relating Product Development Design Requirements to the Essential Question and Total Analytical Error

Control of Analytical Error
• Design Requirements – Allocation of Total Allowable Error
• Design Control – Control of Calibrator and Calibration Error by Design
• Production Testing and Field Monitoring – Delivering the Right Design over Time

Summary
Sources of Analytical Error

All Key sources of Total Analytical Error Must be understood and addressed during System Design and Development

Total Analytical Error

Systematic Error
(Inaccuracy / Bias)
- Constant
- Dynamic
- Random
  - Stability
  - Drift

Random Error
(Imprecision)
- Imprecision (EP5)
  - Day
  - Run
  - Rep

Outliers

Ref Calibrator Value Assignment
- Instrument between Units
- Reagent Lot Variability
- Calibration Error
- Calibrator Mfg. Variability
- Commodities Lot to Lot
Translating TEa into Design Requirements

Error budgeting a Total Allowable Error (TEa) Design Input is a key foundation to building effective design specifications.

Design Objectives:
- Will the design meet requirements?
- With what confidence?
- How robust is the product over time?

Error Budgeting of TEa
Translates the TEa requirements into lower level component specifications.

It realistically accounts for sources of error in the system design and the allocations that set the foundation of the product design specifications.

Instrument and Assay Design and Process specs are established to maintain this budget over time.
Method Decision Chart

Evaluating the Analytical System relative to Medical Utility Guides Our Development Efforts

Total Allowable Analytical Error (TEa) = 20%

- < 2 Sigma
- > 2 Sigma

Westgard: Six Sigma and Quality Control
**Method Decision Chart**

*Evaluating the Analytical System relative to Medical Utility Guides Our Development Efforts*

**Sigma Value**

\[
\text{Sigma Value} = \frac{\text{TE}_a - \text{BIAS}_a}{\%\text{CV}_a}
\]

**Method Decision Chart**

<table>
<thead>
<tr>
<th>Bias (%)</th>
<th>Imprecision (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2%</td>
<td>2%</td>
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<tr>
<td>4%</td>
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<td>6%</td>
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<td>12%</td>
<td>12%</td>
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<tr>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

**To target 6 Sigma Performance, we allocate maximum bias levels for each of the drivers of analytical bias**

**Allocations to Sources of Analytical Bias in Design**

- Ref Calibrator
- Value Assignment
- Calibration
- Mfg. Variability
- Reagent Mfg. Variation
- Lot to Lot
- Stability Effects
- Reagent and Calibrator
- Between Instrument Variation

**Westgard: Quality Control**
Calibrator’s Role in Error Transmission

The calibrator set is the foundation for establishing the dose-response curve and allows us to report consistent results for patient specimens under varying conditions.

We rely upon calibration to tune out differences in the dose-response curve due to:

- **variation in reagent potency** due to the manufacturing process
- change in reagent potency over the **shelf life** of the reagent
- differences in **instruments** (optics, etc.)
Translating Requirements into Specs

The role of R&D Scientists and Engineers is to identify the relationships in the translation process and design a robust product with this knowledge.

Calibrator Design

Traceability

Production Specs

Design Specifications (Product and Process)

Calibrator Kit

Assay Design

Total Allowable Error

User / Medical Requirement

High Level Design Expectations

Stability Shift

Imprecision

Rgnt Lot Var

Calibrator Lot Var

Calibrator Design

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**Calibrator Manufacturing**

Uncertainty in the true value of a calibrator due to manufacturing or testing error in the Working Reference must be accounted for in impact to materials customer receive.

- **Reference Manufacturing**
  - LSL (-1%)
  - Target
  - USL (+1%)

- **True Mean**

- **Customer Manufacturing**
  - LSL (-1%)
  - Target
  - USL (+1%)

- **True Mean**

- **Calibrator Bias that Must be Accounted for in the Design Allocation**

Primary/Working Reference Calibrator → Customer Calibrator
Translating Rqmts into Specs: IA Calibrator Example

**Design Input Requirement:**
Total Allowable Analytical Error not to exceed ± 20% at 95% confidence about the medical decision pt.

**Error Budget**
1/3 of Total Error allotted to Bias.
Calibrator + Reagent Lot Allocation of Random Bias < ±5% about the Medical Decision Point

**Kit Level Design Requirements:**
Allocations Based on DOEs, Calibration Design, etc.
- Calibrator Ref Bias < ±1%
- Calibrator Kit Lot Bias < ±1.5%
- Reagent Lot Bias < ±2.5%

**Component Level Specifications:**
Calibrator Lot Var: Based on Calibration Analysis
- Calibrator 1 ± 1.2%
- Calibrator 2 ± 1.1%
- Calibrator X ± 1.3%

**Acceptance Spec**
Detection Mode of Control
Calibrator 1: ±1.0% Product Test

**Process Risk Control Plans**

**Calibrator Mfg Eval.**
Process Selection, Characterization and Capability Evaluation

**Production Docs**

**Test Validity Spec**
w/i run %CV<1.3%

**Black = Rqmts / Specs**
**Blue = Trace to Rqmt**
**Red = Risk Management**

Proprietary and confidential — do not distribute
Translation of Requirements into Production Specifications

FDA Guidance on Design Control

“Design controls are an interrelated set of practices and procedures that are incorporated into the design and development process, i.e., a system of checks and balances.”

Requirement: Documented functions, conditions or capabilities that a medical device or process must meet to satisfy a user’s needs, standards, or regulatory expectations.

Specification: Any requirement with which a product, process, service or other activity must conform.
Calibration Robustness Study Overview

R&D Quality Engineering
Technical Risk Map and Risk Reduction Process

Tracking and understanding technical risks critical to successful system development. Rigorous technical risk management standard practice including risk reduction tracking.

Early Feasibility Phase
Risk Mapping and Control

Risk Identification
Tracking and understanding technical risks critical to successful system development.

Risk Monitoring and Control
Rigorous technical risk management standard practice including risk reduction tracking.

A typical Risk Analysis may assess >1,000 potential risks and associated controls
Proactive Control of Quality – Example Pressure Monitoring

Detection of abnormal pressure profiles due to various induced failure modes

Evaluation of Aspirate Profile

- **Front End**: Aspirate Begin
- **Back End**: Aspirate End
- **PSI_Discord**: Possible Air Aspirate
- **Shape_Score**: Possible Partial Aspirate or Foam
- **Slope_Score**: Possible Foam or Insufficient Sample
- **Clot_Score**: Possible Clot

Aspirate Pressure vs. Time
Proactive Control of Quality – Example Pressure Monitoring

Detection of abnormal pressure profiles due to various induced failure modes

Aspiration Fault Types – Pressure Monitoring Profiles

Normal

Air/Large Bubble

Foam

Insufficient Sample

Soft Clot

Clot/Viscous Sample
What this Means to Our Customers and to Patients
More Accurate Results for Our Patients and Less issues with Calibration and QC for Our Laboratory Customers

Performance – Best In Class Performance of Products through Design

Sigma Metric Performance of Alinity System vs. ARCHITECT

• >90% of the IA and CC products were 5 sigma or greater.

• No assays were <3 Sigma.

Fig. 1. Normalized Method Decision Chart for Alinity c Clinical Chemistry Assays.
Our Customers’ View – Growing Customer Satisfaction

*Our customers are noticing our improvement and would recommend us.*

NPS above +50 is considered “Excellent,” and above 70 is considered “World-class.”

https://www.questionpro.com/blog/nps-considered-good-net-promoter-score/
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Thank You!!!

Grazie
Dhanyawaad
Arigato
Xie Xie
Danke
Shukran
Spasibo
Obrigado
Dziekuje
Gracias
Merci

A Promise for Life
Back-up Materials
More Accurate Results for Our Patients and Less issues with Calibration and QC

*Performance – Best In Class Performance of Products*

Sigma Metrics for 30 Abbott Diagnostics
ARCHITECT
Clinical Chemistry Tests