Quality Control of Laboratory Testing

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Baystate Health System
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- Leading provider of healthcare services in Western MA
- >10,000 employees, Gross revenues >$1.4 billion
- Baystate Medical Center - tertiary care
- Hybrid Academic/Private Practice >1400 physicians
- 653 beds; 3rd largest acute care in NE
  - 37,000 admissions annually
  - 600,000 ambulatory visits
  - 147,000 emergency visits (Level One Trauma Center)
- Western Campus Tufts School of Medicine 240 faculty
- Franklin Medical Center (90 beds) > 4700 admissions
- Mary Lane Hospital (31 beds) >1600 admissions annually
What is Quality?

1. a. peculiar and essential character: NATURE [her ethereal quality]
   b. inherent feature: PROPERTY [had a quality of stridence, dissonance]

2. a. degree of excellence: GRADE [the quality of competing air service]
   b. superiority in kind [merchandise of quality]

QA versus QC

• Quality Assurance – the practice that encompasses all procedures and activities directed toward ensuring that a specified quality of product is achieved and maintained

• Quality Control – the set of procedures designed to monitor the test method and the results to ensure appropriate test system performance
History of Quality Control

• 1900s Folin & Wu glucose method for quantifying blood sugar:
  • prepare reagents from basic chemicals,
  • perform test using standard procedures
  • Measure reaction product in colorimeter
  • Estimate analyte concentration from std curve

• 1950’s industrial process control models introduced formal QC to clinical analyses

• Industrial model of quality in analytical process – analyze a surrogate sample – called a control, containing known amount of measured analyte.
Quality Control

• Controls useful in:
  • Verifying the suitability of analytical systems (sample, reagents, instruments, and/or users)
  • Monitoring the precision and trueness of measurement results
  • Preventing false-negative and false-positive results
  • Preventing fault conditions that could lead to inaccurate results
  • Troubleshooting problems that require corrective action

Types of Quality Control

• “On-Board” or Analyzer QC – built in device controls or system checks
• Internal QC – laboratory analyzed surrogate sample controls.
• External QC – blind proficiency survey, samples sent a few times a year to grade an individual laboratory’s performance against other labs
United States QC Regulations

• CLIA ’67 – required daily QC as integral part of testing process for each test—applied to all labs involved with interstate transport of samples.
• CLIA ’88 - reaffirmed “two levels of QC per test per day” (blood gases every 8 hours), applied to all labs performing clinical testing.
• CAP began to advocate daily QC through inspection and accreditation.
• Joint Commission focus on patient safety and preanalytic, analytic and postanalytic processes.
Waived Testing Trends

• Since CLIA ’88, waived labs must:
  • Enroll in CLIA Program
  • Pay biennial certification fees
  • Follow manufacturer’s test instructions
• Number of waived tests grown from 8 to >40
• Number waived labs increased from 20% to 64% of the 203,000 CLIA labs.
Consequences of Poor Quality

• Complaints about SMBG devices represent the largest number filed with the FDA for any medical device (by 1993, over 3200 incidents, including 16 deaths). Greyson J. Diabetes Care 1993;16:1306-8.


• Nine patients at two nursing facilities in Southern California were diagnosed with hepatitis B infection transmitted in association with blood glucose monitoring. State of California Health and Human Services, Department of Health Services, Licensing and Certification Program. Recommendations on the prevention and control of HBV transmission in diabetic patients who require blood glucose testing. July 2000.
Consequences of Poor Quality

- Centers for Medicare and Medicaid Services (CMS) Pilot Study in 1999 Ohio and Colorado inspections found over 50% of labs had significant quality issues.
- 2001 CMS expanded pilot inspected 2.5% (436 waived and PPM labs) in 8 states:
  - 32% did not perform QC as required
  - 16% failed to follow manufacturers’ instructions
  - 7% did not perform calibration as required by the manufacturer
CMS Waived Lab Pilot Study

- Of the waived labs, in addition:
  - 23% had certificate issues (change name, director, address)
  - 20% cut occult blood cards and urine dipsticks to obtain more tests from a single card/dipstick.
  - 19% had personnel without training/competency evaluation
  - 9% did not follow manufacturer’s storage and handling instructions
  - 6% were using expired reagents/kits

DHHS Office of Inspector General Enrollment and Certification Processes in the CLIA Program. August 2001. OEI-05-00-00251
CMS Waived Lab Follow-Up

- CMS initiating on-site visits to 2% labs
- CMS listed 15 Professional Societies and groups that offer educational opportunities
- State-by-State revisits to original 8 pilots
  - Varying improvement 7/8 states (total 74% or 61/82 labs)
  - No improvement 26% (26/82 labs)
- Most labs want to do proper testing, but don’t know what is required or how to best control a laboratory process
Quality Laboratory Testing

• Test results that are reliable
• Appropriate use of technology
• Documentation of results in medical record
• Compliance with national, regional and local laboratory accreditation regulations
Quality Systems Approach

- Quality Systems Essentials apply across the path of workflow regardless of the service and set a basis management philosophy of quality.
  - Organization
  - Personnel
  - Equipment & Reagents
  - Purchasing & Inventory
  - Process Control (pre, analytic, post)
  - Documents and Records
  - Occurrence Management
  - Internal and External Assessment
  - Process Improvement
  - Service and Satisfaction
  - Safety

Sources of Laboratory Error

• Environmental:
  • Temperature
  • Humidity
  • Air flow
  • Light intensity
  • Altitude

• Operator:
  • Improper specimen prep, handling
  • Incorrect test interpretation
  • Failure to follow test system instructions

• Analysis:
  • Calibration factor incorrect
  • Mechanical failure
Systematic Errors

- Errors which affect every test in a constant and predictable manner
- Can occur from one point forward or for a limited period of time
- Surrogate, liquid sample QC does a good job at detecting systematic errors, like:
  - Reagent deterioration or preparation
  - Improper storage or shipment conditions
  - Incorrect operator technique (dilution, pipette setting)
  - Calibration errors – wrong setpoint, factors
Random Errors

• Errors which affect individual samples in a random and unpredictable fashion, like:
  • Clots
  • Bubbles
  • Interfering substances

• Surrogate sample QC does a poor job at detecting random errors unless the error specifically occurred with the QC sample.
QC and Lab Errors

- QC daily at 09:00, two levels
- Line leak occurs at 11:00, dispenses partial reagent causing 25% decrease in values, not detected until next day QC at 09:00. (Systematic Error), must reanalyze all specimens since previous QC at 09:00, the previous day.
- Hemolyzed specimen (Random error) affects one sample
Quality Control

• A stabilized surrogate sample of known concentration analyzed like a patient sample to determine assay recovery and result stability over time

• Advantages
  • QC has target values, if assay recovers target, then everything is assumed stable (instrument, reagent, operator, sample)
  • QC monitors the end product (result) of the entire test system

• Disadvantages
  • Patients can be reported before problem detected
  • When problem detected must go back and reanalyze patients since last “good” QC

• Need to get to fully automated analyzers that eliminate errors upfront, provides assured quality with every sample
  • Until that time, need a robust QC program to ensure result quality
Manufacturer Checks – Device Built-In or On-Board QC

- Some devices have internal checks which are performed automatically with every specimen:
  - Development of a line (Pregnancy test, Occult blood)
  - Sensor signal (blood gas analyzer, clots)
  - Flow resistance and liquid sensors (clots or bubbles in analyzer pipettes)
- Other checks engineered into device:
  - Temperature indicator in shipping carton
  - Barcoding of reagent expiration dates (prevents use)
  - Lockout features that require successful QC
  - Disposable analyzer cuvettes/pipette tips (carry-over)
Variety of New Devices and Control Configurations

- Unique device methods/control configurations
  - Immunoassay – hCG, Drug Testing, Occult blood with internal controls
  - Glucose and Coagulation – Electronic monitors
  - Blood Gas
    - Multi-use Cartridges with liquid control/calibrators
    - Individual tests and readers with internal controls on both
  - In-vivo – continuous pH/glucose monitors, indwelling catheters
  - Alternative specimens – breath alcohol
  - Transcutaneous – neonatal bilirubin, pulse oximeters
- Traditional QC requirements, 2 levels/day, may not apply
- Emerging field and emerging accreditation requirements
Quality Control

• Laboratory directors have ultimate responsibility for determining appropriate quality control procedures for their labs.

• Manufacturers if *in vitro* devices have responsibility for providing adequate information about the performance of devices, means to control risks, and verify performance within specification.

• In practice, quality control is a shared responsibility of manufacturers and users of devices.

Quality Control

• No single quality control procedure can cover all devices, since devices may differ in design, technology, function, and intended use.
• QC practices developed over the years have provided labs with some degree of assurance that results are valid.
• Newer devices have built-in electronic controls, and “on-board” chemical and biological controls.
• Quality control information from the manufacturer increases the user’s understanding of device overall quality assurance requirements so that informed decisions can be made regarding suitable control procedures.

Risk Management Process

Life-Cycle Risk Management Process

Risk Analysis

- Hazard Identification
- Probability of Harm
- Severity of Harm

Risk Assessment

- Risk Estimation
- Risk Evaluation
- Risk Control
- Risk Monitoring
- Failure Investigation

Questions:
- New Hazard?
- Greater severity?
- Increased frequency?
Total Quality Assurance

• Holistic or global approach to QA
• Every instrument or device is different
• Hazard identification and risk management
  • Hazard identification defines the sources of potential error for an instrument or device, the frequency of those errors and potential consequences from not detecting an error
  • Risk management involves the identification of potential risks, assessment of risk consequences, development of risk controls, checks or other means for detecting and preventing a potential error, and monitoring effectiveness of these risk mitigations.
Risk Estimation

• Probability of Harm = Frequency of error x Probability error undetected
  • Frequent = once per week
  • Probable = once per month
  • Occasional = once per year
  • Remote = once every few years
  • Improbable = once in the life of the test system

• Severity of harm
  • Negligible = Inconvenience or temporary discomfort,
  • Minor = Temporary injury or impairment not requiring professional medical intervention,
  • Serious = Injury or impairment requiring professional medical intervention,
  • Critical = Permanent impairment or life-threatening injury,
  • Catastrophic = Results in patient death
## Risk Acceptability Matrix

<table>
<thead>
<tr>
<th>Probability of Harm</th>
<th>Negligible</th>
<th>Minor</th>
<th>Serious</th>
<th>Critical</th>
<th>Catastrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Probable</td>
<td>Acceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Occasional</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Remote</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Improbable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>
Lab-Manufacturer Partnership

- Developing a quality program surrounding the implementation of a new device requires a partnership between the manufacturer and the laboratory.
- Some sources of error may be detected automatically by the device and prevented, while others may require the laboratory to do something, like analyze external QC on receipt of new lots of reagents.
- Clear communication of potential sources of error and delineation of lab and manufacturer roles for how to detect and prevent those risks.
CLSI Project: EP22

• Presentation of Manufacturer’s Risk Mitigation Information for Users of *in vitro* Diagnostic Devices.
• Chairholder – Greg Cooper (Bio-Rad)
• EP22 provides guidance to manufacturer on disclosure of information to users regarding the design features intended to mitigate risk from device failures that can affect the accuracy of test results
• This information includes potential failure modes, how the risk mitigation design feature operate, and the evidence to support the effectiveness of those features.
CLSI Project: EP23

- A separate CLSI Subcommittee has been formed to develop guidelines based on manufacturer QC information.
- Proposed title: Laboratory Quality Control Based on Risk Management.
- James H. Nichols, Ph.D., Chairholder
- EP23 describes good laboratory practice for developing a quality control plan based on manufacturer’s risk mitigation information, applicable regulatory and accreditation requirements, and the individual healthcare and laboratory setting
EP23 Laboratory QC Based on Risk Management

Input Information
- Regulatory and Accreditation Requirements
- Manufacturer Provided and Other Product Information
- Individual Healthcare and Laboratory Setting

Process
- Risk Assessment

Output
- Laboratory Director’s QC Plan

CQI
- Post Implementation Monitoring
# Manufacturer Risk Assessment

## EP22/EP23 Glucose Example

<table>
<thead>
<tr>
<th>Targeted Failure Mode (Hazard)</th>
<th>Device Feature or Recommended Action</th>
<th>How feature or action performs intended function</th>
<th>Known limitations of feature or action</th>
<th>Actions required to address known limitations</th>
<th>Studies to verify intended feature or action achieves intended purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect results due to sample carryover</td>
<td>Wash mechanism for probes</td>
<td>Wash mechanism reduces risk of sample carryover</td>
<td>Inadequate washing following high glucose sample can cause subsequent sample to be falsely elevated</td>
<td>Run surrogate sample QC periodically and perform routine maintenance - check probe</td>
<td>Sample carryover study</td>
</tr>
</tbody>
</table>
Laboratory Risk Assessment

• Washing mechanism cleans sample probe after each aliquot.

• Manufacturer recommends periodic surrogate QC to detect dirty probes and routine maintenance to clean and replace probes.

• Limitation – process may fail to clear a high sample. Studies <15% bias for samples up to 486 mg/dL. What about diabetic ketoacidosis, high glucose?
Laboratory Risk Assessment

- Lab director could conduct own carry-over study (using higher glucose samples) or repeat next sample after any glucose >500 mg/dL until sufficient data is collected.
- Residual risk with probe wash and repeating next sample after a high patient
  - Probability of carry-over – occasional that operator may miss high glucose and fail to repeat sample following high result
  - Severity – serious – unknown effect > 500 mg/dL
  - Residual risk – clinically acceptable
- QC elements (manufacturer probe wash plus laboratory repeat next sample after > 500 mg/dL result) are added to a Lab Risk Assessment and QC Plan
## Lab Director’s Risk Assessment
### EP22/EP23 Glucose Example

<table>
<thead>
<tr>
<th>Targeted Failure Mode (Hazard)</th>
<th>Automated Control Effective?</th>
<th>Quality Control Plan</th>
<th>Is Residual Risk Acceptable? (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect results due to sample carryover</td>
<td>Partial (wash mechanism has not been evaluated above 480 mg/dL (26.7 mmol/L) glucose, Carry-over above this level is uncertain)</td>
<td>Run surrogate samples periodically, and perform routine maintenance as recommended by the manufacturer. Repeat next sample following a glucose &gt; 480 mg/dL. In the hospital central lab, report results without autoverification, and utilize lab information system to notify operator of high glucose specimens.</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Laboratory Risk Assessment

- Process is repeated for each risk identified, whether from manufacturer or lab identified.
- For each risk, a mitigation strategy is found that will reduce the residual risk to an acceptable level.
- Sum of all QC elements (manufacturer provided and laboratory added) becomes the laboratory’s QC plan specific to this device and the laboratory environment.
- This plan is then checked against manufacturer QC and local regulatory requirements.
A summary of key points:

- A quality control program is necessary for result quality.
- QC should be customized to the device and the device should dictate the control processes required to ensure quality of test results, rather than fitting a device into a specific QC process.
- Laboratories should become familiar with risk management and the changing regulatory environment.