Objectives of This Presentation

• Define risk management.
• Compare the types of control processes.
• Examine the key points of CLSI document EP23-A, Laboratory Quality Control Based on Risk Management.

History

• 1990’s – Internal quality control (QC) processes being introduced. What is balance of internal and liquid QC?
• 2004 – Centers for Medicare and Medicaid services (CMS) introduces 3 options for equivalent QC (EQC). Scientific basis for EQC questioned
• EP23 developed as a rational approach to allow the laboratory director to develop a QC plan based on risk for their instrumentation and laboratory.
Risk Management

- Risk management is not a new concept, labs:
  - Evaluate the performance of new devices
  - Troubleshoot instrument problems
  - Respond to physician complaints
  - Estimate harm to a patient from incorrect results
  - Take actions to prevent errors
- Risk management is a formal term for what clinical laboratories are already doing every day.

Risk Management Definition

- Systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk (ISO 14971)

Risk Definition

- Risk – the chance of suffering or encountering harm or loss (Webster’s Dictionary and Thesaurus. Ashland, OH: Landall, Inc.; 1993.)
- Risk can be estimated through a combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).
- Risk essentially is the potential for an error to occur.
Risk Management Misnomers

- Risk management is not a means to reduce or eliminate QC!
- Risk management identifies hazards in a laboratory procedure and determines the appropriate control to reduce the risk to a clinically acceptable level.
- In some instances, liquid QC may be replaced with built-in control processes, and in other cases, increased frequency of liquid QC or other control processes may be necessary.

Process Map

- Outlines the analytical process

- Preexamination (Preanalytic) → Examination (Analytic) → Postexamination (Postanalytic)
Some Sources of Laboratory Error

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

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

• Analysis:
  – Calibration factor incorrect
  – Mechanical failure

Fishbone Diagram

Historical Quality Control

• QC historically documents stability of an analytical system (environment, operator, and analyzer).

• 1950s industrial model of quality

• Analyze a surrogate sample (a control) containing known amount of measured analyte.

• If the analytical system recovers the target result using the control, then the system is stable and quality patient results are being produced
Quality Control and Systematic Errors

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

Quality Control and Random Errors

- Errors that affect individual samples in a random and unpredictable fashion, such as:
  - Clots
  - Bubbles
  - Interfering substances
- Surrogate sample QC does a poor job of detecting random errors.

Quality Control

- Advantages
  - QC monitors the end product (result).
  - QC has target values: if assay recovers target, then assumed stable (instrument, reagent, operator, sample)
- Disadvantages
  - When problem detected, must go back and reanalyze patients since last “good” QC
  - If results released, results may need to be corrected
- Need to get to fully automated analyzers that eliminate errors up front.
  - Until that time, need a robust QC plan (QCP)
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
• Other types of QC – control processes either engineered by a manufacturer or enacted by a laboratory to ensure result reliability

Manufacturer Checks

• Some devices have internal checks that are performed automatically with every specimen:
  – Development of a line (pregnancy test, occult blood)
  – Sensor signal (blood gas analyzer, protein build-up, clots)
  – Flow resistance and liquid sensors (clots or bubbles)
• Other checks engineered into device:
  – Temperature indicator in shipping carton
  – Barcoding of reagent expiration dates (prevents use)
  – QC lockout features
  – Disposable analyzer cuvettes/pipette tips (carryover)
Quality Control Limitations

• No single QC procedure can cover all devices, because devices may differ.
• QC practices developed over the years have provided laboratories with some degree that results are valid.
• Newer devices have built-in electronic controls, and "on-board" chemical and biological controls.
• QC information from the manufacturer increases the user’s understanding of devices overall quality assurance requirements.


Laboratory-Manufacturer Partnership

• Laboratory directors have ultimate responsibility for determining appropriate QC procedures for their laboratories.
• Manufacturers of in vitro diagnostic devices have responsibility for providing adequate information about the performance of devices, the means to control risks, and the verification of performance within specification.
• In practice, QC is a shared responsibility of manufacturers and users of devices.


Laboratory-Manufacturer Partnership

• Developing a quality plan surrounding a laboratory 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 take action, like analyze surrogate sample QC on receipt of new lots of reagents.
• Clear communication of potential sources of error and delineation of laboratory and manufacturer roles for how to detect and prevent those risks is necessary.
CLSI Document EP23

- **Laboratory Quality Control Based on Risk Management**
- James H. Nichols, PhD, DABCC, FACB, Chairholder of the document development committee
- EP23 describes good laboratory practice for developing a QCP based on manufacturer’s risk mitigation information, applicable regulatory and accreditation requirements, and the individual health care and laboratory setting.

---

### Laboratory Quality Control Based on Risk Management

![Diagram of Laboratory Quality Control Based on Risk Management]

**MEASURING SYSTEM INFORMATION**
- Medical Requirements for the Test Results
- Regulatory and Accreditation Requirements
- Measuring System Information Provided by the Manufacturer
- Information About Health Care and Test Site Setting

**PROCESSES**
- Risk Assessment
- Quality Control Plan
- Postimplementation Monitoring

**OUTPUT**

---

### EP23 Risk Assessment

**Risk Assessment**

- Identify the risk(s) and the level of importance of each risk
- Identify the potential effect of the risk(s)
- Develop a control strategy for each risk
- Implement the control strategy
- Monitor the control strategy

**Risk Evaluation**

- Evaluate the risk using a risk assessment matrix
- Determine the likelihood and impact of the risk
- Assign a risk priority number (RPN)
- Prioritize the risks

**Risk Mitigation**

- Implement risk mitigation strategies
- Document the implementation of the risk mitigation strategies
- Monitor the effectiveness of the risk mitigation strategies
- Review and update the risk assessment and mitigation strategies as needed

---

---
Risk Example for a Simple Device

- Simple, single-use lateral flow pregnancy test
- One year expiration, room temperature storage
- Concern #1 of test degradation due to shipping — Temperature exposure
- Concern #2 of test degradation during storage — Refrigeration 4 – 10°C recommended
- Manufacturer has built-in control process, a separate antigen/antibody (Ag-Ab) reaction from hCG — If test degraded, the control line will not develop.

hCG Risk Example
Reagent Degradation During Shipping

- Exposed to temperature during shipment
- Can’t confirm how long and at what temperature tests may degrade
- Internal QC process may not be as sensitive to temperature as hCG test reaction
- Analyzing surrogate QC with arrival of each shipment confirms reagent viability
- Event driven QC — with each shipment

<table>
<thead>
<tr>
<th>Targeted Failure Mode (Hazard)</th>
<th>Measuring System Feature or Recommended Action</th>
<th>Known Limitations of Feature or Recommended Action</th>
<th>Control Process Effective?</th>
<th>The QCP Actions Required to Address Known Limitations</th>
<th>Residual Risk Acceptable?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect results due to reagent degradation during shipment</td>
<td>Built-in control process. Separate Ag-Ab reaction exposed to same conditions as hCG Ag-Ab reaction forms 2nd line on test.</td>
<td>Control reaction may not be as sensitive to temp as hCG reaction (more robust than hCG Ab).</td>
<td>Partial</td>
<td><strong>Yes</strong></td>
<td></td>
</tr>
</tbody>
</table>
hCG Risk Example
Reagent Degradation During Storage

- Manufacturer requires test stored refrigerated temp range
- Residual risk of staff failing to monitor and record temperature, or take action when out of range
  - Probability of harm from failing to record temperature and not taking action (once a year) = occasional
  - Severity of harm – serious – could lead to fetal harm if patient is pregnant and test is compromised (false negative) = serious
  - Residual risk = clinically acceptable
- QCP: Monitor internal control line with each test AND monitor/record storage temperature

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 medical intervention
  - Critical = Permanent impairment or life-threatening injury
  - Catastrophic = Results in patient death

Sources for Risk Estimation

- Medical literature
- Health hazard evaluations
- Adverse event reports
- Medical judgment
- Additional resources
  - Historical failure data;
  - Method evaluation/verification data
  - Reliability estimates
  - Site environmental assessments
  - QC and proficiency testing information
  - Failure rejection experiments
  - Failure simulations
**Risk Acceptability Matrix**

<table>
<thead>
<tr>
<th>Severity of Harm</th>
<th>Probability of Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negligible</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Minor</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Serious</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Critical</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Catastrophic</td>
<td>Unacceptable</td>
</tr>
</tbody>
</table>

**hCG Risk Example**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect results due to reagent degradation during shipment</td>
<td>Built-in control process. Separate Ag-Ab reaction exposed to same conditions as hCG.</td>
<td>Control reaction may not be as sensitive to temp as hCG reaction (more robust than hCG Ab).</td>
<td>Partial</td>
<td>Monitor storage conditions (keep kits within suggested range).</td>
<td>Yes</td>
<td>Unacceptable</td>
</tr>
</tbody>
</table>

**hCG Example: Partial Quality Control Plan**

- Analyze surrogate QC with arrival of each shipment confirms reagent viability
- Monitor/record storage temperature
- Monitor internal control line with each test
- Plus any additional control processes determined by laboratory’s hazard identification and risk assessment
**hCG Risk Example**

- If manufacturer and regulated QC processes provide clinically acceptable risk, no further controls may be necessary.
- If risk is unacceptable, then laboratory needs additional control processes to reduce risk.
- Storage conditions – Cost balance: refrigerated reagent quality depends on reliability of staff monitoring (continuous monitoring added expense)
- Reagent viability – verified by analyzing QC samples
  - Increase frequency of analysis to enhance assurance in reagent stability.

**Laboratory Risk Assessment**

- Medical application – QC sample frequency
  - Inpatient – acute care; rapid decisions without time for follow-up require more frequent QC sample analysis
  - Outpatient – may be confirmed against symptoms or other testing, may discharge patient before action occurs; time to confirm diagnosis may - require less frequent QC sample analysis
- Optimal mix of control processes dependent on Laboratory Director, device, medical application of the test, and local regulations.

**hCG Risk Example**

**QCP Implementation**

- No process is ever free of risk!
- Laboratory should benchmark quality (continued errors in face of QCP)
- Determine source of continued errors and modify QCP as needed
  - New hazard not identified in risk assessment
  - Increase frequency – higher occurrence
  - Increased harm – more severity than estimated
  - Detection control process not as effective
hCG Risk Example
QCP Implementation

- Risk Management is subjective, but can be made very quantitative with better information
- Weak risk assessment in developing a QCP will be evident - continued errors after implementation
- More time developing a QCP can be predicted to present with fewer errors after implementation
- Can never get to zero risk, simply a level that is clinically acceptable for the test, clinical application and setting

Laboratory Quality Control Based on Risk Management

- Challenge is for laboratories to conduct risk assessment:
  - Risk = probability an event might occur that could cause harm to the patient (or lab tech)
  - Rank risks: occurrence x severity harm x detection
  - Risk mitigations selecting an effective combination of available control processes (eg, analyze liquid QC samples in conjunction with other control processes)

EP23 Outcomes

- Laboratories become aware of their own sources of error.
  - Preexamination, examination, postexamination
- Laboratories are alerted to conditions that could lead to patient or staff harm.
  - Facility design – heat, lack of space, power, environ.
  - Staff turnover
  - Immediacy of result application – rapid treatment
  - Operation of equipment by inexperienced staff
EP23 Outcomes

- Manufacturer/laboratory partnership
- Need for more information about risks and performance from the manufacturer
- Laboratories should request risk information from manufacturer if not readily available

EP23 Outcomes

- Design a QCP that is right for the test.
  - Based on:
    - Test performance and reliability
    - Number of patient samples tested and reported between QC events
    - Medical application of the test and laboratory
  - Some tests may require more frequent analysis of QC samples; others may require less QC.
    - Scientifically founded on objective evidence that supports the plan

Summary

- Risk management is something laboratories are already doing. EP23 simply formalizes this.
- A QCP is necessary for result quality and each QCP is unique.
- The QCP is scientifically based. It depends upon the extent to which the device’s features achieve their intended purpose in union with the laboratory’s expectation for ensuring quality results.
- Once implemented, the QCP is monitored for effectiveness and modified as needed to maintain risk to a clinically acceptable level.