Appropriate Quality Control for Diverse and Evolving Test Systems

Rhonda Whalen, M.S.
Chief, Laboratory Practice Standards Branch
Division of Public Health Partnerships
Laboratory Systems

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Background

CLIA Law

"The Secretary shall issue standards to assure consistent performance by laboratories… Such standards shall require each laboratory… to maintain a **quality assurance and quality control program adequate and appropriate for the validity and reliability of the laboratory examinations and other procedures of the laboratory …"**

1992 CLIA Regulations

- Based standards on test complexity
- Regardless of test complexity, specified laboratory director responsibility for quality testing, quality control (QC) procedures
- Through phase-in QC provisions, allowed previously unregulated laboratories time to become familiar with requirements
- Required laboratories to follow manufacturer's instructions for test performance
- Defined minimum QC requirements
- QC requirements divided into
  - General
  - Specialty/subspecialty

2003 CLIA Regulations

- Responded to public comments, CLIAC recommendations
- Ended phase-in QC requirements
- Re-formatted requirements to parallel specimen flow through laboratory
- Incorporated quality system concept throughout testing process (new subpart-Quality System)

2003 CLIA Regulations

- Created one set of non-waived requirements
  - General
  - Specialty/subspecialty
- In determining control procedures, clarified that director needs to consider environment (including patient population), test system, and personnel
- Continue to require laboratory to follow manufacturer's instructions for test performance

Current Status - Regulations and Guidance

Regulation	Guidance
• Establishes minimum requirements	• Provides examples of mechanisms to meet requirements
• One (or limited) size to fit all testing	• Clarifies applicability of requirements
• General requirements with broad application	• Specifies exceptions/alternatives to requirements
• Little flexibility	• Addresses new technology
• Requires rulemaking for revisions	• Requires agency clearance

Quality System Regulations – Analytic Phase

- Verification of performance specifications
- Calibration
- Calibration verification
- Control testing

Verification of Performance Specifications – Regulation

- Before reporting patient results, laboratory must verify test performance specifications for the following:
  - Accuracy
  - Precision
  - Test reportable range
  - Patient reference intervals (normal values)
- Based on verification of performance specifications, laboratory determines calibration and control procedures

Verification of Performance Specifications – Guidance Needed

- To assure flexibility, there is no specific guidance as to:
  - Number of assays to perform
  - How many materials to use
  - Time period for evaluations
  - Acceptability criteria
- May need to clarify minimum acceptable procedures for laboratory verification of performance specifications
- Could manufacturers recommend procedures for laboratory to follow?

Calibration – Regulation

Perform calibration

- Following manufacturer's instructions
  - Using calibration materials provided or specified
  - At the frequency recommended by the manufacturer
- Using criteria determined by the laboratory through verification of performance specifications
- If possible, calibration material should be traceable to a reference method or reference material of known value

Calibration – Generally Manufacturer Defined

- Initial calibration may be factory performed
- Manufacturer may define laboratory calibration/re-calibration frequency in labeling
- Number, type, concentration, acceptable limits of calibration materials, and frequency should be included in labeling

Calibration Verification – Regulation

- Must include at minimum three calibrators: a zero, a midpoint, and a maximum value near the upper end of the laboratory's reportable range.
- Must be performed, at a minimum, every 6 months or whenever
  - A change of reagents occurs
  - Major maintenance or critical test system component changes occur
  - Laboratory detects trends or shifts in test values
  - Laboratory determines more frequent verification is needed

Calibration Verification – Guidance Needed

- Should there be exceptions to 3 point calibration verification?
- Should calibration verification be required following major maintenance (e.g., electrode change, etc.)?
- Could the same material be used to calibrate and verify calibration (not currently acceptable)?

Control Procedures – Regulation

- Based on verification of test performance specifications, laboratory must establish the number, type, and frequency of testing control materials
- Laboratory is responsible for having control procedures that monitor accuracy and precision of the complete analytic process

Control Procedures – Regulation

- Control procedures must
  - Detect immediate errors due to
    - Test system failure
    - Adverse environmental conditions
    - Operator performance
  - Monitor over time accuracy/precision of test performance influenced by changes in
    - Test system performance
    - Environmental conditions
    - Operator variance

Control Testing – Regulation

- Test two controls of different concentrations
- Test control material in same manner as patient samples
- Same material may not be used to meet calibration and control requirements

Control Procedures – Guidance Needed

- Current guidelines specify alternative/equivalent quality control (EQC) procedures to accommodate stable test systems, test systems with built in QC
- Need additional guidance for alternative control procedures
- Consider exception for testing control(s) in same manner as patient samples (e.g., blood gases)

Dilemma

ALL TEST SYSTEMS, LABORATORIES (TESTING CONDITIONS) ARE NOT THE SAME

QC Regulations – General

- Typically applicable to all test systems with little flexibility to address new, evolving technologies
- Cannot specifically address individual test systems/methodologies
- Not always practical/appropriate
- QC materials sometimes not available
- Inconsistent application to similar test systems in different specialties

QC Regulations – Specialty/subspecialty

- Laboratory specialties/subspecialties no longer distinct/clear-cut
- A single instrument may include tests for
  - Coagulation/Chemistry
  - Blood gases/Chemistry/Microbiology
  - Molecular testing/Chemistry/Microbiology
  - Cytology/Chemistry

Problematic Test Systems

- Unitized test systems
- Test systems that incorporate multiple components or reactions
  - Immunohematology antibody screening panels
  - Allergen-specific IgE tests
  - Genetic testing micro-arrays
  - Microbiology identification systems

Manufacturers' Instructions

- CLIA requires laboratories to follow manufacturers' instructions
- Manufacturers' instructions need to identify components monitored/checked by built in QC
- Instructions for some test systems
  - Provide insufficient information
  - Are ambiguous
- QC information is
  - Not explicit or conflicting
  - Located throughout product literature

Need For Uniform Process

- Currently, exceptions for checking methodology/reagents are based on data collection/evaluation strategies
- Data collection may not be feasible for rapidly expanding new technologies
- Uniform approach/process needed to
  - Determine applicability of QC requirements
  - Assist laboratories in reasonably/appropriately complying with CLIA requirements

Considerations

Control Procedures

- Overall QC scheme would need to consider
  - Built-in or inherent or inherent QC checks (electronic QC, procedural QC) included in test system
  - Other checks/balances in the testing process
  - Test is part of a testing algorithm
  - Testing environment
  - Knowledge and skills of testing personnel

QC Materials / Mechanisms

- What test components must be monitored by QC?
- To what extent can QC be manufactured into the test/device?
- If test systems incorporate multiple components or reactions in a single device format, is QC for each component necessary?
- What type of controls are appropriate to verify accuracy and precision?
  - Electronic/built-in checks/procedural
  - Liquid
  - Other

QC Frequency

- How much QC is necessary to assure patient safety?
- At what frequency should these controls be tested?
- If other processes are employed
  - Would traditional controls need to be tested?
  - At what frequency?

Alternatives

- Would focusing only on vulnerable areas of testing (using risk analysis) be sufficient in determining appropriate QC?
- Could a network of laboratories using specific test systems collect data needed for the evaluation of QC alternatives?

Evidence-based Data

- On what basis should laboratories make decisions about their QC program?
- Would studies need to be conducted to collect performance data?
  - Manufacturer's responsibility - help provide initial data
  - Laboratory's responsibility – long term data collection
- Could a data template be developed?
  - Would need to describe all testing variables
    - Test system sources of error
    - Operator's skills and training
    - Environmental conditions
    - Patient population

Responsibility for Data Evaluation

- Who would complete the template?
- Who would review and evaluate the template data?
- Could these responsibilities be shared by
  - Industry
  - Laboratory/professional organizations
  - Government
  - Partnership (industry/laboratory community/government)?

Last Thoughts

QC Protocols

- Need to balance flexibility while adhering to accepted standards of quality practice
- Traditional QC and alternative QC schemes need to coexist
  - CLIA applies to all laboratory testing sites
  - CLIA needs to accommodate existing and diverse technologies, as well as evolving methodologies
  - New rulemaking unlikely