QUALITY ASSURANCE ISSUES IN THE TB LAB

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Outline

- Test method validation/verification
  - FDA-cleared & approved; modified; LDTs
    - Non-approved specimen types for FDA-cleared tests
  - MALDI-TOF
- Individualized Quality Control Plan (IQCP)

Disclosures

- No relevant conflicts to disclose

Validation/Verification General Concepts

- Validation and verification terms often interchanged

	Verification	Validation
CLIA, CLSI	**One-time process** to demonstrate that test system performs according to specifications	**On-going** process; test continues to perform as per specifications (aka quality assurance)
CAP	**One-time process**; unmodified tests	**One-time process**; modified tests and LDTs

Validation/Verification General Concepts

- Val/Ver regulations pertain to a complete “test system”
- Under CLIA, laboratories must:
  - Verify performance characteristics of unmodified, FDA-cleared or approved test systems
  - Establish perf. characteristics of modified tests and laboratory-developed tests (LDTs)
- Most available guidance pertains to diagnostic tests. Less guidance on identification tests (e.g. MALDI-TOF) and antibiotic susceptibility testing

Validation/Verification Guidance

How are the final regulations being implemented?

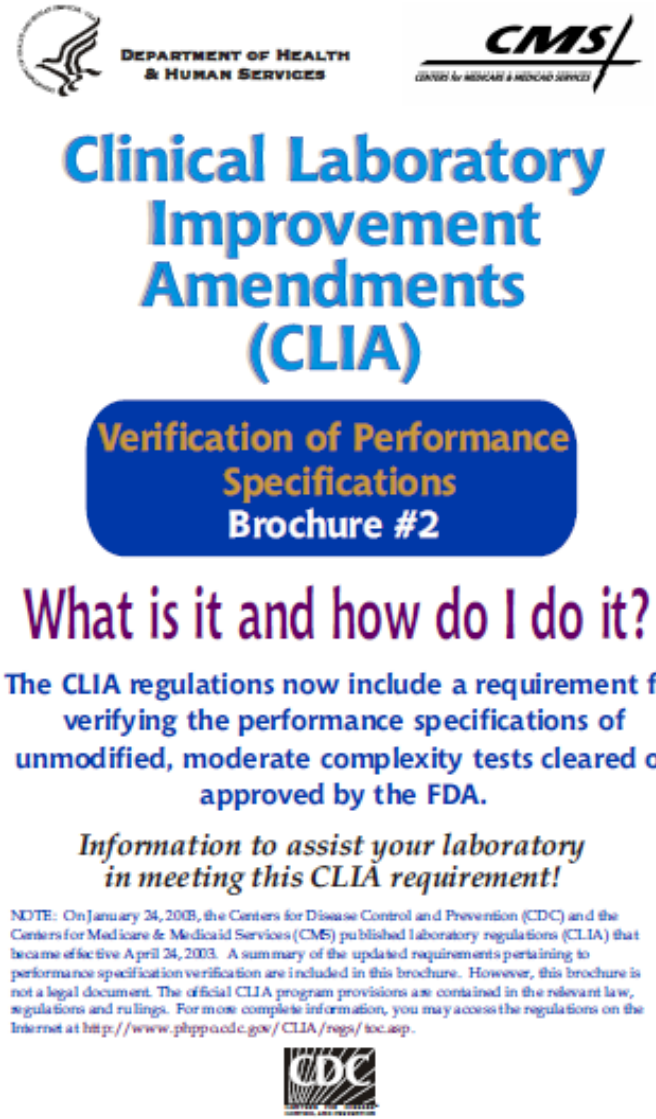
CMS is allowing each laboratory that it inspects to have one educational survey following the April 24, 2003, effective date of the regulations. This will give laboratories time (2 years) and the opportunity to receive the technical assistance that may be needed to meet the updated requirements.

Where can I find additional information and guidance?

Assistance for meeting the requirements is provided in Appendix C of the State Operations Manual (CMS Publication 7), which is posted on CMS's CLIA Website. Information about CLIA and links to other laboratory-related resources can be found on the following Websites:

CDC: www.phppo.cdc.gov/clia/default.asp
CMS: www.cms.hhs.gov/clia/default.asp
FDA: www.fda.gov/cdrh/CLIA/index.html (for a listing of waived, moderate complexity and high complexity tests)

http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Brochures.html



BACKGROUND

The CLIA Quality System Regulations became effective on April 24, 2003. Now the laboratory is required to check (verify) the manufacturer's performance specifications provided in the package insert--for accuracy, precision, reportable range, and reference ranges--for each new unmodified, moderate complexity test that the laboratory performs before reporting patient test results. The verification process helps to assure that the test, when used in your laboratory by your testing personnel for your patient population, is performing as the manufacturer intended.

This requirement applies when the laboratory **REPLACES** a test system or instrument (with the same model or a different model); **ADDS** a new test; or **CHANGES** the manufacturer of a test kit.

The requirement does not apply to tests performed by the laboratory before April 24, 2003.

TIP! ***While the laboratory's technical consultant or director should be involved in the planning and evaluation of the performance specification checks, the test system manufacturer may also assist by providing a verification protocol and appropriate samples for the evaluation.***

ACCURACY

Are your test results correct?

The laboratory needs to compare the accuracy of the test results it obtains when using a test system with the manufacturer's accuracy claims. This can be done by testing commercially available calibrators/calibration and quality control materials with known values, proficiency testing materials that have established values, and previously tested patient specimens with established values. If test results for these samples fall within the manufacturer's stated acceptable limits, accuracy is verified.

PRECISION

Can you obtain the same test result time after time?

The laboratory is responsible for verifying that it can repeatedly test the same samples on the same day, and on different days and get the same or comparable results (reproducible), regardless of which member of the laboratory's testing personnel performs the test (operator variance). Several of the laboratory's testing personnel should participate in this evaluation to help determine overall laboratory variance. Exception: For fully automated test systems that are not operator dependent, operator variance should not affect the test's precision and may not need to be evaluated by more than one person.

REPORTABLE RANGE

How high and how low can test result values be and still be accurate?

To verify the manufacturer's established reportable range for the test, choose samples with known values at the highest and lowest levels the manufacturer claims accurate results can be produced by the test system. The laboratory may only report patient test results that fall within the verified levels. The laboratory director and/or the technical consultant will need to decide how the laboratory will report results that are greater than the highest verified level or less than the lowest verified level.

REFERENCE RANGES/INTERVALS (NORMAL VALUES)

Do the reference ranges provided by the test system's manufacturer fit your patient population?

You may begin patient testing using the manufacturer's suggested reference range(s) or you may use other published reference ranges from a textbook or a journal publication. Reference ranges can vary based on the type of patient (e.g., pediatric, male, female). Over time, you may need to adjust your reference range(s) to better fit the patient population(s) you routinely test. When you test known normal patients, the results should be within your reference range and with abnormal patients, you should expect results outside the reference range.

How many samples do I need to test?

While testing 20 samples is considered the "rule of thumb" for statistical purposes, this is not a magic number. Depending on the test system and the laboratory's testing volume, the actual number of specimens needed for each part of the verification study may vary.

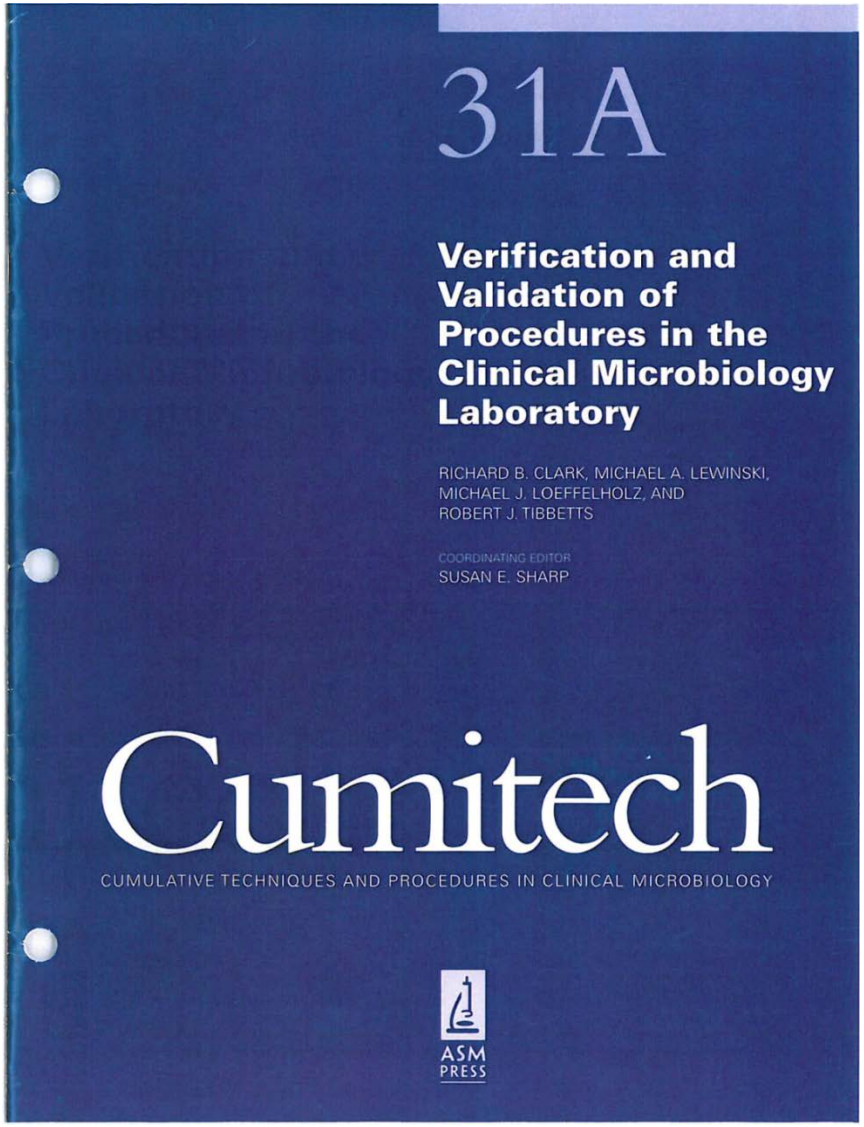
Once the laboratory director has reviewed and approved the results of the verification studies, the laboratory may begin using the test system for routine testing and reporting patient test results. Conversely, if the study results indicate that the test is not accurate or results cannot be consistently reproduced, the laboratory's technical consultant and the test system manufacturer should be consulted regarding steps to resolve the problem.

TIPS! ***With planning, verifying a test system's accuracy; precision, including operator variance; and reportable range may be performed using the same samples. For example, you may test samples with known values at the upper and lower end of the manufacturer's reportable range along with samples that are in the normal range for your patient population, in different runs, on different days, using several of the personnel who will normally perform the testing. The activities of the personnel verifying the test system will also facilitate meeting CLIA's personnel competency requirements for these employees. In addition, the laboratory director may use the verification process to meet the CLIA requirements for establishing the test system's quality control protocol, an essential component of the laboratory's overall quality system.***

Where can I find additional information about the CLIA requirements pertaining to the verification of performance specifications?

You may refer to the State Operations Manual, Appendix C-Interpretive Guidelines, §493.1253, available on the CMS website at: www.cms.hhs.gov/clia.

Validation/Verification Guidance



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Validation/Verification Guidance

- Clinical and Laboratory Standards Institute (CLSI)
  - MM03-ED3; *Molecular Diagnostic Methods for Infectious Diseases, 3rd Edition*
  - MM17A; *Verification and Validation of Multiplex Nucleic Acid Assays; Approved Guideline*
  - EP12-A2; *User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline - Second Edition*

Validation/Verification Standards

- CLIA 493.1253. Establishment and verification of performance characteristics
- College of American Pathologists
  - All Common Checklist
  - Microbiology Checklist, Molecular Microbiology section

Verification of FDA-Cleared Tests

- Demonstrating that your laboratory can reproduce results claimed by manufacturer
- Extensive clinical trial data already exist
- Verification requirements
  - Accuracy (method produces correct results)
  - Reproducibility (method produces correct results inter-run, intra-run, inter-operator)
  - Reportable range (method produces correct positive results over a range of analyte)
  - Reference range (cutoff or normal range is appropriate for your lab's patient population; or samples lacking analyte produce negative result)

Verification of Modified Tests and LDTs

- Accuracy, reproducibility, reportable and reference ranges
- Plus,
  - Analytical sensitivity (limit of detection)
  - Analytical specificity & interfering substances
  - Others, as required

Examples of Test Modifications

- Pre-analytical
  - Additional sample type (e.g. Xpert MTB/RIF assay on non-pulmonary specimens, IGRA on non-blood specimens)
  - Different patient population (e.g. Xpert MTB/RIF assay on pediatric patients)
- Analytical
  - Eliminating or changing sample extraction step
  - Different extraction or amplification platform
- Post-analytical
  - Adjusted cutoff (e.g. TB antigen or control cutoff for IGRA/adjusting IGRA indeterminate range)
  - Different intended use
- Confused if a procedure or use is a modification? Check the manufacturer's package insert!

Verification of MALDI-TOF

- MALDI-TOF is an identification test
  - Accurate and reproducible identifications
  - Reportable and reference ranges do not apply
- Standards/guidance on identification tests is limited
  - ASM Cumitech 31A. *"Verification of automated, multi-analyte test systems for identification…to the species level should be conducted with a minimum of 20 isolates representing a wide range of clinically relevant organisms…"* (e.g. biochemical panels)
    - MALDI-TOF is more comprehensive.
- FDA-cleared database
  - Suggest ~20 isolates total (each) GN, GP, anaerobes, yeast, etc.
- Non-FDA-cleared database (e.g. mycobacteria)
  - Suggest ~20 isolates total for each species?

Verification of MALDI-TOF

- Reproducibility
  - Select several isolates to repeat on different days (subcultures), runs, operators
- Using media not specified by MALDI manufacturer is off-label. Requires establishment of performance.

Ongoing Validation, aka Quality Assurance

- Personnel competency assessment and training
- Proficiency testing
- Quality control
- Instrument maintenance
  - Comparison of multiples
  - Calibration
- Review of historical data (+’ve rates)
- Complaint investigations

Quality Control

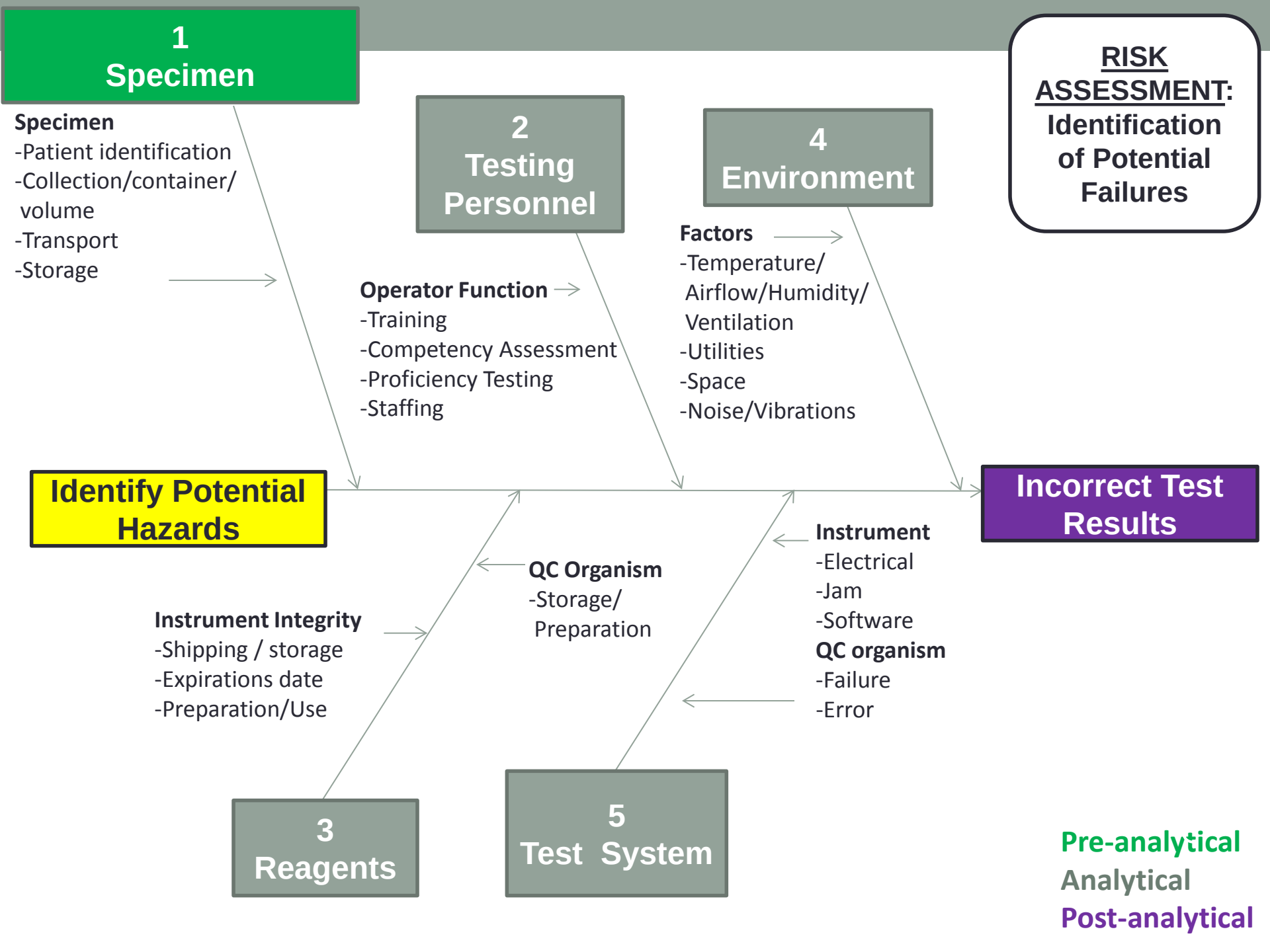
- Equivalent QC Procedures
  - Reduced testing frequency of external QC materials, if test system includes internal monitoring system (internal control)
- Eq QC to be replaced by Individualized Quality Control Plan (IQCP) in January 2016
  - IQCP is Eq QC plus individualized risk assessment for each test system. CLSI, CAP, ASM are developing guidance

IQCP Components

- Risk assessment
  - Collect data. Note areas where errors could occur (pre-analytical, analytical, post-analytical)
  - Assess frequency of errors and potential harm
- Quality control plan
  - Define control mechanisms in place to detect and prevent errors
  - Define QC and acceptability criteria
- Quality assessment
  - Monitor and ensure effectiveness of QCP

IQCP—Risk Assessment

- Identify risks (sources of potential failures and errors associated with test system
  - Risk assessment components
    - Specimen (collection, labeling, transport, storage, etc.)
    - Test system (instruments, controls, reporting, etc.)
    - Reagents (shipping, storage, preparation, etc.)
    - Environment (temp, humidity, etc.)
    - Testing personnel (training, competency, etc.)
  - Evaluate the frequency of those failures/errors
  - Evaluate impact (harm) due to failures/errors
- Resulting “Risk Assessment” is used to develop QCP (how to control for the risks)


1
Specimen
2
Testing
Personnel
4
Environment
RISK ASSESSMENT:
Identification of Potential Failures
Specimen
-Patient identification
-Collection/container/ volume
-Transport
-Storage
Operator Function
-Training
-Competency Assessment
-Proficiency Testing
-Staffing
Factors
-Temperature/ Airflow/Humidity/ Ventilation
-Utilities
-Space
-Noise/Vibrations
Identify Potential Hazards
Incorrect Test Results
QC Organism
-Storage/ Preparation
Instrument
-Electrical
-Jam
-Software
QC organism
-Failure
-Error
Instrument Integrity
-Shipping / storage
-Expirations date
-Preparation/Use
3
Reagents
5
Test System
Pre-analytical
Analytical
Post-analytical

Risk Evaluation

Frequency

- Unlikely (1/2-3 yrs)
- Occasional (1/mo-yr)
- Frequent (1/wk)

Impact

- Negligible (temporary discomfort)
- Minor (temporary injury; not requiring medical intervention)
- Critical (permanent impairment requiring medical intervention)

IQCP—Quality Control Plan

- Document that describes process to control the quality of test system
  - All phases of testing
  - Monitor accuracy and precision of test performance
  - Number, type, frequency of QC
  - Criteria for acceptability of QC

Example QCP

- Build tables to include risks identified in fishbone diagram
- Determine probability of occurrence and severity of harm for each risk
- Identify measures to reduce risks/errors (where are these measures found in procedures, logs, etc?)

Reagents	Frequency	Severity of Harm	Measures to control risk	Relevant SOP
Shipping / Storage	Occasional	Minor – Critical	Reagents are shipped & stored according to manufacturer's instruc.	SOP.xxxx
Expiration dates	Occasional	Minor – Critical	Reagents are used within expiration dates.	SOP.xxxx
Preparation / Use	Occasional	Critical	All reagents prepared/used according to manufacturer's instructions.	SOP.xxxx
QC organism storage/prep	Occasional	Minor – Critical	Results for all QC organisms are within acceptable limits.	SOP.xxxx

IQCP—Quality Assessment

- Establish system for ongoing monitoring of effectiveness of QCP
  - Includes all 5 Risk Assessment components (specimens, test system, reagents, environment, testing personnel)
- When test process failure/error occurs
  - Conduct and document investigation to identify cause
  - Determine impact
  - Make appropriate modifications to QCP

IQCP—Quality Assessment

- All instrument or QC organism failures will be brought to attention of the supervisor/designee for investigation (see SOP.xxxx)
- Documented review of QC will be performed to see that QC is accurately performed and documented (see SOP.xxxx)
- Remediation of QC failures is addressed in SOP.xxxx
- Remediation of PT failures is addressed in SOP.xxxx
- Reporting errors are investigated timely (see SOP.xxxx)
- For all QC/PT failures, laboratory reporting errors, complaints, etc., a reassessment of risk will be performed and adjustments made to the QCP as necessary. The reason for failure will be identified and addressed in a new/updated risk assessment answering the following:
  - Has a new hazard been identified?
  - Does this hazard change the frequency of risk?
  - Does this hazard change the severity of harm?
- Additional control measures will be implemented if necessary as determined by the new risk assessment.

IQCP Example

- Based on our
  - Risk assessment
  - QC program
  - Overall QA program
    - Specimen handling/storage, competency assessment, PT, QC, Environment monitoring, reagent labelling/storage, Instrument PM, QC/instrument failure investigation, Unexpected error investigation, reporting errors, complaint investigation…
- The QCP for our “xyz” test system will consist of following the instructions in SOP.xxxx and recording results on QC-FORM.xxxx
- QC will consist of:
  - Testing [XX] controls per lot/shipment before or concurrently with placing these materials into service
  - [Enter a Time Frame: Weekly, bi-weekly, monthly….] testing [XX] controls
  - Testing [XX] controls after each major system maintenance or soft ware upgrade before or concurrently with placing the instrument back into service
- QC acceptability criteria defined in SOP.xxxx

pre-analytical
analytical
post-analytical

IQCP Questions?

- CMS: http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Individualized_Quality_Control_Plan_IQCP.html
- ASM: Clin Micro Portal → Lab Management

http://clinmicro.asm.org/index.php/lab-management/laboratory-management/445-iqcp-iqcp

- Step-by-step guideline for developing an IQCP at: http://wwwn.cdc.gov/CLIA/Resources/IQCP/

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