OneLab
A Unified Response to Training Needs

The Life of a Test Method: Validation, Verification, and Managing Quality

Presented by Rex Astles

June 30, 2021

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Agenda

- Introduction
  - Today's Presenters
  - New OneLab-relevant Resources
- Life of a Test Method: Validation, Verification, and Managing Quality
- Q&A
- Upcoming Events

Presenters

Triona Henderson-Samuel, MD

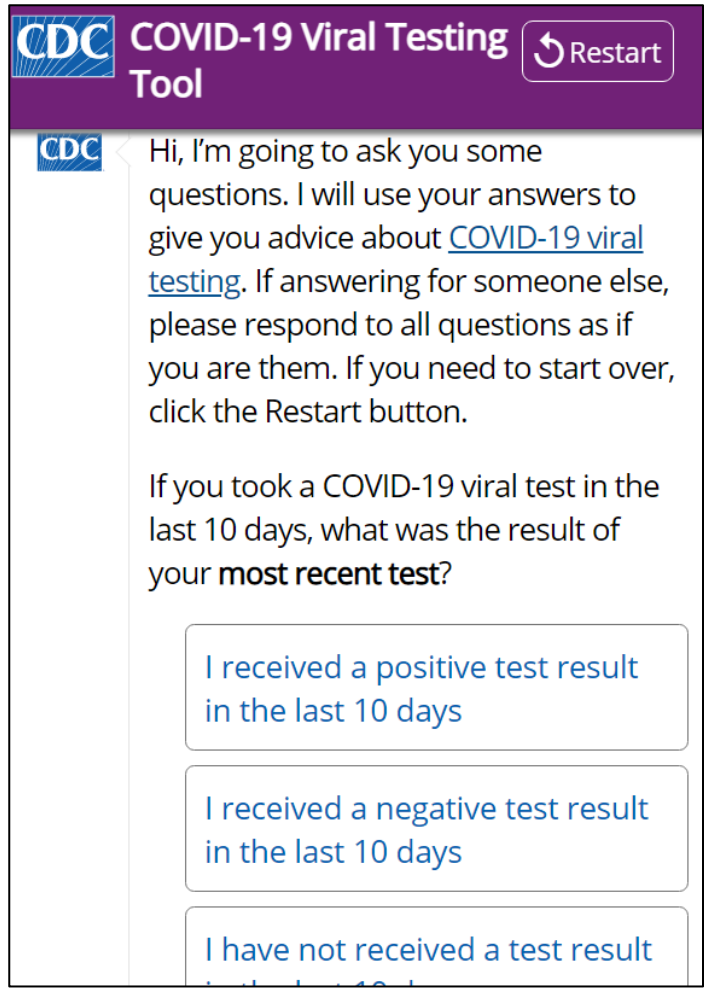
Physician (Public Health, Clinical Pathology)
Training and Workforce Development Branch, DLS, Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), CDC

Rex Astles, Ph.D

Health Scientist
Informatics and Data Science Branch, DLS, Center for Surveillance, Epidemiology, and Laboratory Services (CSLES), CDC

New Resource: COVID-19 Viral Testing Tool

- Provides clinical decision support to help determine what type of COVID-19 (caused by SARS-CoV-2) testing should be performed.
- Healthcare providers can use this tool to access information and aid in making decisions about next steps.
- Individuals can use this tool to determine what type of test to get, or determine the appropriate next step(s), if any, based on a test result
- Located on the COVID-19 Testing Page



New Resource: Clinical Laboratory COVID-19 Response (CLCR) Calls Update on Activities for SARS-CoV-2 Variant Surveillance

- Recording and slides from 6/14 will be posted to the CLCR call website
- Presentation of current prevalence of SARS-CoV-2 by regions and lineages – these are updated every Tuesday afternoon
- Tim Stenzel from the Food and Drug Administration answered questions regarding the effect of variants on testing validity and laboratory safety practices

Packing and Shipping Job Aid

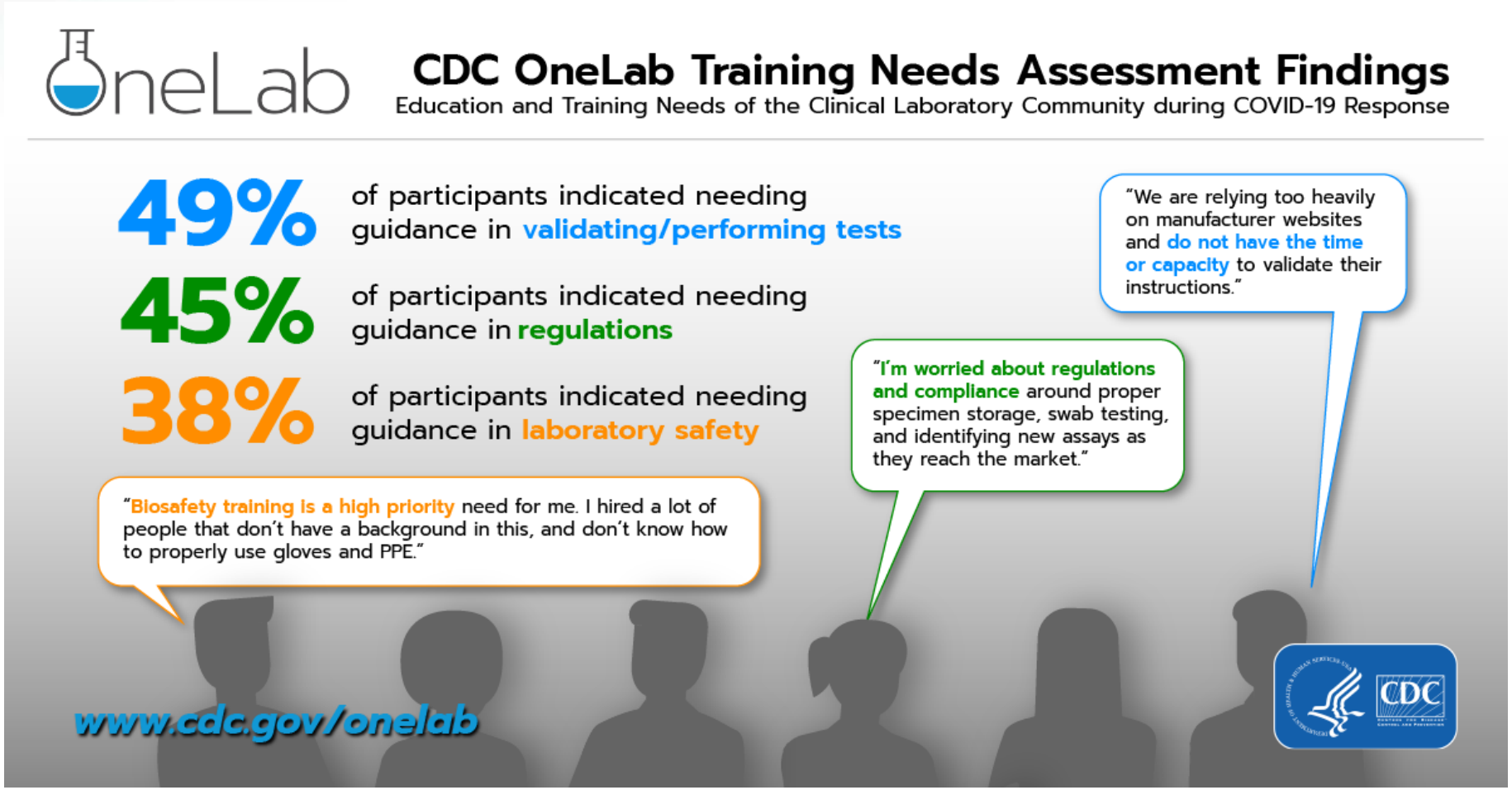
https://www.cdc.gov/coronavirus/2019-ncov/downloads/lab/COVID-19-Pack-and-Ship-Job-Aid-508.pdf

Quick reference guide for personnel trained to pack and ship suspected or confirmed SARS-CoV-2 specimens as UN 3373 Biological Substance, Category B

POLL QUESTIONS

LIFE OF A TEST METHOD - VALIDATION, VERIFICATION, AND MANAGING QUALITY

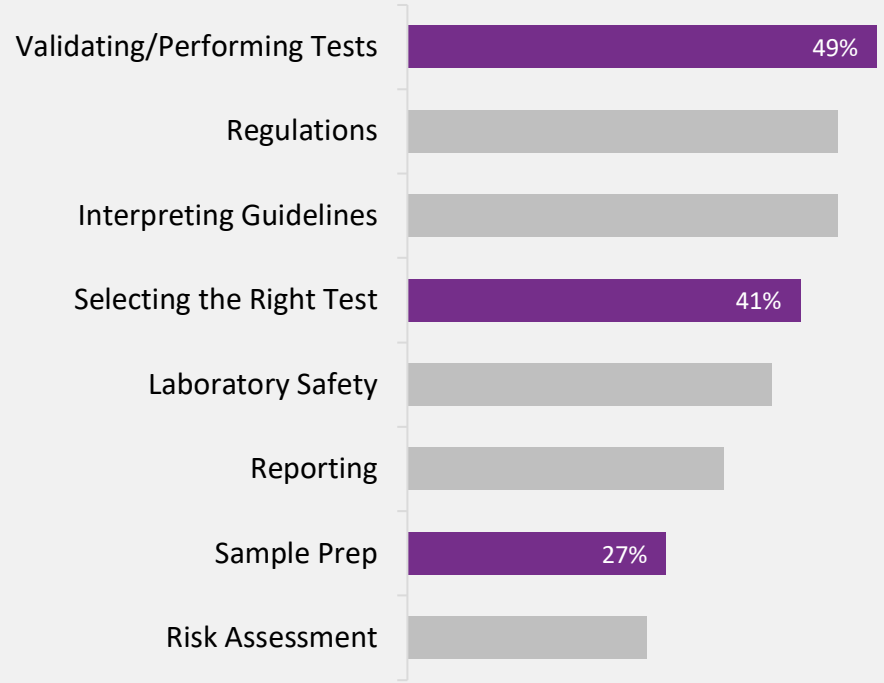
Laboratory Education and Training Needs



Laboratory Scientific and Technical Education and Training Needs

Clinical laboratory professionals are finding existing scientific and technical trainings regarding COVID-19 testing and laboratory quality to be insufficient and challenging to locate and access

Critical COVID-19 Related Education and Training Needs



"If we switch specimens or swabs that came with a kit, does it take us back to step one of the **validation process**?"

"We are **relying too heavily on manufacturer websites** and do not have the time or capacity to validate their instructions."

"[Our primary] challenges are understanding antibody and antigen testing. We don't have clarity – what is an **acceptable sensitivity** of these tests?"

"It would be great to have a virtual training for **sample collection**, which has a great influence on SARS-CoV-2 test results."

"LIFE OF A TEST METHOD: VALIDATION, VERIFICATION, AND MANAGING QUALITY”

REX ASTLES, PHD, DABCC, FAACC
DIVISION OF LABORATORY SYSTEMS

What is it?

- You have successfully implemented an assay that you recently purchased. You continue to perform quality control as required by the manufacturer and are performing all function checks. Is this ongoing process…
  - *validation* of acceptable performance
  - *verification* of adequate performance, or
  - *demonstration* of ongoing acceptable quality?

Background

- Purpose
  - Describe functions of the laboratory system when there is **not** a public health emergency
- Learning objectives
  - Describe the “test method life” model
  - Differentiate test method validation and verification
  - List instructional resources that explain the life of a test method

Outline

- Roles in the Laboratory System
- Complexity Model
- The “Test Method Life” Paradigm
- Important Terminology used by the FDA and CLIA
- Importance of “Instructions For Use”

Roles in the Laboratory System

Manufacturers

Federal agencies
CDC, CMS, FDA

Accreditation organizations
Approved by CMS

Exempt states

Professional organizations

Standard-setting organizations
CLSI, ISO

Clinical laboratories

Public health laboratories

Agency Roles – Food and Drug Administration (FDA)

- **Review** and may allow marketing of 3 main premarket submission types
  1. Waiver
  2. Premarket Notification (510(k))
  3. Premarket Approval Application (PMA)
- **Grant** waiver determinations
- **Categorize** diagnostic tests by their CLIA complexity

Agency Roles – Centers for Medicare & Medicaid Services (CMS)

- **Issue** laboratory certificates
- **Collect** fees
- **Conduct** inspections and enforce regulatory compliance
- **Approve** accreditation organization deemed status and state exemptions
- **Monitor** laboratory performance on proficiency testing (PT) and approve PT programs
- **Publish** Clinical Laboratory Improvement Amendments (CLIA) rules

Agency Roles – Centers for Disease Control and Prevention (CDC)

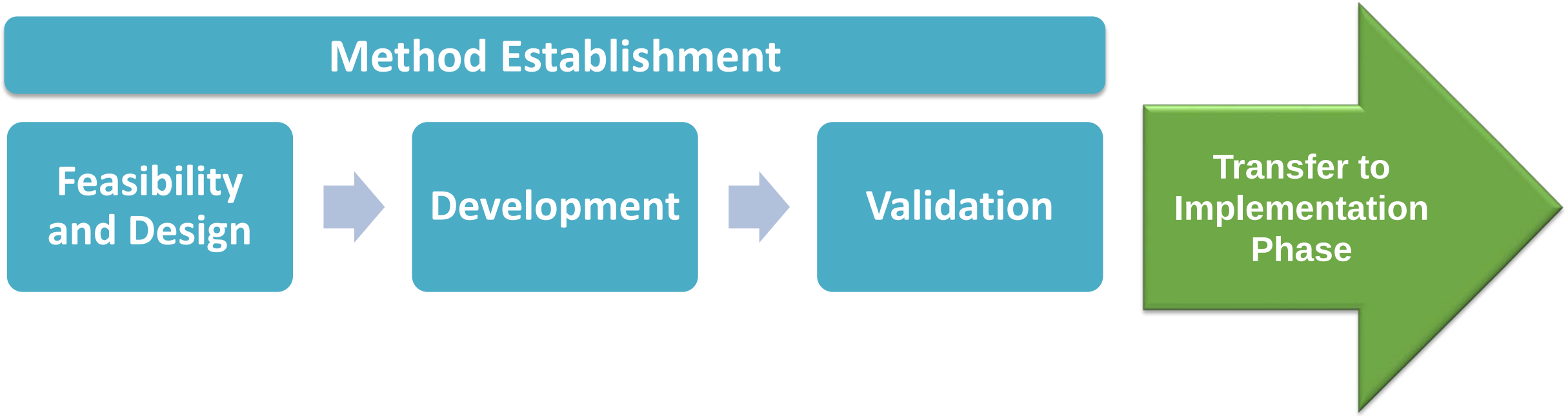
CDC's Division of Laboratory Systems

- **Develop/revise** technical standards in collaboration with CMS
- **Conduct** studies and provide technical consultation
- **Monitor** PT program performance
- **Manage** Clinical Laboratory Improvement Advisory Committee (CLIAC)
- **Develop/distribute** technical information and educational materials
- **Strengthen** partnerships with laboratory medicine stakeholders

CLIA Complexity Model

- **Laboratories with a CLIA Certificate of Waiver can only perform test methods determined to be waived by FDA**
  - No requirement for performance verification of waived test methods
- **Laboratories qualified to perform moderate complexity testing**
  - Must *verify* manufacturer's performance claims for moderate complexity test methods
  - Cannot perform high complexity test methods
  - Must have a technical consultant role
- **Laboratories qualified to perform high complexity testing**
  - Can perform all testing complexities
    - Including laboratory developed tests (LDTs) and modified commercial test methods. For these, performance must be established and verified.
  - Must have general supervisor and technical supervisor roles

Phases of the Test Method Life: Establishment



Manufacturers “Establish” Method Performance

- Feasibility and Design
- Development
- Validation
- With FDA approval, clearance or waiver, the test method can be marketed and ultimately, implemented by end-users

Note: When laboratories create LDTs or modify IVD test methods, they are acting as manufacturers, and they must establish acceptable performance is achieved.

Important Terms for Validation

- **Intended Use** – usage by the end user laboratory, as specified by the test method manufacturer, as originally designed and described in its instructions for use. It includes definition of the measurand, i.e., the analyte and specimen matrix, the target condition and clinical use, including whether it is for screening, diagnosis, prognosis or monitoring.

Important Terms for Validation

- **Target population** – specific population for which the test method was validated, possibly including patient age, sex, or occurrence of other medical conditions.

Important Terms for Validation

- **Detection capability** – ability to detect an analyte, including infectious agents, at very low concentrations. It is sometimes called “analytical sensitivity,” or simply “sensitivity,” but it should not be confused with clinical sensitivity. Refer to CLSI EP18 for related definitions of “Limit of Detection” and “Limit of Quantitation.”

Important Terms for Validation and Verification

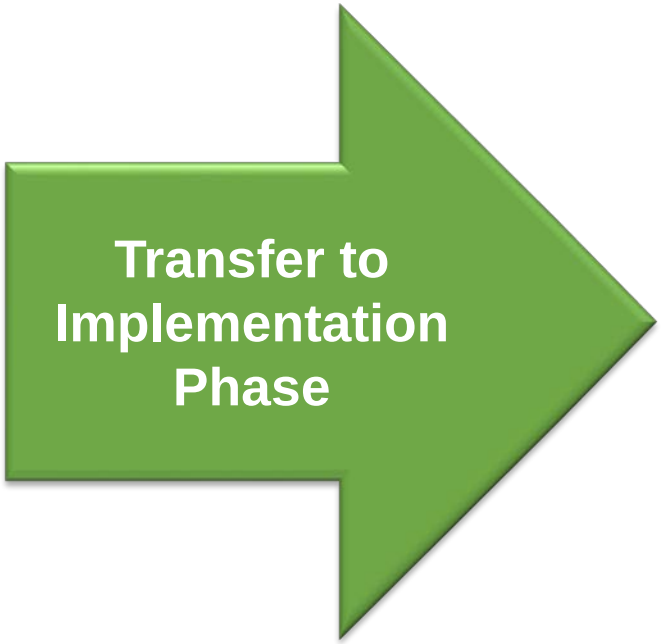
- **Performance claims** – The analytical and clinical characteristics of the test method, as validated and stated by the manufacturer.

CLIA Requirements for Establishment of Performance of a Test Method

CLIA requires that performance specifications must be **established** before performing patient testing §493.1253(b)(2)

- Accuracy
- Precision
- Analytical sensitivity, aka detection capability
- Analytical specificity
- Reportable range of test results
- Reference intervals
- Any other required performance characteristics
- There is no specific requirement in CLIA for clinical validation
- Requirements for reagent stability assessment are addressed through calibration verification and QC

Phases of the Test Method Life: Implementation



Method Implementation

Preliminary Evaluation → Verification → Launch → Method Maintenance → Method Retirement

Laboratories “Implement” Validated Methods

- Preliminary Evaluation
- Verification
- Launch
- Method Maintenance
- Method Retirement

CLIA Requirements Applicable to Implementation

Determination of calibration procedures and control procedures based upon performance specifications previously established or verified §493.1253(b)(3)

Appropriate control procedures (QC) §493.1256

- Monitor the accuracy and precision of the complete analytic process
- Establish the number, type, and frequency of QC testing
- Detect immediate errors due to test system failure, adverse environmental conditions, operator performance
- Monitor over time the accuracy and precision that may be influenced by the above three factors
- Adhere to requirements in §493.1256(d) for specific QC practices
  - Unless using Individualized Quality Control Procedure (IQCP)

CLIA Requirements for Verification

Verification of Test Performance is applicable to:

- unmodified, FDA-cleared or approved test system §493.1253(b)(1)

Demonstrate the laboratory can obtain performance specifications comparable to those established by the manufacturer

- Accuracy, Precision, Reportable range of test results §493.1253(b)(1)(i)(A-C)
- Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population §493.1253(b)(1)(ii)

CLIA Requirements for Verification

CLIA regulations <u>don't</u> specify that performance <u>previously established by a laboratory</u> must be verified, but CLSI EP19 recommends it.

No specific requirements in CLIA for verification of:

- Detection capability
- Performance of qualitative tests
  - *However, CLIA requirements apply for*:
    - Verification of Accuracy, Precision, Reportable range of test results §493.1253(b)(1)(i)(A-C)
    - Verification that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population §493.1253(b)(1)(ii), and
    - Determination of calibration procedures §493.1253(b)(3) and control procedures §493.1256 based upon performance specifications previously established or verified

Importance of “Instructions For Use”

In Vitro Diagnostic Device Labeling Requirements (FDA)

- The established and proprietary names of the product
- The intended use or uses, e.g., pregnancy detection
- Storage instructions – both reagents and specimen stability
- Limitations of the procedure
- Expected values including how the range(s) was established and identification of the populations on which it was established
- Specific performance characteristics as appropriate including accuracy, specificity, precision, and sensitivity

What if…?

What if you…

1) Modify a manufacturer's procedure (product insert)?
2) Want to use unauthorized reagents or materials?
3) Test for 'off-label' specimen type, target population, or diagnostic purpose?
4) Disregard instructions in the product insert including required QC or training?
5) Want to use a non-waived test in a Certificate of Waiver setting?

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  - *verification* of adequate performance, or
  - *demonstration* of ongoing acceptable quality?- CORRECT

Resources

CDC Division of Laboratory Systems

- Laboratory Training
- Laboratory Quality
- Ready? Set? Test? Booklet
- Clinical Laboratory Improvement Amendments (CLIA)
- Clinical Laboratory Improvement Advisory Committee (CLIAC)
- Laboratory Outreach Communication System (LOCS)

FDA

- Introduction to FDA's Regulation of Medical Devices
- FDA CLIA Test Database

CMS

- Clinical Laboratory Improvement Amendments (CLIA) Information

Electronic Code of Federal Regulations

- Part 493 – Laboratory Requirements (CLIA regulations)

Clinical and Laboratory Standards Institute (CLSI)

- EP19 "A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures"
- Help Validate and Verify Laboratory Developed Tests: Using EP19, A Framework for Using CLSI Documents (Webinar)
- Harmonized Terminology Database

Supplemental Table

Technical Requirements and CLSI Guidelines for Laboratory Test Method Life Phases
Updated June 2021 from presentation at the 2019 American Association for Clinical Chemistry Annual Meeting
"Using CLSI Guidelines to Meet quality requirements established by FDA, CLIA, and ISO throughout the Laboratory Test Method Life"

			REQUIREMENTS				CLSI GUIDELINES**
	Phases	**Activity**	**FDA QSR[1]**	**CLIA[2]**	**NYS[3]***	**ISO[4-8]**	
Establishment	**1. Feasibility and Design**		21 CFR 820.30		QMS FS; S1-S7 Director: DR FS; S1-S5 Human Resources: HR FS; S1-S10	**ISO 9001:2015** Clauses: 8.2.1, 8.2.2, 8.2.3, 8.3.1 through 8.3.6	General: EP12, QSRLDT Process Management: EP19, QMS13 Documents: QSRLDT, QMS02
	2. Development	General	820.30, 820.50, 820.181, 820.40, 820.60, 820.65		Facility: FD FS; S1-S3 Safety: LS FS; S1-S17 Resources: RM FS; GRM S1-S7 Equipment LEI S1-S9 Reagents: RGM S1-S5 QC S1	**ISO 9001:2015** Clauses 8.3.1 through 8.3.6 **ISO 13485:2016** Clauses 7.1 through 7.3	Facilities: QSRLDT Suppliers: QSRLDT, QMS21 Equipment: QSRLDT, QMS01, QMS13, AUTO08 Process Management: EP19, QMS18, QSRLDT, EP23, EP12 Documents: QMS13, QMS26, QSRLDT
		Risk Analysis, Evaluation, and Control		493.1253(b)(3) & c, 493.1256	QC S2	**ISO 14971:2019** **ISO 17025:2017** Clause 8.5 **ISO 22367:2020**	EP18, EP21
	3. Validation	General	820.30 820.75 820.86	493.1253(a), 493.1253(b)(2), 493.1253(b)(2)(vii), 493.1253(c), 493.1254(b)	Test Performance Specifications: TPS S2-S4	**ISO 13485:2016** Clauses 7.5, 7.6 **ISO 17025:2017** Clause 7.2.2 **ISO 15189:2012** Clauses 5.5.1.1, 5.5.1.3,	General: EP19, QMS18 Process Management: EP19, QMS18 Documents: QMS02, QMS26, QSRLDT Process Management: EP12 NCE Management: QSRLDT Assessment: QSRLDT

Thank you!

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Use of trade names is for identification only and does not imply endorsement by U.S. Centers for Disease Control and Prevention.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of Centers for Disease Control and Prevention.

Q&A

Note: There will be a future event focused on EUAs

July OneLab Network Event

OneLab Network: COVID-19 – Leading in Times of Crisis

Friday, July 16 | 1 to 2 PM EST

Presented by
Leslie Ann Dauphin, PhD

Director (acting)
Center for Surveillance, Epidemiology, and Laboratory Services
Centers for Disease Control and Prevention

Register