Recommended Quality Practices to move from LDT to Medical Device

Best Practices for LDT Companies with Assays Developed Under CLIA to Work Towards Medical Device

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Agenda

- LDT Definition
- 21 CFR §820 regulation compared to 42 CFR §493
  - Differences
  - Similarities
- Suggestions for compliance

What is a Laboratory Developed Test (LDT)?

- A Laboratory Developed Test is defined as a type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory.
- FDA first obtained comprehensive authority to regulate all in vitro diagnostics as devices in 1976.
- FDA has generally not enforced premarket review and other applicable FDA requirements because LDTs were relatively simple lab tests and available on a limited basis. While LDTs have increased in complexity, FDA continues to exercise enforcement discretion.
- LDTs are currently under CMS purview – CLIA regulations

Reference: Discussion Paper on LDTs, Jan 2017
https://www.fda.gov/media/102367/download

- You have a laboratory developed test, and now want to obtain FDA marketing authorization.
- What improvements are needed for your quality system?
- There are many similarities between the requirements, as well as some key differences.
  - FDA quality system requirements 21 CFR Part 820 vs. CLIA quality systems requirements 42 CFR Part 493*
- 21 CFR Parts 801, 803, 806, 807, 809 also need consideration

(*CLSI Quality System Regulation for Laboratory-Developed Tests: A Practical Guide for the Laboratory. CLSI document QSRLDT, 2015)

21 CFR Part 820: Quality System Regulation

Sets forth requirements for current Good Manufacturing Practice (cGMP) for Medical Devices.

- General Provisions
- Quality System Requirements
- Design Controls
- Purchasing Controls
- Identification and Traceability
- Production and Process Controls
- Nonconforming Product
- Corrective and Preventive Action
- Labeling and Packaging Control
- Handling Storage, Distribution and Installation
- Records
- Servicing
- Statistical Techniques

CLIA Regulation: 42CFR Part 493 (aka: CLIA ‘88)

- Sets Clinical Laboratory requirements including
  - Laboratory registration/certification
    - Fees as set by Health and Human Services (HHS)
- Spells out specific responsibilities, education and training requirements for
  - Testing personnel
  - Laboratory management

CLIA Regulation: 42CFR Part 493

- Subpart K - Laboratory Quality System for Nonwaived testing
  - **§ 493.1200 Introduction.**
  - (a) Each laboratory that performs nonwaived testing must establish and maintain written policies and procedures that implement and monitor a quality system for all phases of the total testing process (that is, preanalytic, analytic, and postanalytic) as well as general laboratory systems.
  - (b) The laboratory's quality systems must include a quality assessment component that ensures continuous improvement of the laboratory's performance and services through ongoing monitoring that identifies, evaluates and resolves problems.
  - (c) The various components of the laboratory's quality system are used to meet the requirements in this part and must be appropriate for the specialties and subspecialties of testing the laboratory performs, services it offers, and clients it serves.

42CFR Part 493: General Laboratory Systems 493.1230

Applies to all testing phases (preanalytic, analytic, postanalytic)

- Patient Confidentiality
- Specimen Identification/integrity
- Complaint Investigations
- Communications
- Personnel Competency Assessment
- Evaluation of Proficiency Testing performance
- Quality Assessment

42CFR Part 493: Preanalytic Systems: 493.1240

- Test Request
- Specimen collection, submission, handling and referral
- Quality assessment

42CFR Part 493: Analytic Systems: 493.1250

- Procedure manual
- Test systems, equipment, instruments, reagents, materials and supplies
- Establish or verify test system performance specifications
- Maintenance and function checks
- Calibration and calibration verification procedures
- Control procedures
- Comparison of test results
- Corrective actions
- Test records
- Quality assessment

42CFR Part 493:
Postanalytic Systems: 493.1290

- Test Report
- Quality Assessment

Key Differences

Quality Organization

No CLIA requirement for a Quality Policy, Management representative or Quality Planning.

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.0 Quality Systems	493.1200-1227 Quality System for Non-waived testing
820.20 Management Responsibility (b) Organization (1) Responsibility and authority	493.1445 Laboratory Director responsibilities 493.1451 Technical Supervisor responsibilities 493.1457 Clinical Consultant responsibilities 493.1495 Testing Personnel responsibilities
820.20 Management Responsibility (b) Organization (2) Resources	493.1200 Introduction (c) Components of the laboratory quality system
820.20 Management Responsibility (c) Management Review	493.1200 Introduction (b) Quality assessment component 493.1230 General Laboratory Systems 493.1239 General Laboratory Quality Assessment
820.20 Management Responsibility (d) Quality System Procedures	493.1200 Introduction (a) Written quality system policies and procedures

Design Controls

No specific CLIA regulation for design controls such as

- Design planning
- Design input
- Design output
- Design verification and validation
- Design Transfer
- Design changes
- Design history file
- Risk management

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.30 Design Controls	493.1241 Test Request 493.1242 Specimen submission, handling and referral 493.1252 Test systems, equipment, reagents, materials and supplies 493.1253 Establishment and verification of performance specifications 493.1290 Post-analytic systems 493.1291 Test Report

Documents and Records

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.40 Document Controls 820.70 Production and process controls (a)(1) Documented instructions, SOPs	493.1251 Procedure Manual
820.186 Quality system record	493.1231 Confidentiality of patient information
No requirement	493.1291 Test Report (a-i)
820.180 General requirements [Records]	493.1101 Facilities (e) Storage of Records 493.1105 Retention requirements 493.1291 Test Report (j) Reports and records maintained by the laboratory
820.181 Device master record	No requirement
820.184 Device history record	493.1283 Test Records

A Laboratory testing procedure might be considered equivalent to a Device master record as it outlines everything needed perform a test successfully.

Assessments

CLIA does not require inspection of the overall quality management system, but rather requires assessment of laboratory processes and systems.

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.22 Quality audit	No requirement
No requirement	493.551 General requirements for laboratories [Accreditation] 493.801-865 Participation in Proficiency Testing for laboratories performing non-waived testing 493.1236 Evaluation of proficiency testing performance 493.1239 General laboratory quality systems assessment 493.1249 Preanalytic systems quality assessment 493.1289 Analytic systems quality assessment 493.1299 Postanalytic systems quality assessment 493.1773 Basic (external) inspection requirements

Personnel

- 21CFR 820 requires personnel with the appropriate education, background, and training to perform tasks.
- CLIA sets minimum educational and training requirements for non-waived testing personnel as well as laboratory management.

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.25 Personnel	493.1235 Personnel competency assessment policies
820.72 Production and process controls (d) Personnel	493.1351-1495 Personnel responsibilities for non-waived testing

Purchasing and Inventory control

- Supplier qualification, approval and management of vendors is expected by as part of purchasing controls in 21CFR 820.50.
- CLIA has no specific requirement for approved vendors; rather most labs will qualify reagents and equipment based on testing needs. These qualifications are stored in the testing validation files.

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.50 Purchasing Controls	493.1252 Test system, equipment, instruments, reagents, materials and supplies (a) Test systems must be selected by the laboratory.
820.150 Storage	493.1252 Test system, equipment, instruments, reagents, materials and supplies (b) proper storage of reagents and specimens.

Similarities

Nonconforming Event Management

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.90 Nonconforming product	493.1239 General laboratory systems quality assessment (b) Review of the effectiveness of corrective actions
820.100 Corrective and preventive actions	493.1282 Corrective actions 493.1291 Test report (k) Errors in reported patient information
820.198 Complaint files	493.1233 Complaint investigations
No requirement *However, refer to 21CFR parts 803 and 806 for reporting requirements*	493.1234 Communications The laboratory must have a system in place to identify and document problems that occur as a result of a breakdown in communication between the laboratory and an authorized person who orders or receives test results.

Facilities and Safety

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.70 Production and process controls (c) Environmental Control	493.1101 Facilities (d) Safety procedures 493.1252 Test systems, equipment, instruments, reagents, materials and supplies (b) (1-4) Essential conditions
820.70 Production and process controls (e) Contamination control	493.1101 Facilities (a) (2) Contamination
820.70 Production and process controls (f) Buildings	493.1101 Facilities (a) (1) Space, ventilation and utilities

Equipment

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.70 Production and process controls (g) Equipment	493.1101 Facilities (b) Appropriate and sufficient equipment and materials 493.1254 Maintenance and function checks
820.70 Production and process controls (i) Automated processes	No requirement
820.72 Inspection, measuring and test equipment	493.1254 Maintenance and function checks

Process Management

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.60 Identification	493.1252 Test systems, equipment, instruments, reagents, materials and supplies
820.70 Traceability	493.1232 Specimen identification and integrity

Process Management

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.70 Production and process controls (a) General	493.1253 Establishment and verification of performance specifications (b)(3) Determination of calibration and control procedures 493.1256 Control procedures 493.1261-1278 Test system control procedures 493.1281 Comparison of test results
820.70 Production and process controls (b) Production and process changes	493.1521 Procedure manual (d) changes in procedures
820.70 Production and process controls (h) Manufacturing material	No requirement

Process Management

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.75 Process validation	493.1253 Establishment and verification of performance specifications 493.1256 Control procedures
820.80 Receiving, in-process and finished device acceptance	493.1242 Specimen submission, handling and referral (a)(7) Specimen acceptability and rejection
820.86 Acceptance testing	No requirement

CLIA 42CFR 493.1252 outlines requirements to ensure testing is performed according to manufacturer's instructions for use. For LDTs it’s important to determine and implement procedures for appropriate receiving, storage and use of reagents and equipment.

Process Management

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.120 Device labeling	493.1251 Procedure Manual (b)(1) Requirements for labeling [patient specimens]
820.130 Device packaging	No requirement
820.140 Handling	493.1242 Specimen submission, handling and referral
820.160 Distribution 820.170 Installation	493.1291 Test Report
820.200 Servicing	No requirement
820.250 Statistical techniques	493.1253 Establishment and verification of performance specifications 493.1256 Control procedures (d)(10)(i) Control materials providing quantitative results

Continuous Improvement

21CFR Part 820 (QSR regulation)	42CFR Part 493 (CLIA)
820.100 Corrective and preventive actions	493.1200 Introduction (b) Quality assessment component that ensures continuous improvement

So, what do you do?

- Gap analysis
  - What's missing from your quality system?
  - Plan to fill those gaps
    - Quality Management Procedures such as:
      - Design Control and Risk Management
      - Medical Device Reporting
      - Management Review
      - Updates to CAPA, Complaint
      - And more

Common Gaps

- No documented design control
- No documented risk assessment/management processes
- No SOP for medical device reporting
- Need to beef up
  - Management Review
  - Quality Audits
  - CAPA
  - Complaint investigation
  - Recall process
    - Corrected report vs. Recall
  - Medical Device Reporting process

Design Controls

- Clinical Laboratories don’t always document the design and development of a LDT, or documentation may be incomplete.
- It may be necessary to backfill design documentation, in particular
  - Design inputs
  - Design specifications
  - Verification/validation of design outputs
  - Design History File

Risk Management

- Risk evaluation and management is not mandated by CLIA regulations.
- FDA recognizes ISO 14971:2019 (Medical Devices – Application of risk management to medical devices)
  - For LDT, prepare to backfill risk analysis and management.
  - Review and document potential risks and mitigations for:
    - Patient
    - Operator
    - Test process
    - Components
    - Test result
    - Cybersecurity
    - (and more)
  - Risk/Benefit report

CLIA: Corrective action

- Corrective action policies and procedures must be available and followed as necessary to maintain the laboratory's operation for testing patient specimens in a manner that ensures accurate and reliable patient test results and reports.
- The postanalytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of postanalytic systems quality assessment reviews with appropriate staff.

§ 493.1282 Standard: Corrective actions.

FDA: Corrective and Preventive Action

- Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action.
  - The expectation is for a medical device manufacturer to have a robust CAPA program:

"The procedures shall include requirements for:

(1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;

(2) Investigating the cause of nonconformities relating to product, processes, and the quality system;

(3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

(4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

(5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;

(6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and

(7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

(b) All activities required under this section, and their results, shall be documented."

§ 820.100 Corrective and preventive action.

Audits

- FDA
  - Audits are performed to determine the effectiveness of the quality system
  - All elements of the quality system are audited
  - Audit findings feed into the CAPA system

- CLIA
  - Quality Assessments, including review of testing quality control
  - Quality assessment findings may result in corrective actions
  - No requirement to audit the quality system, or determine the effectiveness of the QMS

Medical Device Reporting/Recalls

- Medical Device Reporting and Recalls are not mandated by CLIA
  - CLIA has rules regarding result error correction; a corrected report is issued to the health care professional:
    - § 493.1299: When errors in the reported patient test results are detected, the laboratory must do the following: (1) Promptly notify the authorized person ordering the test and, if applicable, the individual using the test results of reporting errors. (2) Issue corrected reports promptly to the authorized person ordering the test and, if applicable, the individual using the test results.
- FDA regulations 21CFR §803 and §806 address expectations for medical device reporting and handling of recalls.

Management Review

- Quality Monitoring (CLIA Lab) vs Management Review
  - CLIA (examples)
    - Proficiency testing
    - QC Trends
    - Laboratory errors and corrections/corrective actions (preanalytic, analytic, postanalytic)
  - 820.20
    - Is the quality system established and adequate for the device?
    - Covers systems
      - Internal audits
      - CAPA
      - Complaint
      - etc.

In Summary

- FDA §820 regulations provide a framework for design, development and manufacturing of medical devices, including IVDs.
- CLIA §493.1200-1299 focuses mainly on what occurs AFTER a test method is manufactured.
  - CLIA requirements operate as a total quality system for clinical laboratories.
- Perform a gap analysis of your quality system and create a plan to fill the gaps before a premarket submission.

References

- 21 CFR § 820
- 42 CFR § 493
- CLSI Quality System Regulation for Laboratory-Developed Tests: A Practical Guide for the Laboratory. CLSI document QSRLDT, 2015