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# Quality System Regulation for Laboratory-Developed Tests

*A Practical Guide for the Laboratory*

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# Table of Contents

# Introduction

This practical guide is intended for the laboratory that is creating laboratory-developed tests (LDTs) that may be subject to the US Food and Drug Administration (FDA) regulations, specifically the Quality System Regulation (QSReg), 21 CFR Part 820. LDTs are those *in vitro* diagnostic devices that are intended for clinical use and are designed, manufactured, and used within a single laboratory. This practical guide is intended to clarify how to implement the QSReg that may be required for some classifications of LDTs. On October 3, 2014, the FDA issued draft guidance for regulating LDTs that included notification or registration of LDTs with the FDA, reporting adverse events, and other requirements. This document only addresses the QSReg that is currently applicable to manufacturers and is expected to become applicable for some classifications. On May 6, 2024, the FDA published a final rule establishing LDTs as devices under the Federal Food, Drug, and Cosmetic Act.

CLSI solicited the help of experts from the *in vitro* diagnostics industry in compiling this guide. These experts have many years of experience in complying with FDA regulations and succeeding with FDA inspections.

The QSReg can be difficult to understand, so the experts explained each section in plain language. The regulation is compared, where appropriate, to the Clinical Laboratory Improvement Amendments (CLIA) regulations. Similarities and differences are identified. This guide attempts to answer the question: "What does the QSReg require, above and beyond what we already do for CLIA?"

Because regulation language can sometimes leave room for interpretation, tips and hints are provided to give the reader ideas about methods for complying that have proven effective. In addition, brief explanations are provided for several terms used in this guide:

**Class I, II, or III:** FDA categorizes laboratory tests by novelty and risk of harm to a patient, should an erroneous result be acted upon. Well-characterized tests with very low risk are typically class I; tests with moderate risk are typically class II; and novel tests with high or unknown risk are typically class III.

**Manufacture:** the process of preparing the LDT for use; eg, measuring and mixing chemicals to make a reagent.

**Manufacturer:** the laboratory that is preparing and using the LDT.

**Product:** the components of the LDT; eg, the reagents.

**Validation and verification:** FDA uses these terms a bit differently from CLIA. For CLIA, manufacturers validate the test and the laboratories verify its performance characteristics before use. For LDTs, the laboratory is the manufacturer, and must validate (prove) that the test is fit for its purpose. The validation may involve conducting studies with patient samples (clinical studies), and comparing the LDT results to patient outcomes or other patient-related parameters. Each new lot of LDT reagent can then be verified to function correctly.

Throughout this document we use icons to draw the reader's attention to important points. The icon indicates clarifying or additional information. The ⚠ icon indicates important points that need to be considered to meet the QSReg requirements.

This practical guide is not intended to replace the QSReg, nor does it in any way usurp the authority of FDA's regulations or guidance documents.

For the reader's convenience, the text of the QSReg is included in its entirety in Appendix A. A crosswalk between the QSReg, the CLIA regulations, and the CLSI quality system essentials is included in Appendix B.

# Abbreviations and Acronyms

| | |
|---|---|
| **% CV** | coefficient of variation expressed as a percentage |
| **BOM** | bill of materials |
| **CAPA** | corrective and preventive action |
| **CFR** | Code of Federal Regulations |
| **CLIA** | Clinical Laboratory Improvement Amendments |
| **CV** | coefficient of variation |
| **DHF** | design history file |
| **DHR** | device history record |
| **DMR** | device master record |
| **FDA** | US Food and Drug Administration |
| **GCP** | good clinical practice |
| **HCl** | hydrochloric acid |
| **HEPA** | high-efficiency particulate air |
| **HR** | human resources |
| **HVAC** | heating, ventilation, and air conditioning |
| **IVD** | *in vitro* diagnostic |
| **LDT** | laboratory-developed test |
| **MDR** | medical device reporting |
| **NaOH** | sodium hydroxide |
| **pH** | negative logarithm of hydrogen ion concentration |
| **QA** | quality assurance |
| **QC** | quality control |
| **QMS** | quality management system |
| **QSE** | quality system essential |
| **QSR** | quality system record |
| **QSReg** | Quality System Regulation |
| **R&D** | Research and Development |
| **rpm** | revolutions per minute |
| **SOP** | standard operating procedure |
| **UDI** | unique device identifier |
| **UPC** | universal product code |

# Chapter 1: Management Responsibility (§ 820.20)

A good quality system is not possible without full management support. The FDA QSReg has specific requirements for the organization's management, which address both responsibilities and actions.

> **Requirement**
> § 820.20(a): *Quality policy.* Management with executive responsibility shall establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

CLIA defines that the laboratory director is responsible for ensuring that QC and quality assessment programs are established and maintained, to ensure the quality of the laboratory services provided and to identify failures in quality as they occur (42 CFR § 493.1445[e][5]).

CLIA requires policies and procedures specific to quality (42 CFR § 493.1200). CLIA also requires laboratories to have a quality policy (42 CFR § 493.1239[a]; 42 CFR § 493.1231 to § 493.1236). This policy is usually a few statements, for example:

> "We will provide high-quality products by ensuring our laboratory-developed tests have good design, excellent technical performance, and actionable test results. We will strive to continuously improve our products, maintain our quality system, and meet all applicable regulatory requirements."

**Management with executive responsibility** means a senior employee (eg, laboratory director) who has the authority to establish and make changes to the quality policy and quality system.

It is important that the quality policy be visible throughout the facility and widely communicated to all levels of the organization.

The quality policy should reflect the goals of the laboratory's quality system in crisp language that is meaningful for the laboratory staff as well as the laboratory's stakeholders and investors. When developing the policy, consider adding elements addressing:

- The laboratory's commitments to its customers and patient safety
- Leadership's commitment to good professional codes and standards
- The quality of the laboratory's services
- Commitment to compliance with the standards and requirements for quality management systems (QMS)
- Leadership's commitment to compliance with applicable regulations and/or obligatory standards
- The laboratory's standard of service

Every laboratory staff member should be able to state the quality policy when asked. Because it does not need to be memorized, it can be printed on the back of entry badges and/or posted in conspicuous places—anywhere that is immediately accessible to staff members.

**Requirement**

§ 820.20(b): *Organization*. Each manufacturer shall establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the requirements of this part.

It is important that the quality manager (or those people responsible for the release of the LDT) is independent from (ie, does not report to) the operation manager (the person responsible for the manufacturing of the LDT).

CLIA has organizational requirements that cover the laboratory testing process, but not necessarily the designer/manufacturer of tests. For example, 42 CFR § 493.1445(e)(11) states that laboratories must "Employ a sufficient number of laboratory personnel with the appropriate education and either experience or training to provide appropriate consultation, properly supervise and accurately perform tests and report test results in accordance with the personnel responsibilities described in this subpart;" and, in Section (e)(15): "Specify, in writing, the responsibilities and duties of each consultant and each supervisor, as well as each person engaged in the performance of the preanalytic, analytic, and postanalytic phases of testing, that identifies which examinations and procedures each individual is authorized to perform, whether supervision is required for specimen processing, test performance or result reporting and whether supervisory or director review is required prior to reporting patient test results."

The laboratory should create an organizational chart. An example of an organizational chart is shown in Figure 1.

**Conclusion:**

There are two causes for this nonconformance:

1. The instrument needs to be redesigned to eliminate the sharp edge.
2. The work area needs to be reconfigured to ensure adequate space for working.

**Actions:**

1. Until a replacement instrument can be obtained, place a piece of thick tape over the sharp edge of the instrument.
2. Reconfigure the workspace to allow adequate space for working.

Figure 8 is an illustration of a fishbone diagram.

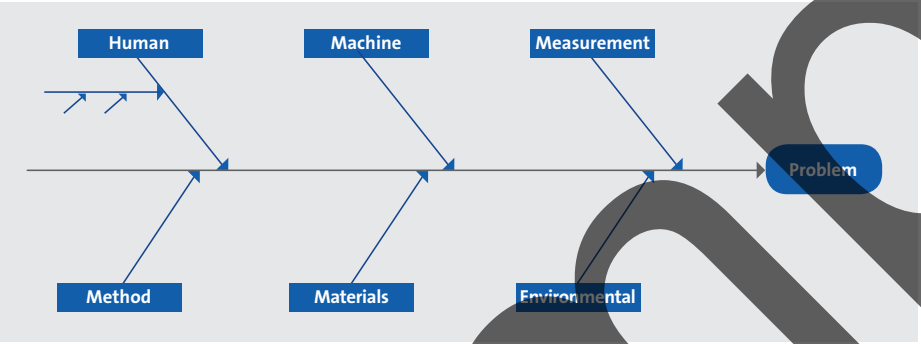


**Figure 8. Example Fishbone (or Ishikawa) Diagram**

Figure 9 is an illustration of a Pareto chart.

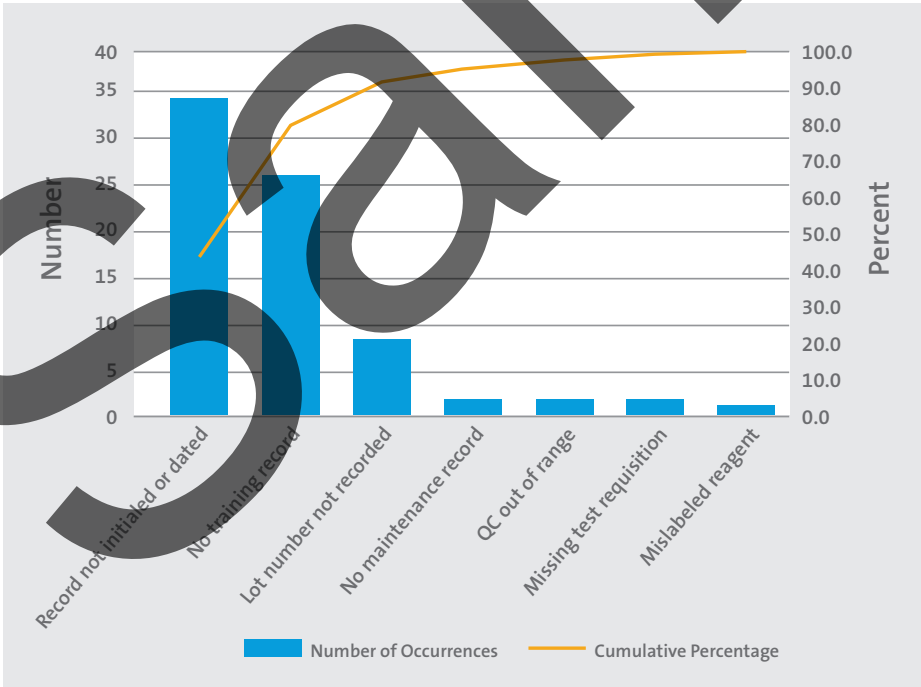


**Figure 9. Example Pareto Chart of Quality Audit Findings**

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