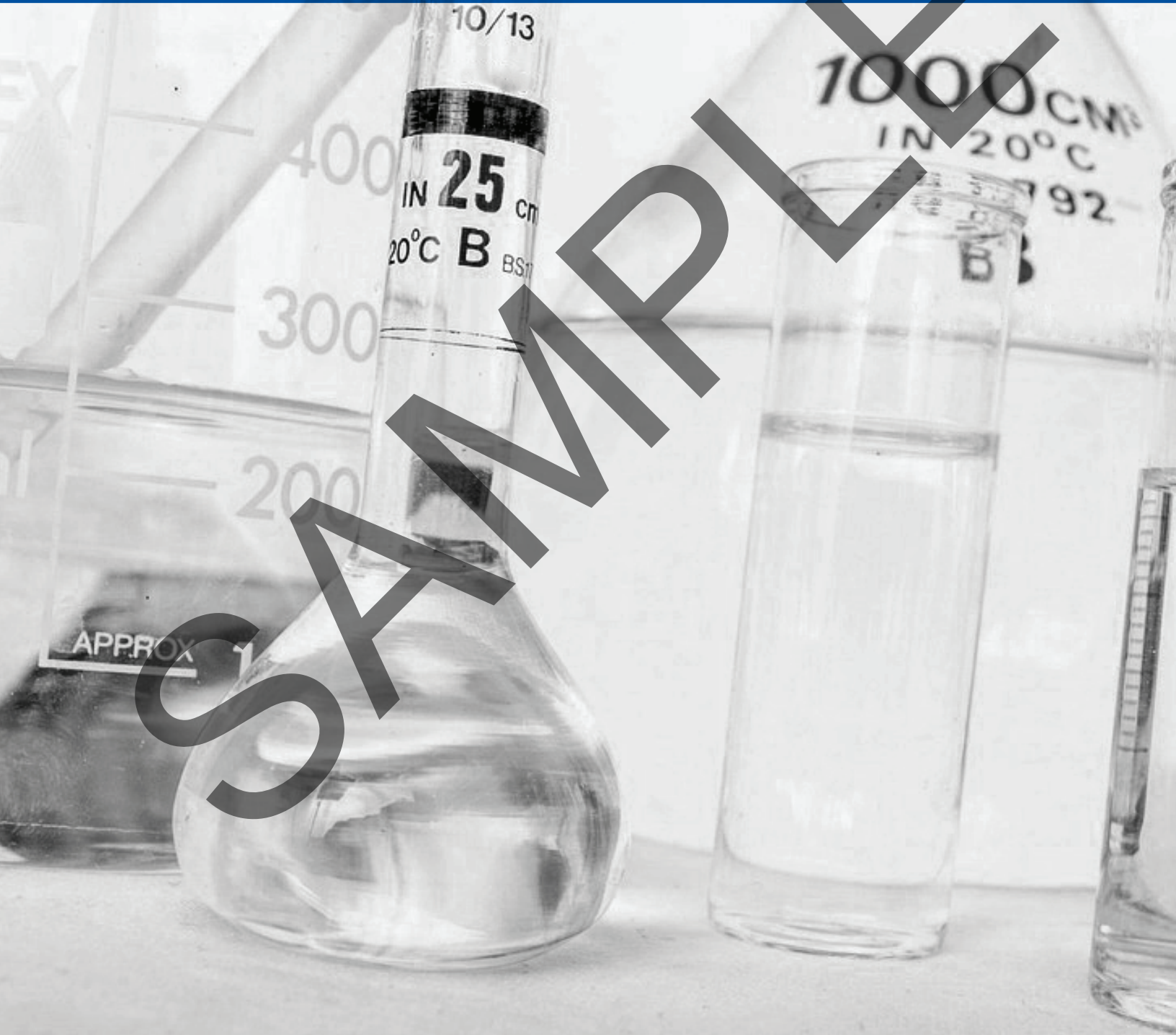


# Quality System Regulation for Laboratory-Developed Tests

*A Practical Guide for the Laboratory*



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## 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 (QSR), 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 QSR 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 On October 3, 2014, the FDA issued draft guidance for regulating LDTs that included notification or registration of LDTs with the FDA, reporting adverse events, and other requirements.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 QSR that is currently applicable to manufacturers and is expected to become applicable for some classifications of LDTs when the final guidance is published.

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 QSR 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 QSR 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. FDA intends to regulate the higher risk tests first.

**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 QSR requirements.

This practical guide is not intended to replace the QSR, 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 QSR is included in its entirety in Appendix A. A crosswalk between the QSR, the CLIA regulations, and the CLSI quality system essentials is included in Appendix B.

# Chapter 1: Management Responsibility (§ 820.20)

A good quality system is not possible without full management support. The FDA QSR 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:

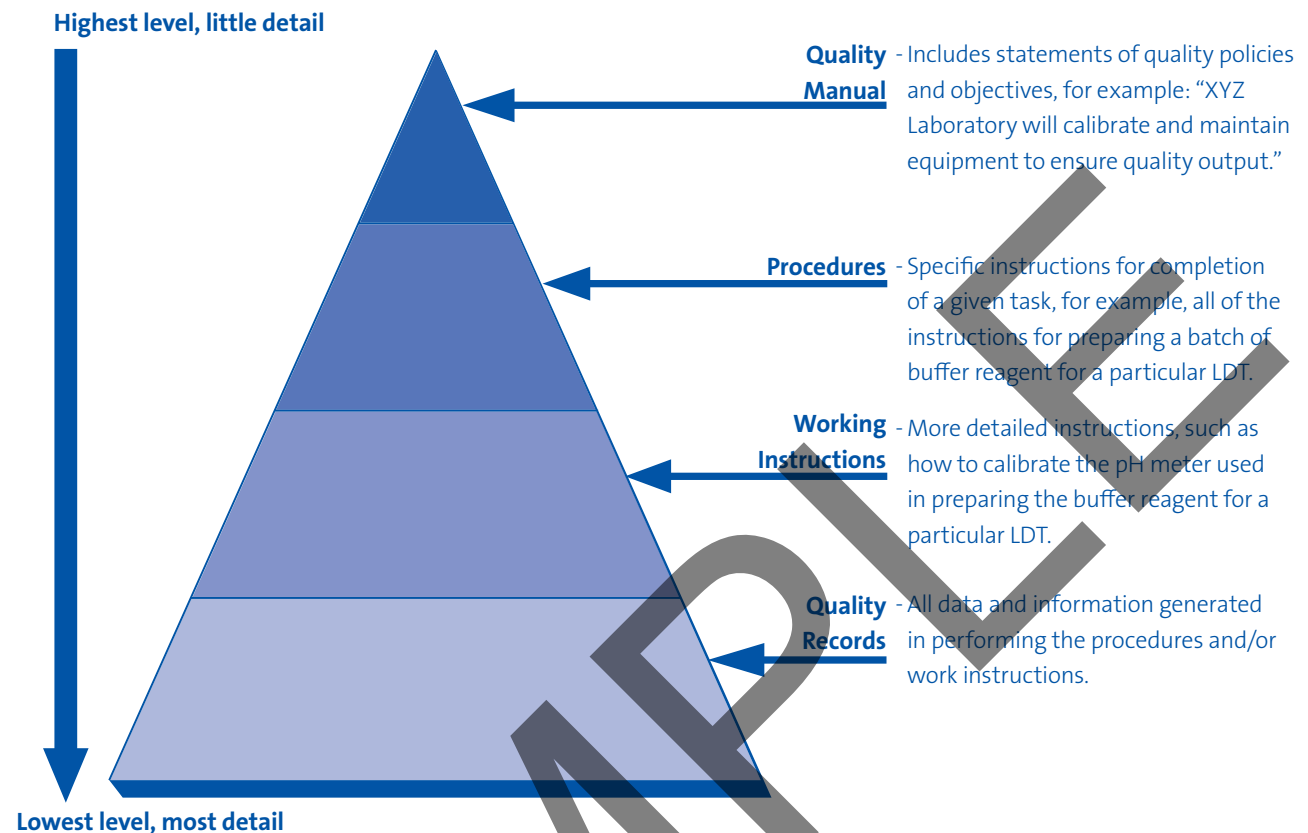
**“We will provide high-quality products by ensuring our laboratory-developed tests have good design, excellent technical performance, and actionable test results. We will strive to continuously improve our products, maintain our quality system, and meet all applicable regulatory requirements.”**



## 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.

Figure 5 outlines the common structure of quality system documentation.



**Figure 5. Example Documentation Pyramid**

The documentation pyramid displays four levels of documentation, which are called tiers.

1. The first tier, and the top of the pyramid, represents the quality manual and policies. The quality manual and policies provide the quality system structure and summarize the quality system.
2. The second tier represents operating procedures and includes the written guidelines that explain what is expected and required.
3. The third tier represents work instructions and provides detailed instruction on how to perform the applicable tasks.
4. The fourth, and last, tier includes quality records, which document the results achieved and provide evidence of activities performed.

The pyramid is used to show that even though the quality manual and policy is important, it is only a small portion of the overall documentation. The bulk of any documentation system is the quality records.

- !** Think about the documentation pyramid as a house; a house is only as stable as the foundation. Quality records are the foundation of a quality system. Records contain significant data that prove:
- ▶ When and what tasks were done, and by whom
  - ▶ Measurements or readings taken
  - ▶ Conditions that were monitored
  - ▶ Whether a product passed or failed testing
  - ▶ Conditions or data that were reviewed and approved or failed



# Chapter 3: Personnel (§ 820.25)

The personnel are the most essential part of any workplace, including the laboratory. Ensuring that there are enough properly trained people is one of the most important functions of the laboratory director.

## Requirements

§ 820.25(a): *General.* Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed.

§ 820.25(b): *Training.* Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented.

§ 820.25(b)(1): As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs.

§ 820.25(b)(2): Personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.

This section of the QSRreg should be easy to comply with, as it aligns with the CLIA regulations (42 CFR § 493.1235, § 493.1445, and § 493.1451). CLIA also requires a “sufficient number of laboratory personnel with the appropriate education and either experience or training.” CLIA requires that before testing patient specimens, all personnel must receive the appropriate training (or retraining, if necessary), and be competent to perform the testing reliably and accurately.

The QSRreg emphasizes that training must include awareness of device defects that might occur due to improper performance of a job, or device defects that an employee might encounter during routine job functions. In this case, “device defects” would refer to problems with the LDT reagents or instruments that lead to unsafe and ineffective devices.



A good way to ensure that every employee has been adequately trained is to keep a documented training plan, customized for each employee or each position within the laboratory. Check off each training as it is completed, including the signature of the trainer and the date.



Training didn't happen if it isn't documented! Good records are the key to compliance!

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