CHAPTER 1

INTRODUCTION TO THE QUALITY SYSTEMS APPROACH TO CGMP COMPLIANCE

1.1 OVERVIEW OF QUALITY SYSTEMS

The Food and Drug Administration (FDA) mandates that a drug firm, and therefore its laboratory, be operated in a state of control by employing conditions and practices that assure compliance with the intent of The Federal Food, Drug, and Cosmetic Act and portions of the Current Good Manufacturing Practice (CGMP) regulations (e.g., 21 CFR Parts 210 and 211) that pertain to it. Activities found in drug firms, including operation of the laboratory, can be organized into systems that are sets of operations and related activities. Control of all systems helps to ensure the firm produces drugs that are safe, have the proper identity and strength, and meet the quality and purity characteristics as intended.

For drug firms, the FDA has outlined the following general scheme of systems that impact the manufacture of drugs and drug products:

1. **Quality System.** This system assures overall compliance with CGMPs and internal procedures and specifications. The system includes the quality control unit and all of its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation
protocols, and reports, etc.). It includes all product defect evaluations and evaluation of returned and salvaged drug products. (See CGMP regulation 21 CFR 211 Subparts B, E, F, G, I, J, and K.)

2. **Facilities and Equipment System.** This system includes measures and activities that provide an appropriate physical environment and resources used in the production of the drugs or drug products, including:
   
   (a) Buildings and facilities with maintenance;
   
   (b) Equipment qualifications (installation and operation), equipment calibration and preventative maintenance, and cleaning and validation of cleaning processes, as appropriate. Process performance qualifications are included as part of process validation done within the system where the process is employed and;
   
   (c) Utilities that are not intended to be incorporated into the product such as HVAC, compressed gases, steam, and water systems. (See CGMP regulation 21 CFR 211 Subparts B, C, D, and J.)

3. **Materials System.** This system includes measures and activities to control finished products and components including water or gases that are incorporated into the product, containers, and closures. It includes validation of computerized inventory control processes, drug storage, distribution controls, and records. (See CGMP regulation 21 CFR 211 Subparts B, E, H, and J.)

4. **Production System.** This system includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures. (See CGMP regulation 21 CFR 211 Subparts B, F, and J.)

5. **Packaging and Labeling System.** This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations. (See CGMP regulation 21 CFR 211 Subparts B, G, and J.)

6. **Laboratory Control System.** This system includes measures and activities related to laboratory procedures, testing, analytical methodology development, validation or qualification/verification, and the stability program. (See CGMP regulation 21 CFR 211 Subparts B, I, J, and K.)

As stated in (6) above, FDA considers a firm’s laboratory control system to be a key element in CGMP compliance. Within the laboratory control
systems are at least seven additional subsystems or subelements which include:

- Laboratory managerial and administrative systems,
- Laboratory documentation practices and standard operating procedures,
- Laboratory equipment qualification and calibration,
- Laboratory facilities,
- Methods validation and technology transfer,
- Laboratory computer systems, and
- Laboratory investigations.

Establishing and maintaining quality systems and subsystems demonstrates control.

1.2 QUALITY SYSTEMS AND COMPLIANCE WITH CGMPs:
REASONS FOR AUDITING YOUR LABORATORY

The purpose for auditing your laboratory is to demonstrate to your organization and ultimately to FDA that you are in control of your laboratory control system. In order to demonstrate control, data is needed to support your position. These data are obtained by executing a well-organized and systematic laboratory audit.

In addition to demonstrating current control, you must show future control. Therefore, you must also have in place a system that to continually monitors the status of compliance within laboratory and corrects deficiencies if discovered.

1.3 GOALS OF AUDITING YOUR LABORATORY

In short, the goals of a laboratory audit are:

- Demonstrate control by conducting the audit and generating data to support your position.
- If not in control then:
  - Show that you know why you are not in control;
  - Show that you know which areas are out of compliance;
  - Show that you know which areas have the greatest impact;
  - Develop interim controls to mitigate the impact of the areas with the greatest risk;
  - Develop a plan to put you back in control;
Implement the plan; and
Generate a system to continually monitor your state of compliance so you stay in control in the future (e.g., sustainable compliance).

1.4 LABORATORY AUDIT PHASES

As stated in the preceding list, a well-organized and systematic laboratory audit must be executed in order to obtain data to prove control. To accomplish this, the audit may be organized into the following phases:

- Preparation phase,
- Audit and data capture phase,
- Reporting phase,
- Corrective action phase,
- Verification phase, and
- Monitoring phase.

Details of the design and implementation for each phase are described in the remaining chapters of this book. In addition, some of the tools, templates, and examples needed to complete such an audit are included in the Appendices.

1.5 INTEGRATION WITH EXISTING PROGRAMS

One of the strengths of the laboratory control system audit process described in this guide is that it allows for easy integration and linkage with existing audit programs and data. Specifically:

- Data collected from previous internal audits, 483 observations, external audits, and gap analyses are linked and compiled via use of the laboratory audit form (LAF) data capture instrument.
- Existing corrective action project plans become part of the corrective action phase of this process and are managed as one coherent effort.

1.6 MODIFIABLE AND SCALABLE APPROACH

In addition to the ability to integrate this approach into existing systems, the guide is also constructed with the following major characteristics:

- Scalable. The audit approach described here is useful regardless of the size of the facility. It works whether your organization has 10, 100, or
several hundred employees. Simply scale the magnitude of the audit based on the availability of resources at your facility and match those laboratories that constitute your quality operations.

- **Modifiable.** The tools and templates outlined in this book are designed not only to instruct but to be copied and modified. Take them and modify them a little or modify them a lot. They are meant to save time and prevent reinvention the wheel.

**REFERENCE**


**BIBLIOGRAPHY**

Food and Drug Administration, Code of Federal Regulations, Food and Drugs, Title 21 Parts 210 and 211 “Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs: General” and “Current Good Manufacturing Practice for Finished Pharmaceutical,” Revised April 1, 2005.


