Chapter 1

General Framework of Drug Analysis and Quality Control

1. Introduction

Non-compliant medicines, including defective, degraded, substandard, or counterfeit products, represent a major public health concern, particularly in developing countries. Their circulation is facilitated by:

- Limited access to essential medicines
- Expansion of informal and parallel markets
- Globalization of pharmaceutical trade
- Weak regulatory enforcement
- Complex international supply chains

National Quality Control Laboratories play a central role in ensuring that medicines available on the market meet required standards of quality, safety, and efficacy. However, limited infrastructure, financial constraints, and shortages of trained personnel may restrict their ability to ensure continuous surveillance across the entire pharmaceutical supply chain.

Pharmaceutical quality control is therefore not only a laboratory activity but a comprehensive regulatory and technical system integrating manufacturing control, regulatory oversight, analytical verification, and post-marketing surveillance.

2. Fundamental Concepts in Drug Quality

2.1 Medicinal Product (Drug)

According to **WHO** and international regulations:

A medicinal product is any substance or combination of substances intended for:

- Prevention of disease
- Diagnosis
- Treatment
- Management of diseases
- Modification of physiological functions

A medicinal product includes:

- Active Pharmaceutical Ingredient (API)
- Excipients
- Finished dosage form

Drugs may be obtained through:

- Chemical synthesis
- Biological extraction
- Biotechnological processes

From a quality perspective, a medicine must comply with:

- Pharmacopoeial standards
- Regulatory requirements
- Good Manufacturing Practices (GMP)

2.2 Pharmaceutical Analysis

Pharmaceutical analysis is:

- The application of analytical chemistry techniques to determine the **identity, purity, content**, and **performance** of pharmaceutical substances and products.

Objectives:

- Confirm identity
- Quantify active ingredient
- Detect impurities
- Verify compliance with specifications
- Ensure batch-to-batch consistency

2.3 Pharmaceutical Control

Pharmaceutical control refers to all regulatory and analytical activities ensuring compliance with established standards.

It includes:

- Marketing Authorization evaluation
- GMP inspections
- Laboratory testing
- Post-marketing surveillance

2.4 Quality in Pharmaceuticals

According to **ISO**:

Quality is the set of characteristics of a product that enables it to satisfy expressed or implied needs.

For medicines, quality is one of the three pillars required for Marketing Authorization:

1. Quality
2. Safety
3. Efficacy

Pharmaceutical quality is defined by:

- Identity
- Strength (content)
- Purity
- Performance

Quality is:

- Designed during development
- Built into manufacturing processes
- Verified through quality control
- Maintained throughout the lifecycle

2.5 Counterfeit / Falsified Medicines

According to **WHO**:

Falsified medicines deliberately misrepresent their identity, composition, or source.

They may:

- Contain no API
- Contain incorrect API
- Contain sub-therapeutic or excessive doses
- Have falsified packaging

Distinction:

- Substandard medicines = quality failure (non-intentional)
- Falsified medicines = intentional fraud

Risks:

- Treatment failure
- Toxicity
- Antimicrobial resistance
- Loss of public trust

Combating counterfeit medicines requires:

- GMP-compliant production
- Secure packaging and serialization
- Reliable analytical testing
- Strong regulatory enforcement

2.6 Stability of Medicines

According to ICH Q1A:

Stability is the ability of a medicinal product to **maintain** its **chemical**, **physical**, **microbiological**, and **therapeutic** properties within specified limits throughout its shelf life.

Types of Stability

1- **Chemical stability:** Ability of the API to maintain its chemical integrity and potency. **Example:**

- **Aspirin** undergoing **hydrolysis** to salicylic acid in humid conditions.
- **Vitamin C** oxidizing when exposed to air.

2- **Physical stability**: Maintenance of physical properties such as appearance, dissolution, and uniformity. **Example**:

- Cream showing phase separation (oil and water layers).
- Tablets becoming soft or cracked due to high humidity.
- Suspension forming hard sediment (caking).

3- **Microbiological stability:** Resistance to microbial growth or contamination during shelf life. **Example:**

- Multi-dose eye drops contaminated after opening.
- Syrup without preservative showing bacterial growth.

4- **Therapeutic stability**: Ability to maintain intended therapeutic effect. **Example:**

- Antibiotic losing potency, leading to treatment failure.
- Insulin losing activity due to improper refrigeration.

5- **Toxicological stability:** Prevention of formation of toxic degradation products.

Example:

- Tetracycline degradation forming toxic compounds causing kidney damage.
- Nitrosamine impurities forming in certain drugs under improper storage.

Main Degradation Pathways

1. **Hydrolysis**: affects esters, amides, lactones, lactams; accelerated by moisture, pH.
2. **Oxidation:** affected by oxygen, metals, and light.

3. **Photodegradation**: caused by UV or visible light; generates reactive radicals.
4. **Racemization**: conversion of a chiral drug into a racemic mixture; accelerated by pH and heat.
5. **Isomerization**: structural rearrangement without molecular formula change; influenced by heat, light, and pH
6. **Polymerization:** formation of larger molecular chains from reactive compounds; promoted by heat, light, and oxygen.

Factors Affecting Stability

- Temperature (Arrhenius law)
- Humidity
- Light
- Oxygen
- pH
- Metal ions
- Microbial contamination

Stability Improvement Strategies

- Lyophilization
- Antioxidants
- Desiccants
- Opaque packaging
- Optimal pH control
- Controlled storage conditions

3. Main Sources of Contamination and Degradation

Medicines may be contaminated during manufacturing, storage, distribution, or use.

3.1 During Manufacturing

- **Cross-contamination:** Transfer of residues from one product to another during production.
- **Equipment residues:** Remaining traces of API, excipients, or cleaning agents left on equipment surfaces.
- **Poor cleaning validation:** Failure to scientifically demonstrate that cleaning procedures effectively remove residues.

- **Human error:** Mistakes made by operators due to inadequate training or failure to follow procedures.
- **Inadequate environmental control:** Poor control of air quality, humidity, temperature, or pressure in production areas.

Cross-Contamination Triangle

- **Source:** The origin of contamination (e.g., previous batch residue, operator, dust)
- **Vector:** The medium that transfers contamination (e.g., air, equipment surface, clothing).
- **Receptor:** The product being contaminated. Contamination occurs only if these three elements interact.

3.2 During Storage

- Excessive temperature
- High humidity
- Light exposure
- Oxygen exposure

3.3 During Distribution

- Break in cold chain
- Poor transportation conditions
- Mechanical stress

3.4 During Use

- Improper reconstitution
- Multi-dose contamination
- Incorrect patient storage

Prevention depends on GMP compliance and risk-based control strategies.

4. Quality Management: QA and QC

Quality management in pharmaceuticals is based on two complementary components: Quality Control (**QC**) and Quality Assurance (**QA**).

4.1 Quality Control (QC)

Quality Control consists of **laboratory techniques** used to **verify compliance** with **specifications**.

QC Activities:

- Sampling of raw materials and finished products
- Establishment of specifications and acceptance criteria
- Analytical testing (HPLC, titration, microbiological tests, etc.)
- Batch release testing before market distribution.

*QC is **product-oriented and reactive**. It detects problems **after production** by testing the finished product.*

4.2 Quality Assurance (QA)

Quality Assurance is a **comprehensive management system** that ensures quality is built into the product from the beginning.

QA ensures:

- GMP implementation
- Proper documentation and traceability
- Process validation
- Quality risk management
- Internal and external audits

*QA is system-oriented and preventive. It aims to **prevent errors before they occur**.*

5. Regulatory Framework

Modern pharmaceutical regulation evolved after public health tragedies such as:

- **Diethylene glycol poisoning (1937)**: even though most issues had been resolved. Unfortunately, in that same year, more than **100 people died** after using a medicinal product (an **elixir of sulfanilamide**) that contained **diethylene glycol**.
- **Thalidomide disaster (1960s):** This drug was used as a **sedative** and **antiemetic**, particularly in **pregnant women**. However, it was later found to have **teratogenic** effects. These adverse effects resulted in **malformations** in approximately **10,000** to **20,000 infants**.

These events led to:

- Mandatory safety evaluation before marketing
- Establishment of regulatory agencies
- Introduction of GMP

6. Main Regulatory References

6.1 Pharmacopoeias

A pharmacopoeia is a legally binding reference defining:

- Specifications
- Analytical methods
- Impurity limits
- Storage conditions

Major pharmacopoeias:

- United States Pharmacopeia **USP**
- European Pharmacopoeia **(Ph. Eur.)** Algeria is an observer member of the European Pharmacopoeia.
- British Pharmacopoeia **BP**
- Japanese Pharmacopoeia **(JP)**

Pharmacopoeial methods are considered authoritative and are used as official references in case of regulatory or legal disputes.

6.2 Good Manufacturing Practices (GMP)

Good Manufacturing Practices (**GMP**) is part of **quality assurance** that ensures medicines are consistently **produced** and **controlled** according to **defined quality standards**. Introduced after the **thalidomide** tragedy, GMP were **first** established in 1963 by the **Food and Drug Administration (FDA)** and later recommended worldwide by the **World Health Organization (WHO)**, becoming legally binding in most countries.

❖ **Current GMP Structure:** Current GMP guidelines include:

- General rules for medicinal products for human use.
- Guidelines for active pharmaceutical ingredients (APIs)
- Related documents such as those from the **International Council for Harmonisation** of Technical Requirements for Pharmaceuticals for Human Use (ICH).

- Specific guidelines for special products (sterile products, radiopharmaceuticals, medical gases, etc.).

❖ **Scope and Objectives :** GMP requirements cover:

Pharmaceutical quality system, Personnel, Premises and equipment, Documentation, Production and quality control, Outsourced activities, Complaints, recalls, and self-inspection

❖ **Ten Key Principles (Simplified)**

GMP can be summarized as:

- **Write** clear procedures
- **Follow** procedures
- **Document** all activities
- **Validate** processes
- **Integrate** quality into design
- **Maintain** facilities and equipment
- **Train** qualified personnel
- **Prevent** contamination
- **Build** quality into products
- **Perform** regular audits

❖ **Ultimate Objective**

The main goal of GMP is to ensure that **medicines** are **manufactured** under **controlled conditions** by **qualified personnel**, resulting in **safe, effective, and high-quality** products.
Since 2014, quality management and risk management principles (based on **ICH** guidelines) have become integral parts of GMP.

6.3 ICH Guidelines

The **I**nternational **C**ouncil for **H**armonisation (**ICH**), established in **1990**, aims to harmonize **pharmaceutical regulatory standards** worldwide to ensure **quality, safety, and efficacy** of medicines.

ICH guidelines focus on three fundamental aspects of medicines:

- **Quality (Q)** – 12 guidelines

- **Safety (S)** – 11 guidelines
- **Efficacy (E)** – 18 guidelines
- **Multidisciplinary (M)** – 8 guidelines

These guidelines aim to **facilitate regulatory** *convergence and promote consistent standards across regions.*

❖ **Key Achievements**

- **Common Technical Document (CTD, ICH M4):** A harmonized format for marketing authorization applications, structured in five modules to streamline regulatory review.
- **Quality Guidelines (Q9 & Q10):** Emphasize quality risk management and effective pharmaceutical quality systems in line with GMP.

❖ **Note on Legal Status**

While widely recommended by regulators, **ICH guidelines** are **not legally binding** and do not confer certification, unlike **ISO** standards. They provide a framework for consistent quality, safety, and efficacy while supporting continuous improvement in pharmaceutical quality management.

6.4. Monograph

The standards of the **European Pharmacopoeia** are presented in the form of **general** or **specific monographs**. The development of general monographs has increased considerably in recent years. All active substances and excipients described in the European Pharmacopoeia are subject to the provisions of the general monograph.

The specifications included in monographs generally comprise the following sections:

a) Title

b) Definition

c) Characteristics

d) Identification

e) Tests

f) Assay

7. Marketing Authorization (MA)

A medicinal product can only be marketed after regulatory approval, which is based on **three key** types of data:

- Pharmaceutical (quality) data
- Non-clinical (preclinical) data
- Clinical data

The approval process is organized using the **Common Technical Document** (**CTD**), structured into **five modules**:

1. Administrative
2. Quality
3. Non-clinical
4. Clinical
5. Regional information

8. Organization of Drug Control Systems

8.1 International Level: Drug regulation and control involve several international organizations that ensure medicine safety, quality, and compliance across borders:

- **WHO:** global health guidance and standards
- **ICH:** harmonization of technical and regulatory requirements
- **Interpol:** fight against counterfeit medicines
- **World Customs Organization:** control of imports and exports
- **EMA(European Medicines Agency):** European Medicines Agency, oversees drug approval in the EU
- **FDA(U.S. Food and Drug Administration):** US regulatory authority for pharmaceuticals and biologics

8.2 National Level (Example: Algeria)

- Ministry of Health
- National Agency for Pharmaceutical Products (ANPP)
- National Laboratory for Pharmaceutical Control
- Customs authorities
- Public and private manufacturers

Regulation integrates:

- GMP
- Pharmacopoeial standards
- Marketing Authorization system

9. Quality Control Laboratories

Quality control laboratories:

- Analyze raw materials
- Test finished products
- Verify MA dossiers
- Support regulatory decisions

WHO requirements:

- Legal authorization
- Qualified personnel
- Validated methods
- Data integrity
- Proper documentation

10. Analytical Methods in Pharmaceuticals

Physical Methods

- Melting point
- Density
- Refractive index
- UV-Vis
- IR
- Atomic absorption

Physico-Chemical Methods

- HPLC
- GC
- TLC
- Electrophoresis
- pH measurement

Chemical Methods

- Titration
- Karl Fischer
- Limit tests

- Assay methods

Biological Methods

- Sterility testing
- Antibiotic assay
- Pyrogen testing

11. Examples of Active Substance Monographs

Example: Paracetamol

Monograph includes:

- Definition (content limits)
- Identification (IR, UV)
- Related substances (HPLC)
- Limit tests
- Assay
- Storage conditions

Example: Amoxicillin

Includes:

- Optical rotation
- Water content (Karl Fischer)
- Related substances
- Potency assay

Modern monographs integrate impurity profiling in accordance with ICH Q3 guidelines.