Unit-1

Pharmaceutical Quality Assurance

B.Pharma 6th Sem Notes

Unit: 1

- **Quality Assurance and Quality Management concepts**: Definition and concept of Qualitycontrol, Quality assurance and GMP
- **Total Quality Management (TQM):** Definition, elements, philosophies
- **ICH Guidelines:** purpose, participants, process of harmonization, Brief overview of QSEM, with special emphasis on Q-series guidelines, ICH stability testing guidelines
- **Quality by design (QbD):** Definition, overview, elements of QbD program, tools
- **ISO 9000 & ISO14000:** Overview, Benefits, Elements, steps for registration
- **NABL accreditation:** Principles and procedures

Quality Management (QM)

Definition: Quality Management is the overarching philosophy and organizational structure that determines and implements the "Quality Policy." It is the total management function that determines the quality policy and its implementation through means such as quality planning, quality control, quality assurance, and quality improvement.

Core Concept:

- **Total Oversight:** It is not just about testing a product; it is about managing the entire organization (staff, infrastructure, suppliers, culture) to ensure quality.
- **Customer Focus:** The primary goal is to meet or exceed customer expectations and regulatory requirements.
- **Continuous Improvement:** QM involves constantly analyzing data to improve processes over time (often associated with TQM or Total Quality Management).

Quality Assurance (QA)

Definition: Quality Assurance is the wide-ranging concept covering *all* matters that individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the object of ensuring that products are of the quality required for their intended use.

Principles:

- **Proactive & Process-Oriented:** QA focuses on *preventing* defects before they happen. It asks, "How can we design the process so mistakes are impossible?"
- **"Building Quality In":** Instead of testing quality *into* a product at the end, QA ensures quality is built into the product during design and development.
- **Documentation:** QA relies heavily on Standard Operating Procedures (SOPs), audits, and documentation to prove that the process was followed correctly.

Functions:

- Process validation.
- Auditing suppliers and internal departments.
- Training personnel.
- Change control (managing changes to processes).

Good Manufacturing Practice (GMP)

Definition: GMP is that part of Quality Assurance which ensures that products are **consistently produced and controlled** to the quality standards appropriate to their intended use and as required by the marketing authorization.

Principles:

- **Consistency is Key:** The main goal of GMP is to ensure that every batch is the same as the clinical trial batches that were proven safe and effective.
- **Risk Minimization:** GMP is designed to minimize risks that cannot be eliminated through testing the final product (e.g., cross-contamination or mix-ups).
- **Compliance:** GMP is a legal requirement in regulated industries (like Pharmaceuticals, Food, and Cosmetics).

Functions:

- **Hygiene:** Strict cleanliness of facilities and personnel.
- **Traceability:** Records must be kept so the history of every batch is traceable.
- **Validation:** Critical steps of manufacturing must be validated (proven to work).

Quality Control (QC)

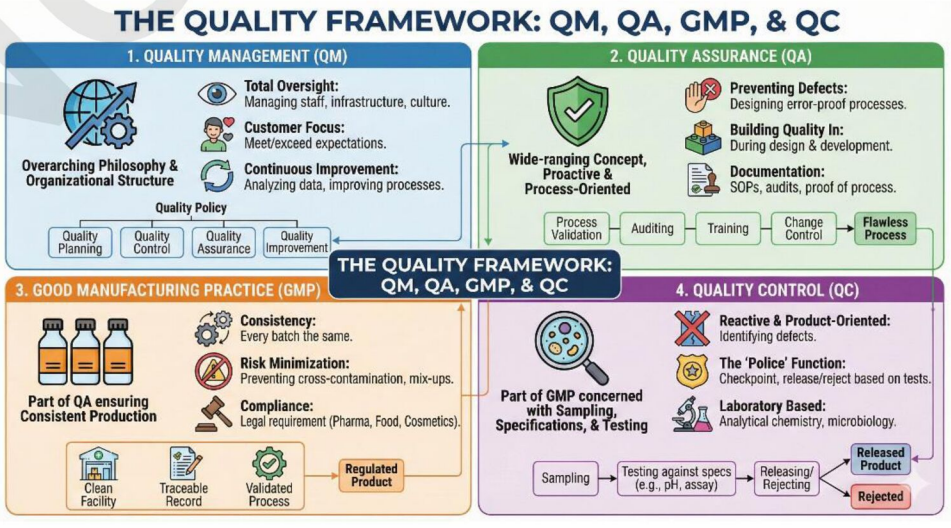
Definition: Quality Control is that part of GMP concerned with **sampling, specifications, and testing**. It ensures that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

Principles:

- **Reactive & Product-Oriented:** QC focuses on *identifying* defects in the finished product or raw materials. It asks, "Does this specific sample meet the criteria?"
- **The "Police" Function:** QC acts as the checkpoint. If a product fails QC testing, it cannot be sold.
- **Laboratory Based:** QC is typically associated with the laboratory environment (analytical chemistry, microbiology).

Functions:

- Sampling raw materials and finished goods.
- Testing against specifications (e.g., pH, assay, dissolution).
- Releasing or rejecting batches based on test results.



Total Quality Management (TQM)

Definition

Total Quality Management (TQM) is a **management approach** focused on continuous improvement of quality in all organizational processes, involving **all employees**, with the primary goal of **customer satisfaction** and long-term organizational success.

In pharmaceuticals, TQM ensures that **quality is embedded in every activity**, from raw material procurement to product distribution.

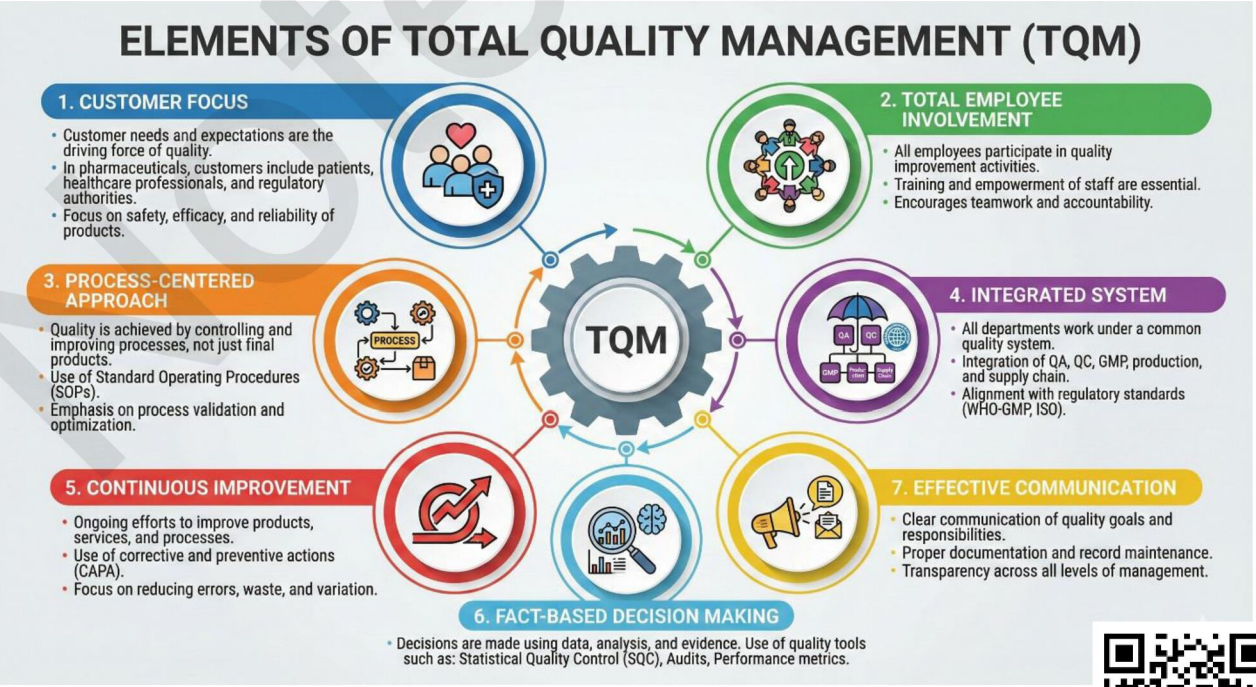
Concept of Total Quality Management

TQM is based on the idea that **quality is everyone's responsibility**, not just the Quality Control or Quality Assurance department. It emphasizes **preventing defects**, improving processes, and fostering a quality-oriented culture across the organization.

TQM integrates:

- Management commitment
- Employee involvement
- Process control
- Continuous improvement
- Customer focus

Elements of Total Quality Management



Philosophies of Total Quality Management

1. Deming's Philosophy (W. Edwards Deming)

- Quality improvement leads to **higher productivity and lower costs**
- Emphasized **14 principles of management**
- Focus on system improvement rather than blaming individuals
- Encouraged leadership and continuous learning

2. Juran's Quality Trilogy (Joseph Juran)

Juran proposed three key components:

1. **Quality Planning** – Identifying customers and their needs
2. **Quality Control** – Monitoring performance and correcting deviations
3. **Quality Improvement** – Continuous enhancement of processes

3. Crosby's Philosophy (Philip Crosby)

- Quality means **conformance to requirements**
- Emphasized **Zero Defects**
- Prevention is better than inspection
- Quality improvement reduces overall cost

4. Kaizen Philosophy

- Japanese concept meaning **continuous, small improvements**
- Involves all employees
- Focus on gradual, sustained enhancement of processes

5. Customer-Driven Quality Philosophy

- Quality is defined by **customer satisfaction**
- Products must meet or exceed customer expectations
- Feedback is used for improvement

Importance of TQM in Pharmaceutical Industry

- Improves product quality and consistency
- Enhances regulatory compliance
- Reduces recalls, complaints, and rejections
- Increases patient safety
- Builds organizational reputation and trust

ICH Guidelines

(International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)

Purpose of ICH Guidelines

The **primary purpose of ICH** is to **harmonize pharmaceutical regulatory requirements** across different countries to ensure that **safe, effective, and high-quality medicines** are developed and registered efficiently.

Objectives:

- To avoid **duplication of clinical trials and studies**
- To reduce **time and cost** of drug development
- To ensure **uniform quality, safety, and efficacy standards**
- To facilitate **global acceptance** of pharmaceutical products
- To protect **public health**

Participants of ICH

ICH brings together **regulatory authorities** and **pharmaceutical industry associations** from major global regions.

Regulatory Authorities:

- **USFDA** – United States
- **EMA** – European Union
- **PMDA / MHLW** – Japan

Industry Associations:

- **PhRMA** – USA
- **EFPIA** – Europe
- **JPMA** – Japan

Observers:

- **WHO**
- **Health Canada**
- **Swissmedic**
- Other regional regulators

Process of Harmonization

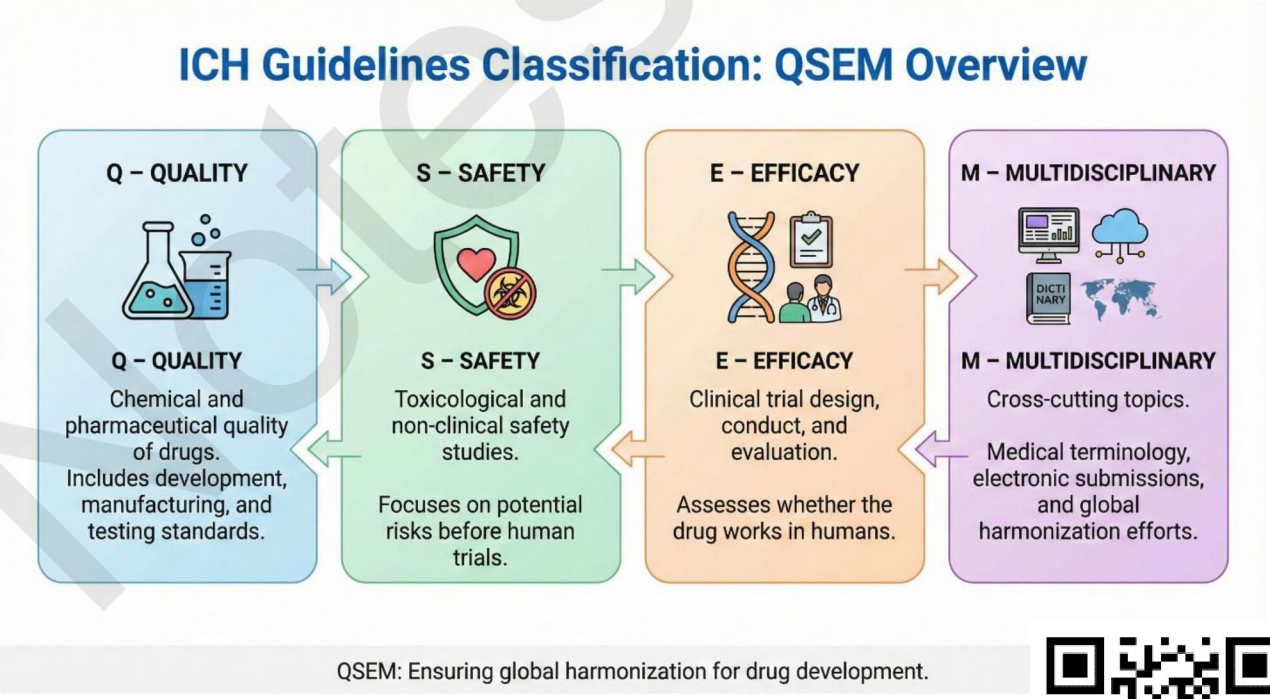
The **ICH harmonization process** involves developing consensus-based guidelines accepted by all participating regions.

Steps in Harmonization:

1. **Consensus Building**
   - Experts from regulatory agencies and industry prepare draft guidelines
2. **Drafting of Guideline**
   - Technical document prepared and reviewed
3. **Public Consultation**
   - Draft is circulated for comments
4. **Revision and Finalization**
   - Comments are incorporated
5. **Adoption**
   - Final guideline is adopted by regulatory authorities
6. **Implementation**
   - Guidelines become part of national regulations

This process ensures **scientific consistency and regulatory acceptance worldwide**.

Brief Overview of QSEM (ICH Guidelines Classification)



QSEM: Ensuring global harmonization for drug development.

ICH Q-Series Guidelines (Quality Guidelines)

The **Q-series** focuses on **quality aspects** of pharmaceutical products.

Major Q-Series Categories:

Category	Area Covered
Q1	Stability testing
Q2	Analytical method validation
Q3	Impurities
Q4	Pharmacopoeial harmonization
Q5	Biotechnological products
Q6	Specifications
Q7	GMP for APIs
Q8	Pharmaceutical development
Q9	Quality risk management
Q10	Pharmaceutical quality system

6. ICH Stability Testing Guidelines (Q1 Series)

Stability testing determines **how the quality of a drug product varies with time** under the influence of environmental factors.

ICH Q1A (R2): Stability Testing of New Drug Substances and Products

Purpose:

- To establish **shelf life and storage conditions**

Stability Conditions:

- **Long-term**: 25°C ± 2°C / 60% RH ± 5%
- **Accelerated**: 40°C ± 2°C / 75% RH ± 5%
- **Intermediate**: 30°C ± 2°C / 65% RH ± 5%

ICH Q1B: Photostability Testing

- Evaluates the effect of **light exposure**
- Ensures protection from light-induced degradation
- Applies to both **drug substance and drug product**

ICH Q1C: Stability Testing for New Dosage Forms

- Applies when a **new dosage form** is developed from an existing drug substance
- Reduced stability data may be acceptable

ICH Q1D: Bracketing and Matrixing Designs

- **Bracketing**: Testing only extreme strengths or sizes
- **Matrixing**: Testing a subset of samples at each time point
- Reduces number of stability studies without compromising data quality

ICH Q1E: Evaluation of Stability Data

- Provides guidance on **data analysis**
- Used to establish **expiry date**
- Includes statistical evaluation of trends

ICH Q1F

- Earlier guideline for **climatic zones**
- Now **withdrawn**, but concepts absorbed into Q1A

Importance of ICH Guidelines in Pharmaceuticals

- Ensures **global regulatory compliance**
- Improves **product quality and consistency**
- Reduces **regulatory burden**
- Facilitates **international marketing**
- Enhances **patient safety**

Quality by Design (QbD)

Definition of Quality by Design (QbD)

Quality by Design (QbD) is a **systematic, science- and risk-based approach** to pharmaceutical development that begins with **predefined objectives** and emphasizes **product and process understanding** and **process control**, based on sound science and quality risk management.

(As per ICH Q8 guideline)

Overview of Quality by Design

Traditional quality systems relied mainly on **end-product testing** to ensure quality. QbD represents a **modern approach**, where quality is **built into the product from the beginning**, rather than tested into it.

Concepts of QbD:

- Quality is **designed into the product**
- Focus on **process understanding**
- Identification and control of **critical variables**
- Use of **risk management tools**
- Lifecycle approach to product quality

In QbD, consistent quality is achieved by understanding:

- How formulation variables affect product quality
- How process parameters influence performance

Objectives of QbD

- To ensure **consistent product quality**
- To reduce batch failures and deviations
- To enhance **process robustness**
- To improve regulatory flexibility
- To ensure patient safety and product efficacy

Elements of QbD Program

Quality Target Product Profile (QTPP)

- A **prospective summary** of quality characteristics of a drug product
- Includes:
    - Dosage form
    - Route of administration

  - Strength
  - Release characteristics
  - Stability
- Forms the **foundation of QbD**

Critical Quality Attributes (CQAs)

- Physical, chemical, biological, or microbiological properties
- Must be within limits to ensure product quality
- Examples:
  - Assay
  - Dissolution
  - Content uniformity
  - Impurity levels

Critical Material Attributes (CMAs)

- Properties of raw materials that affect CQAs
- Examples:
  - Particle size
  - Polymorphic form
  - Moisture content
- Applies to APIs and excipients

Critical Process Parameters (CPPs)

- Process parameters that have a direct impact on CQAs
- Examples:
  - Mixing time
  - Granulation temperature
  - Compression force
- Must be monitored and controlled

Design Space

- The **multidimensional combination** of CMAs and CPPs
- Proven to assure quality
- Operating within design space is **not considered a regulatory change**

Control Strategy

- Planned set of controls to ensure product quality
- Includes:
  - Raw material controls
  - In-process controls
  - Finished product testing
- Ensures consistent performance

Lifecycle Management

- Continuous monitoring and improvement
- Applies throughout the product life cycle
- Supported by ICH Q10 Pharmaceutical Quality System

Tools Used in Quality by Design

Quality Risk Management Tools (ICH Q9)

- Failure Mode and Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Hazard Analysis and Critical Control Points (HACCP)
- Risk ranking and filtering

Design of Experiments (DoE)

- Statistical tool to study multiple variables simultaneously
- Identifies relationships between CMAs, CPPs, and CQAs
- Reduces number of experiments
- Improves process understanding

Process Analytical Technology (PAT)

- Real-time monitoring of critical parameters
- Enables immediate process control
- Improves consistency and efficiency

Statistical Tools

- Control charts
- Regression analysis
- Trend analysis
- Capability analysis

Knowledge Management Tools

- Historical data analysis
- Scientific literature
- Prior development knowledge

Advantages of QbD

- Improved product quality and consistency
- Reduced manufacturing failures
- Better regulatory confidence
- Increased process efficiency

- Enhanced patient safety

QbD and ICH Guidelines

- **ICH Q8** – Pharmaceutical Development
- **ICH Q9** – Quality Risk Management
- **ICH Q10** – Pharmaceutical Quality System

Together, these guidelines form the **foundation of QbD implementation**.

ISO Standards

ISO (International Organization for Standardization) is an international body that develops standards to ensure **quality, safety, efficiency, and environmental responsibility** of products and services worldwide.

ISO 9000 SERIES

1. ISO 9000: Overview

The **ISO 9000 series** is a set of international standards related to **Quality Management Systems (QMS)**. It helps organizations ensure that they consistently meet **customer and regulatory requirements**.

The most important standard for certification is **ISO 9001**.

ISO 9000 Family Includes:

- **ISO 9000** – Fundamentals and vocabulary
- **ISO 9001** – Requirements for Quality Management System
- **ISO 9004** – Guidelines for performance improvement

Benefits of ISO 9000

- Improved **product and service quality**
- Increased **customer satisfaction**
- Better **process control and consistency**
- Reduction in errors, rework, and waste
- Enhanced **organizational efficiency**
- International recognition and credibility
- Improved regulatory compliance

Elements of ISO 9000 (Quality Management Principles)

ISO 9000 is based on the following key principles:

1. **Customer Focus**
   - Understanding and meeting customer needs
2. **Leadership**
   - Top management commitment to quality
3. **Involvement of People**
   - Employee participation at all levels
4. **Process Approach**
   - Managing activities as processes
5. **System Approach to Management**
   - Integrated quality management system
6. **Continual Improvement**
   - Ongoing improvement of processes
7. **Evidence-Based Decision Making**
   - Decisions based on data and analysis
8. **Relationship Management**
   - Good supplier and stakeholder relationships

Steps for ISO 9000 Registration

1. **Management Commitment**
   - Decision to implement ISO 9001
2. **Gap Analysis**
   - Compare existing system with ISO requirements
3. **Documentation**
   - Preparation of Quality Manual, SOPs, records
4. **Implementation**
   - Training and system implementation
5. **Internal Audit**
   - Identify non-conformities
6. **Management Review**
   - Review system effectiveness
7. **Certification Audit**
   - Conducted by accredited certification body
8. **Registration**
   - ISO 9001 certificate issued (valid for 3 years)

ISO 14000 SERIES

1. ISO 14000: Overview

The **ISO 14000 series** deals with **Environmental Management Systems (EMS)**. It helps organizations minimize their **environmental impact** and comply with environmental regulations.

The main certifiable standard is **ISO 14001**.

ISO 14000 Family Includes:

- **ISO 14001** – Environmental Management System requirements
- **ISO 14004** – EMS guidelines
- **ISO 14010–14012** – Environmental auditing (older standards)

Benefits of ISO 14000

- Reduced environmental pollution
- Compliance with environmental laws
- Efficient use of natural resources
- Improved waste management
- Enhanced corporate image
- Cost savings through energy and resource conservation
- Sustainable development

Elements of ISO 14000 (Environmental Management System)

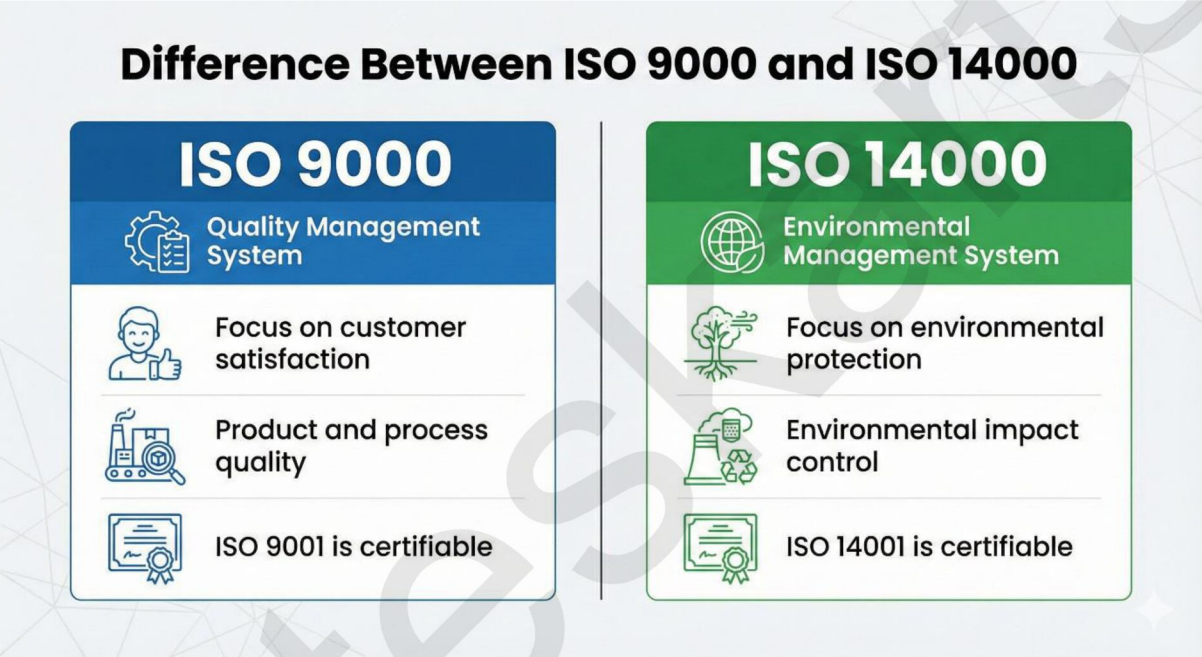
1. **Environmental Policy**
   - Commitment to environmental protection
2. **Planning**
   - Identification of environmental aspects and impacts
   - Legal and regulatory requirements
3. **Implementation and Operation**
   - Roles, responsibilities, and training
   - Documentation and operational control
4. **Checking and Corrective Action**
   - Monitoring and measurement
   - Handling non-conformities
5. **Management Review**
   - Periodic evaluation of EMS performance

Steps for ISO 14000 Registration

1. **Top Management Commitment**
   - Establish environmental policy
2. **Environmental Review**
   - Identify environmental impacts and risks
3. **Planning**
   - Set environmental objectives and targets
4. **Documentation**
   - EMS manual, procedures, and records
5. **Implementation**
   - Training and operational control

6. **Internal Environmental Audit**
   - Identify gaps and non-compliances
7. **Management Review**
   - Review EMS effectiveness
8. **Certification Audit**
   - Conducted by accredited body
9. **Registration**
   - ISO 14001 certificate issued

Difference Between ISO 9000 and ISO 14000



NABL Accreditation

(National Accreditation Board for Testing and Calibration Laboratories)

Introduction to NABL

NABL is an autonomous body under the **Quality Council of India (QCI)**, established to provide **accreditation to testing, calibration, and medical laboratories** in accordance with international standards.

NABL accreditation ensures **technical competence, reliability, and global acceptance** of laboratory test and calibration results.

Principles of NABL Accreditation

NABL accreditation is based on internationally accepted principles that ensure **confidence in laboratory results**.

Technical Competence

- Laboratories must demonstrate **competent personnel**, validated methods, and calibrated equipment
- Ensures accuracy, precision, and reliability of test results

Impartiality

- Laboratory activities must be **free from bias and conflicts of interest**
- Results should not be influenced by commercial, financial, or other pressures

Confidentiality

- Protection of **client information and test data**
- Secure handling of reports and records

Traceability

- All measurements must be **traceable to national or international standards**
- Ensures consistency and comparability of results

Consistency and Reliability

- Uniform application of procedures
- Reproducible and dependable test results

Compliance with International Standards

NABL follows:

- **ISO/IEC 17025** – Testing and calibration laboratories
- **ISO 15189** – Medical laboratories
- **ISO/IEC 17020** – Inspection bodies

Objectives of NABL Accreditation

- To ensure **quality and reliability of laboratory services**
- To promote **international acceptance** of test results
- To improve laboratory management and technical competence
- To enhance confidence of regulators, industries, and customers
- To support pharmaceutical quality assurance and regulatory compliance

Procedures for NABL Accreditation

The NABL accreditation process is **systematic and stepwise**.

Step 1: Application

- Laboratory submits an **online application** to NABL
- Selects relevant standard (e.g., ISO/IEC 17025)
- Defines **scope of accreditation**

Step 2: Submission of Documents

Key documents include:

- Quality Manual
- Standard Operating Procedures (SOPs)
- Test methods and validation data
- Equipment calibration records
- Personnel qualification and training records

Step 3: Pre-Assessment (Optional)

- Conducted to identify **gaps and non-conformities**
- Helps laboratories prepare for final assessment

Step 4: Final Assessment

- NABL appoints **qualified assessors and technical experts**
- On-site evaluation of:
  - Technical competence
  - Implementation of quality system
  - Testing and calibration practices

Step 5: Corrective Actions

- Laboratory addresses **non-conformities** identified during assessment
- Submits corrective action reports within a specified time

Step 6: Accreditation Committee Review

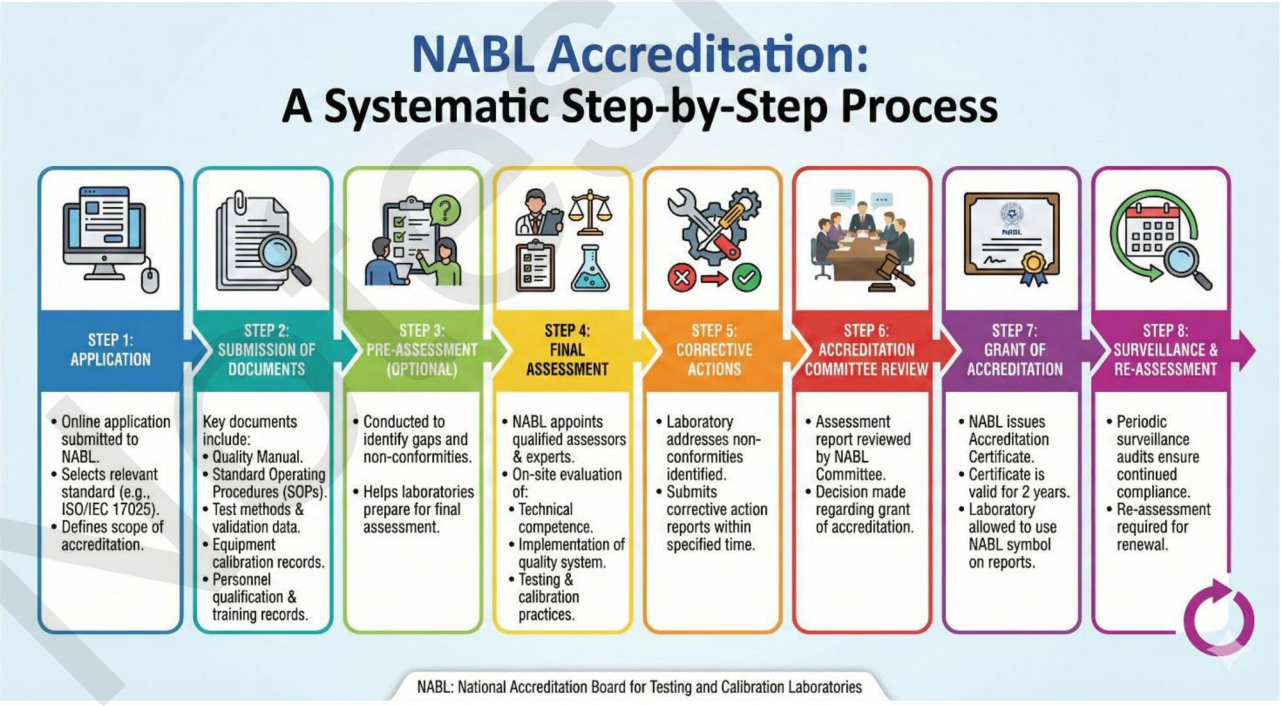
- Assessment report reviewed by NABL Accreditation Committee
- Decision made regarding grant of accreditation

Step 7: Grant of Accreditation

- NABL issues **Accreditation Certificate**
- Certificate is valid for **2 years**
- Laboratory allowed to use **NABL symbol** on reports

Step 8: Surveillance and Re-Assessment

- Periodic surveillance audits ensure continued compliance
- Re-assessment required for renewal



Benefits of NABL Accreditation

- International acceptance of test reports
- Enhanced credibility and customer confidence
- Improved laboratory efficiency and accuracy
- Compliance with regulatory requirements

- Reduction in re-testing and disputes
- Competitive advantage in pharmaceutical and healthcare sectors

Importance of NABL in Pharmaceutical Industry

- Ensures accuracy of **quality control testing**
- Supports **GMP and regulatory inspections**
- Essential for **stability testing, raw material testing, and finished product analysis**
- Enhances trust in analytical data

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