# UNIT –4-QUALITY MANAGEMENT SYSTEMS

## POINTS TO BE COVERED IN THIS TOPIC

### QUALITY MANAGEMENT & CERTIFICATIONS

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# UNIT –4-QUALITY MANAGEMENT SYSTEMS

## POINTS TO BE COVERED IN THIS TOPIC

- **INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO 14000)**
  - ❖ STANDARDS UNDER ISO 14000 SERIES
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- **GLP (GOOD LABORATORY PRACTICES)**

# QUALITY MANAGEMENT & CERTIFICATIONS

## ❖ INTRODUCTION

- A quality management system is a **management technique** used to **communicate** to **employees** what is required to **produce** the **desired quality** of products and services and to influence employee actions to complete tasks according to the **quality specifications.**

### ➢ Purpose of Quality Management System

| | |
|---|---|
| 1. | Establishes a vision for the employees. |
| 2. | Builds motivation within the company. |
| 3. | Sets standards for employees. |
| 4. | Sets goals for employees. |
| 5. | Helps fight the resistance to change within organizations. |
| 6. | Helps direct the corporate culture |

## ❖ CONCEPT OF QUALITY

**Quality** – Quality, as it applies to an object (product, service, process), is defined as the "Degree to which a set of inherent characteristics (attributes) of the object satisfies a set of requirements."

- Therefore, the Quality of an object is determined by comparing a **predetermined set** of characteristics against a **set of requirements.**
- If those characteristics conform to the requirements, **high quality** is achieved, but if those characteristics do not conform, a low or poor level of **quality** is achieved.

## ➢ Importance of Quality

- **Business success** may simply be the extent to which your **organization** can produce a **higher-quality product** or **service** than your competitors are able to do at a **competitive price.**
- When **quality** is the key to a **company's success**, quality management systems allow organizations to keep up with and meet current quality levels, meet the consumer's requirement for quality, retain employees through competitive **compensation programs**, and keep up with the **latest technology.**

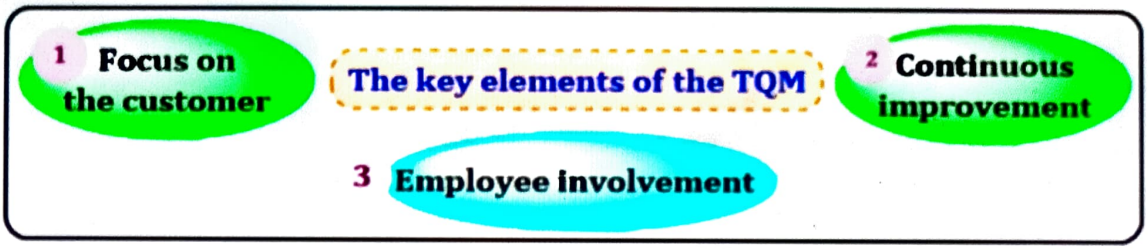

## ❖ TOTAL QUALITY MANAGEMENT

- TQM is a **management approach** in which quality is emphasized in every aspect of the **business** and **organization**.
- Its goals are aimed at **long-term development** of quality products and services.

| | |
|---|---|
| **TOTAL** | Made up of the whole |
| **QUALITY** | Degree of excellence a product or service provides |
| **MANAGEMENT** | Act, art, or manner of planning, controlling and Directing. Therefore, TQM is the art of managing the whole to achieve excellence. |

- Therefore, TQM is the art of managing the whole to achieve excellence.

## The key elements of the TQM




## Principles of TQM

1. Customer focus
2. Leadership
3. People involvement
4. Process approach
5. System approach to management
6. Continual improvement
7. Factual approach to decision making
8. Mutually beneficial supplier relationships


## Characteristics of TQM

- ✓ **Committed management.**
- ✓ **Adopting and communicating about total quality management.**
- ✓ **Closer customer relations.**
- ✓ **Closer provider relations.**
- ✓ **Benchmarking.**
- ✓ **Increased training.**
- ✓ **Open organization**
- ✓ **Employee empowerment.**
- ✓ **Flexible production.**
- ✓ **Process improvements.**
- ✓ **Process measuring**

## Benefits Of TQM

- ✓ Improved quality.
- ✓ Employee participation.
- ✓ Team work.
- ✓ Working relationships.
- ✓ Customer satisfaction.
- ✓ Employee satisfaction.
- ✓ Productivity.
- ✓ Communication.
- ✓ Profitability.
- ✓ Market share.

## Advantages & Disadvantages Of TQM

| ADVANTAGES | DISADVANTAGES |
|---|---|
| • Improves reputation- faults and problems are spotted and sorted quicker. | • Initial introduction cost. |
| • Higher employee morale- workers motivated by extra responsibility, teamwork and involvement indecisions of TQM. | • Benefits may not be seen for several years. |
| • Lower cost. | • Workers may be resistant to change |
| • Decrease waste as fewer defective products and no need for separate. | |

## Importance of TQM in pharma industry Handling

### 1. Drugs

- Containers should be opened carefully and subsequently resealed in an approved manner.
- Highly sensitizing material such as penicillin's and cephalosporins should be handled in separate production areas.
- Highly active or toxic API (e.g. certain steroids, cytostatic substances) should be manufactured in a dedicated area and using dedicated equipment.
- Pure and final API should be handled in an environment giving adequate protection against contamination.

### 2. Storage

- Secure storage facilities should be designated for use to prevent damage or deterioration of materials.
- These should be kept clean and tidy and subject to appropriate pest control measures.
- Environmental conditions should be recorded.

- The condition of stored material should be assessed at **appropriate intervals.**
- **Storage conditions** for API should be based upon stability studies considering time, temperature, humidity, light etc.

## 3. Packaging

- Labelling and packaging processes should be defined and controlled to ensure that **correct packaging materials** are used correctly, and other specified requirements are met.
- **Printed labels** should be securely stored to avoid mix-ups arising.
- Marking and labelling should be legible and durable, provide sufficient information, for accurate identification and indicate, if appropriate, required **storage conditions, retest and/or expiry date.**

## 4. Facilities and equipment

- The location, design, and construction of buildings should be suitable for the type and stage of manufacture involved, protecting the product from contamination (including cross-contamination) and protecting operators and the **environment from the product.**
- Equipment surfaces in contact with materials used in API manufacture should be **nonreactive**.

## 5. Sterile area

- **Personnel suffering** from an infectious disease or having open lesions on the exposed surface of the body should avoid activities which could compromise the **quality of API.**
- Smoking, eating, drinking, chewing and storage of food should be restricted to designated areas separated from **production** or **control areas**.

## 6. Labelling

- Each container should be identified by an **appropriate label**, showing at least the **product identification** and the **assigned batch code**, or any other easily understandable combination of both.

## 7. Computerized systems

- Computer systems should be designed and operated to prevent **unauthorized entries** or changes to the **programme**.
- In the case of manual entry of **quality critical data** there should be a second independent check to verify accuracy of the initial entry.
- A **back-up system** should be provided of all quality critical data.

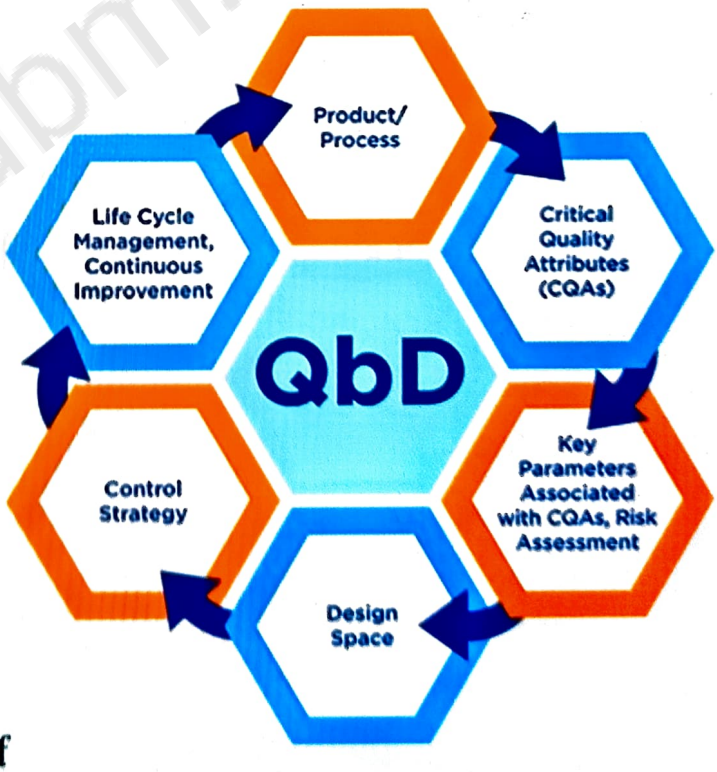
# ❖ QUALITY BY DESIGN

## ➢ Definition

- "A systematic approach to development that begins with **predefined objectives** and **emphasizes product** and process understanding and **process control**, based on sound science and quality risk management"
- The concept of QBD was mention in **ICH Q8 guidelines**, which states that, **"To identify quality cannot be tested in products, i.e. Quality should be built into product by design.**

## ➢ Benefits of QBD

- QbD is good Business
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Organizational learning is an investment in the future
- QbD is good Science
- Better development decisions
- Empowerment of technical staff




## ➢ Steps Involved in Quality by Design Products

### 1. Development of new molecular entity

- Preclinical study
- Nonclinical study
- Clinical Study

- Scale up
- Submission for market Approval

## 2. Manufacturing

- Design Space
- Process Analytical Technology
- Real time Quality Control

## 3. Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance


## ➢ Quality Target Product Profile

- It is the summary of the drug development program described in terms of labeling concepts and it mainly focus on the safety and efficacy.

| |
|---|
| ✓ Description |
| ✓ Clinical Pharmacology |
| ✓ Indications and Usage |
| ✓ Contraindications |
| ✓ Warnings |
| ✓ Precautions |
| ✓ Adverse Reactions |
| ✓ Drug Abuse and Dependence |
| ✓ Over dosage |
| ✓ Dosage and Administration |
| ✓ How Supplied |
| ✓ Animal Pharmacology and/or Animal Toxicology |
| ✓ Clinical Studies |

- A drug product **designed**, **developed** and **manufactured** according to Quality Target Product Profile with specification (such as dissolution/release acceptance criteria) consistent with the desired in vivo performance of the product.

## ➢ Critical Quality Attributes

- A CQA is a **physical**, **chemical**, **biological**, or **microbiological** property or characteristic that should be within an appropriate limit, range, or distribution to ensure the **desired product quality.**
- CQAs are generally associated with the drug substance, **excipients**, intermediates (in-process materials), and **drug product.**
- CQAs of **solid oral dosage forms** are typically those aspects affecting product **purity, strength, drug release**, and **stability**.
- CQAs for **other delivery systems** can additionally include more product specific aspects, such as aerodynamic properties for **inhaled products, sterility for parenteral, and adhesion properties for transdermal patches.**
- For drug substances, raw materials, and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs.

## ➢ Certain Key Aspects of QBD

### 1.The Target Product Quality Profile (TPQP)

- Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development — **"planning with the end in mind."**
- More recently an expanded use of the TPP in development planning, clinical and **commercial decision making**, regulatory agency interactions, and risk management has started to evolve.

### 2.Drug substance and Excipients properties

- To consistently achieve the **drug-product quality** specified in the label, the drug substance needs to be thoroughly characterized with respect to its **physical, chemical, biological**, and **mechanical** properties such as solubility, polymorphism, stability, particle size, and flow properties.

## 2. Manufacturing Process Design and Development

- Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process.
- Process design is the **initial stage** of process development, in which an outline of the **commercial manufacturing processes** is documented, including the intended scales of manufacturing.
- The outline should include all the factors that need to be considered for the design of the process, including **facility, equipment, material transfer,** and **manufacturing variables.**

### ❖ SIX SIGMA CONCEPT


- Six sigma was developed at **Motorola** in the **1980s** as a method to measure and improve **high-volume production processes.**
- Its overall goal was to measure and eliminate waste by attempting to **achieve near perfect results.**
- The term *six sigma* refers to a **statistical measure** with no more than 3.4 defects per million
- Six sigma is a statistically oriented approach to process improvement that uses a variety of tools, **including statistical process control (SPC), total quality management (TQM),** and **design of experiments (DOE).**
- It can be coordinated with other major initiatives and systems, such as **New product development, materials requirement planning(MRP),** and **just-in-time (JIT) inventory control.**
- Six Sigma is a very clever way of **branding** and **packaging** many aspects of Total Quality Management (TQM). ( TQM is a management approach to long–term success through customer satisfaction.)
- Manufacturing methods of six sigma are used in **Batch production, Job production & Mass production.**

## ➢ The Characteristics of Six Sigma

### 1. Statistical Quality Control

- Six sigma is clearly derived from **Greek letter sigma** which is used to denote standard deviation in statistics which is used to measure **nonconformance** as far quality output is concerned.

### 2. Methodical Approach

- The six sigma is not merely quality improvement strategy in the theory as it features a **well-defined methodical approach** of application in **DMAIC** and **DMADV** which can be used for quality production.

### 3. Fact and Data Based Approach

- The **statistical** and **methodical aspects** of Six Sigma show the scientific basis of the technique. This accentuates an important aspect of Six Sigma that it is fact and data based.

### 4. Project and Objective Based Focus

- The Six Sigma process is implemented for an **organization's project** tailored to its specifications and requirement.
- The process is flexed to suit the requirements and conditions in which a project is operating to get the **best results.**
- Apart from that, the Six Sigma is also **objective based.** The management needs some incentive to invest in the Six Sigma process. It is aimed to enhance profitability and to generate financial.

### 5. The Customer Focus

- The Customer focus is fundamental to the Six Sigma approach.
- The quality improvement and control standards are based on the explicit **customer requirements.**

### 5. Teamwork Approach to Quality Management

- The Six Sigma process requires organizations to get organized when it comes to **controlling** and **improving quality.**

- Six Sigma involves a lot of training depending on the role of an individual in the Quality Management team.

## ➢ Six Sigma Objectives

| S.NO | OBJECTIVES | DEFINATIONS |
|---|---|---|
| 1. | OVERALL BUSINESS IMPROVEMENT | • Six Sigma methodology focuses on business improvement.<br>• Beyond reducing the number of defects present in any given number of products. |
| 2. | REMEDY DEFECTS/ VARIABILITY | • Any business seeking improved numbers must reduce the number of defective products or services it produces.<br>• Defective products can harm customer satisfaction levels. |
| 3. | REDUCE COSTS | • Reduced costs equal increased profits.<br>• A company implementing Six Sigma principles must look to reduce costs wherever it possibly can-without reducing quality. |
| 4. | IMPROVE CYCLE TIME | • Any reduction in the amount of time it takes to produce a product or perform a service means money saved, both in maintenance costs and personnel wages.<br>• Additionally, customer satisfaction improves when both retailers and end users receive products sooner than expected.<br>• The company that can get a product to its customer faster may win her business. |
| 5. | INCREASE CUSTOMER SATISFACTION | • Customer satisfaction depends upon successful resolution of all Six Sigma's other objectives.<br>• But customer satisfaction is an objective all its own. |

## ➢ Methodologies

Six Sigma projects follow two project methodologies:

1. DMAIC
2. DMADV

1. **DMAIC:**

- DMAIC is used for projects aimed at improving an existing business process.
- The DMAIC project methodology has Five phases:
  1. Define 2. Measure 3. Analyze 4. Improve 5. Control

2. **DMADV:**

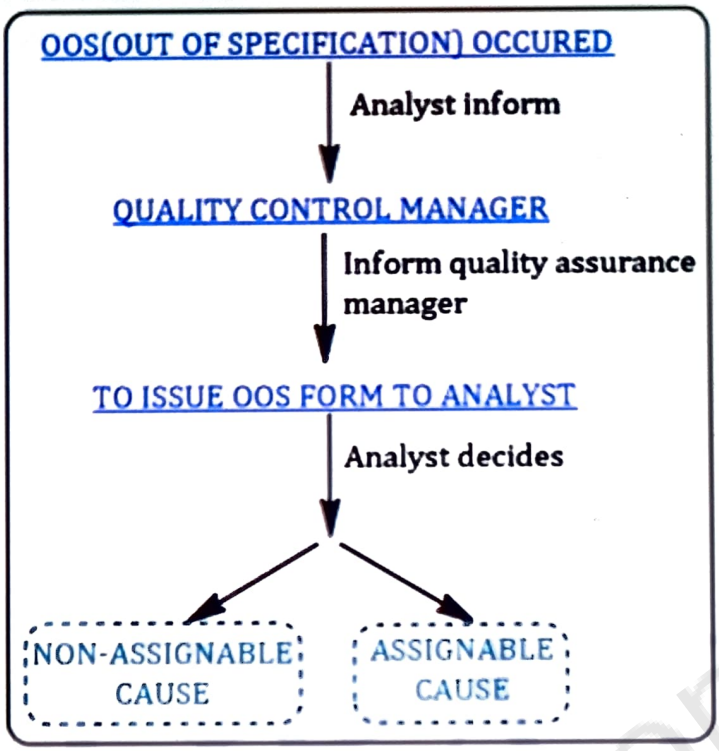
- DMADV is used for projects aimed at creating new product or process designs.
- DMADV project methodology has Five phase:
  1. Define 2. Measure 3. Analyze 4. Design 5. Verify

# ❖ OUT OF SPECIFICATIONS

## ➢ Definitions

- The term OOS (out of specification), is defined as those results of in **process** or **finished product testing**, which falling out of specified limits, that are mentioned in compendia, drug master file, or drug application.
- The OOS, may arise due to deviations in product manufacturing process, errors in testing procedure, or due to malfunctioning of **analytical equipment.**
- The reasons for OOS can be classified as:
  1. **Assignable**
  2. **And Non-Assignable**

## ➢ Schematic representation




# ❖ CHANGE CONTROL

## ➢ Definition

- Change control is a **systematic approach** to managing all changes made to a product or system.
- The purpose is to ensure that **no unnecessary changes** are made, that all changes are documented, that services are not unnecessarily disrupted and that resources are used efficiently.

## ➢ Procedure

1. The **initiating department** shall initiate the change as per the change control format
2. The initiating department shall furnish the details very clearly in the form for present process/use, proposed change, Justification & impact analysis and acceptance criteria.
3. The initiating department shall also define changes as major or minor based on product quality or its impact of safety, health, and environmental aspects. Some of the major and minor changes are listed below:

✓ **Major Changes:**

- For a substance of **chemical** and **microbiological quality evaluation**.
- **Addition** or **deletion** of a step or addition of an **alternative/new step** in the formulation manufacturing process.
- Addition of a **new manufacturing site** with modification of the formulation manufacturing process described in the original **dossier/document.**
- Change in input quantities of **formulation manufacturing process.**
- Changes in the quality of raw material(s) or key intermediate(s) used in the formulation manufacturing process.

✓ **Minor Changes:**

- Change in the **administrative references** (name/company name, address) of the certificate holder.
- Change in the **references** (name/company name, address) of the manufacturing site.
- Change or updating of the methods of analysis used to test the substance.
- Change in the **specifications** of the substance.
- Change in **supplier of starting** and **packing material**.
- Change in the **batch size.**
- Addition of a **new manufacturing site** in the same site as described in the **original dossier.**
- Change in the **documents** like SOPs etc.

## ➢ Key Benefits of Change Control System

- **Structured** and **consistent approach** towards **managing change.**
- Documenting the **details of change.**
- Routing of change requests to appropriate individuals/team for approvals.
- Documentation of **change approvals** and **implementation**.
- Maintenance of **change history** and **easy retrieval of information.**
- Tracking changes effectively and providing an audit trail.
- Demonstrate compliance to **FDA regulations.**

# INTRODUCTION TO ISO 9000 SERIES OF QUALITY SYSTEMS STANDARDS

## ❖ INTRODUCTION

1. The ISO 9000 family of standards is related to quality management systems and designed to help organizations ensure that they meet the needs of customers and other stakeholders while **meeting statutory** and **regulatory requirements.**
2. ISO 9000 deals with the fundamentals of **quality management systems**, including the eight management principles on which the family of standards is based.
3. **International standards** promote international trade by providing one consistent set of requirements recognized around the world.
4. ISO 9000 can help a company satisfy its customers, meet **regulatory requirements** and achieve **continual improvement**. It provides the base level of a quality system, not a complete guarantee of quality.
5. Originally published in 1987 by the International Organization for Standardization (ISO), a specialized international agency for standardization composed of the national standards bodies of 90 countries.

## ❖ ISO 9000 SERIES

- **ISO 9000:** Explains fundamental quality concepts and provides guidelines for the selection and application of each standard.
- **ISO 9001:** Model for quality assurance in design, development, production, installation, and servicing.
- **ISO 9002:** Model for quality assurance in the production and installation of manufacturing systems.
- **ISO 9003:** Quality assurance in final inspection and testing.
- **ISO 9004:** Guidelines for the applications of standards in quality management and quality systems.

## ❖ ADVANTAGES

- **Quality** is maintained
- ISO registration also has a significant bearing on **market credibility** as well.
- **Opportunity** to compete with larger companies.
- More time spent on **customer focus.**
- **Confirmation** that your company is committed to quality.
- May facilitate **trade** and **increased market** and **Opportunities**.
- Can increase **customer confidence** and **Satisfaction**.


## INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO 14000)

- ISO is an **international standard-setting body** composed of representatives from various national standards organizations.
- Founded on 23 February 1947, the organization' promotes worldwide proprietary, industrial and commercial standards.
- It is headquartered in **Geneva, Switzerland.**
- ISO 14000 is a family of standards related to **environmental management** that exists to help organizations.
- Minimize how their **operations** (processes etc.) negatively affect the environment (i.e. cause adverse changes to air, water, or land).
- Comply with **applicable laws**, **regulations**, and other environmentally oriented requirements continually improve in the above.

## ❖ STANDARDS UNDER ISO 14000 SERIES

- ✓ **ISO 14001** is an EMS standard.
- ✓ **ISO 14010** series of standards are about auditing.
- ✓ **ISO 14020** is about environmental labeling.
- ✓ **ISO 14030** is a standard on environmental performance evaluation.
- ✓ **ISO 14040** series are on environmental life cycle assessment(LAC).

## ❖ ISO 14001 STANDARD

- ISO 14001 is known as a **generic management system standard**, meaning that it is relevant to any organization seeking to improve and manage resources more effectively. This includes:
  - ✓ **Single site to large multi-national companies.**
  - ✓ **High risk companies to low risk service organizations.**
  - ✓ **Manufacturing, process and the service industries; including local governments.**
  - ✓ **All industry sectors including public and private sectors.**
  - ✓ **Original equipment manufacturers and their suppliers.**

## ❖ BENEFITS

- It can be applied to any type of **organization**.
- It helps in maintaining an **efficient quality system** in an organization.
- It creates confidence in customer on the **quality of product supplied.**
- It acts as **competitive barrier.**

## NATIONAL ACCREDITATION BOARD FOR TESTING AND CALIBRATION LABORATORIES (NABL)

- NABL specifies the **general requirements** for the competence to carry out **tests** and **calibrations**, including sampling. It covers testing and calibration performed using standard methods, nonstandard methods, and laboratory-developed methods.
- NABL is an **autonomous society providing Accreditation (Recognition)** of Technical competence of a testing, calibration, medical laboratory & Proficiency testing provider (PTP) & **Reference Material Producer (RMP).**
- NABL stands for **National Accreditation Board for Testing And Calibration Laboratories.**
- NABL has agreements with ILAC (International Laboratory Accreditation Conference) and APLAC (Asia Pacific Laboratory Accreditation Cooperation).

- These are especially valuable for **International recognition** and **mutual acceptance** of test results. In short accreditation has worldwide acceptance.

## ❖ NABL MISSION

- To strengthen the **accreditation system** accepted across the globe by providing high quality, value driven services, **fostering APLAC/ILAC MRA**, empanelling competent assessors, creating awareness among the stake holders, **initiating new programs** supporting accreditation activities and pursuing organizational excellence.

## ❖ BENEFITS OF ACCREDITATION

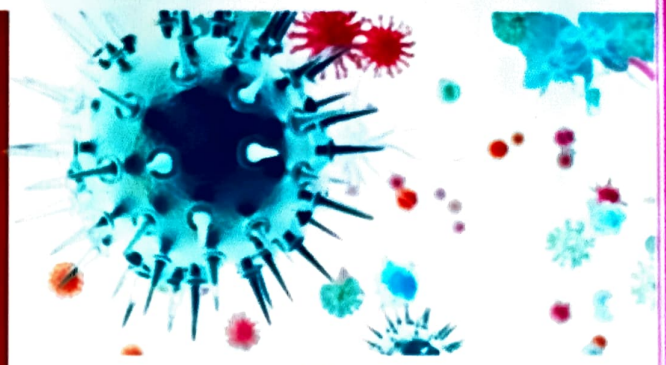
- ✓ Potential increase in business due to enhanced **customer confidence** and **satisfaction**. Savings in terms of time and money due to reduction or elimination of the need for **re-testing**.
- ✓ Better control of **laboratory operations** and feedback to laboratories as to whether they have sound **Quality Assurance System** and are technically competent.

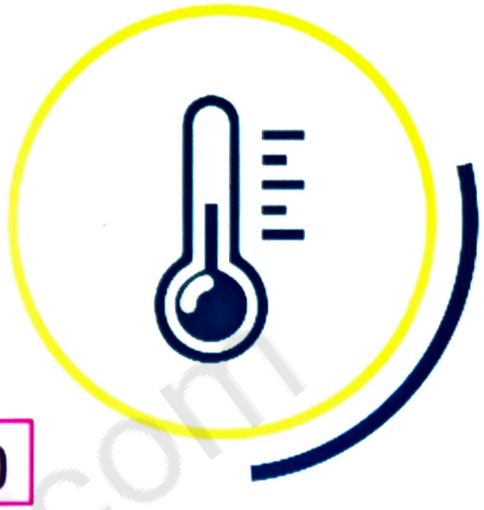
NABL ACCREDITED

- ✓ Increase of confidence in **Testing / Calibration data** and **personnel performing work.**
- ✓ Customers can **search** and **identify** the laboratories accredited by NABL for their specific requirements from the directory of **Accredited Laboratories.**
- ✓ Users of accredited laboratories will enjoy greater access for their products, in both domestic and international markets, when tested by accredited laboratories.
- ✓ **Proficiency testing providers** play an important role in the value chain for assurance of products and services. Being an accredited PTP gives the organization credibility for their PT services.

**NABL Accreditation is currently given in the following fields and disciplines:**

- Biological
- Chemical
- Electrical
- Electronics
- Fluid-Flow
- Mechanical
- Non-Destructive Testing
- Radiological
- Thermal
- Forensic





# GOOD LABORATORY PRACTICES (GLP)

## ❖ DEFINITION

- **GLP embodies a set of principles that provides a framework within which laboratory studies are planned performed, monitored, and archived and reported.**

## ❖ PURPOSE OF GLPS

1. GLP is to certify that every step of the analysis is valid or Not.
2. Assure the **quality** & **integrity of data** submitted to FDA in support of the safety of regulated products.
3. GLPs have **heavy emphasis** on **data recording, record & specimen retention.**

## ❖ PRINCIPLES OF GOOD LABORATORY PRACTICES

| | | | |
|---|---|---|---|
| **1.** | Test Facility Organization and Personnel. | **4.** | Test systems |
| **2.** | Quality Assurance Programme (QAP) | **5.** | Test and Reference Substances |
| **3.** | Facilities | **6.** | Standard Operating Procedures(SOP) |

| | | | |
|---|---|---|---|
| 7. | Apparatus, Material and Reagents. | 9. | Performance of The Study |
| 8. | Reporting of Study Results | 10. | Storage and Retention of Records and materials |

## ❖ BENEFITS OF GOOD LABORATORY PRACTICES

1. It will give **better image** of company as a **Quality producer** in Global market.
2. Provide hot tips on **analysis of data** as well as measure uncertainty and perfect record keeping.
3. Provide guidelines for doing **testing** and **measurement** in detail.
4. Provide guidelines and better control for maintenance of **instruments, environment control, preservation of test records etc.**