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UNIT-IV

# Quality Management Systems

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**Abstract:** Quality management & Certifications: Concept of Quality, Total Quality Management, Quality by Design (QbD), Six Sigma concept, Out of Specifications (OOS), Change control, Introduction to ISO 9000 series of quality systems standards, ISO 14000, NABL, GLP

**Keywords**: Adoption, Collaboration, Deployment, Innovation, Knowledge, Transfer

## 1.1 Total Quality Management

**Total:** composed of the entire

**Quality** is the level of quality that a good or service offers;

**Management** is the art, practice, or act of planning, guiding, and managing. Thus, Total Quality Management (TQM) is the art of managing everything to achieve perfection.

**Characteristics of TQM**

- Devoted administration.
- Implementing & disseminating complete quality management.
- Improved customer service.
- Closer relationships with providers.
- Setting benchmarks.
- More instruction.
- An open structure
- Empowerment of employees.
- Adaptable manufacturing.
- Enhancements to the process.

- Measurement of the process

**Principles of TQM**

- Deliver high-quality work each and every time.
- Pay attention to the client.
- Approach improvement strategically.
- Make constant progress.
- Promote cooperation and respect for one another.

**TQM's components**

- Pay attention to the client.
- Participation of employees
- Continuous improvement

**Focus on the customer**

- External customers use the company's goods or services; it is crucial to identify the company's clients.
- Since quality is regarded as everyone's responsibility, employees should participate in quality initiatives.
- Employees who receive the products of other employees are known as internal customers.
- Considering frontline staff members are likely to interact with external clients the most, they can contribute the most to quality.
- Therefore, the ability to innovate and enhance quality must be granted to personnel.

**Continuous Improvement**

- In the never-ending quest for quality, people are always looking to improve the product or service's functionality, speed, and feature count.
- The idea behind continuous improvement is that small, regular enhancements will eventually result in a notable improvement in quality.
- To continually enhance every function, the Total Quality Management (TQM) management approach is employed.
- It is a constant, continual commitment to improvement.
- A concept of management that encourages achieving customer needs via ongoing improvement forms the basis of total quality.

**Continuous Process Improvement**

Consider every task as a commercial and production process, including design, invoicing, purchasing, and so forth.

- Inputs, processes, and results.
- Process enhancement: higher levels of client satisfaction.
- There are five ways to improve: cut down on resources, cut down on mistakes, satisfy downstream customers expectations, make the process safer, and increase worker satisfaction

**Benefits Of TQM:**

- Better quality.
- The involvement of employees.
- Cooperation.
- Collaborations.
- Client contentment.
- Worker contentment.
- Efficiency.
- Interaction.
- Profitability.

**Importance of TQM in pharma industry Handling:**

- Gently open containers, then reseal them using the proper procedure. Examples of highly sensitising substances that should be handled in separate manufacturing facilities are cephalosporin's and penicillin's.
- APIs that are extremely poisonous or powerful (like some steroids or cytostatic compounds) ought to be produced in a specific location with specialized machinery.
- Handling pure and completed API in a setting that provides sufficient protection against contamination is essential.

**Storage:**

- To avoid material deterioration or damage, secure storage facilities should be designated for use, maintained tidy and orderly, and subjected to the proper pest control techniques.It is essential to record environmental conditions.

- At suitable intervals, the state of the substance being stored should be evaluated.
- Stability studies that take into account factors like time, temperature, humidity, light, etc. should serve as the foundation for api storage conditions.

**Packaging:**

- To guarantee that the right materials are utilized and that other requirements are fulfilled, labelling and packing procedures should be created and monitored.
- Printed labels should be kept in a secure location to prevent confusion.
- Labels and markings should be readable, durable, and, if appropriate, include the expiration date, retest requirements, and/or required storage conditions in addition to providing sufficient information for accurate identification.

**Facilities and equipment:**

- Building placement, design, and construction should be appropriate for the type and stage of manufacture in order to protect the product from contamination, including cross-contamination, as well as to protect the environment and operators from the product.
- Equipment surfaces that come into contact with api-making materials shouldn't react.

**Sterile area**

- Employees with infectious disorders or open lesions on exposed body parts should refrain from activities that could compromise the quality of API.
- Only places that are separate from production or control areas should be used for eating, drinking, chewing, smoking, and storing food.
- Labelling
- The product identity, the batch code, or any other clearly comprehensible combination of the two must be printed on the proper label for every container.
- Additional labels could be needed for containers intended for external distribution.

**Computerised system:**

- When manually entering quality-critical data, a second independent check should be made to ensure the accuracy of the first entry.
- Computer systems ought to be constructed and operated to guard against illegal access or program changes.
- Every significant piece of high-quality data needs a backup system. **Advantages of TQM**

- Enhances reputation by promptly identifying and resolving issues and flaws.
- Improved morale among staff members: Greater responsibility, collaboration, and participation in TQM decisions inspire staff members.
- More affordable.
- Less waste because fewer products are defective and extra packaging is not required.

**Disadvantages of TQM**

- The adoption's upfront costs.
- It may take several years before the benefits become evident.
- Employees may be reluctant to adapt. An organizational management model.

**Benefits Total Quality Management**

- The option to charge higher rather than competitive rates, better sales and investment returns, and lower expenses are some of the financial advantages.
- Greater client retention rates, easier access to international markets, and less
- The amount of time needed to create innovative technologies and establish a solid reputation as an industry leader.
- One such strategy is Total Quality Management (TQM), which aims to raise performance and quality to either meet or surpass customer expectations.
- **CONCLUSION:**
- Rework is reduced to nearly zero when quality management is used, which is a realistic objective.
- TQM encourages managers, employees, and the company as a whole to get involved. Effective organisation is the only way for pharmaceutical producers to fulfil their significant legal, social, and professional responsibilities to guarantee the quality of their goods.
- The workplace culture and employees' complete involvement. It should be recognised that the application of both national and international regulations must be methodical.
- Strict control must be used.
- TQM, an organisational strategy that prioritises quality as an overarching objective, seeks to avoid errors rather than identify them. Quality is therefore a key element of

modern organisational success.

## 1.2 Quality By Design (QbD)

**Definition:**

"A methodical approach to development that starts with predetermined goals and places an emphasis on understanding products and processes as well as process control, based on sound science and quality risk."

The concept of QBD was brought up in relation to the ICH Q8 criteria, which state that "Quality cannot be tested in products; quality should be built into product by design."

**Advantages:**

- Benefits to the sector
- A better comprehension of the procedure.
- The number of batch failures has decreased.
- Change management that is more successful and efficient.

**Additional opportunities:**

- A drop in submissions following approval.
- A more efficient transfer of technologies to manufacturing.
- A methodology and identification based on risk.
- New methods for validating processes.

**Objectives:**

- The primary goal of QBD is to guarantee superior products; in order to do this, process and product qualities that are essential to planned performance must result from a combination of fresh estimation made during development and information already in existence.
- With this information and data, desirable attributes can be produced and the process can be measured.
- Assures the integration of process and product expertise acquired during development.

**Key Aspects of QbD:**


**Fig. No. 4.1:** Key Aspects of QbD

**The Target Product Quality Profile (TPQP)**

To ensure that a medicinal product's intended quality and, by extension, its safety and efficacy is realised, TPQP is defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved."

TPP serves as the foundation for product design in the following ways:

- Administration route for dosage forms
- Strength Release.
- A feature of pharmacology
- Requirements for pharmaceutical product quality.
- The sophistication of drugs.

**Critical Quality Attributes (CQAs):**

- Finding the pertinent CQAs comes next after TPQP is established.
- A CQA is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distributed" to guarantee the quality of the intended product.

- To do these risk evaluations, prior product data is essential, such as the entire laboratory, nonclinical, and clinical experience with a particular product-quality attribute.

**Critical Process Parameters (CPPs) :**

- CPPs are defined as "parameters whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality."
- The ability of a process to exhibit satisfactory quality and performance while simultaneously withstanding input unpredictability is known as process resilience.

**Risk Assessment:**

- Quality risk management is the systematic process of assessing, managing, discussing, and re-examining risks to the quality of the pharmaceutical product during the course of its lifecycle.
- Quality risk assessment (QRA) can be quite thorough even though it aids in reducing the initial list of possible criteria that could affect CQAs.

**Design Space:**

- The design space, as defined by ICH Q8(R2), is a complex interplay between input variables (such material characteristics) and process parameters that have been demonstrated to ensure quality.
- Design space work is not considered a modification. One change that usually initiates the post-approval regulatory change process is leaving the design space.

**Control Strategy:**

- According to the definition of control strategy, "a planned set of controls, derived from current product and process understanding that assures process performance and product quality"
- The ability to use process data, which typically comprises of a valid combination of process controls and measurable material attributes, to evaluate and ensure the quality of the final product and/or the product produced throughout the process. ICH Q8 (R2).
- Some of the components that may be part of the control strategy are procedure controls, in-process controls, lot release testing, process monitoring, characterisation testing, comparability testing, and stability testing.

**Life Cycle Management:**

- With fewer post-approval filings, process improvements in terms of consistency and throughput could take place across the product life cycle.
- Why because process modifications within the design space do not require examination or permission when using the QBD paradigm.

**Significance:**

- The process of designing and developing manufacturing processes and formulations to provide a specific level of quality is referred to as "quality by design."
- Quality by Design necessitates knowledge of how formulation and manufacturing process elements affect product quality.
- Quality by Design ensures high-quality products through efficient control methods.

## 1.3 Six Sigma

Six Sigma seeks to improve the quality of process outputs by identifying and removing the underlying causes of defects. The statistical and managerial defects in a product are compiled by the Six Sigma approach. The concept of variation states that "NO two items will be exactly the same." In a process that has achieved six sigma capability, the variance is negligible in relation to the specification limit. According to statistical predictions, 99.9999966% of products made with the six-sigma approach should be free of defects (3.4 faults per million). Many TQM (total quality management) components can be creatively packaged and branded using the Six Sigma methodology. (TQM is a management approach that leverages customer satisfaction to attain sustained performance.) Six Sigma manufacturing methods are used in batches.

**Characteristics of Six Sigma:**

- The word "six sigma" comes from Greek letter "sigma," which in statistics stands for standard deviation, which is used to measure output quality nonconformance.
- Methodical Approach: Six Sigma has a well-defined methodical application in DMAIC and DMADV that can be applied to high-quality production, making it more than just a quality improvement approach, according to the theory.
- Fact-and-Data-Based Method: Six Sigma's systematic and statistical components demonstrate the technique's scientific foundation. This highlights a key component of Six Sigma, which is its fact-and-data-based methodology.
- Project and Objective-Based Focus: The Six Sigma methodology is used to execute

a project that is customized to a business's requirements and specifications. To get the greatest results, the strategy is adjusted to fit the needs and circumstances of a project. Additionally, Six Sigma is based on objective data.

- To invest in the Six Sigma process, management requires some sort of incentive. Its goal is to increase profitability and produce revenue.
- A key component of the Six Sigma methodology is the customer focus. The criteria for quality improvement and control are based on the particular requirements of the client.
- Cooperation Methodology for Quality Control: Businesses must set up their internal structures in accordance with the Six Sigma process in order to manage and enhance quality. The Six Sigma approach consists of

**Six Sigma Objectives:**

- Overall Business Improvement: The Six Sigma methodology's main goal is to improve business. beyond lowering the quantity of flaws in a specific quantity of goods.
- Address Variability/Defects: Any company that wants to expand needs to create fewer faulty goods or services. Items with flaws could negatively impact consumer satisfaction.
- Reduce Costs: Lower expenses translate into more profits. When using Six Sigma principles, a company should aim to reduce expenses wherever possible without compromising.
- Reduce Cycle Time: Any decrease in the time required to manufacture a good or provide a service results in cost savings on staff compensation and maintenance. When retailers and end users receive things earlier than anticipated, customer happiness also increases. The business can acquire a product.

**Methodologies**

There are two project approaches used in Six Sigma projects:
1.DMAIC
2.DMADV

1.DMAIC: Projects that strive to enhance an existing business process employ DMAIC. There are five stages in the DMAIC project methodology:

1.Describe
2. Step
3. Examine
4. Enhance
5. Command

2.DMADV: Projects aiming at developing new process or product designs employ

DMADV. The five phases of the DMADV project approach are:

1.Describe
2. Step
3. Examine
4. Design
5. Check

## 1.4 Out Of Specification (Oos)

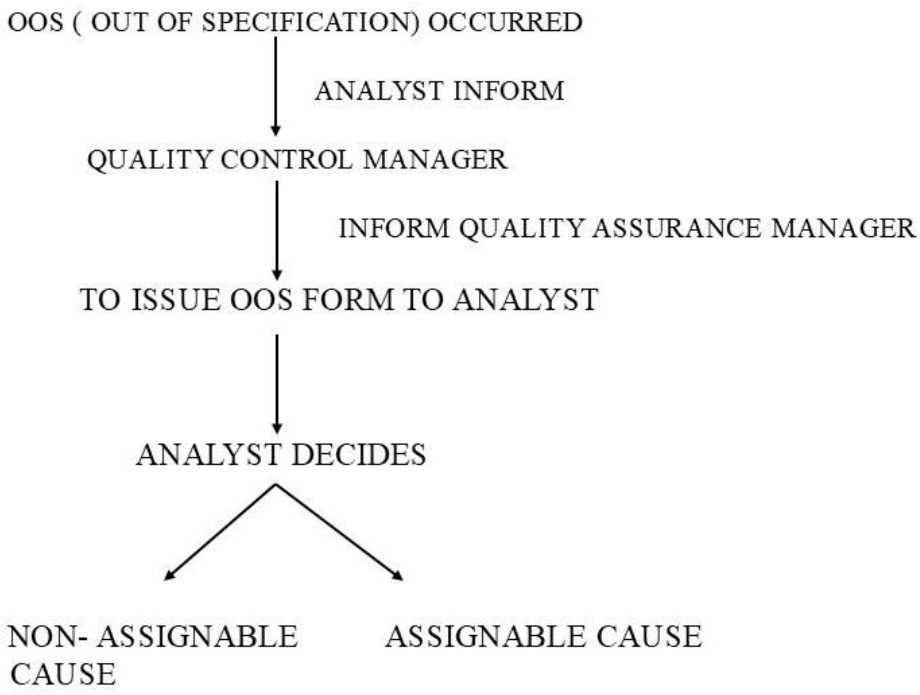
Test results from in-process or finished goods that deviate from established parameters are referred to as "out of specification," or "OOS," and are recorded in compendia, drug master files, or drug applications.

An OOS may be caused by flawed analytical equipment, anomalies in the product production process, or mistakes in the testing procedure.

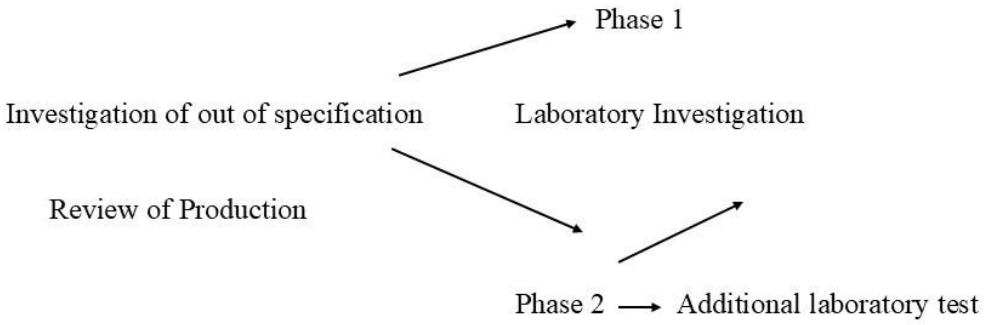
One group of factors that contribute to OOS is

1. Assignable
2.Non assignable

**Schematic representation:**



**Investigation of OOS results:**




## 1.5 Change Control

The methodical process of keeping an eye on modifications made to a system or product is known as change control. The goal is to make sure that resources are used effectively, that no needless changes are made, that all changes are documented, and that services are not abruptly stopped.

**Procedure:**

a. Initiating department will use change control format to begin the modification.

b. The proposed change, the current procedure or use, the effect analysis and rationale,

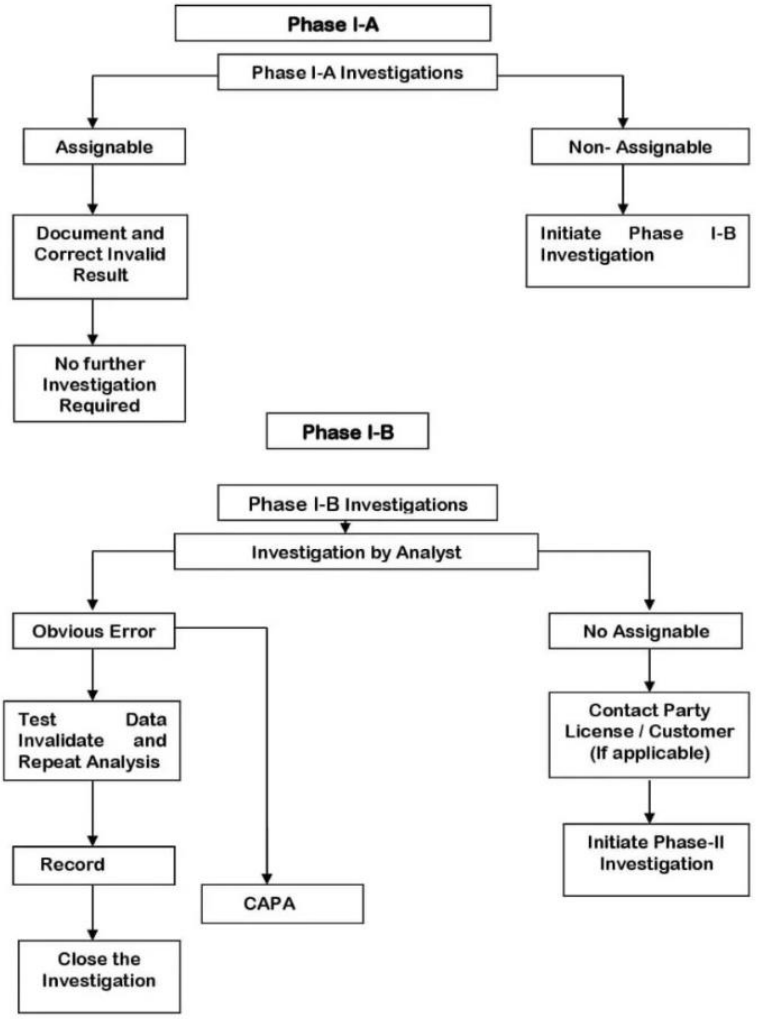
and the acceptance criteria must all be explicitly stated in the form by the initiating department.

c. The initiating department will also decide if the changes are significant or minor based on the quality of the product or how it impacts environmental, health, and safety aspects. some of the major and minor changes is provided below:

**Major Changes:**

- An evaluation the quality of a chemical and microbiological substance. Changing the formulation production process by adding a new step or eliminating an existing one.
- A new production site is added, and the formulation manufacturing process that was previously detailed in the dossier or document is modified.

- A shift in the quantity of input utilized during the manufacturing process of formulation.
- Variations in the primary raw material's or intermediate's quality throughout the formulation production process.



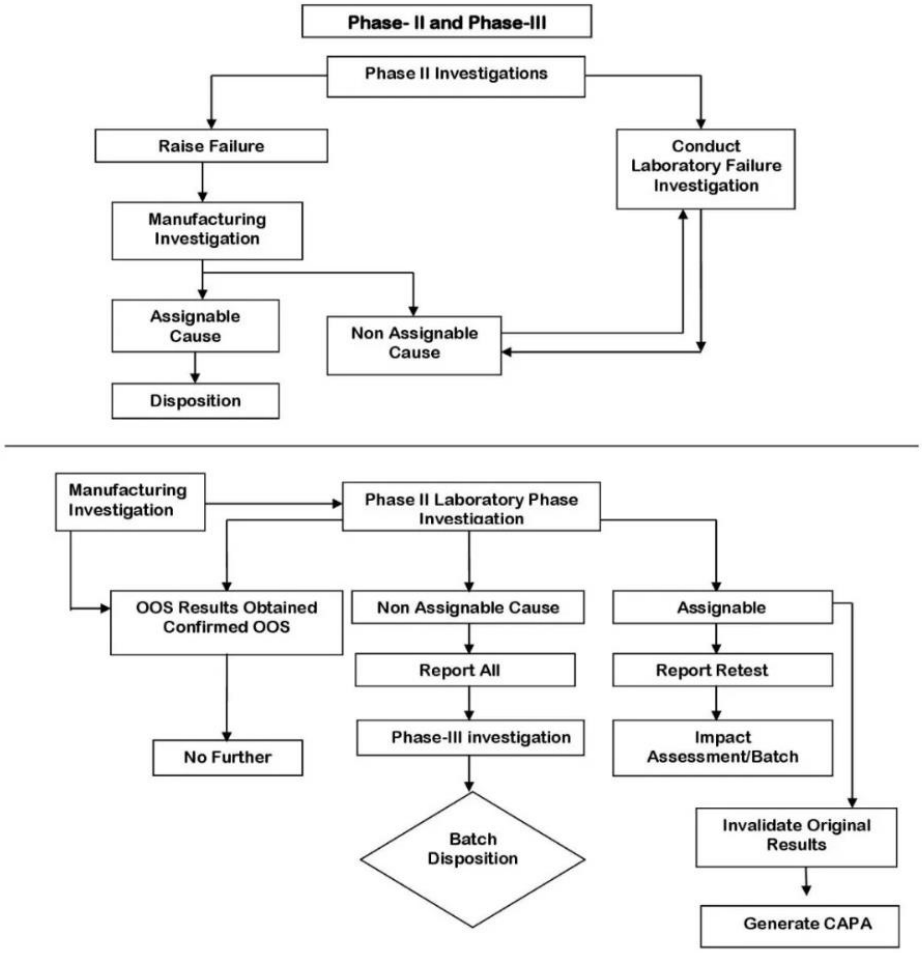



**Table No.4.2:** Schematic representation of OOS for phase I and II

**Minor Changes:**

- The certificate holder's administrative references, including name, firm name, and address, have been changed.
- A change to the references (name, address, and firm name) for the manufacturing facility.
- Modernisation or modification of the analytical methods for material testing.
- A change to the substance's specifications.
- An initial shift and a supply of packing materials.

- A change in batch size.
- The construction of new production plant on land that was initially described in the dossier.
- Changes to other publications and SOPs.
- The primary benefits of the Change Control System are:
- A consistent, deliberate approach to change management
- Documenting the modification's specifics.
- Sending requests for modifications to the appropriate individual or group for approval documentation of the changes' implementation and approval.
- Simple information retrieval and change history preservation.
- Keeping an eye on changes

## 1.6 Quality Standard – ISO 9000

1. Regarding quality management systems, the ISO 9000 set of standards is designed to help businesses meet their legal and regulatory requirements as well as the demands of stakeholders and clients.
2. ISO 9000 covers the fundamentals of quality management systems, including the eight management principles that serve as the framework for the family of standards.
3. International standards promote international trade by providing a single, universally recognised set of requirements.
4. A business can accomplish continuous improvement, regulatory compliance, and customer satisfaction using ISO 9000. Although it offers the foundation for a quality system, quality is not always guaranteed.
5. The International Organisation for Standardisation (ISO), a global standardisation body composed of 90 national standards organisations, first published it in 1987.

**Eight Quality Management Principles:**

i. Customer-focused
ii. Individual participation
iii. Process-based leadership approach
iv. Management based on systems
v. Continuous improvement
vi. A decision-making process grounded in facts
vii. Supplier partnerships that are mutually advantageous

**ISO 9000 Series:**

1. ISO 9000: Outlines fundamental quality concepts & provides guidance on selecting and applying each standard.
2. ISO 9001: Design, development, manufacture, installation, and maintenance quality assurance methodology.

3. ISO 9002: Quality Assurance Model for Production and Installation of Manufacturing Systems.
4. Ensuring quality in final inspection and testing (ISO 9003).
5. ISO 9004: Guidelines for Using Standards in Quality Management &Systems

**Advantages**

- Preserving quality and upholding
- Market trust is significantly impacted by ISO registration.
- An opportunity to compete with larger companies.
- The customer is given more consideration.
- Confirmation of your company's commitment to excellence.
- Could increase market opportunities and encourage trade.
  May increase client confidence & satisfaction.

## 1.7 International Organization For Standardization (ISO 14000)

- ISO is an international standard-setting body composed of representatives from various national standards organisations that was founded on February 23, 1947. Promoting international proprietary, industrial, and commercial standards is its goal. Its headquarters are in Geneva, Switzerland.
- Businesses are intended to benefit from the ISO 14000 set of environmental management standards.
- Minimise their operations' adverse consequences on environment (i.e., harmful alterations to water, land , or air).
- Continually improve the previously described while abiding by applicable laws, regulations, and other ecologically minded standards.

**ENVIRONMENTAL MANAGEMENT SYSTEM:**

A framework known as an Environmental Management System (EMS) helps a company govern its operations consistently so that it can achieve its environmental objectives. It is anticipated that this enhanced oversight will lead to an improvement in the company's environmental performance.

**STANDARDS UNDER ISO 14000 SERIES:**

- ISO 14001 is an EMS standard.
- ISO 14010 series of standards are about auditing.
- ISO 14020 is about environmental labelling.

- ISO 14030 is a standard on environmental performance evaluation.
- ISO 14040 series are on environmental life cycle assessment(LAC)

**ISO 14001 STANDARD:**

ISO 14001, sometimes referred to as a general management system standard, is applicable to any company that wants to improve and manage its resources. This includes:

- A single location for large, global companies.
- From high-risk companies to service providers with minimal risk.
- The governmental and private sectors, as well as every industry segment
- Original equipment producers and suppliers
- Municipal governments as well as the manufacturing, process, and service sectors.

**BASIC PRINCIPLES AND METHODOLOGY:**

- To Plan
- To Do
- To Check
- To Act

**Advantages:**

- Assists a company in upholding an efficient quality system
- Any type of organisation can use it.
- It reassures the customer about the quality of the products being sold.
- It acts as an obstacle to competition.

## 1.8 National Accreditation Board for Testing and Calibration Laboratories (NABL)

NABL specifies the general prerequisites for performing tests and calibrations, including sampling. It includes testing and calibration using both standard and non-standard methods as well as methods created in laboratories.

Technical competence accreditation (recognition) is provided for medical laboratories, proficiency testing providers (PTPs), reference material producers (RMPs), and testing and calibration services by an independent organisation know as NABL NABL stands for National Accreditation Board for Testing and Calibration Laboratories. The International Laboratory Accreditation Conference (ILAC) and the Asia Pacific Laboratory Accreditation Cooperation (APLAC) have agreements with NABL. These are very helpful for worldwide recognition of test results and for mutual acceptance. In

conclusion, certification is recognised globally.

**NABL Mission:**

By providing top-notch, value-driven services, creating APLAC/ILAC MRA, employing certified assessors, increasing stakeholder awareness, starting new projects to support accreditation activities, and aiming for organisational excellence, NABL hopes to improve the internationally renowned accreditation system.

**Advantage of accreditation:**

1. Possibility of higher sales as a result of improved client satisfaction and confidence. time and cost savings due to the necessity for fewer or no retests.
2. Enhanced monitoring of lab operations and feedback to labs on the soundness of their QAS and technical proficiency.
3. Increased confidence in the testing/calibration data and the individuals doing the work.
4. Customers can search for and identify NABL-accredited laboratories that match their specific needs by using the Accredited Laboratories database.
5. Their users will have more access to both domestic and international markets when their items are evaluated by accredited laboratories.
6. In order to guarantee the quality of products and services, proficiency testing providers are essential to the value chain. A PTP that has been approved gives the business's physical therapy services credibility. The benefits of proficiency testing are well accepted.

- A performance evaluation of a facility relative to other participating (peer) institutions.
- The performance of the facility is continuously monitored.
- After an inquiry, the cause or causes of poor PT performance were found, and corrective actions were put in place to stop a recurrence, test and calibration performance improved.
- Method evaluation, which entails determining the procedures' level of precision and accuracy.
- Establishing credibility with regulators, accrediting organizations, and consumers.

## 1.9 Good Laboratory Practices (GLP)

**Definition:** GLP is a set of rules that creates a framework for planning, conducting, supervising, recording, and reporting laboratory research.

**Purpose of GLPs:**

1. GLP is in charge of confirming the validity of every phase of the analysis.
2. Verify the accuracy and consistency of the information provided to the FDA to support the safety of regulated products.
3. In GLPs, data collection, documentation, and specimen preservation are highly regarded.

**Good Laboratory Practices Principles.**

1. The Test Facility's Staff and Organisation.
2. The Quality Assurance Program, or QAP.
3. Facilities.
4. Equipment, Reagents, and Materials.
5. Examine the systems.
6. Materials for Reference and Testing.
7. Standard operating procedures, or SOPs.
8. The study's performance.
9. Presenting the study's conclusions.
10. Storage &Retention of Materials & Records.

**Benefits of good laboratory practices:**

1. Enhance the business's standing as a superior producer in the international marketplace.
2. Give practical guidance on measuring uncertainty, analysing data, and maintaining correct documentation.
3. Provide thorough guidelines on how to carry out measurements and testing.

   Provide suggestions and enhanced safeguards for, among other things, environmental management, instrument upkeep, and test record retention.

## Review Questions

**Short Answer 02 marks**

1. Define quality. Emphasize the value of quality kinds.
2. Describe TQM. Incorporate the TQM ideas.
3. Describe TQM. What goals does TQM aim to achieve?
4. Describe the QbD goals.

5. Describe QbD. Discuss about the QbD software.
6. List the benefits and drawbacks of QbD.
7. Outline the Six Sigma goals.
8. Describe ISO 9000. Explain the Significance of ISO 9000
9. Describe ISO 14000. Explain the Significance of ISO 14000

**Short Essay 05 marks**

1. Describe QbD and its essential components.
2. Discuss about the fundamentals of ISO 9000.
3. Briefly describe the TQM tenets and the components of QbD.
4. Write a brief message explaining the Six Sigma idea.
5. Distinguish between DMAIC and DMADV.
6. Describe change management. Talk about the process and advantages of change control.
7. Write on NABL

**Long Essay 10 marks**

1. Describe the SIX SIGMA idea using a variety of approaches.
2. Describe the steps of investigation used to determine the Out of Specifications (OOS).

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