INDUSTRIAL PHARMACY – II (BP702T)

UNIT- IV

TOTAL QUALITY MANAGEMENT:

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.

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

Principles of TQM

1. Produce quality work the first time and every time.
2. Focus on the customer.
3. Have a strategic approach to improvement.
4. Improve continuously.
5. Encourage mutual respect and teamwork

The key elements of the TQM

- Focus on the customer.
- Employee involvement
- Continuous improvement

Focus on the customer

• It is important to identify the organization's customers.
• External customers consume the organization's product or service.
• Internal customers are employees who receive the output of other employees.
• Since the quality is considered the job of all employees, employees should be involved in quality initiatives.

• Front line employees are likely to have the closest contact with external customers and thus can make the most valuable contribution to quality.
• Therefore, employees must have the authority to innovate and improve quality.

Continuous Improvement

• The quest for quality is a never-ending process in which people are continuously working to improve the performance, speed, and number of features of the product or service.
• Continuous improvement means that small, incremental improvement that occurs on a regular basis will eventually add up to vast improvement in quality.
• TQM is the management process used to make continuous improvements to all functions.
• TQM represents an ongoing, continuous commitment to improvement.
• The foundation of total quality is a management philosophy that supports meeting customer requirements through continuous improvement.

Continuous Process Improvement

▪ View all work as process – production and business.
▪ Process – purchasing, design, invoicing, etc.
▪ Inputs – process – outputs.
▪ Process improvement – increased customer satisfaction.
▪ Improvement – 5 ways:
▪ reduce resources, reduce errors, meet expectations of downstream customers, make process safer, make process more satisfying to the person doing

Benefits Of TQM:

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

Importance of TQM in pharma industry Handling:

• Containers should be opened carefully and subsequently resealed in an approved manner.

• Highly sensitising material such as penicillins 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.

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

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.

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 non-reactive.

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.

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.

• . Containers for external distribution may require additional labels.

Computerisedsystems :

• . Computer systems should be designed and operated to prevent unauthorised 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.

Advantages of tqm

• Improves reputation- faults and problems are spotted and sorted quicker.
• Higher employee morale- workers motivated by extra responsibility, teamwork and involvement indecisions of tqm.
• Lower cost.
• Decrease waste as fewer defective products and no need for separate.

Disadvantages of tqm:

• Initial introduction cost.
• Benefits may not be seen for several years.
• Workers may be resistant to change.
A model for organization management.

BENEFITS OF TOTAL QUALITY MANAGEMENT

• Financial benefits include lower costs, higher returns on sales and investment, and the ability to charge higher rather than competitive prices.
• Improved access to global markets, higher customer retention levels, less
• Time required to develop new innovations, and a reputation as a quality firm.
• Total quality management (tqm) is one such approach that seeks to improve quality and
• Performance which will meet or exceed customer expectations.

CONCLUSION:

• TQM encourages participation amongst employees, managers, and organization as whole.
• Using Quality management reduces rework nearly to zero in an achievable goal .The responsibilities either its professional, social, legal one that rest with the pharmaceutical manufacturer for the assurance of quality of product are tremendous and it can only be achieved by well organised.
• Work culture and complete engagement of the employees at the workplace. It should be realised that national & international regulations must be implemented systematically and process.

• Control should be practiced rigorously.
• Thus quality is critically important ingredient to organisational success today which can be achieved by TQM, an organisational approach that focusses on quality as an over achieving goals, aimed at aimed at the prevention of defects rather than detection of defects..

QUALITY BY DESIGN(QbD)

Definition:

'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.

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.

Advantages:

- Benefits for Industry:
- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.

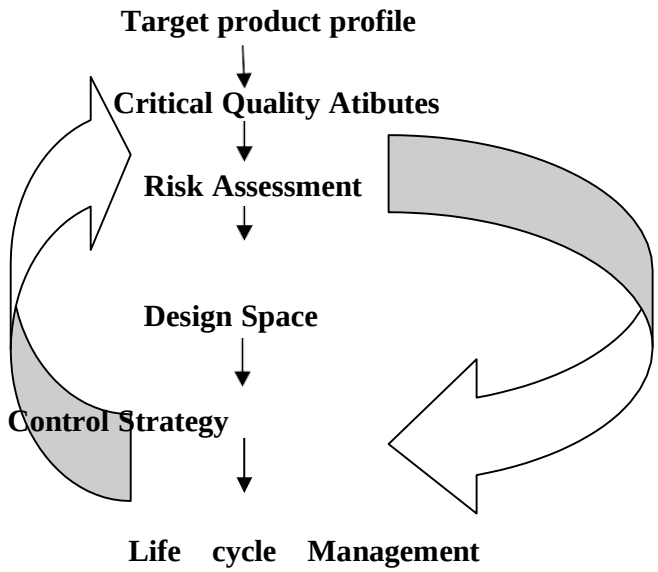
Additional opportunities:

- Reduction of post-approval submissions.
- More efficient technology transfer to manufacturing.
- Risk-based approach and identification.
- Innovative process validation approaches.

Objectives:

- The main objectives of QBD is to ensure the quality products, for that product & process characteristics important to desired performance must be resulting from a combination of prior knowledge & new estimation during development.
- From this knowledge & data process measurement & desired attributes may be constructed.
- Ensures combination of product & process knowledge gained during development.

Key Aspects of QbD:



The Target Product Quality Profile (TPQP):

TPQP has been defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized.

TPP forms the basis for product design in the following way

- Dosage form Route of administration
- Strength Release.
- Pharmacological characteristic
- Drug product quality criteria.
- Pharmaceutical elegance.

Critical Quality Attribute (CQA):

- Once TPQP has been identified, the next step is} to identify the relevant CQAs.
- A CQA has been defined as "a physical, chemical,} biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distributed to ensure the desired product quality.
- Prior product knowledge, such as the} accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments.

Critical Process Parameter (CPPs) :

- Critical process parameters (CPPs) are defined as “parameters whose variability have an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality.
- Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time.

Risk Assessment:

- Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.
- The initial list of potential parameters which can affect CQAs can be quite extensive but can be reduced by quality risk assessment (QRA).

Design Space:

- The ICH Q8(R2) States that the design space is multi-dimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- Working within the design space is not} considered as a change. Movement out of the design space is a change and would normally initiate a regulatory post approval change process.

Control Strategy:

- Control strategy is defined as “a planned set of controls, derived from current product and process understanding that assures process performance and product quality”.
- The ability to evaluate and ensure the quality of in process and/or final product based on process data which typically include a valid combination of measured material attributes and process controls. ICH Q8(R2).
- The control strategy can include the following elements: procedural controls, in process controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing.

Life Cycle Management:

- In the QBD paradigm, process changes within} the design space will not require review or approval.
- Therefore, process improvements during the} product life cycle with regard to process consistency and throughput could take place with fewer post approval submissions.

Significance:

- Quality by Design means –designing and developing formulations and manufacturing processes to ensure a predefined quality.
- Quality by Design requires – understanding how} formulation and manufacturing process variables influence product quality.
- Quality by Design ensures – Product quality with effective control strategy.

SIX SIGMA

Six Sigma seeks to improve the quality of process outputs by identifying and removing the causes of defects. Six Sigma approach is a collection of managerial and statistical deficiencies in product. The concept of Variation states "NO two items will be perfectly identical.

In a process that has achieved six sigma capability, the variation is small compared to the range of specification limit.

A six-sigma process is one in which 99.9999966% of the products manufactured are statistically expected to be free of defects (3.4 defects per million).

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:

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.

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.

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

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.

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.

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:

Overall Business Improvement: Six Sigma methodology focuses on business improvement. Beyond reducing the number of defects present in any given number of products.

***Remedy Defects/Variability*:** Any business seeking improved numbers must reduce the number of defective products or services it produces. Defective products can harm customer satisfaction levels.

Reduce Costs: Reduced costs equal increased profits. A company implementing Six Sigma principles must look to reduce costs wherever it possibly can--without reducing quality.

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. Additionally, customer satisfaction improves when both retailers and end users receive products sooner than expected. The company that can get a product to its customer faster may win her business.

Increase Customer Satisfaction: Customer satisfaction depends upon successful resolution of all Six Sigma's other objectives. 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

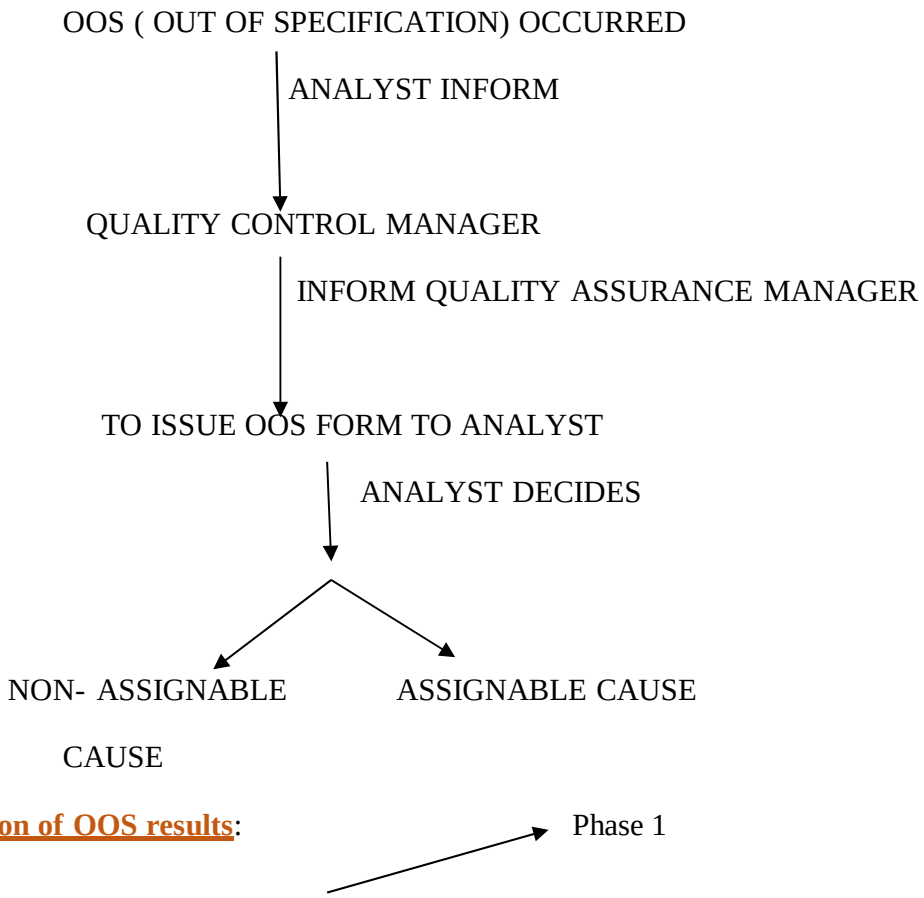
OUT OF SPECIFICATION (OOS)

Definition: 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.

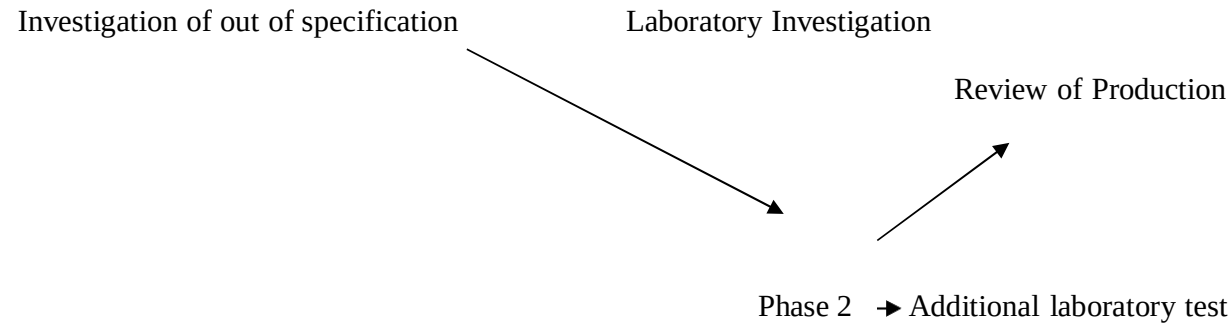
The OOS, may arise due to deviations in product manufacturing process, errors in testing procedure, or due to malfunctioning of analytical equipment.

The reasons for OOS can be classified as
1.Assignable
2.And Non-Assignable.

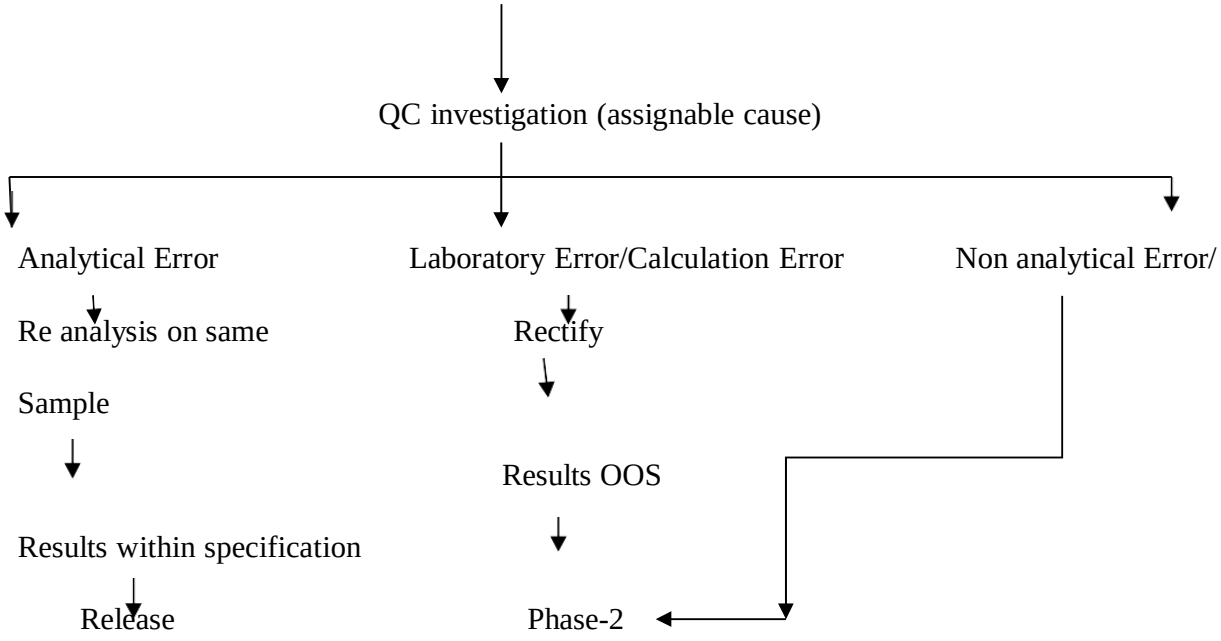
Schematic representation:



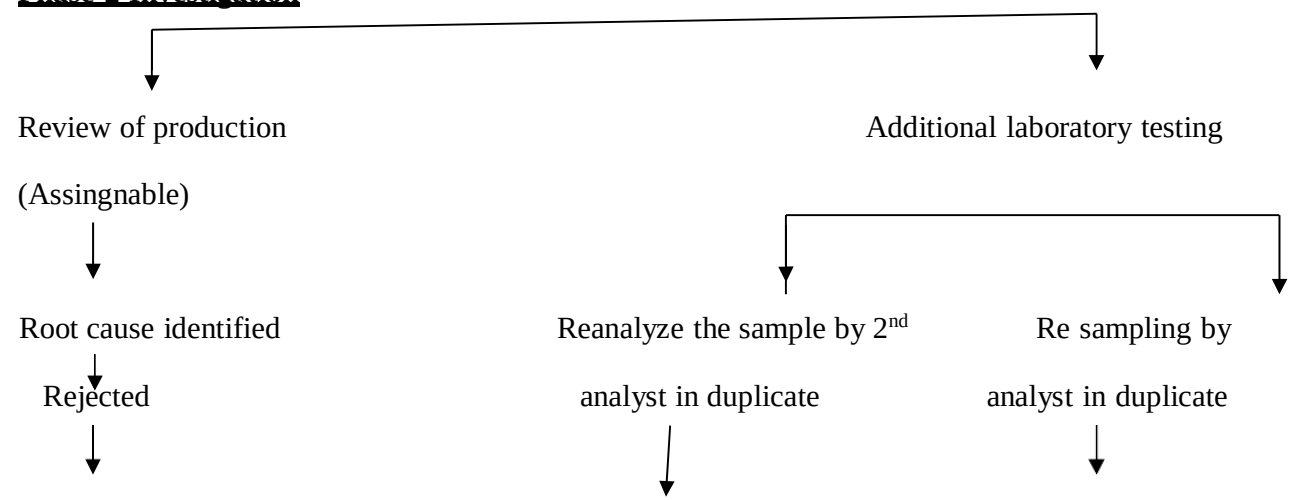
Investigation of OOS results: Phase 1

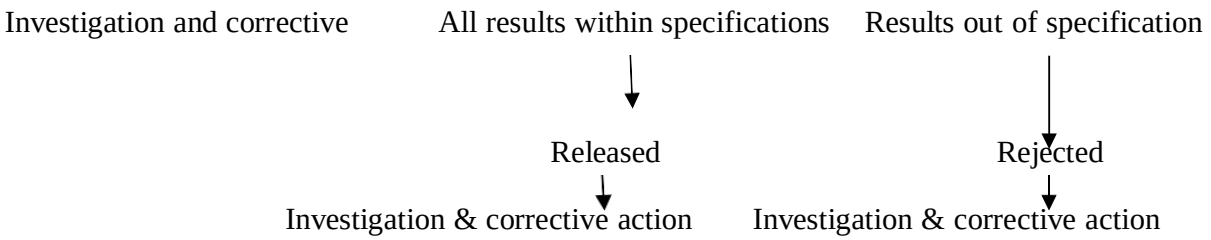


Phase-1 Investigation



<u>Phase-2 Investigation</u>





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.

Quality Standard – ISO 9000

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.

Eight Quality Management Principles:

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

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 bearingon 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 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.

ENVIRONMENTAL MANAGEMENT SYSTEM:

An Environmental Management System (EMS) is a framework that helps a company achieve its environmental goals through consistent control of its operations. The assumption is that this increased control will improve the environmental performance of the company.

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.

BASIC PRINCIPLES AND METHODOLOGY:

- Plan
- Do
- Check
- Act

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, non-standard 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 organisational excellence.

Benefits of Accreditation:

1. 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 .
2. Better control of laboratory operations and feedback to laboratories as to whether they have sound Quality Assurance System and are technically competent.
3. Increase of confidence in Testing / Calibration data and personnel performing work.
4. Customers can search and identify the laboratories accredited by NABL for their specific requirements from the directory of Accredited Laboratories.
5. Users of accredited laboratories will enjoy greater access for their products, in both domestic and international markets, when tested by accredited laboratories.
6. 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. The benefits of proficiency testing are widely recognized. These include
    - Comparison of a facility's performance with that of other participating (peer) facilities.
    - Monitoring of a long-term facility performance.
    - Improvement in the performance of tests/calibrations following investigation and identification of the cause(s) of unsatisfactory PT performance, and the introduction of corrective action to prevent re-occurrence.
    - Evaluation of methods, including the establishment of method precision and accuracy.
    - Confidence building with interested parties, e.g. customers, accreditation bodies, regulators.

    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.

GOOD LABORATORY PRACTICES PRINCIPLES.

1. Test Facility Organisation and Personnel.
2. Quality Assurance Programme(QAP).
3. Facilities.
4. Apparatus, Material and Reagents.
5. Test systems.
6. Test and Reference Substances.
7. Standard Operating Procedures(SOP).
8. Performance of The Study.
9. 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.

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