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CHAPTER -4 Quality Management Systems

SYLLABUS: Quality management and 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.

Syllabus Topic: Quality Management System: Concept of Quality

Introduction:

Quality Management System (QMS) is an important aspect for the pharmaceutical industry for maintaining the quality and safety for their products and services. QMS relies on the regulations and guidelines to maintain the effective quality in pharmaceutical industries.

According to US FDA, the international harmonized guidance is intended to assist pharmaceutical manufacturers by describing a model for an effective quality management system for the pharmaceutical industry. This guidance is referred as ICH (International Council for Harmonization) guideline.

Quality

Quality can be defined according to US FDA as; "A measure of a product's or service's ability to satisfy the customer's stated or implied needs."

Quality in Pharma Industry

Due to the effect of globalization, market competition, cost constrains, supply and demand, complexity of supply chain system and development of international guidelines and regulations, the environment of pharmaceutical industry is changing day by day. The quality, safety and efficacy cannot be ignored or compromised as pharma-industry is directly concerned with the patients to provide them zero defect products.

Quality Assurance (QA)

According to WHO, "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

Quality Control (QC)

QC is that part of GMP concerned with sampling, specification, testing, documentation and release procedures which ensure that the necessary and relevant tests are performed and the product is released for use only after ascertaining its quality.

Scope of Pharmaceutical QMS

According to US FDA, pharmaceutical QMS is applied to the development and manufacture of pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle. For the purpose of this guidance, the following technical activities can be included:

Pharmaceutical Development:

- Drug substance development.
- Formulation development (including container/closure system).
- Manufacture of investigational products.
- Delivery system development (where relevant).
- Manufacturing process development and scale-up.
- Analytical method development.

Technology Transfer:

- New product transfers during development through manufacturing.
- Transfers within or between manufacturing and testing sites for marketed products.

Commercial Manufacturing:

- Acquisition and control of materials.
- Provision of facilities, utilities and equipment.
- Production (including packaging and labeling).
- Quality control and assurance.

ICH Guidelines

ICH guideline is intended for bringing together the regulatory authorities and pharmaceutical industries together for the discussion of the scientific and technical aspects of drug registration.

It is divided into four categories (QSEM):

Q: Quality guidelines - It includes stability, impurities testing, GMP.

S: Safety guidelines - It includes carcinogenicity, genotoxicity, reprotoxicity.

E: Efficacy guidelines - It includes clinical, pharmacogenomics.

M: Multidisciplinary guidelines - It includes medical dictionary for regulatory activities, electronic standards, non-clinical safety studies, common technical document (CTD).

1. Quality Guidelines:

Harmonization achievements in the quality area include pivotal milestones such as the conduct of stability studies defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quantity based on good manufacturing practice (GMP) risk management.

It includes the following guidelines:

Q1 (A-F): Stability
Q2: Analytical validation
Q3 (A-D): Impurities
Q4 (A-B): Pharmacopoeias
Q5 (A-E): Quality of biotechnological products
Q6 (A-B): Specifications (Test procedures and acceptance criteria for new drug substances and biological products)
Q7: Good Manufacturing Practice
Q8: Pharmaceutical development
Q9: Quality Risk Management
Q10: Pharmaceutical Quality System
Q11: Development and manufacture of drug substances
Q12: Lifecycle management
Q13: Continuous manufacturing of drug substances and drug products
Q14: Analytical process development

2. Safety Guidelines:
ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity.

S1 (A-C): Carcinogenicity studies
S2: Genotoxicity studies
S3 (A-B): Toxicokinetics and Pharmacokinetics
S4: Toxicity Testing
S5: Reproductive Toxicology
S6: Biotechnological Products
S7 (A-B): Pharmacology Studies
S8: Immunotoxicology studies
S9: Non-clinical evaluation for Anticancer Pharmaceuticals
S10: Photosafety evaluation
S11: Non-clinical pediatric safety
S12: Non-clinical bio-distribution Studies for Gene Therapy Products

3. Efficacy guidelines:
It is concerned with the design, conduct, safety and reporting of clinical trials.

E1: Clinical Safety for Drugs used in Long Term Treatment
E2 (A-F): Pharmacovigilance
E3: Clinical Study Reports
E4: Dose-Response Studies
E5: Ethnic Factors (in the Acceptability of Foreign Clinical Data)
E6: Good Clinical Practice
E7: Clinical Trials in Geriatric Population
E8: General Considerations for Clinical Trials
E9: Statistical Principles for Clinical Trials
E10: Choice of Control group in Clinical Trials
E11: Clinical Trials in Pediatric Population
E12: Clinical Evaluation by Therapeutic Category
E14: Clinical evaluation
E15: Definitions in Pharmacogenetics
E16: Qualification in Genomic Biomarkers
E17: Multi-Regional Clinical Trials
E18: Genomic Sampling
E19: Safety Data Collection
E20: Adaptive Clinical Trials

4. Multidisciplinary Guidelines:
Some highlights of this guideline are:

M1: ICH medical terminology	**M6:** Gene Therapy
M2: Electronic Standards	**M7:** Mutagenic impurities
M3: Nonclinical Safety Studies	**M10:** Bioanalytical Method Validation
M4: Common Technical Document-CTD	**M12:** Drug Interaction Studies

Sources of Quality Variation
1. Materials:
(a) Variations among suppliers of same substances.
(b) Variations among batches from same suppliers.
(c) Variations within a batch.

2. Machines:
(a) Variation of equipment of same process.
(b) Difference in adjustments of equipment.
(c) Aging of machines and improper care.

3. Methods:
(a) Wrong procedure.
(b) Inadequate procedure.
(c) Negligence in procedure by chance.

4. Personnel:
(a) Improper working conditions.
(b) Inadequate training and understanding.
(c) Lack of interest and emotional upheavals.
(d) Dishonesty fatigue and carelessness.

Control of Quality Variation
The mistakes can be controlled, minimized or eliminated by material control; packaging control and GMP variations can be controlled when Quality Control, Quality Function, and Quality Assurance work side by side.
Controlling each and every step of process can control variations. Control can be divided into:

1. Material control
2. Manufacturing practice control
3. Packaging control
4. Distribution control

Syllabus Topic: Total Quality Management

Introduction
The pharmaceutical industry is key part of the health care system. The regulation of this

industry is very important because one mistake in production or design can cause more severe condition in relation to health care system. So, the maintenance of the quality of the drugs is so important in pharmaceutical industries because the poor quality of drugs can cause health hazards and economical burden for both the government and patients. Total quality management is improvised in the industries to maintain the quality and safety of the drugs and prevention of the defects rather than the detection. The pharmaceutical quality system is described under ICH guideline Q10. The concepts, key points of quality improvement of TQM were proposed by several eminents like Edward Deming, Joseph Juran, Philip Crosby, Genichi Taguchi, etc.

Definition

As per International Organization of Standard (ISO), TQM is defined as: "A management approach of an organization centered on quality, based on participation of all its members and aiming at long term benefits to all members of the organization and society".

Focus of TQM

There are three main key components of TQM:

1. Consumer/Customer focus
2. Involvement of employee
3. Continuous improvement

TQM is controlled by customer focus, process (planning, management and improvement) and total participations. According to previous literature (Mazumder et al, 2011), the key ingredients of TQM are:

1. Strategic commitment by the management
2. Employee involvement
3. Materials used in the organizations
4. Precise techniques used by the organizations and
5. Improved methods

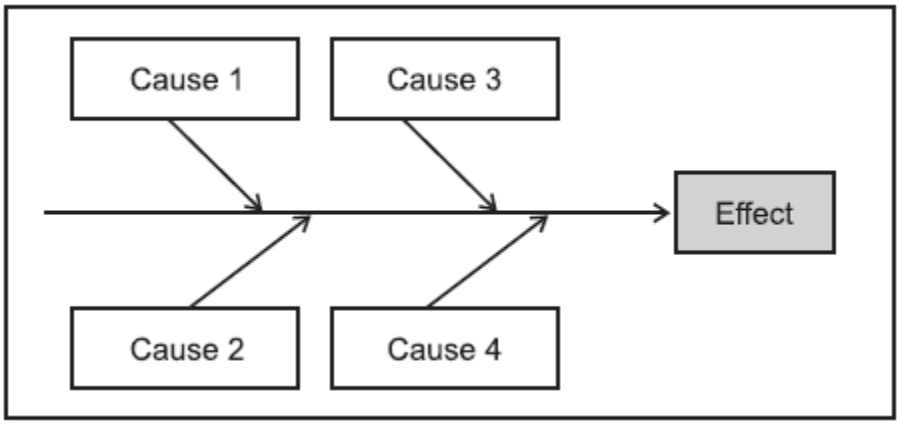
Statistical Quality Control

To achieve accuracy, statistics play an important role in quality management systems. The seven major tools used for statistical process control are:

1. Histogram: A histogram is an accurate representation of the distribution of numerical data (related with one variable).

2. Pareto chart: A Pareto chart is a type of chart that contains both bars and a line graph, where individual values are represented in descending order by bars, and the cumulative total is represented by the line.

3. Cause and effect diagram (Fish bone diagram): It helps to identify the possible causes of a specific problem or quality characteristic.



Cause and effect diagram

4. Defect concentration diagram.

5. Control chart: The control chart is a graph used to study how a process changes over time. Data are plotted in time order. A control chart always has a central line for the average, an upper line for the upper control limit and a lower line for the lower control limit.

6. Scatter diagram: The scatter diagram graphs pairs of numerical data, with one variable on each axis, to look for a relationship between them. If the variables are correlated, the points will fall along a line or curve.

7. Check sheet: The check sheet is a form or document used to collect data in real time at the location where the data is generated.

Advantages
1. Improve in quality and safety of the drugs.
2. Improvement of customer satisfaction.
3. Improvement of reputation of industry.
4. Total involvement of employee with higher moral and responsibilities.
5. Lower economic burden.

Syllabus Topic: Quality By Design (QbD)

Introduction
Pharmaceutical industries always rely on the continuous improvement in safety, quality and efficacy of the products. The pharmaceutical products are intended for the patient care. So, the priority is enhanced therapeutic benefits and absence of impurities. Therefore, the product should be designed to meet patients' needs and the intended product performance. The product quality and performance are regulated by finished product testing, with understanding of the process and critical process parameters. The US FDA (Food and Drug Administration) has adopted the principles of QbD in the development, manufacturing and regulation of pharmaceutical products. ICH guidelines also focus on the principles of QbD through its guidelines mentioned as ICH Q8 (R2)-Pharmaceutical Development, ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality System) and ICH Q11 (Development and manufacture of drug substances).

Definition
According to US FDA and ICH Q8 (R2) the QbD is a systematic approach to development which includes the prior knowledge of product and process understanding based on the results of studies using design of experiments, use of quality risk management and use of knowledge management.

Objectives of QbD

The main objectives of QbD are as follows:
1. Increasing manufacturing efficiency.
2. Increasing the efficiency in product development.
3. Enhancement of product quality and performances to meet patients' needs.
4. Increase in process capability.
5. Avoidance of regulatory compliances.
6. Incorporation of risk management.
7. Reduction in production costs and waste.
8. Reduction in product variability, defects and rejections.

The main outcomes of QbD are as follows:
1. Maintenance of product quality to meet expected clinical performances.
2. Maintenance of product quality by efficient manufacturing and formulation process.

Elements of QbD

The following elements can be included in the study of QbD:
1. QTPP (Quality Target Product Profile): This profile is related to quality, safety and efficacy.
2. CQAs (Critical Quality Attributes): The study of CQAs helps in the study and controlling of the product characteristics that have impact on product quality.
3. Determination of CQAs of drug substances, excipients, etc. and the selection of the excipients to attain the desired drug quality.
4. Suitable manufacturing process selection.
5. Risk assessment:
• CMAs (Critical Material Attributes)
• CPPs (Critical Process Parameters)
6. Defining a control strategy.

Quality Target Product Profile (QTPP)
It includes:
1. Dosage forms, route of administration, delivery systems.
2. Strength of doses.
3. Container closure system.
4. Pharmacokinetic properties.
5. Drug product quality criteria.

Critical Quality Attributes (CQA)
CQA is related with drug substance, excipients, intermediates (in-process materials) and

drug product. CQA is a physical, chemical, biological or microbiological property (should be within an appropriate limit, range, or distribution) to ensure the desired product quality.

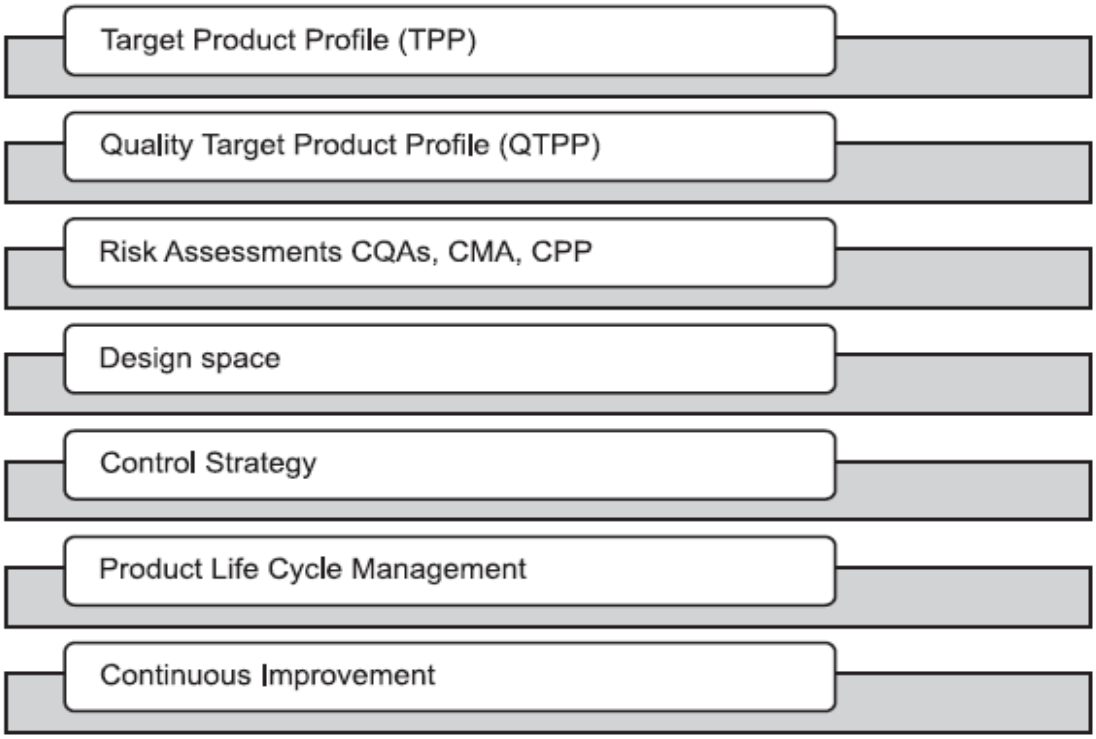
Risk Assessment: CMAs (Critical Material Attributes) and CPPs (Critical Process Parameters)

Risk assessment, a science-based method or process, is used in QRM (Quality Risk Management, mentioned in ICH Q9). This assessment identifies materials attributes and process parameters effectively that have an effect on product CQAs. This process is utilized in prior pharmaceutical development process which makes available more information and knowledge about the development process. Based on prior knowledge and initial experimental data, risk assessment method helps to identify and rank different parameters like process, equipments and input materials with potential that have an impact on product quality.

Control Strategy

The pharmaceutical product should be produced with required quality in consistent fashion and the control strategy ensures this. It includes the following elements:

1. Control of input material attributes *viz.,* drug substance, excipients, packaging materials, considering their utilization and effect on product quality.
2. Product specifications.
3. Controls of unit operations that have a role to maintain the product quality. The operations may include granulation, drying, degradation, particle size distribution, etc.
4. In-process testing.
5. Finished product testing.
6. Testing of products at every stage at regular intervals (Monitoring program).



Quality by Design (QbD)

Syllabus Topic: Six Sigma Concepts

Introduction

Six sigma concepts are a principle for the process improvement. Six sigma represents the quality level which is implemented for reducing the operational costs in pharmaceutical industry and serving the best customer satisfaction and services. Six sigma is symbolized as "6σ". Six sigma is a statistical measurement of product variables. This concept helps to achieve stable and predictable process results with continuous quality improvement.

Aim of Six Sigma Concept

The main aims of the six sigma concept are as follows:

1. Process improvement

2. Improved methodology

3. Improved quality

4. Customer satisfaction

5. Reduction in process variation

6. Reduction in costs

7. Fewer defects to achieve the goal

8. Continuous quality improvement

4.4.3 Six Sigma Process

The concept is designed in "DMAIC" process. DMAIC stands for Define, Measure, Analyze, Improve and Control.

1. Define: 'Define' is the first and more difficult step of six sigma approach. The basic aim of this step is defining the problems and objectives. 'Define' explains project goal, aim, difficulties, target magnitude and time span to achieve the improved process.

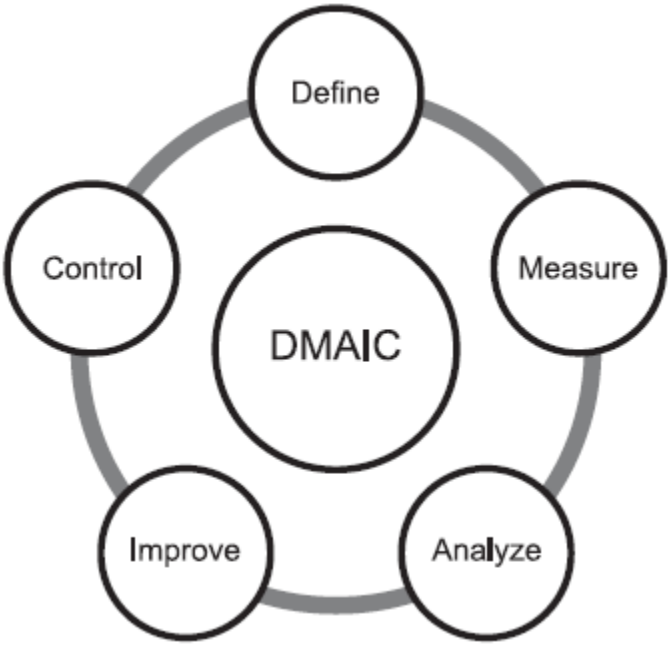
2. Measure: This is the process of collecting expected future data. The data will help to understand the magnitude of improvement and will answer either the expected improvement can be measured or not. The data is not necessarily quantitative.

3. Analyze: This process includes the analysis of the whole process and helps to understand the factors of influence. This is nothing but the analysis of raw data to establish a correlation between input variables and the possible output that implies critical quality attributes (CQAs).

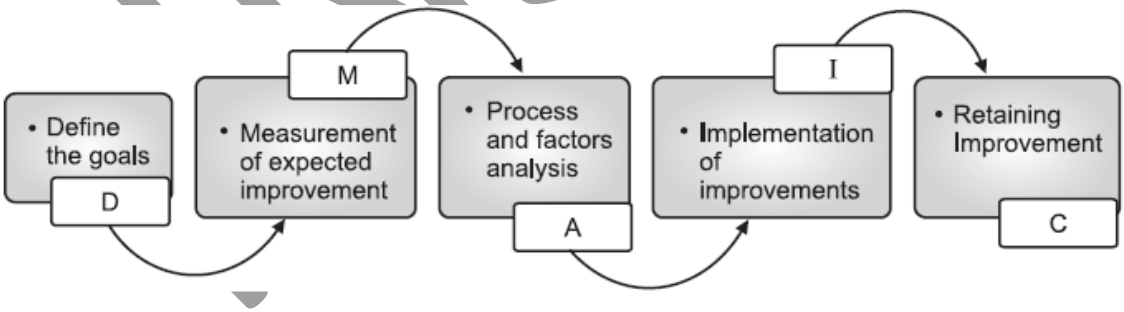
4. Improve: The next step is improvement of the process that has been outlined in the define step to achieve the expected outcome and result. The principles, specifications

and process outflow selected in the first step should be improved and incorporated in the lifecycle with fewer defects.

5. Control: The improvement done in the last step should be retained and additional procedures may be included in the workflow.



Six Sigma Concept: DMAIC



Six Sigma Process: DMAIC

Syllabus Topic: Out of Specifications (OOS)

Introduction

When an analytical or test result of any batch or material is out of prescribed and predetermined limits or specifications, it is called as OOS. OOS may be raised in the case of stability testing, analysis of in-process, test of raw materials, intermediates and

finished goods (API). Investigation for OOS may be performed while getting any unacceptable and questionable results.

Identification of OOS: Reports of Laboratory Investigation

This investigation is conducted when OOS is found in analysis. The main purpose of obtaining OOS reports is to find out the source of the results which fall outside the specifications. In this initial investigation, all the results should be recorded and well documented. The data should be conveyed and forwarded to quality control department, so that full scale analysis can be performed.

Responsibility of Analyst and Supervisor

An analyst has the primary responsibility for the laboratory testing results. He should have sound knowledge about the principle, primary requirements and process of the investigations. The accurate and precise results are expected, if any wrong results are found that should be informed to concern superior department and assessment should be initiated with immediate effect. The supervisor of the laboratory should discuss the problems and the malfunctioned result with the analyst. He should verify the followed correct procedure and knowledge of the analyst. He should overlook the following points:

1. Raw data of the result.

2. Calculations of the result.

3. Proper functioning of instruments.

4. Procedure performed by the analyst.

5. Quality parameters of solvents, reagents, standard solutions.

6. Knowledge of the analyst regarding investigation.

7. Method validation and evaluation of performance.

8. Preservation of the results obtained.

Identification of OOS: Reports of Full-Scale Investigation

When an initial analysis does not confirm the errors caused by OOS result from lab investigations, full scale investigations with proper design should be performed. The identification of the source of the errors and the action taken for the correctness are the main objectives of this investigation. The following are the important aspects of OOS results identification with respect to full scale investigation.

1. Review of manufacturing, production and sampling.

2. Review of lab investigation result.

3. Supplementary laboratory testing procedure.

Review of Manufacturing, Production and Sampling

To find out the OOS results, review of manufacturing, production and sampling is very important. The errors and problems should be investigated and identified. The documents and records of manufacturing and production should be reviewed. The investigations should be reviewed through a well-documented manner.

Review of Lab Investigation Result

It contains the following information:

• Cause of the investigation.

• Review and summary of manufacturing process (which may have identified as malfunctioned or cause of OOS results).

• Review of previous results to find out the possible causes of OOS results.

• Review of documented records to analyze the possible factors of wrong results.

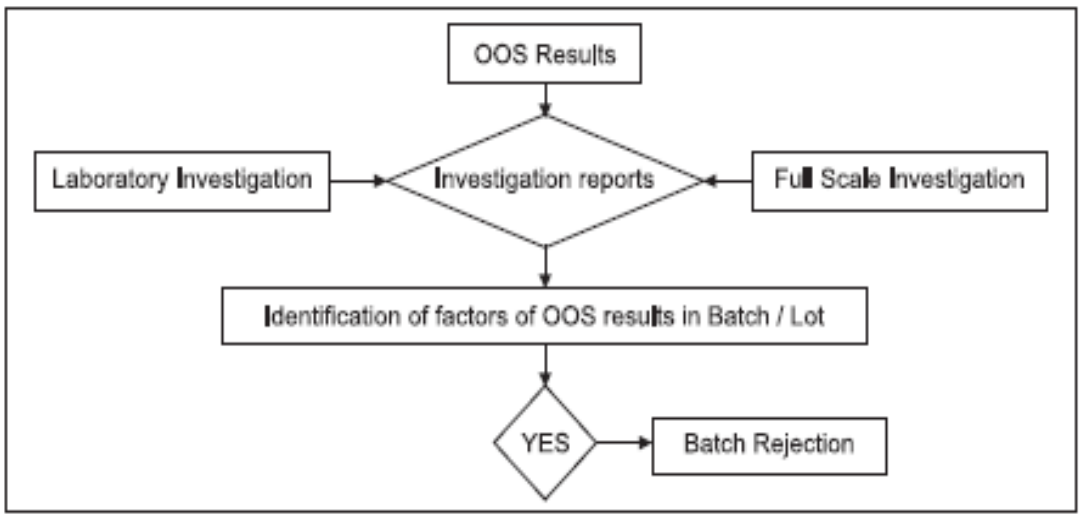
• The actions taken to correct the process.

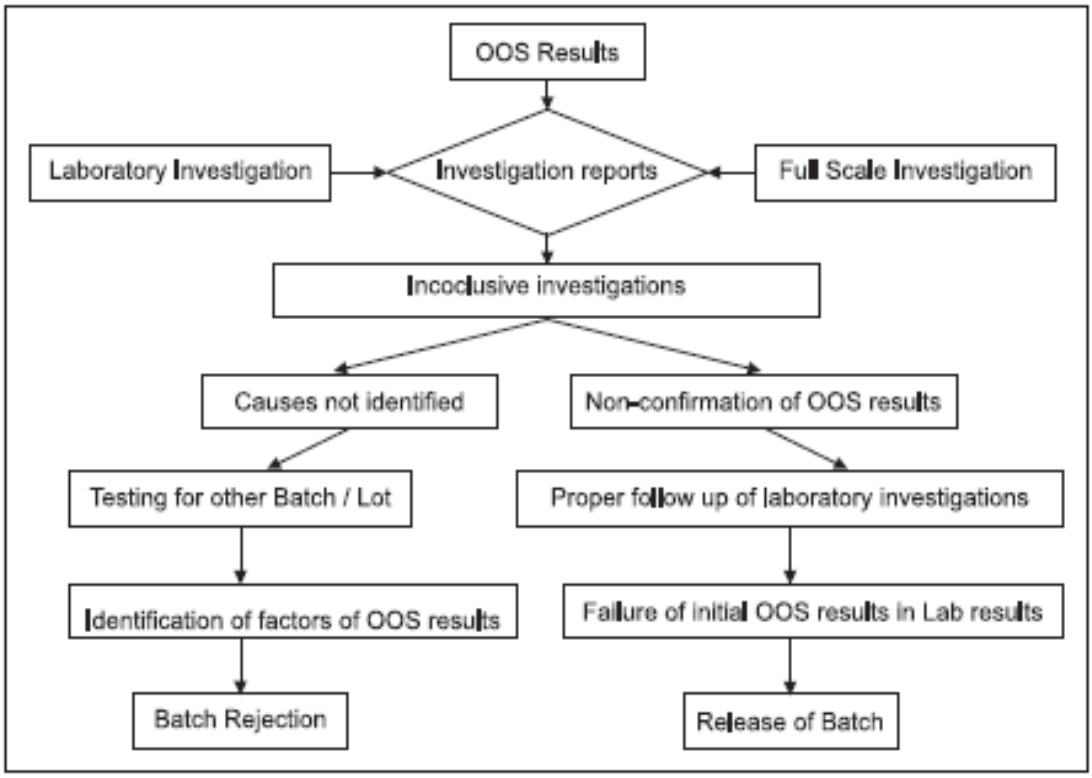
Supplementary Laboratory Testing Procedure

To investigate OOS results in full scale, additional laboratory testing may be performed. This includes Re-testing and Re-sampling. In Re-testing, a portion of original samples are tested again according to the standard procedures. The results are kept in a well documented manner. This process helps to find out the problems encountered due to error in instruments, process, dilution or sample handling. In Re-sampling, a specimen is collected from any additional units from original sample or a new sample is prepared from the same batch and analyzed further.

Analysis of Investigated Results

The reported results should be analyzed and interpreted to find out the possible, probable and actual causes of OOS results. Some possibilities are discussed below:





Analysis of investigated results

Syllabus Topic: Change Control

Introduction

In pharmaceutical industry change control is an important part of quality assurance. The changes proposed and made in any procedure or process should be reviewed, established, documented and approved by the concerned authorities. Change control is the system to implement this approved change to confirm the regulatory requirements.

Definition

Change control can be defined as; "A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state". (EU GMP Guidelines, Annexure 15).

Function

Any change in manufacturing process, equipment, materials used that may cause alteration in product quality should be validated.

The main functions of change control are:

1. Identification of the changes made.

2. Review of the change.

3. Approval of the change.

4. Validating the changes which can alter the product quality, regulatory or GMP (Good manufacturing process) requirements.

5. Analysis of the change and monitoring of the impact of change.

4.6.4 Area of Change

1. Manufacture: Following changes are concerned:

• Raw materials

• Equipments

• Process/parameters

• Testing/validation procedures

• Packaging materials

• Cleaning process

2. Quality control and quality assurance: Following changes are considered:

• Quality testing parameters

• Sampling size

• Validation process

• Specifications of raw materials, intermediates and final product

• Documentation

• Standard operating procedures (SOPs)

3. Research and development: It includes the change in;

• Manufacturing process (any addition of elimination of steps)

• Raw materials (any addition of omission of the product)

• Specifications of raw materials, intermediates and final product

• Quantitative aspects of raw materials and finished products

• Manufacturing conditions and storage conditions

• Testing/validation procedures

4. Engineering: It includes the following changes in:

• Equipment used

• Validation of the equipment

• Parts of equipment

• Working and design layout

• Software/ Hardware or Change in any program

5. Marketing.

Written Procedures and Documentation

Procedures in writing should be kept at the proper place to describe the changes made related to the materials, equipment and method of manufacturing or testing conditions or any other change that can affect the quality of the product. Standard operating procedure (SOP) and records of change control documents are required for the documentation. The Change Control Form (CCF) is an important documentation part of change control. It contains the form related to initiate department for the proposed change, proposed change details, comments from QA Head, category of the changes, supportive documents, management review form and assessment of CCF.

Change control log book

Change control (CC) No.	Initiated Department	Originator Name	Proposed Change	Category of change	Approval/ Rejection of CC	Date of Change	Verified by QA Head (Sign and Date)	Any remark

Syllabus Topic: ISO Quality Standards

Quality Management System (QMS)

The quality policy and objectives of any organization are implemented, defined and established by QMS. QMS allows documenting and implementing the procedures for an organization to attain the goals. The procedures should be carried out consistently, related problems should be identified and dissolved, and continuous improvement in the procedures through extensive reviews should be done to improve the quality of the products and service. Proper implementation of QMS will ensure the better service and customers' satisfaction.

Relationship among QMS, QA, GMP and QC

ISO Quality Standards

International Organization for Standardization (ISO) is an international standard of QMS. This written international standard is implemented by ISO. It is an independent organization with more than 150 national standard bodies.

To serve the satisfaction to the customers, an organization needs standards through QMS and ISO. The needs of standard are for the following points:

• For customer satisfaction and safety, which depend on output of the organization.

• For maintaining the quality system that is auditable and verifiable with continuous mode.

• For the continuous improvement and effectiveness of the organization with main focus on customer.

ISO standard is concerned with the

• Standard development based on global expert opinion.

• Capacity building activities by technical assistance.

• Research and training for the education about standards.

The history of ISO though began in 1946, in 1947 ISO started officially its operation and in 1951 the first ISO standard was published.

ISO 9000

The ISO 9000 family of standards is designed to help organizations to ensure the customers' needs, the statutory and regulatory requirements. It does not certify any organization. It certifies the QMS of any organization. The basic quality management principles (QMP) of ISO 9000 are:

QMP 1: Customer focus
QMP 2: Leadership
QMP 3: Engagement of people
QMP 4: Process approach
QMP 5: Improvement
QMP 6: Evidence based decision making
QMP 7: Relationship management

ISO 9000 Series

ISO 9000: Quality assurance and quality management concepts, guidelines for selection and use.

ISO 9001: Concepts for QA in design, production and development of the system, along with service and installation.

ISO 9002: Concepts for QA in production, service and installation.

ISO 9003: Model for QA in final inspection and finished good testing.

ISO 9004: Guidelines for quality assurance and quality management planning, implementation, efficiency and improvement.

Requirements of ISO 9000 Series

To establish an effective QMS through ISO 9000 series the following points are necessary:

1. Responsibility of the Management of the Organization: The policy to maintain the quality should be ensured by the management of the organization. The quality policy should be implemented and maintained in all the spheres of the organization.

2. Quality System and Design Control: The supplier of raw materials should maintain the quality and documents regarding specifications of the materials. The products should meet predetermined quality and standards.

3. Documentation regarding Stakeholder's Contract and Purchasing: The well documented contract review with different suppliers should be maintained by the management. The capability of the contractor should be defined and documented. The details of purchasing and all data should be in documentation and maintained for the record to attain the desired quality management in the organization.

4. Process Control: The design of work flow should be decided, planned, defined and implemented. The responsibilities should be defined to the personnel for the equipment, process and the change if any in the protocols that should be well documented, reviewed and proposed for the prior approval from the higher and concerned authorities. The production plan, installation and service should be finalized by keeping in mind that the variations in reaction condition shall alter the quality of the finished products. The inspection of validation of equipment, calibration process and efficiency are the important concerns.

5. Final Inspection and Testing of Finished Goods: The inspection and analysis for the finished products should be well documented and, test procedure and result should be reviewed and maintained for the record. The product that does not meet certain specifications should be prevented for the further process and installation.

6. Actions taken to Overcome the Errors: The possible causes for the errors should be identified and eliminated. The non-conformities of the products can affect the quality parameters and to maintain the quality management, the preventive actions should be

taken, reported and documented. The implementations of the corrective measures should be confirmed.

7. Internal Audits: The effectiveness of the organization and system is determined by the quality internal audits. The audit report will assure the functioning of the system is adequate or not to maintain the desired quality of the products. The audit report shall be maintained and the corrective steps should be taken by the responsible individual in their respective areas if any deficiencies found. The audit in regular intervals assures the quality of the process in the organization.

8. Training and Providing Education/Awareness regarding the Standards: The personnel involved in the system shall be provided training, proper education or workshops about the standards as per requirement. The training report shall be documented and maintained.

9. Statistical Analysis: To analyze and control the process capability, statistical analysis shall be documented and implemented.

Advantages of ISO Certification

1. Increment in marketability.

2. International recognitions.

3. Reliability in the market.

4. Capability of providing quality products to satisfy the customer.

5. Improvement in relationship with customers and stakeholders.

Syllabus Topic: ISO 14000

Introduction

ISO 14000 family provides practical tools to manage the environmental responsibilities of companies and organizations. It was initially published in 1996 and revised in 2004. This standard is related to Environmental Management System (EMS). ISO 14000 is considered as generic management system and it is applicable for the following:

• Any organization (single-site to large MNCs, high risk to low risk companies).

• The manufacturing industries (equipment manufacturers and suppliers), process industries and service industries.

• All industries of local government, public and private sectors.

The basic features of ISO 14000 are:

• Minimum harmful effects on environment.

• Continuous improvement to achieve the desired performances.

Principle of ISO 14000

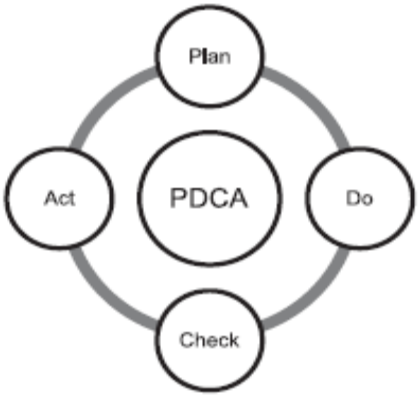
The principle of ISO 14000 is explained by PDCA Model.

1. Plan: Designing of aim, objective and processes to achieve the desired result.

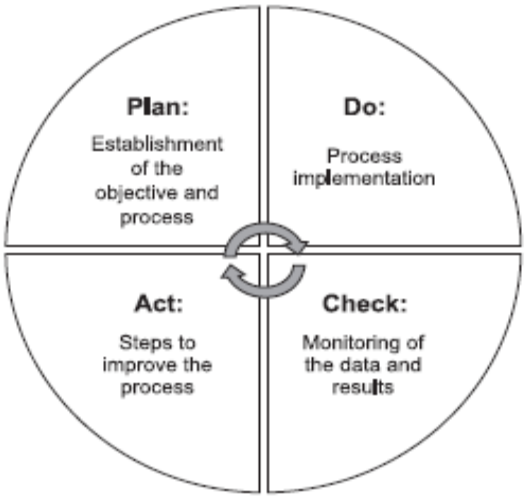
2. Do: Designed process should be performed step by step. The changes are noted and data is stored to analyze the results.

3. Check: The evaluation of the data and results recorded in the previous steps.

4. Act: The evaluation of the data and results helps to improve the process. In this step, the problems of the result are rectified for the continuous improvement, for this purpose, Do and Check steps may be repeated several times for the better outcome. The causes of the difference in the results are identified and improved. This step is often named as 'Adjust'.



PDCA Model



Working of ISO 14000

Features of ISO 14000

The features of ISO 14000 are mentioned:

1. EMS (Environmental Management System).

2. Environmental related evaluations, investigations and auditing.

3. The investigation of the process performances.

4. Environmental labels and declarations.

Advantages of ISO 14000

By getting ISO certification any organization can maintain their conformation to the environmental regulations. This certification can help an organization by the following ways:

• Better marketability.

• Better utilization of resources.

• Environmental responsibilities.

• Better quality of finished goods and products.

• Customers' satisfaction.

• Enhancement of the reputation and reliability of the organization.

• Improvement of the relationship among management, employees, customers and investors.

• Reduction in cost.

ISO 14000 Series

- **ISO 14001 (2015)**
  EMS: Requirements with guidance for use
- **ISO 14004 (2016)**
  EMS*: General guidelines on implementation
- **ISO 14006 (2011)**
  EMS: Guidelines for incorporating ecodesign
- **ISO 14015 (2001)**
  EM#: Environmental assessment of sites and organizations (EASO)
- **ISO 14020 to 14025 (2000)**
  EM: Environmental labels and declarations
- **ISO 14031 (2013)**
  EM: Guidelines for environmental performance evaluation
- **ISO 14040 (2001)**
  EM: Life cycle assessment, environment goal setting
- **ISO 14050 (2009)**
  EM: Vocabulary (terms and definitions)
- **ISO 14063 (2006)**
  EM: Guidelines and examples of environmental communication
- **ISO 14064 (2006)**
  Quantification of emitted Greenhouse gases and their reduction

(**Note:** EM# and EMS* stand for Environment Management and Environment Management System respectively).

Process of ISO 14001 Certification

Registration and Certification procedure of ISO 14001

Environmental Management System (EMS)

EMS is a system which monitors, reviews, summarizes, evaluates, reports and improves the environmental performances to achieve the environmental goal. EMS helps to reduce the environmental impact and to increase the efficiency. Waste reduction is one of the important goals of EMS.

Features of EMS

The EMS has the following features:

1. Improvement of environmental performances.

2. Controlling and managing of environmental policies in organization in systematic way to maintain the long-term effect of better products, service and customer satisfaction.

3. Process design to control the pollution and waste reduction.

4. Reducing the impact of environmental factors.

5. Training of the personnel about the process and control.

6. Assistance of planning, controlling and monitoring the environmental policies in organization.

7. Continuous improvement to meet the desired goal and result.

8. Maintains the accountability between the management and employee personnel.

Syllabus Topic: NABL (National Accreditation Board for Testing and Calibration Laboratories)

Introduction

NABL is an autonomous constituent board of quality council of India. NABL stands for "National Accreditation Board for Testing and Calibration Laboratories". NABL has been established and constituted for providing accreditation to the Government, industry associations and individual industry or organizations. The accreditation is related to the thirdparty assessment of the technical competence of testing which includes medical and calibration laboratories, proficiency testing providers (PTP) and reference material producers (RMP).

NABL and ISO Principles

The accreditation service is based on the following ISO principles:

1. Accreditation Systems: ISO/IEC 17011 (2017) (Conformity assessment-requirements for accreditation bodies accrediting conformity assessment bodies).

2. Testing and Calibration Laboratories: ISO/IEC 17025 (2005) and ISO/IEC 17025 (2017) (General requirements for the competence of testing and calibration laboratories).

3. Medical Laboratories: ISO 15189 (2012) (Medical laboratories-requirements for quality and competence).

4. PTP (Proficiency Testing Providers): SO/IEC 17043 (2010) (Conformity Assessment-General requirements for proficiency testing).

5. RMP (Reference Material Producers):ISO 17034 (2016) (General requirements for the competence of reference material producers).

Need of NABL

To achieve an international level acceptance for any laboratories, proficiency testing providers or RMPs, there is a need of a formal recognition to follow the international standards and acceptability to omit extensive re-testing. NABL is an authoritative body which provides the formal recognition for specific tests/ measurements by following international standards and third-party assessment.

Recognition of NABL in International Level

NABL maintains the relationship with several international bodies like:

1. International Laboratory Accreditation Co-operation (ILAC).

2. Asia Pacific Accreditation Co-operation (APAC).

Scope of NABL

In the following fields NABL accreditation is currently issued.

Testing Laboratories	• Biological • Chemical • Electrical • Electronics • Fluid-Flow • Mechanical • Non-Destructive Testing (NDT) • Photometry • Radiological • Forensic
Calibration Laboratories	• Electro-Technical • Mechanical • Fluid Flow • Thermal • Optical • Radiological • Medical Devices
Medical Laboratories	• Clinical Biochemistry • Clinical Pathology • Haematology and Immunohematology • Microbiology and Infectious Disease Serology • Histopathology • Cytopathology
Medical Imaging-Conformity Assessment Bodies	• Projectional Radiography: X-Ray, Bone Densitometry (DEXA), Dental X-Ray-OPG • Fluoroscopy • Computed Tomography (CT) • Magnetic Resonance Imaging (MRI) • Ultrasound • Colour Doppler
Proficiency Testing Providers (PTP)	• Testing • Calibration • Medical • Inspection
Reference Material Producers (RMP)	• Chemical Composition • Biological and Clinical Properties • Physical Properties • Engineering Properties • Miscellaneous Properties

Advantages of NABL

NABL accreditation has many advantages for the organizations, PTPs and RMPs. Some of them are:

1. Increases credibility of the testing reports (issued by the specific lab).

2. Building up of confidence for the organization in calibrating and testing the reports.

3. Accreditation ensures the quality assurance systems of the organization.

4. Customers' satisfaction.

5. Customers of these accredited organizations/ laboratories can have greater access for their products, in both domestic and international markets.

6. Market acceptability and increased potential in business.

7. Elimination of need of re-testing.

8. Monitoring of maintenance of efficacy for long time.

9. Improvement in the process.

10. Employee's/Staff's education and training can be overlooked.

11. Increases market opportunity for RMPs.

12. The accreditation assures the quality control methods, validation methods, quality assurance, calibrations for the RM (reference materials), so, the use of CRM (certified reference materials) build the confidence for the RMPs and also the re-checking of CRM can be eliminated.

Syllabus Topic: GLP (Good Laboratory Practice)

Introduction

GLP was introduced for the non-clinical safety studies in 1976. In late 90's this practice along with OECD (Organization for Economic Co-operation and Development) was accepted as industry standards. GLP has been introduced due to the poor and dishonest practice in laboratory in the early 70's. The poor lab practices include wrong calibration of equipments, inaccurate test systems and accounts. In 1983, Industrial Bio Test Laboratory (1952-1978) of New York was found guilty as it provided wrong and inaccurate research data to the Government. The company provided fake, fabricated and concealed data of the tests on rodents involving Trichlorobanilide (deodorant soap additives), Naprosyn (arthritis drug), Sencor (Herbicide) and Nemacur (Pesticide).

Definition

According to Valcarcel M., GLP is a set of rules, operating procedures and practices established by an organization to ensure the quality and accurate results in a laboratory practice. In this practice, the given organization sets the principles and the laboratory works are planned, operated, overlooked and reported.

Fundamentals of GLP

Resources

It includes the following:

1. Organization and Management: Management has the overall responsibility for the implementation of both good science and good organization within their institutions. Good science includes proper definition of experimental design, knowledge of scientific principles, documentation of experimental and environmental variables, complete evaluation of the results and reporting of results. Whereas, good organization should provide proper planning of studies, qualified skilled personnel, adequate facilities, infrastructures, proper conduction of studies and verification process for the study results.

2. Personnel: The detailed records should be maintained for every individual staff of the institution. The records include the detail curriculum vitae, training records and their job descriptions. These records should meet the GLP requirements and these are maintained to establish that every staff has the competence, education, experience and training to perform the tests.

3. Availability of Facilities: Adequate facilities with state-of-the-art infrastructure should be provided by the institution and management to ensure the validation of the studies. The cleaning, maintenance and documents of the site plan should satisfy the guidelines.

4. Availability of Equipments: Adequate equipments must be available for the study in the organization. The suitability of the equipment and calibrated instruments should be provided by the management.

Characterization

It includes:

1. Test Items: It may be an active ingredient for a medicine, a pesticide, a food additive, a vaccine, an industrially used chemical, a biomass or an extraction from plants. These items are characterized by analytical profile like chemical identification test, solubility, stability etc. The test items should be stored properly to avoid the contamination.

2. Test Systems: The test systems could be the animals, bacteria, cells, organs and plants. Sometimes they may be analytical equipments also. The test systems should be handled in such a way that it must comply with the GLP guidelines and with the national animal welfare law.

Rules

1. Study Protocols: The study plan or protocol describes how the study is designed and how it is to be conducted. The plan should include the expected timeframe of the study.

2. Written Procedures: Written procedures are often known as SOPs (Standard Operating Procedures). SOPs provide the instructions how each technical procedure should be performed, how to ensure the sound organization of the study, environmental variables and data.

Results

It includes raw data, final reports and data archiving.

1. Raw Data: The original record and the data needed for the reconstruction should be recorded. The raw data should include '*what*' was done, '*how*' it was done, '*when*' the work was done and '*who*' performed the work. The recorded data should clarify the process by which it is generated and should confirm the process has been performed as per the guidelines and SOPs.

2. Final Results: Final results are the responsibility of the study director. These results should describe the study accurately and the scientific interpretation. The results should reflect accurately the raw data. The review and audit of these reports should be done. All accepted changes in the results approved by the reviewer should be incorporated before the finalization of the results.

3. Archives: Archiving is a safe depositing of all information. It is considered to be a center for the compilation and distribution of summary documents. The archiving of document helps the reconstruction of studies performed earlier.

Quality Assurance

The requirement of the quality assurance is to validate the experimental results. Quality assurance unit (QAU) or simply QA must review all phases of preclinical research, organization framework, staff documents, study procedures and SOPs. The internal audits and inspections should be performed by the QA officers. The QA performs the study-based audit, facility and systems-based inspection and process-based inspections.

GLP Principles

GLP principles are set of organizational requirements. GLP is a regulation covering the quality management of non-clinical safety studies. The aim of the regulation is to encourage scientists to organize and perform their studies in a way which promotes the quality and validity of the test data. GLP deals with the following issues:

- The facility provided by the organization.
- Efficient and trained personnel.
- Quality of validated equipment and reagents.
- Predetermined study design.

• SOPs, process validation and test procedures.

• Correctness of the results.

• Quality assurance laboratory (QAL) and Quality assurance program (QAP).

• Recorded and documented results and their storage.

The organizations should fulfill all the criteria to provide all the facilities for the good practice in laboratory. The personnel should have enough knowledge about the principles and working of the practices. In the elements of GLP, SOP is an important part with respect to quality assurance. To maintain the productivity of the result, a well documented SOP is required; moreover, the personnel should have complete information mentioned in SOPs. SOPs define the complete process flow and work steps which help to achieve the accurate and precised results. Validated modern equipments and adequate facilities should be provided by the organization to maintain the good practice in laboratory. The complete specifications and storage of reagents and materials should be provided. QA laboratory should have the proper test procedures (physical, chemical and biological) and characterized data for both the test and reference materials.

Quality assurance unit (QAU) bears the responsibility to assure the GLP and this unit is attached with QAL and QAP. The audit of the laboratory and verification of the quality parameters are the major responsibilities of the QAU. The reported study results should be stored and retained with well documented manner.

Aim of GLP

1. GLP helps to reduce the number of false negatives arising from the studies. False negative result for a toxicity study falsely intimated that the test item is not toxic, but in real the item is toxic.

2. GLP also helps to reduce the chance of false positives. In the case of a non-clinical safety study, the results wrongly predict that the test item is toxic, when really it is not.

3. GLP promotes international recognition of study data. When studies are performed according to OECD GLP principles, then the acceptability and reliability of the data are recognized in the international level by the OECD member states.

THANK YOU