PHARMACEUTICAL QUALITY ASSURANCE

UNIT 1

Quality Assurance and Quality Management concepts:

- DEFINITION OF QUALITY

Quality is defined in some dictionaries as "DEGREE OF EXCELLENCE", while the International Organization for Standardization (ISO) defines it as "The totality of features and Characteristics of product of service that bear on its ability satisfy stated/implied needs".

- DEFINITION OF QUALITY CONTROL Definition of Q.C by WHO

"Q.C is a part of GMP which is concerned with sampling, specification, testing with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are neither released for use, nor products released for sale or supply, until their quality has been found satisfactory".

CONCEPT OF QUALITY CONTROL

- QC is a set of activities for ensuring quality in products, the activities focus on identifying defects in actual product produced.
- QC is a corrective tool.
- QC aims to identify defects in finished products and the aim of QC is to identify defects after a product is developed and before it is released.
- QC works by finding and eliminating sources of quality problems through tools and equipments so to meet customer's requirement.

Quality Control system should ensure that

- There should be Adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing Raw materials, packaging materials, intermediate products, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
- Samples of starting materials, packaging materials, intermediate products, bulk products and finished products should be taken by personnel according to the methods approved by Quality Control.
- Test methods should be validated.
- Records should be made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated.

Responsibilities of Q.C Department

- QC is responsible for the day-to-day control of quality within the company.
- QC department is responsible for analytical testing of incoming raw materials and inspection of packaging components, including labeling.
- To conduct in-process testing when required, perform environmental monitoring, and inspect operations for compliance.
- They also conduct the required tests on finished dosage form. • QC plays a major role in the selection of qualified vendors from whom raw materials are purchased.
- Maintenance of all documents related to Q.C department.

DEFINITION OF QUALITY ASSURANCE

Definition of Q.A by WHO

"Quality assurance is a wide ranging concept covering all matters that individually or collectively influence the quality of product. The totality of the arrangement made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use and QA also includes GMP and other factors such as product design and development."

CONCEPT OF QUALITY ASSURANCE

- QA is a set of activities for ensuring quality in the process by which the products are developed.
- QA is a managerial tool.
- QA aims to prevent defects with a focus on process used to make the product.
- The goal of QA is to improve development and test processes so that defects do not arise in when the product is being developed.

Quality Assurance system should ensure that

- Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice.
- Production and control operations are clearly specified and Good Manufacturing Practice adopted.
- Managerial responsibilities are clearly specified.
- Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials.
- All necessary controls on intermediate products and any other in process controls and validations are carried out.
- The finished product is correctly processed and checked, according to the defined procedures.

Responsibilities of Q.A Department

- QA department is responsible for ensuring that the quality policies adopted by a company are followed to meet quality requirements.
- To identify and prepare the necessary SOP's related to the control of quality.
- QA department ensures that the product meets all the applicable specifications and that it was manufactured according to the standards of GMP.
- QA also holds responsibility for quality monitoring or audit.
- QA functions to assess operations continually and to advise and guide them towards full compliance with all applicable internal and external regulations.

GMP (GOOD MANUFACTURING PRACTICES)

DEFINITION OF GMP AS PER WHO "GMP is that part of Quality Assurance, which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization".

CONCEPT OF GMP

Our quality control systems were designed on the concept that, if a formulation conformed to the prescribed standards, it should be taken as product of quality, safety and efficacy.

But this concept did not hold good as evidenced by various drug mishaps in several countries, hence the concept of GMPs emerged in 1960's in United States of America, The first version of GMP

guidelines for manufacturing, processing, packaging and holding of finished pharmaceuticals was introduced by USFDA in 1963.

GMP guidelines represent minimal standards that are necessary conditions for marketing authorization, drugs are considered to be adulterated, if GMP's are not met

GMP guidelines typically comprise strong recommendations on quality management, personnel, production facilities and equipments, documentation and records, production and in-process controls, packaging and labeling, storage and distribution, laboratory controls, validation, complaints and recalls.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

1. All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal yling products of the required quality and complying with their specifications and/or as bas marketing authorization;

2. Critical steps of manufacturing processes and significant changes to the process are validated.

3. All necessary facilities for GMP are provided including:

- Appropriately qualified and trained personnel.
- Adequate premises and space.
- Suitable equipment and services.
- Correct materials, containers and labels.
- Approved procedures and instructions.

GMP COVERS

1. Personnel

2. Building and facilities

3. Equipment

4. Sanitation and Hygiene

5. Control of components, Drug product containers and closures

6. Production and Process controls

7. Packaging and Labeling controls

8. Holding and distribution

9. Laboratory controls

10. Returned and Salvaged drug products 11. Reports and records (Documentation)

1. PERSONNEL

•The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of quality products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer.

•Individual responsibilities should be clearly understood by the individuals and recorded.

•All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions.

•The manufacturer should have an adequate number of personnel with the necessary

qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

Personnel Training

1. The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2. Beside the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. mode songe

3. Training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept. 20019

4. Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

Personnel Hygiene

1. Detailed hygiene programs should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel.

2. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programs should be promoted by management and widely discussed during training sessions.

3. All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge.

4. Steps should be taken to ensure as far as is practicable that no person affected by an Beinfectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

5. Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

6. Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited

2.BUILDING AND FACILITIES

Design and construction features

1. Buildings should be of suitable size, construction location to facilitate cleaning, maintenance, and proper operations.

2. Space should be adequate for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers and closures, labeling, in - process materials, or drug products and to prevent contamination.

3. The movement of components and product through the building must be designed to prevent contamination.

4. Operations should be performed within specifically defined areas having adequate control systems to prevent contamination or mix-ups during each of the following procedures: Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, and release for manufacturing or packaging.

5. Holding rejected materials. 6. Storage of released components, drug product containers, closures, and labeling.

7. Storage of in-process materials.

8. Manufacturing and processing operations.

9. Packaging and labeling operations.

10.Quarantine storage before release of drug products.

11.Storage of drug products after release.

12. Aseptic processing

13. An air supply filtered through High Efficiency Particulate Air (HEPA) filters under positive

14. Air handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for humans.

15. Sanitation: Any building used for manufacture, processing, packing, or holding of a drug product should be maintained in a clean and sanitary condition. Such buildings should be free of infestation by rodents, birds, insects, and other vermin, Trash and organic waste matter should be held and disposed of in a timely and sanitary manner.

3. EQUIPMENTS

1. Equipment should be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for cleaning and maintenance.

2. Equipment construction: (a) Equipment should be constructed so that surfaces that contact components, in-process materials, or drug products should not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond official or other established requirements.

(b) Any substance required for operation such as lubricants or coolants shall not come into contact with drug products, containers, and so on, so as to alter the safety, identity, strength, quality, or purity of the drug product beyond established requirements.

3. Equipment cleaning and maintenance:

a) Equipment and utensils should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the drug product beyond the official requirement

b) Written procedures must be established and followed for cleaning and maintenance of equipment and utensils used in the processing of a drug product. These procedures must include but are not limited to the following:

i. Assignment of responsibility for cleaning and maintaining equipment.
ii. Maintenance and cleaning schedules, including sanitizing schedules if appropriate.
iii. A sufficiently detailed description of the methods, equipment, and materials used in cleaning and maintenance operations and the methods of disassembling and reassembling equipment as a part of cleaning and maintenance.
iv. Removal or obliteration of previous batch identification.
v. Protection of clean equipment from contamination prior to use.
vi. Inspection of equipment for cleanliness immediately before use.

4.SANITATION AND HYGIENE

1. A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of pharmaceutical products.

2. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.

3. Potential sources of contamination should be eliminated through an integrated comprehensive program of sanitation and hygiene.

4. The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and in general, any adverse effect on the quality of products.

5. Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross contamination and facilitate cleaning

5.CONTROL OF COMPONENTS, DRUG PRODUCT CONTAINERS AND CLOSURES

1. General requirements:

a) There must be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of product components, containers, and closures. Of course, all such procedures must be followed. It is quite common and even more embarrassing to be cited for not following your own written procedures

b) All components listed above must be handled and stored in a manner that will prevent contamination.

c) Bagged or boxed components should be stored off the floor. Spacing should allow cleaning and inspection.

d) Every container of components must be identified with a distinctive code or lot number for each receival of that product. Even if the next receival is the same vendor lot number, it must be a new identifying number by the pharmaceutical manufacturer

2. Receipt and storage of untested components:

a) Upon receipt each container of components must be visually examined for appropriate labeling and any damage or contamination to the component container.

b) Components must be stored under quarantine until they have been tested as appropriate and released for use.

3. Testing and approval or rejection of components:

a) Each lot of components shall be withheld from use until it has been sampled, tested, and released by the quality control unit.

b) Representative samples must be taken from receival of every component. d every

c) The number or amount of component to be sampled should be based on component appearance, statistical confidence levels, the past history of the supplier, and the quantity needed to analyze and reserve samples if required

4. Use of approved components (including drug product containers and closures) must be rotated to assure that the oldest approved stock is used first.

5. Components must be retested and/or reexamined after storage for a long period of 915 time or after exposure to the atmosphere, heat, or other condition that might adversely affect the component.

6. Rejected components should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing.

7. Containers and closures:

a) Containers and closures must not be reactive, additive, or absorbent so as to alter the drug beyond established acceptance criteria.

b) Container closure systems must provide adequate protection against foreseeable external factors in storage that can cause deterioration or contamination of the product.

c) Containers and closures should be clean and, if necessary, sterile and processed to remove pyrogens.

d) Standards or specification, methods of testing, and, if appropriate, sterilization and depyrogenation must be written and followed.

6.PRODUCTION AND PROCESS CONTROLS

1. Written procedures and procedure deviations:

a) Written procedures for production and process control must be written and followed. ed These procedures should be designed to assure that the drug products have the identity, strength, quality and purity they are represented to possess. These procedures must include all requirements given below and must be drafted, reviewed, and approved by the affected organizational units and reviewed and approved by the quality control unit.

b) When following the above identified procedures, all actions must be documented at the time of performance. Any deviations from the written procedure must be recorded and justified

2. Charge in of component: written production and control procedures must include the following, which are designed to assure that the drug products produced meet all specifications and standards.

a) The batch must be formulated with the intent to provide not less than 100% of the labeled amount of active ingredient.

b) Components used must be weighed, measured, or subdivided appropriately. c) If a component is removed from its original container and placed in another, the new container should be identified with the following information:

i. Component name and/or item code.

ii. Receiving or control number

iii. Weight or measure of material in the new container

3.Actual yield and percentage of theoretical yield should be determined at the completion of each appropriate phase of manufacturing, processing, packaging, or holding. These calculations should be performed by one person and independently verified by a second individual.

4. Equipment identification:

a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product must be properly identified at all times to indicate their contents and the phase of processing of the batch.

b) Major equipment should be identified by a distinctive identification that shall be recorded in the batch production record to indicate the specific equipment used. In cases where only one of a particular type of equipment exists in a given manufacturing facility, the name of the equipment may be used instead of creating a distinctive identification.

5. Sampling and testing of in- process materials and drug products:

a) To assure batch uniformity and integrity, it is necessary to write and follow procedures that describe the in-process controls and tests or examinations that will be conducted on samples taken according to procedure. Procedures should be written to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the product being manufactured.

7.PACKAGING AND LABELING CONTROLS

1. Materials examination and usage criteria:

a) Written procedures describing in detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials must be no developed, approved, and followed. These materials must be representatively sampled, tu examined, or tested on receipt and accepted by the quality control unit before use.

b) Any materials that do not fully meet acceptance criteria must be rejected to prevent their use

c) Records of each receival of each different label and packaging material must be maintained indicating receipt, examination or testing, and whether accepted or rejected.

d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents must be stored separately with suitable identification.

e) Obsolete and outdated labels, labeling, and other packaging materials must be quarantined and destroyed.

2.Issuance of labeling

a)Strict control should be exercised over the issuance of labeling, for use in drug product labeling operations.

b) Labeling materials issued for a batch must be carefully examined for identity and conformity to the labeling specified in the batch production record.

c) Procedures should be written and followed for reconciliation of the quantities of labeling issued, used, destroyed, and returned. Procedures should require evaluation of discrepancies found between the number of packages finished and the amount of labeling issued if discrepancies outside narrow preset limits occur

d) All excess labeling bearing a lot or control number must be destroyed.

e) Returned labeling should be maintained and stored in a manner to prevent mix-ups.

f) Written procedures should describe the control procedures used for the issuance of labeling.

3.Expiration dating :

a) All packaged drug products must carry an expiration date that has been determined gril from appropriate stability testing.

b) Expiration dates must be related to the recommended storage conditions stated on the label as determined by stability studies

c) If the drug product is to be reconstituted at the time of dispensing, its label must carry doubexpiration information for both the reconstituted and un-reconstituted forms.

d) Expiration dates must appear on labeling in accordance with the requirements stated ylinelsewhere in this regulation.

8.HOLDING AND DISTRIBUTION

1. Warehousing procedures: Written procedures describing the warehousing of drug products must be written and followed. These procedures should include:

i. Quarantine of drug products before release by the quality control unit.

ii. Storage of drug products under appropriate conditions of temperature, humidity, and light so that the quality of the drug products is not affected.

2. Distribution procedures: Written procedures concerning the distribution of drug products must be established and followed. These procedures should include:

i. A procedure that assures the distribution of the oldest approved stock First. Deviation from this procedure is acceptable if it is temporary and appropriate.

ii.A system for documenting distribution so that distribution of each lot of drug product can be readily determined to facilitate its recall if required

9.LABORATORY CONTROLS

1. General requirements:

a) The establishment of any specifications, standards, sampling plans, test processes, or other laboratory control mechanism required by this part of the regulation, including any changes to the above must be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

b) Laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that all materials conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls should include:

i. Determination of conformance to written specifications for the acceptance of each lot within each shipment of raw materials. The specifications should include a description of the sampling and testing procedures used. Samples must be representative and adequately identified.

ii. Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials.

iii. The calibration of instruments, apparatus, gauges, and recording devices at specified intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event that the limits are not met.

2.Testing and release for distribution :

a) Laboratory testing of each lot of drug product must be conducted to establish conformance to final specifications for the product. Testing must include identity and strength of each active ingredient

b) Each batch of product required to be free of objectionable microorganisms must be tested appropriately.

c) All sampling and testing plans must be described in written procedures that include the method of sampling and the number of units to be tested.

e) The accuracy, sensitivity, specificity, and reproducibility of test methods used must be established and documented

3.Stability testing

a) A There must be a written testing program designed to assess the stability characteristics boof every drug product. The results of such testing must be used to determine appropriate dr storage conditions and expiration dates. The written program must include:

i. Sample size and test intervals based on statistical criteria for each attribute examined.

ii. Storage conditions for sampled retained for testing.

iii. Reliable, meaningful and specific test methods.

iv. Testing of the product in the same container - closure system as the one in which the Jovis product is to be marketed.

V. Testing of drug products for reconstitution at the time of dispensing as well as after they are reconstituted.

10.RETURNED AND SALVAGED DRUG PRODUCTS

1. Returned drug products: Returned drug products must be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during the return or the condition of the drug product, its container, carton, or labeling is a result of storage or shipping casts doubt on the safety, identity, strength, quality, or purity of the drug product, the returned drug product must be destroyed unless examination testing or other investigation proves the drug product meets appropriate standard

2. Drug product salvaging: Drug products that have been subjected to improper storage conditions, including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fi res, accidents, or equipment failures, must not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is:

a) Evidence from laboratory tests and assays that the drug products meet all applicable standards of identity, strength, quality, and purity.

b) Evidence from inspection of the premises that the drug products and associated packaging were not subjected to improper storage conditions as a result of the disaster or accident

11.REPORTS AND RECORDS (DOCUMENTATION)

1. General Requirements:

a) Any production, control, or distribution record that is associated with a batch of a drug 910 must be retained for at least one year after the expiration date of the batch OR, for OTC drug products that do not have expiration dates, three years after complete distribution of the batch

b) Retained records may be original records or true copies such as photocopies, microfilm, microfiche, or other accurate reproduction of the original.

2. A written record of major equipment cleaning, maintenance (except routine maintenance), relating to GMP brought and use must be included in individual equipment logs that show the date, time, product, and lot number of each batch processed.

3. Component, drug product container, closure, and labeling records must include the following:

a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling.

b) The results of any test or examination performed and any conclusions derived from these results.

4.Master production and control records Batch production and control records should be prepared for each batch of drug product produced and must include complete information about the production and control of that batch. These records must include:

a) A full and complete reproduction of the appropriate master production or control record.

The copy must be checked for accuracy, dated, and signed.

b) Documentation that each significant step in the manufacture, processing, packaging,

❖ TOTAL QUALITY MANAGEMENT

DEFINITION OF TQM

"TQM is a management approach for an organization, centered on quality, based on the participation of all its members and aiming at long-term success through customer satisfaction, and benefits to all members of the organization and to society.

ELEMENTS OF TQM

There are Eight Key elements of TQM these elements can be divided into four groups according to their function.

- Foundation: Ethics, Integrity and Trust.
- Building Bricks: Training, Teamwork and Leadership.
- Binding Mortar : Communication.
- Roof: Recognition.

1.Ethics.

- Ethics is concerned with good and bad in any situation.
- It is two faceted subject represented by organizational and individual ethics.
- Ethics teach an individual/ employee to follow code of conduct of organization and adhere to rules and regulations.

2.Integrity.

- Integrity implies honesty, morals, values, fairness and adherence to the facts and sincerity.
- You need to respect your organization's policies. Avoid spreading unnecessary rumors about your fellow workers.
- Total Quality Management does not work in an environment where employees criticize and backstab each other.

3. TRUST

- Trust is one of the most important factors necessary for implementation of total quality management.
- Employees need to trust each other to ensure participation of each and every individual.
- Trust improves relationship among employees and eventually helps in better decision making which further helps in implementing total quality management successfully.
- Without trust, the framework TQM cannot be built.
- Trust build's the cooperative environment essential for TQM.

4. TRAINING

- Employees need to be trained on Total Quality Management.
- Managers need to make their fellow workers aware of the benefits of total quality management and how would it make a difference in their product quality and eventually yield profits for their organization.
- Employees need to be trained on interpersonal skills, the ability to work as a team member, technical know-how, decision making skills, problem solving skills and so on.
- Training enables employees to implement TQM effectively within their departments and to also make them indispensable resources

5.TEAMWORK

- To become successful in business team work is a key element.
- With the use of teams, the business will receive quicker and better solutions to problem.
- Team also provides more permanent improvements in processes and operations.

- In teams, peoples feel more comfortable to bring the problems that occur and get help from other workers to find a solution.

There are three Types of teams that organizations adopt

1. Quality improvement team or excellence team:

These are the temporary teams with the purpose of dealing with specific problems that often re-occur.

2. Problem solving team

These are temporary teams to solve certain problems and also to identify and overcome the causes of problem.

3)Natural working team.

These teams consist of small group of skilled workers who share tasks and responsibilities.

6. LEADERSHIP

- It is the most important element in TQM.
- It appears everywhere in organization.
- Leadership provides a direction to the entire process of Total Quality Management
- Total Quality Management needs to have a supervisor who acts as a strong source of inspiration for other members and can assist them in decision making,
- A leader himself needs to believe in the entire process of TQM for others to believe in the same.

7. COMMUNICATION

- It binds everything together, starting from foundation to roof of TQM.
- It acts as a vital link between all elements of TQM.
- Communication means a common understanding of ideas between the sender and receiver.
- Employees need to interact with each other to come up with problems existing in the system and find their solutions as well.
- The success of TQM demands communication with and among all the organizational members, suppliers and customers.

There are different ways of communication

1. Downward communication

This is the dominant form of communication in an organization, in this Flow of information takes place from the management to the employees.

2. Upward communication

By this lower level of employees are able to provide suggestions to upper management, in this Flow of information takes place from the employees to the top level management.

3. Communication also takes place between various departments.

8.RECOGNITION

- Recognition is the final element of Total Quality Management.

- Recognition is the most important factor which acts as a catalyst and drives employees to work hard as a team and deliver their lever best. Every individual is hungry for appreciation and recognition.
- Employees who come up with improvement ideas and perform exceptionally well must be appreciated in front of all.
- They should be suitably rewarded to expect a brilliant performance from them even the next time

❖ PHILOSOPHIES OF TOTAL QUALITY MANAGEMENT

1. Walter A. Shewhart

- Contributed to understanding of process variability.
- Developed concept of statistical control charts.

2. W. Edwards Deming

- Stressed management's responsibility for quality.
- Developed "14 Points" to guide companies in quality improvement.

3. Joseph M. Juran

- Defined quality as "fitness for use."
- Developed concept of cost of quality.

4. Armand V. Feigenbaum

Introduced concept of total quality control.

5. Philip B. Crosby

- Coined phrase "quality is free."
- Introduced concept of zero defects.

6. Kaoru Ishikawa

- Developed cause-and-effect diagrams.
- Identified concept of "internal customer."

7. Genichi Taguchi

- Focused on product design quality.
- Developed Taguchi loss function.

1.WALTER A. SHEWHART

- Walter A. Shewhart was a statistician at Bell Labs during the 1920s and 1930s. Shewhart studied randomness and recognized that variability existed in all Jns manufacturing processes.
- He developed quality control charts that are used to identify whether the variability in the process is random or due to an assignable cause, such as poor workers or mis-calibrated machinery.
- He stressed that eliminating variability improves quality. His work created the foundation for today's statistical process control, and he is often referred to as the "grandfather of 299 quality control

2. W.EDWARs DEMING

- W. Edwards Deming is often referred to as the "father of quality control." He was a statistics professor at New York University in the 1940s. After World War II he assisted many Japanese companies in improving quality.
- The Japanese regarded him so highly that in 1951 they established the Deming Prize, an annual award given to firms that demonstrate outstanding quality. It was almost 30 years later that American businesses began adopting Deming's philosophy.
- A number of elements of Deming's philosophy depart from traditional notions of quality. The first is the role management should play in a company's quality improvement effort. Historically, poor quality was blamed on workers on their lack of productivity, laziness, or carelessness

3. JOSEPH M. JURAN

- Dr. Joseph Juran is considered to have had the greatest impact on quality management. Juran originally worked in the quality program at Western Electric. He became better known in 1951, after the publication of his book Quality Control Handbook.
- In 1954 he went to Japan to work with manufacturers and teach classes on quality. Though his philosophy is similar to Deming's, there are some differences. Whereas Deming stressed the need for an organizational "transformation," Juran believes that implementing quality initiatives should not require such a dramatic change and that quality management should be embedded in the organization.
- One of Juran's significant contributions is his focus on the definition of quality and the cost of quality.
- Juran is credited with defining quality as fitness for use rather than simply conformance to specifications. As we have learned in this chapter, defining quality as fitness for use takes into account customer intentions for use of the product, instead of only focusing on technical specifications.

4. ARMAND V FEIGENBAUM

- Another quality leader is Armand V. Feigenbaum, who introduced the concept of total od quality control. In his 1961 book Total Quality Control, he outlined his quality principles in 40 steps.
- Feigenbaum took a total system approach to quality. He promoted the idea of a work environment where quality developments are integrated throughout the entire organization, where management and employees have a total commitment to improve quality, and people learn from each other's successes.

5. PHILLIP B. CROSBY

- Philip B. Crosby is another recognized guru in the area of TQM. He worked in the area of quality for many years, first at Martin Marietta and then, in the 1970s, as the vice president for quality at ITT.
- He developed the phrase "Do it right the first time" and the notion of zero defects, arguing that no amount of defects should be considered acceptable.
- He scorned the idea that a small number of defects are a normal part of the operating 259 process because systems and workers are imperfect. Instead, he stressed the idea of prevention.

6. KAORU ISHIKAWA

- Kaoru Ishikawa is best known for the development of quality tools called cause-and effect diagrams, also called fishbone or Ishikawa diagrams.

- These diagrams are used for quality problem solving, and we will look at them in detail later in the chapter.
- He was the first quality guru to emphasize the importance of the "internal customer," the next person in the production process.
- He was also one of the first to stress the importance of total company quality control, vil rather than just focusing on products and services.
- Dr. Ishikawa believed that everyone in the company needed to be united with a shared ins/vision and a common goal.
- He stressed that quality initiatives should be pursued at every level of the organization and that all employees should be involved.

7. Genichi Taguchi

- Dr. Genichi Taguchi is a Japanese quality expert known for his work in the area of product design. He estimates that as much as 80 percent of all defective items are caused by poor product design.
- Taguchi stresses that companies should focus their quality efforts on the design stage, as it is much cheaper and easier to make changes during the product design stage than later during the production process.
- Taguchi is known for applying a concept called design of experiment to product design. This method is an engineering approach that is based on developing robust design, a design that results in products that can perform over a wide range of conditions.

❖ ICH GUIDELINES

(INTERNATIONAL CONFERENCE ON HARMONIZATION)

- Harmonization of Technical Requirements for ICH is the "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use",
- It is a unique project that brings together the regulatory authorities of Europe, Japan and USA and experts from the pharmaceutical industry in these three regions to discuss scientific and technical aspects of product registration
- ICH is a joint initiative involving both regulators and research-based industry representatives of the EU, Japan and the US in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines.

PURPOSE

The purpose of ICH is to make recommendation on ways to achieve greater Harmonization in the interpretation and application of technical guidelines and requirements for Product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

OBJECTIVES

- To increase international harmonization of technical requirements to ensure that safe, effective and high quality medicines are developed.
- To harmonize technical requirements for registration or marketing approval.
- To develop and register pharmaceuticals in the most efficient and cost effective manner.
- To promote public health.
- To prevent unnecessary duplication of clinical trials on humans.
- To minimize the use of animal testing without compromising safety and effectiveness of drug.

ICH PROCESS OF HARMONIZATION

1. OVERVIEW

- There is a mechanism to harmonize new technical requirements resulting from scientific progress and developments in innovative drug research and also there is process for updating and supplementing the current ICH guideline, when necessary and monitoring their use so that the benefits of harmonization achieved so far are not lost.
- Working procedures have been agreed to ensure that these objectives are met.
- Major topics are handled under the full ICH Process and Minor is handled through the abbreviated Maintenance process.

2. INITIATION OF ICH HARMONIZATION ACTION

Proposals for Harmonization action.

- Formal proposals for ICH action must be channeled through one of the six parties to
- ICH or one of the observers on the steering committee. Proposals for harmonization action might fall into one of the following categories.

1. New types of medicinal product.

2. Lack of harmonization in current technical requirements.

3. Transition to technically improved testing procedures.

4. Review of an existing ICH guideline.

5. Maintenance of an existing guideline

3.FULL ICH PROCESS FOR MAJOR HARMONIZATION TOPICS

Topic selection

The steering committee agenda will, routinely include an item on proposals for new topics.

The sponsoring party or observer will have circulated the concept paper to coordinators and the secretariat in advance and the concept paper and any comments will be submitted to the steering committee, a preliminary determination will be made on whether the topic is of sufficient interest to all parties and can be accommodated within the ICH work program

Topic selection and participation of interested parties: once a preliminary determination has been made that a topic is worthwhile and interested parties beyond the six ICH sponsors and three observers are identified, the steering committee will invite, as appropriate, those additional parties to discussion on the topic, just prior to its acceptance by steering committee as an ICH Topic.

Steering committee Action

When a topic is adopted for harmonization action the steering committee will:

a. Confirm the objectives and expected outcome of harmonization action

b. Confirm the composition of the Expert Working Group (EWG) appointed to discuss the technical issues.

c. Set a Timetable and Action Plan for the EWG.

The Concept Paper will be revised and updated to reflect these decisions.

Expert Working Group

- Each of the six ICH parties (EC, EFPIA, MHLW, JPMA, FDA and PHRMA) will be asked to designate a topic leader for the new topic.
- The topic leaders will participate in the EWG meetings and be the point of contact for any consultations carried out between meetings by correspondence, fax, e-mail etc. A deputy Topic leader may also be designated.
- In case of EWGs with extended membership, the secretariat will invite the designated organization to nominate an expert to participate in the EWG and act as the contact point for receipt of document on technical issues

Time table and action plan

- The steering committee will agree a "target" timetable for development of scientific consensus in the expert working group for each new harmonization topic.
- This would not normally exceed 2 years.
- One of the six ICH Parties will be designated to nominate the Rapporteur and all involved parties will be asked to nominate their respective expert within a fixed time limit.

4. ABBREVIATED PROCESS FOR MAINTENANCE OF ICH AGREEMENTS

The "Maintenance" process is intended to provide rapid and flexible way of making minor changes and revisions to existing ICH guidelines.

The procedure is intended to provide results quickly and efficiently using the minimum amount of resources consistent with the achievement of a scientifically valid result. As far as possible, maintenance work should be completed via a written procedure with recourse to meetings only in exceptional cases**.**

5.TYPES OF MAINTENANCE: UPDATING BASED ON NEW INFORMATION

Proposal of a "permitted daily exposure" (PDE) for a new solvent or a revised PDE for dond to an already classified solvent is submitted directly to the ICH secretariat with supporting information through an ICH region coordinator.

Revision of an established PDE will be considered only on presentation of previously unrecognized toxicity data sufficient to result in a significant change.

The ICH secretariat will distribute the proposal to the Representatives of the ICH Ad hoc Expert Working Group on Residual Solvents.

The regulatory representative will ordinarily rely on correspondence or teleconferencing to avoid unnecessary travel. Based on the discussion, with request for further information to the proposing group and/or individual as appropriate, the representative will prepare an assessment report based on committee approval with a recommendation to accept, with or without modifications, or reject the proposed PDE

❖ Steps in the ICH Process

The Five step process which proved successful for the first phase of ICH activities will be maintained, with appropriate modification to accommodate the extended EWGS.

Step -1: Consensus Building

The Representative prepares an initial draft of a guideline or recommendation, based on the objectives set out in the concept paper, and in consultation with expert designated to the EWG.

The initial draft and successive revisions are circulated for comment, giving fixed deadlines for receipt of those comments**.**

To the extent possible, consultation will be carried out by correspondence, using fax and E-mail.

Meeting of the expert working will normally takes place at the time and venue of the biannual steering committee meetings

Step -2: Start of Regulatory Action

Step 2 is reached when the steering committee agrees on the basis of the report from the EWG, that there is sufficient scientific consensus on the technical issues.

For the draft guideline or recommendation to proceed to the next stage of regulatory consultation, this agreement is confirmed by steering committee members for each of the six ICH parties signing their assent.

Step -3: Regulatory Consultation

At this stage, the guideline or recommendation embodying the scientific consensus leaves the ICH process and becomes the subject of normal wide ranging regulatory consultation in the three regions.

In EU it is published as a draft CPMP guideline, in USA it is published as draft guidance in the Federal register and in Japan it is translated and issued by MHLW, for internal and external consultation.

The difference from normal, national/EU procedures for consultations on guidelines is that the regulatory parties exchange information on the comments they have received in order to arrive at a single, harmonized text.

Step 4: Adoption of Tripartite Harmonized Text

At step 4, the topic returns to the ICH forum where the steering committee receives a report from the regulatory Representatives. If both, regulatory and industry parties are satisfied that the consensus achieved at step 2 is not substantially altered as a result of consultation, the text is adopted by the steering committee.

The adoption takes place on the signatures from the three regulatory parties to ICH affirming that the Guideline is recommended for adoption by the regulatory bodies in the three regions

Step -5: Implementation

Having reached step 4 the tripartite harmonized text moves immediately into the final 997 step of the process which is the regulatory implementation.

This is carried out according to the same national/regional procedures that apply to other regulatory guidelines and requirements, in the European Union, Japan and the USA.

Information on the regulatory action taken and implementation dates are reported back or to the steering committee and published by the Secretariat.

❖ BRIEF OVERVIEW QSEM GUIDELINES

Q-Quality: "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 quality based on Good Manufacturing Practice (GMP) risk management."

S- Safety: "ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years."

E-Efficacy: "The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, and safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ genomics techniques to produce better targeted medicines.

M- Multidisciplinary: "Those are the cross-cutting topics which do not fit uniquely 1ol into one of the Quality, Safety and Efficacy categories. It includes the ICH medical gri terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI)

❖ ICH Q-SERIES GUIDELINES

Q1 GUIDELINE IS FOR STABILITY

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

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product.

Q1B: Photo stability Testing of New Drug Substances and Products: TUGive guidance on the basic testing protocol required to evaluate the light sensitivity and di stability of new drugs and products.

Q1C: Stability Testing for New Dosage Forms: or Gives guidelines for new formulations of already approved medicines and defines the bris circumstances under which reduced stability data can be accepted.

Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances 101 and Products

Q1E: Evaluation of Stability Data:

This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. The Har guideline provides Recommendations on establishing shelf lives for drug substances and drug products intended for storage at or below "room temperature".

Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV. Describes harmonized global stability testing requirements in order to facilitate access to medicines by reducing the number of different storage conditions. WHO conducted a survey amongst their member states to find consensus on 30°C/65% RH as the long term storage conditions for hot-dry and hot-humid regions

❖ ICH STABILITY TESTING GUIDELINES

ICH guidelines for stability studies

Q1A(R2)- Stability Testing of New Drug Substances and Products.

Q1B- Stability Testing: Photo stability Testing of New Drug Substances and Products. anisi
Q1C-Stability Testing for New Dosage Forms.

Q1D- Bracketing and Matrixing Designs for Stability: Testing of New Drug Substances and Products.

Q1E- Evaluation of Stability Data.

Q1F- Stability Data Package for Registration: Applications in Climatic Zones III and IV.

ICH GUIDELINE Q1-A (STABILITY STUDIES)

Objective of the guideline

It defines stability of drug substance and drug product for registration of application of NCE or associated drug, within three regions of ICH i.e. EU, Japan, USA.

Principles of guideline

1. Purpose of stability testing is to provide evidence how quality varies with time under influence of tube

- Temperature
- Humidity
- Light

2.To establish shelf life for drug products.

3. Recommendation of storage conditions.

4. Gives Test conditions based on analysis of effects of climatic conditions in the three sregions of the EU, Japan, and USA.

5. Gives mean kinetic temperature which is derived from climatic data

Stress testing

- Stress testing means to validate the stability indicating power of the analytical procedures. To identify stability-affecting factors such as ambient temperature, humidity and light and to select packing materials that protects the formulation against such effects.
- To identify potential degradants of the API and assess if they can be formed during manufacture or storage of the formulation.
- To select manufacturing process for particular drug substance.

Selection of Batches

Data from formal stability studies should be provided and at least three primary batches are selected.

- From batches manufactured to a minimum of pilot scale.
- From batches having same synthetic route.
- From a batch where method of manufacture and procedure simulates final process.

Stability Commitment

When Re-test period is not covered or not mentioned, long term stability data do not cover proposed re-test period, it is granted at the time of approval, commitment should be made to

continue post approval to establish re-test period and it is not required for Submission which includes data from 3 production batches, commitment to continue through proposed re-test period.

Statements/Labeling

Storage Statement Storage statement established for labeling should be in accordance with national/regional requirements and statement based on stability evaluation

Re-test date: Re-test date derived from stability information and the re-test date should be displayed on the container label.

- **Types of Stability Testing**

1. Real-time testing: This involves testing drug product for a longer duration to find out what is the maximum product degradation when stored as recommended.

2. Accelerated stability testing: Here, product is subjected to stress in the form of higher temperatures, moisture, agitation, light, pH, and packaging conditions to study its degradation profile.

3. Retained sample stability testing: This is testing of samples retained from each batch that has been sent into the market.

4. Cyclic temperature stress testing: Not routinely used. It involves subjecting the products to temperature stresses in a way to mimic likely market storage conditions

❖ Quality by Design (QBD)

DEFINITION: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

OBJECTIVES OF QBD

1. The main objective 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.

2. From this knowledge & data process measurement, desired attributes may be constructed. 3. Experimental study would be viewed as positive performance testing of the model ability through Design space.

3. Experimental study would be viewed as positive performance testing of the model ability through Design space.

4. Ensures combination of product & process knowledge gained during development.

SALIENT FEATURES OF QBD

1. Product is designed to meet patient needs and performance requirements.

2. Process is designed consistently to meet the product quality attributes.

3. Understand the impact of raw materials and process parameters on product quality.

4. The critical sources of process variability are identified and controlled

BRIEF OVERVIEW

- Quality by Design is a concept first outlined by Dr. Joseph M. Juran.
- Dr. Joseph M. Juran explained that most of quality crises and issues in product emerge due to a lack of importance assigned to it during product planning.
- Food Drug and Administration (FDA) in its current Good Manufacturing Practices in 21st century initiated QbD with an objective to build quality into the product from its inception.
- QbD is described in ICH Q8, Q9 and Q10 guidelines.
- For ensuring quality of the manufactured products, QbD is an important transition from the traditional quality by testing (QbT) perspective, which ascertains the product's quality by verifying it with approved regulatory specifications at the end of the manufacturing process.
- FDA has encouraged the application of QbD principles to pharmaceutical development, since it promotes product and process understanding to build quality into a product.
- QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality.
- QbD requires an Understanding and controlling formulation and manufacturing process variables that affect product quality.
- QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics.

BENEFITS OF QBD

For industry

1. Better understanding of the process.

2. Less Batch failure.

3. Ensure better design of products with fewer problems in manufacturing.

4.Allows for continuous improvement in products & manufacturing process.

For FDA

1.Enhances scientific base for analysis.

2. Provide better consistency.

3. Provide for more flexibility in decision making.

4. Ensures decisions made on science & not on observed information.

ELEMENTS OF QBD PROGRAM

1. Quality Target Product Profile (QTPP)

2. Critical Quality Attributes (CQA)

3. Risk Assessment

4. Design Space

5. Control Strategy

6. Continuous Improvement

1.QUALITY TARGET PRODUCT PROFILE (QTPP)

- QTTP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.
- It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised on the label.
- It includes identity, assay, dosage form, purity and stability.
- The QTPP guides the formulation scientists to establish formulation strategies to develop a product of optimum quality.
- QTPP forms the basis for design and development of the product.
- TPP is an abstract of the essential properties of the drug and its intended use. These properties define the objectives of the drug development program.

2. CRITICAL QUALITY ATTRIBUTES (CQA)

- A property or characteristic that when controlled within a defined limit, range, or distribution ensures the desired product quality.
- A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q 8 R2)
- CQA is used to describe elements of the QTTP and aspects of product performance and determinants of product performance.
- CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material.
- CQAS are derived from the QTPP and guide product and process development.

3. RISK ASSESSMENT

- Quality Risk Management (ICH Q9) defines Risk management; it indicates that, the manufacturing and use of a drug product necessarily entail some degree of risk.
- Risk assessment is a valuable science based process used in science-quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAS.
- Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.
- Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data.

4. DESIGN SPACE

- ICH Q8 (R1) defines Design space as, the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.

- The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAS (Critical Quality Attributes) and CPPs
- It describes the multivariate functional relationships between CQAS and the CPPs that impact them, and should include their linkage to or across unit operations.
- The Design Space also contains the proven acceptable ranges (PAR) for CPPs and acceptable values for their associated CQAS.
- Normal operating ranges are a subset of the Design Space and are managed under the company Pharmaceutical quality System.

5. CONTROL STRATEGY

ICH Q8 (R1) defines control strategy as: A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

The control strategy may include:

- Control of input material attributes (e.g., drug substance, excipients, and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specifications
- Practical controls
- Facility controls, such as utilities, environmental systems and operating condition

6. CONTINUOUS IMPROVEMENT

- "Continuous improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics."
- QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement (reduction of variability).
- The backbone for Continuous Improvement is the Pharmaceutical Quality System.

❖ ISO 9000 & ISO 14000

- ISO [International organization for standardization] is a non-governmental organization established in 1946 in Geneva, Switzerland.
- It is derived from the Greek word "isos" that means "equal".
- ISO is the world's largest developer of standards.
- ISO's principal activity is the development of technical document.
- ISO standards are extremely useful not only to the manufacturers but also to the whole society as they contribute in the development, manufacturing and supply of products and services which are more efficient, safer and cleaner.

ROLE OF ISO

ISO makes trade between countries easier and fairer.

ISO provide governments with a technical base for health, safety and environmental legislation.

ISO helps in transferring technology to developing countries.

ISO standards ensure safety and quality of products and services to customers and other users

❖ ISO 9000 (BRIEF OVERVIEW)

- ISO 9000 is a family of quality management systems standards is designed to help organizations ensure that they meet the needs of customers and other stakeholders while meeting statutory and regulatory requirements related to a product or service".
- ISO 9000 deals with the fundamentals of quality management systems, including the eight management principles on which the family of standards is based.
- 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.
- It was originally published in 1987 by the International Organization for Standardization (ISO).

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 sevicing
- 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 management and quality systems

OBJECTIVES OF ISO 9000

- Achieve, maintain and seek to continuously improvement in product quality. Improve the quality of operations.
- Provide confidence to internal management.
- Provide confidence to customers.
- Provide confidence that quality system requirements are fulfilled.

BENEFITS OF ISO 9000

- Increased marketability.
- Reduced operational expenses.
- Better management control.
- Increased customer satisfaction.
- Improved internal communication.
- Improved customer service.
- Reduction of product-liability risks.
- Enhanced product quality and reliability at a reasonable price.
- Improved health, safety and reduction of waste

ELEMENTS OF ISO 9000

Customer Focus :The customer is the primary focus of a business. By understanding and responding to the needs of customers, an organization can correctly targeting key demographics and therefore increase revenue by delivering the products and services that the customer is looking for. With knowledge of customer needs, resources can be allocated appropriately and efficiently.

Good Leadership: A team of good leaders will establish unity and direction quickly in a business environment. Their goal is to motivate everyone working on the project, and successful leaders will minimize miscommunication within and between departments.

Involvement of people: The inclusion of everyone on a business team is critical to its success. Involvement of substance will lead to a personal investment in a project and in turn create motivated, committed workers. These people will tend towards innovation and creativity, and utilize their full abilities to complete a project. If people have a vested interest in performance, they will be eager to participate in the continual improvement that ISO 9000 facilitates.

Process approach to quality management: The best results are achieved when activities and resources are managed together. This process approach to quality management can lower costs through the effective use of resources personnel, and time. If a process is controlled as a whole, management can focus on goals that are important to the big picture, and prioritize objectives to maximize maximize effectiveness.

Management system approach: Combining management groups may seem dangerous, but if done correctly can result in an efficient and effective management system. If leaders are dedicated to the goals of an organization, they will aid each other to achieve improved productivity. Some results include integration and alignment of key processes. Additionally, interested parties will recognize the consistency, effectiveness, and efficiency that come with a management system. Both suppliers and customers will gain confidence in a business's abilities**.**

Continual Improvement: The importance of this principle is paramount, and should a permanent objective of every organization. Through increased performance, a company can increase profits and gain an advantage over competitors. If a whole business is dedicated to continual improvement, improvement activities will be aligned, leading to faster and more efficient development.

Factual approach to decision making

Effective decisions are based on the analysis and interpretation of information and data. By making informed decisions, an organization will be more likely to make the right decision. As companies make this a habit, they will be able to demonstrate the effectiveness of past decisions. This will put confidence in current and future decisions

Supplier relationships

It is important to establish a mutually beneficial supplier relationship; such a relationship creates value for both parties. A supplier that recognizes a mutually beneficial relationship will be quick to react when a business needs to respond to customer needs or market changes. Through close contact and interaction with a supplier, both organizations will be able to optimize resources and costs

❖ ISO 14000(BRIEF OVERVIEW)

ISO 14000 is a set of international standards brings a worldwide focus to the environment, thus encouraging a cleaner, safer, healthier world for us all. The existence of the standards allows organizations to focus on environmental efforts against internationally accepted criteria.

The ISO 14000 series of standards effectively address the needs of organizations Worldwide by providing a common framework for managing environmental issues. They promise to effect a broadly based improvement in environmental management, which in turn can facilitate trade and improve environmental performance worldwide.

ISO 14000 Series

- ISO 14001: Environmental Management Systems - Specification with Guidance for Use.

- ISO 14004: Environmental Management Systems - General Guidelines on Principles, Systems and Supporting Techniques.
- ISO 14010: Guidelines for Environmental Auditing - General Principles of Environmental It Auditing.
- ISO 14011: Guidelines for Environmental Auditing - Audit Procedures - Part 1: Auditing of Environmental Management Systems.
- ISO 14012: Guidelines for Environmental Auditing - Qualification Criteria for Environmental Auditors.
- ISO 14013/15: Guidelines for Environmental Auditing - Audit Programs, Reviews & Assessments.

ELEMENTS OF ISO 14000

Environmental Management Systems (EMS):EMS" is the name for the entire environmental program planned by a company. It also forms the main component of the company's registration plan for ISO 14001. The EMS maybe documented in an environmental manual, or maintained in sections of the company quality or operations manual. In either case, the EMS should be defined in detail, with the company's environmental goals clearly stated.

Environmental Auditing (EA): The ISO 14000 series, like the ISO 9000 International Quality Standards, relies heavily on auditing to ensure that the standard requirements are met. Audits are mandated by the ISO 14000 standards. The standard states that, "Audits may be performed by personnel from within the organization (but they should be independent of function to be audited) or by external persons

Environmental Performance Evaluation (EPE): Environmental performance standards are detailed in ISO 14030, a supporting document to ISO 14001 in the ISO 14000 series. ISO 14030 defined the evaluation of environmental performance by management systems, and provides general information about the process. The ultimate goal of these guidance documents is to provide an objective measurement criterion.

Environmental Labeling (EL): Many business use environmental claims (labels, advertising and marketing) as an enticement for buyers to purchase their products. It is also anticipated that ISO 14000 registration will provide similar labeling opportunity. Guidelines for the development of environmental claims are found in ISO 14020, 14021, 14022, 14023 and 14024.

Life-Cycle Assessment (LCA): The support documents providing guidance about LCA detail procedures to examine raw material, generation, storage, manufacture, sales, use, and disposal, and resulting environmental impacts associated with a company's product or service.

Environmental Aspects in Product Standards (EAPS): Guidelines for environmental aspects in product standards are contained in ISO 14060. The objective is to develop guidance for standards writers to consider environmental impacts in their standards-writing process for reducing environmental effects, while ensuring that products perform to quality standards.

BENEFITS OF ISO 14000

- Lower Management Cost.
- Lower Treatment/Disposal Cost.
- Reduced Energy Consumption.
- Increased Productivity.
- Auditing and Report Savings.
- Reduced Regulatory Exposures.
- Improved Relationship with Regulators.

- Increased Compliance.
- Increased Revenue and Profitability.
- Enhanced Image through Environmental Stewardship.
- Meet Supplier/Customer Needs.
- Enhanced Export Potential.

❖ NABL ACCREDIATION

- National Accreditation Board for Testing and Calibration Laboratories (NABL) is an autonomous body under the aegis of Department of Science & Technology, Government of India, and is registered under the Societies Act.
- NABL was established with the objective to provide Government, Industry and Society in general with a scheme for third-party assessment of the quality and technical competence of testing and calibration laboratories.
- Government of India has authorized NABL as the sole accreditation body for Testing and Calibration laboratories**.**
- 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 VISION:"To be the world's leading accreditation body and to enhance stakeholders' confidence in its services

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

BENEFITS OF NABL ACCREDITATION

- Potential increase in business due to enhanced customer confidence and satisfaction.
- Savings in terms of time and money due to reduction or elimination of the need for re testing of products
- Better control of laboratory operations and feedback to laboratories as to whether they have sound Quality Assurance System and are technically competent.
- Increase of confidence in Testing / Calibration data and personnel performing work.

BASIC PRINCIPLE/CONCEPT OF NABL ACCREDITATION

- The concept of Laboratory Accreditation was developed to provide a means for third party certification of the competence of laboratories to perform specific type(s) of testing 990 and calibration.
- Laboratory Accreditation provides formal recognition of competent laboratories, thus providing a ready means for customers to find reliable testing and calibration services in order to meet their demands.
- Laboratory Accreditation enhances customer confidence in accepting testing / calibration reports issued by accredited laboratories.
- Reducing trade barriers and providing greater thrust to exports.

PROCESS OF NABL ACCREDITATION

STAGE I (FILLING OF APPLICATION)

- Prepare your laboratory's application for NABL accreditation, giving all desired. information and enlisting the test(s) / calibration(s) along with range and measurement uncertainty for which the laboratory has the competence to perform.

- Laboratory can apply either for all or part of their testing / calibration facilities. Formats NABL 151, NABL 152 & NABL 153 are to be used by Testing, Calibration and Medical Laboratories respectively for applying to NABL for accreditation.
- Laboratory has to take special care in filling the scope of accreditation for which the laboratory wishes to apply. In case, the laboratory finds any clause (in part or full) not applicable to the laboratory, it shall furnish the reasons.

STAGE II (PRE-ASSESSMENT AUDIT)

- NABL Secretariat shall organize the Pre-Assessment audit, which shall normally be carried by Lead Assessor at the laboratory sites.
- The pre-assessment helps the laboratory to be better prepared for the Final Assessment. It also helps the Lead Assessor to assess the preparedness of the laboratory to undergo Final Assessment apart from Technical Assessor(s).
- A copy of Pre-Assessment Report will be provided to Laboratory for taking necessary corrective action on the concerns raised during audit, if any.
- The laboratory shall submit Corrective Action Report to NABL Secretariat.
- After laboratory confirms the completion of corrective actions, Final Assessment of the laboratory shall be organized by NABL

STAGE III (FINAL ASSESSMENT)

- NABL Secretariat shall organize the Final Assessment at the laboratory site(s) for its compliance to NABL Criteria and for that purpose appoint an assessment team.
- The Assessment Team shall comprise of a Lead Assessor and other Technical Assessor(s) in the relevant fields depending upon the scope to be assessed.
- Assessors shall raise the Non-Conformance(s), if any, and provide it to the laboratory in prescribed format so that it gets the opportunity to close as many Non-Conformance(s) as they can before closing meeting of the Assessment.
- The Lead Assessor will provide a copy of consolidated report of the assessment to the laboratory and send the original copy to NABL Secretariat.
- Laboratory shall take necessary corrective action on the remaining Non-Conformance(s) 21/other concerns and shall submit a report to NABL within a maximum period of 2 months

STAGE IV (CORRECTIVE REASSESSMENT)

- After satisfactory corrective action by the laboratory, the Accreditation Committee examines the findings of the Assessment Team and recommends additional corrective action, if any, by the laboratory.
- Accreditation Committee determines whether the recommendations in the assessment es report is consistent with NABL requirements as well as commensurate with the claims made by the laboratory in its application.
- Laboratory shall have to take corrective action on any concerns raised by the Accreditation Committee.
- Accreditation Committee shall make the appropriate recommendations regarding accreditation of a laboratory to NABL Secretariat.

STAGE V (GRANTING OF ACCREDITATION)

- Accreditation to a laboratory shall be valid for a period of 3 years and NABL shall conduct periodical Surveillance of the laboratory at intervals of one year.
- Laboratory shall apply for Renewal of accreditation to it at least 6 months before the expiry of the validity of accreditation.

UNIT 2

- **ORGANIZATION AND PERSONNEL**
- **PERSONAL RESPONSIBILITIES**
  - In a pharmaceutical industry different jobs are performed by different persons and hence it becomes more important that each employee have a clarity and understanding of the job description.
  - A detailed job description or responsibilities should be prepared in writing, explained and assigned the same to the Person who is going to perform the job and his acceptance must be sought in writing by the person to the Authority person to whom he is going to report.
  - A job description is an organized and factual statement of the responsibilities of a specific job, in brief, it should tell the work, tasks, duties and responsibilities of a job.
  - Basically the job description should indicate what is done, why it is done, where it is done, and in brief how it is done, and then it will result in satisfactory performance and results

Ideally a job description may include:

- Organizational positions and operating relationships clearly mentioning job description and reporting
- Job summary in detail.
- Working conditions and hazards related to the job.
- Jobs/Duties, roles, responsibilities and accountability.

All the important positions in pharmaceutical industry/organization must have written, authorized and accepted job descriptions

KEY PERSONNEL

"It is defined as those positions in the organization, which have a direct impact on the working of the organization and quality of the products produced".

Some key personnel and their responsibilities

1.The Head of Quality Control department:

i. To approve or reject starting, packaging material.
ii. To approve or reject intermediate, bulk and finished products.
iii. To evaluate records related to batch.
iv. To ensure that all necessary testing related to product is carried out.

2.The Head of Production department:

i. To ensure that products are produced and stored according to the appropriate procedures and documentation in order to obtain the required quality.
ii. To approve the instructions relating to production operation, in process controls, and to ensure its strict implementations according to procedures.
iii. To ensure that productions records are evaluated and signed by a designated person before they are made available to the quality control department for further use.
iv. To check the maintenance of the production department, its premises and equipment.

3.Joint Responsibilities of Head of Q.C. and Production Departments:

i. To authorize written procedures, records other documents.
ii. To monitor and control the manufacturing environment.
iii. Plant hygiene.

iv. Process validations and calibrations of analytical apparatus.
v. Training, including the applications and principles of quality assurance and GMP.

4.Responsibilities of Authorized person:

i. Compliance with technical and regulatory requirements.
ii. Approval of the release of finished product for sale.
iii. Establishment and implementation of quality system.
iv. Development of quality manual.

- **TRAINING:** A person is called "Trained person", when he has appropriate knowledge, skill and attitude towards work.

Knowledge: It refers to the theoretical background expected in a person regarding the job to be performed and also the knowledge about the principles of all aspects of GMP, which may affect his area of work.

Skill: It refers to the practical experience he has and his ability to use his theoretical knowledge to perform a particular task give.

Attitude: Attitude is a behavioral trait of a person who is performing a task. He must have knowledge, skill and positive attitude towards performing work assigned to him by authority.

Under a quality system, managers are expected to establish training programs for staff that include:

- Evaluation of training needs.
- Provision of training to satisfy these needs.
- Evaluation of effectiveness of training. Documentation of training and/or re-training.
- Developing, maintaining, and administering the facility training plan.

In Pharmaceutical industries there are different levels of operations and jobs, they may start from production to formulation and lastly release of product.

The different abilities are required at different levels by Personnel. • Personnel must be trained in all these levels to perform the designated jobs.

Organization must identify the different level tasks, sets of knowledge, skills and attitudes required to make a person able to perform his task and train them accordingly.

Authorities must Design and conduct training programs according to tasks and jobs to enhance the Knowledge, skills and abilities of personnel.

Where contamination is a hazard including clean areas or Areas where highly active, toxic, infectious, sensitizing materials are handled, specific should be provided to the staff

Training may include: Training on:

- Concepts and Elements of GMP, GLP and other regulatory guidelines.
- Standards of drugs
- Calibration and validation o Handling of materials
- Sampling

- **HYGIENE :**
  - All the persons involved in manufacturing must be healthy and should practice good sanitation.
  - Organization should develop detailed hygiene programs for their employees and such programs must be implemented.
  - Eating, drinking, chewing and smoking or the storage of food, drink, smoking materials and personal medication should not be permitted within manufacturing areas or in any other area where they might adversely influence product quality.
  - There should be pre-employment medical checks and at regular intervals
  - Steps should be taken to see that no person with disease in a communicable form or with open lesion on the exposed surface of the body is engaged in the manufacture of pharmaceutical products.
  - Direct contact should be avoided between the operators hands products (other than when they are in closed containers), as well as with any part of the equipment that comes in contact with the product.
  - Staff should be required to report infections and skin lesion and defined procedure followed when they are reported. Supervisory staff should look for the signs and symptoms of these conditions.
  - Habit of hand washing must be inculcated in all the employees.
  - A detailed Dress-code procedure should be implemented. This should also cover use of other accessories used for human body protection.
  - Hygiene programs should be promoted by management and widely discussed during training sessions.
  - Requirements regarding personal hygiene and protective clothing apply to all persons entering production or other areas.
  - Only authorized persons shall enter these areas of buildings and facilities designated as limited access areas.
  - All personnel's should be trained in the practices of personal hygiene.
  - A high level of personal hygiene should be maintained by staff working in manufacturing areas

- **PERSONAL RECORDS:**
  - Personnel Records are records pertaining to employees of an organization.
  - Personnel records Contain factual and comprehensive information related to personnel.
  - It contains all the information with effect to human resources in the organization and it is kept in a systematic order.
  - Such records are helpful to a manager in various decisions making areas.
  - Personnel records are maintained for formulating and reviewing personnel policies and procedures.

PURPOSES OF PERSONAL RECORDS

- It helps to supply crucial information to managers regarding the employees. To keep an update record of leaves, lockouts, transfers, turnover, etc. of the employees.
- It helps the managers in framing various training and development programs on the basis of present scenario.

- It helps the managers to make salary revisions, allowances and other benefits related to salaries.
- It also helps the researchers to carry in depth study with respect to industrial relations and goodwill of the firm in the market.

- **PREMISES:**
- **DESIGN,LOCATION, SURROUNDINGS AND GENERAL REQUIREMENTS**
  - Any building used in the manufacture, processing, packaging or holding of drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, manufacturing and proper operation.
  - The factory building used for manufacturing of drug product shall be so situated and shall have such measures to avoid the risk of contamination from external environment
  - including open sewage, drain, public lavatory or any other factory producing disagreeable or harmful fumes, odor, dust and smoke, chemical or biological emission.
  - The premises/building shall conform to all conditions laid down in Factories act 1948. The premises used for manufacturing, processing, warehousing, packaging, labeling and testing should be compatible with manufacturing operations carried out in same area. Adequate space should be provided for logical and orderly placement of equipments and free movement of staff to avoid the risk of cross contamination.
  - The premises/building should be designed and constructed to prevent the entry of insects,birds, rodents etc.
  - HVAC system should be there where it is required (For environmental monitoring). • Proper drainage and waste disposal system should be there and the system should be designed to avoid the back-flow and entry of rodents and insects to the manufacturing areas.
  - The walls and floors of the areas should be free from cracks to avoid dust accumulation.
  - The walls and floors should be smooth and washable to facilitate ease of cleaning in the areas.
  - Premises should be carefully maintained and it should be ensured that repair and maintenance operations do not prevent any hazard to the quality of the products.
  - Premises should be cleaned and where applicable disinfected according to the written standard operating procedures.
  - Electric supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect directly or indirectly either the pharmaceutical product during their manufacturing and storage of the accurate functioning of the equipment.

A. Some principle areas of premises:

1. Ancillary areas Ancillary areas covers:

- Rest and Refreshment rooms.
- Toilets and Washrooms.
- Clothes storage areas. ••Changing rooms for employees.
- Rest and Refreshment Rooms should be separate from other areas.
- Facilities for Toilets should not communicate directly with production or storage areas. .
- Areas for change rooms and storage of clothes and for washing, and toilet purpose should be easily accessible and appropriate for the number of users.

2. Warehousing Areas: Storage areas should have sufficient capacity to allow orderly storage of the various categories of materials and products like:

i. Raw materials.
ii. Packaging Materials.

iii. Intermediates quarantine
iv. Bulk and finished products.
v. Products in quarantine.
vi. Released, returned, rejected and recalled products.

Storage areas should be designed to meet the required environmental conditions like: Temperature and Humidity and Records of such environmental conditions monitoring should be maintained.

Separate sampling areas should be provided for active and raw materials. Such sampling cubicles may be designed with suitable size and also provided with cleaning, drying and storage for sampling tools.

3. Production Areas:

- General category products (other than antibiotics, ctyotoxic and hormones.) should be manufactured in separate manufacturing facilities.
- Highly potent, sensitive or live micro-organism etc. should be produced in separate areas to avoid cross contamination.
- Premises should be designed to have logical flow of materials, well organized layout of plant and machinery and ease of cleaning, both equipment and facility. Depending on the volumes of materials being handled, adequate space should be provided to avoid mix-ups.
- Production areas should be effectively ventilated with suitable designed HVAC system, are appropriate to products being handled; to the operations undertaken and to the external environment.
- Production areas should be regularly monitored during production and non-production periods to ensure compliance with their design specifications.

4. Quality Control Areas

- QC. laboratories should be separate from production areas.
- Areas where biological, microbiological, or radio isotope test methods are employed should be separate from each other.
- Q.C. laboratories should be designed to provide facilities for:
  i. chemical analysis
  ii. Instrumental analysis.
  iii. Microbiological and biological analysis etc.
  iv. Storage for control samples, glassware's, chemicals, microbiological media books, documents etc.

B. Drainage system

- Potable water shall be supplied under continuous pressure in a plumbing system free of defects that could contribute contamination to any drug product.
- Water not meeting such standards of regulatory guidelines shall not be permitted in the potable water system.
- Drains shall be of adequate size.
- Drainage should be connected directly to the sewer and it should be provided with an air break or other mechanical devices to prevent back Spoilage. Drainage system maintenance in the manufacturing facilities is very critical from the point of view of cleaning and sanitation of the facilities.
- A detailed SOP should be there for cleaning and sanitation of drains and their records should be maintained and reviewed periodically

C. Disposal of waste:

- Sewage, waste and biomedical waste in and from the building premises shall be disposedof in a safe and sanitary manner according to the laws.
- The disposal of sewage and effluents (solid, liquid, and gas) from the manufacturing premises should be done in conformity with the requirements of the Environment Pollution Control Board.
- All biomedical waste shall be destroyed as per the provision of Bio-Medical Waste (Management and Handling) Rules, 1996.
- Additional precautions shall be taken for the storage and disposal of rejected drugs/ materials and all the Records shall be maintained for disposal of waste.
- Provisions shall be made for proper and safe storage of waste materials awaiting disposal.
- Hazardous, harmful, toxic substances and inflammable materials shall be stored in suitably designed and separate enclosed areas in conformity with Central and State Legislation.
- Records of all disposed material must be kept and should be available for inspection or audit when required.

- **MAINTENANCE**

Any building, premises used in the manufacture, processing, packing or storage of a drug product shall be in a good state of repair.

Facility maintenance includes maintenance of following things:

- Leakage from ceiling or other surfaces.
- Leakages from pipe lines of waters, steam, gases etc.
- Plumbing problems.
- Loose or broken tiles.
- Improper closing of doors, windows.
- Improper electrical wiring
- Improper electrical fittings/fixtures.
- A detailed check list may be prepared for maintenance.

During routine inspection of the facilities the deficiencies should be identified andcorrected immediately and the facility must always be maintained in a state of good.

Deterioration of building and facilities represents poor image of facilities and it can affect product quality.

Cracks/ holes in walls, ceilings etc. can provide access to the rodents, insects, microorganisms and it can directly affect the quality of the product, sanitation and hygiene.

Roof leakage can affect the quality of materials and may cause damage to the equipments.

- **SANITATION**
  - Any building/premises used in the manufacture, processing, packing or holding of a drug product shall be maintained in a clean and sanitary condition".
  - All the premises shall be free of infestation by rodents, birds, insects, and other vermin's (other than laboratory animals).
  - There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used in the cleaning the buildings and facilities; such written procedures shall be followed.
  - There shall be written procedures for use of suitable Rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents.

- Such written procedures shall be designed to prevent the contamination of equipment, components, drug product container and closures, packaging, labeling material or drug products and shall be followed.
- Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticides, Fungicides and Rodenticide Act.
- Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full time employee during the ordinary.
- SOPs should be available even for cleaning and sanitation of external areas of the facilities like roads, lawns etc. .
- In pharmaceutical industries, operations have to be carried out in clean areas to avoid contamination, cleaning of areas, equipments and microbial monitoring, disinfection of areas and equipments are very important and have to be carried out regularly.
- In order to maintain sanitation and cleaning we have to consider following points:
    a. Create and maintain safe working environment.
    b. Remove dust and dirt which can affect product quality,
    c. Minimize the risk of cross-contamination occurring between products.
    d. Lastly, reduce the levels of microbial contamination

- **ENVIRONMENTAL CONTROL IN STERILE AREAS**

Sterile products are very critical and sensitive in nature hence it requires very high degree of precaution and prevention is required in its preparation and there shall be strict compliance with standards prescribed by regulatory authorities.

1. Air handling units for sterile product manufacturing shall be different from those of other areas.

2. Critical areas such as aseptic filling areas, sterilized components unloading areas and changing room should conform to grades B, C and D respectively and shall have separate "Air handling units". The filter configuration in the Air handling unit shall be suitably designed to achieve the grade of air

3. For products which are filled aseptically, the filling room shall meet Grade B condition at rest.

4 The Filling operation shall take place under Grade A condition which shall be demonstrated under working of simulated conditions which shall be achieved by providing Laminar air flow work station with suitable HEPA Filters.

5.For products which are terminally sterilized, the filling room shall meet Grade C conditions at rest. & Manufacturing and component preparation areas shall meet Grade C conditions.

7. After Completion of preparation, Washed components and vessels shall be protected with Grade C background.

8. The minimum air changes for Grade B and Grade C areas shall not be less than 20 air changes per Hour in a room with good air flow pattern and appropriate HEPA filters.

- **UTILITIES AND MAINTENANCE IN STERILE AREAS**

  Sterile areas/ aseptic processing areas should have:

  1) Smooth and easily cleanable Floors, Walls and Ceilings. 2
  2) Temperature and humidity controls.
  3) Air supply with HEPA filters under positive pressure.
  4) Environmental conditions monitoring system.
  5) A system for Cleaning and disinfecting to produce aseptic/ sterile conditions.

  Floors, walls and ceilings of sterile areas should be subjected to intensive and frequent cleaning and sanitation.

- **CONTROL OF CONTAMINATION IN STERILE AREAS:**

1. Control of contamination- areas/Facilities

- In the areas/Facilities where sterile products are manufactured air should be supplied under positive differential pressure with HEPA filters designed to keep Microorganisms and other particles at low level.
- In sterile areas all the surfaces of floors, walls, ceilings etc should be hard and free from cracks to avoid dust and microorganism accumulation and should permit easy cleaning.
- Access to sterile areas must be Controlled/ Restricted to people and entry and exit to sterile areas should be only permitted through change areas.

2. Control of Contamination - People

All the personnel working in aseptic/sterile areas should emphasize on following points to control the contamination:

i. Keep Body, hair, face, hands and nails clean.
ii. Report illness, injury, respiratory and skin problems. Follow the written changing and wash-up procedures.
iii. Do not use cosmetic and wear jewellery and wrist watches.
iv. Do not take papers and documents in sterile area.
v. Avoid eating, chewing, drinking and smoking in sterile areas.

3. Control of contamination by cleaning and disinfection

i. The written procedures regarding Cleaning and disinfection should be followed exactly and strictly.
ii. Before disinfection, it is necessary to clean the area completely.
iii. All the cleaning and disinfecting agents and materials themselves should be clean
iv. Avoid cleaning by mops use equipments.
Use vacuum cleaners for sucking dust.
v. Always start cleaning walls and ceiling from top to avoid recontamination.

- **EQUIPMENTS AND RAW MATERIALS:**

DEFINITION OF EQUIPMENT: Equipment may be defined as any piece of plant, machinery, instrument etc, which is used for carrying out a specific activity or operation e.g. mixer, dryer, HPLC etc. Equipment can be a single piece or it may consists of a set of integrated pieces to perform a common activity e.g. water purification plant.

- **EQUIPMENT SELECTION**: While selecting the equipment, following points should be considered:

1.Design: The design of the equipment should meet user requirements, for which the equipment is selected. For this purpose User Requirement Specification (URS) should be prepared. URS will vary from equipment to equipment but this should at least answer the following questions:

a) Which kind of operation we are going to perform using this equipment?

b)What capacity it should have in terms of holding and in terms of output?

c)Which materials we are going to use in this equipment and do they have any interaction with the material of construction?

d) How this equipment will be cleaned?

2.Size: Size of the equipment is decided based on the volumes of materials, which we are going to handle. Batch sizes are also directly related to the size of the processing equipment.

In case of size of equipment following things should be considered:

a) Physical dimensions of the machinery (length x height x width).

b) size of the room in which the machine is going to be installed and the path in the plant through, which it will be transported.

c) Holding and output capacity of the equipment.

3.Location: Decision of locating the equipment in the plant depends upon the logical process movement Following are the factors which influence the location of the equipment:

a) Utility services required.

b) Potential danger of contamination and mix-ups. c) Material handling and movement.

d) Movement for processing and cleaning

e) Men movement for repair and maintenance.

4.Construction: Following four main factors should be considered:

a) Ease of cleaning the equipment and surrounding area.

b) Ease of operation of the equipment. c) Ease of maintenance of the equipment.

d) The material of construction (MOC)

- **DOCUMENTS REQUIRED WITH EQUIPMENT**

(1) Machine/Equipment manuals/SOP.

(ii) Machine/Equipment layout drawing, showing the position of the equipment in the rooms.

(iii) Equipment validation reports.

- **PURCHASE SPECIFICATIONS FOR EQUIPMENTS**

While purchasing equipment following parameters/specifications should be considered:

a) Operating criteria are adequate for the process- size, speed and effectiveness. Availability of spares and servicing (Spare parts should be easily available).

b) Ease of maintenance and cleaning.

c) Environmental issues (Equipments disseminating dust may cause contamination to other products being manufactured and Equipment producing noise)

d) Construction material (material used for construction of equipment should be non reactive with A.P.I. Raw materials and products being manufactured).

e) Availability of process controls (e.g. Automatic weight adjustment on tablet press and temperature records on oven).

- **MAINTENANCE OF EQUIPMENTS:**

a) Equipments shall be maintained at appropriate intervals to prevent the malfunction that can affect the process used for manufacturing.

b) Written procedures shall be established and followed for the maintenance of equipments used for manufacturing and the procedures shall include:

i. Maintenance schedule (Frequency of maintenance, calibration, validation).

ii. Assignment of responsibility for maintenance of equipment.

iii. A description of method/procedures used for maintenance.

iv. Protection of equipment.

v. Inspection of equipment before use. c) All the records related to equipment maintenance shall be kept for further use.

- **DEFINITION OF RAW MATERIAL:** "It is defined as the starting material used in manufacturing of finished product".

- **PURCHASE SPECIFICATIONS FOR RAW MATERIALS:**

Regarding purchasing of raw materials following points should be

a) Cost of raw material.

b) Identity, purity and quality of raw material

c) Vendor selection: Materials should be purchased and sourced only from approved suppliers and manufacturers. Choice of vendor should be primarily based on quality consideration and Supplier/Manufacturer of the material should have his name listed in companies approved vendors list.

d) All raw materials should be checked for following things:

i. Name of the manufacturer/supplier.
ii. Name of the product/material.
iii. Batch numbers.
iv. Date of manufacture and date of expiry.
v. Quantity received and number of containers or packages.
vi. vi. Condition of containers and materials.

e) Storage conditions: (Appropriate special storage conditions e.g. store at low temperature, low humidity away from direct light etc. or sterile material etc.) should be clearly mentioned.

- **MAINTENANCE OF STORE FOR RAW MATERIALS**

STORAGE AREA

a) There should be a sufficient area/Capacity for the storage of raw materials.

b) The area used for storage of raw materials should be clean, dry and maintained within acceptable limits of environmental conditions.

c) There should be a well equipped and appropriately designed reception area for receipt raw materials.

d) There should be a Separate area for sampling

e) There should be separate areas for storage of rejected, recalled or returned material.

STORAGE CONDITIONS

The raw materials in the store should be stored according to its storage conditions required:

For example:

a.For general product: Room temperature should be 30° C and Relative humidity should be 60%.

b. Products requiring storage in air conditioning (Temperature should be 25±2°C & Relative humidity should be 45 to 55%)

c,Products requiring Low temperature storage (Temperature should be 2 to 8 °C)

d. Separate area for sterile product storage in A.C under sterile conditions.

LABELING OF MATERIAL IN STORAGE AREA

a) Designated name of product and code

b) Batch no, given by supplier

c) Storage conditions d) Handling procedure

e) Hazards and risks associated with it f) Precaution to be taken

g) Safety measures h) Status of Content

i) Expiry date or date beyond which retesting is necessary

UNIT 3

Quality Control of Packaging Material

DEFINITION OF PACKAGING

Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale, and use. Packaging also refers to the process of designing, evaluating, and producing packages. Packaging can be described as a coordinated system of preparing goods for transport, warehousing, logistics, sale, and end use.

OR

Packaging is also defined as "The process by which the pharmaceuticals are suitably packed so that they should retain their therapeutic effectiveness from the time of their packaging till they are consumed".

IMPORTANCE OF PACKAGING

1) Protect against all adverse external influences that can alter the properties of the product.
2) Protect against biological contamination.
3) Protect against physical damage.
4) Carry the correct information and identification of the product. Tamper evident / Child resistance/ Anti counterfeiting

FUNCTIONS OF PACKAGING

Packaging provides protection against: Light, Moisture, Oxygen, Biological contamination, Mechanical damage etc.

PRIMARY AND SECONDARY PACKAGING

1. Primary packaging: Packaging which is in direct contact with the product. e.g. bottle, closure, blisters etc.

2. Secondary packaging: These additional packaging materials that improve the appearance of the product and do not make direct contact with the product. e.g. Wrappers, labels etc.

TYPES OF PACKAGING MATERIAL USED FOR PHARMACEUTICAL PRODUCTS

Glass, Metal, Plastic ,rubber ,paper board

❖ QC TESTS FOR CONTAINERS

Q.C TESTS FOR GLASS CONTAINERS

i.Chemical resistance of glass containers

a. Powdered Glass test

b. Water attack test

ii. Hydrolytic resistance of glass containers

iii. Arsenic test

iv. Thermal shock test

v. Internal bursting pressure test

vi. Leakage test

vii. Light transmission test (For coloured glass containers)

i. Chemical resistance of glass containers

A. Powdered glass test

This test is done to estimate the amount of alkali leached from the powdered glass which usually happens at the elevated temperatures. When the glass is powdered, leaching of alkali is enhanced, which can be titrated with 0.02N sulphuric acid using methyl red as an indicator

Step-1: Preparation of glass specimen: Take Few containers rinse them thoroughly with purified water and dry with stream of clean air, Grind the containers in a mortar to a fine powder and pass through sieve no.20 and 50.

Step-2: Washing the specimen: Take 10gm of the above specimen in 250 ml conical flask and wash it with 30 ml of acetone. Repeat the washing, decant the acetone, dry and use it within 48 hr

Procedure :

Take 10 gm of sample in 250ml of flask; add 50 ml of highly purified water.

Place the flask in autoclave at 121p C+2p C for 30min.

Remove the flask after 30 minutes and cool it under running water.

Decant the solution in other flask and again wash with 50ml of highly purified water.

Then titrate the above solution immediately with 0.02N sulphuric acid using methyl red as an indicator and record the volume..

B. Water attack test

This test is only for treated soda lime (Type II) glass containers under the controlled humidity conditions and the basic principle involved in this test is that whether the alkali is leaching or not from the surface of the container.

Procedure :

Rinse the container thoroughly with high purity water. Fill each container to 90% of its overflow capacity with water and autoclave at 121p C for 30 min

Then cool the liquid and titrate with 0.02N sulphuric acid using methyl red as an indicator. The volume of sulphuric acid consumed is the measure of the amount of alkaline oxides present in the glass containers.

ii. Hydrolytic resistance of glass containers

Procedure :

Rinse each container at least 3times with CO2 free water and fill with the same to their filling volume, also fill & Cover the vials and bottles and keep in autoclave.

Heat up to 100p C for 10min and allow the steam to issue from the vent cork.

Raise the temperature from 100p C to 121p C over 20 min. Maintain the temperature at 121p C to 122p C for 60 min. angu ni polqmst er

Lower the temperature from 121p C to 100C over 40 min venting to prevent vacuum.. Remove the container from autoclave, cool and combine the liquids being examined.

Measure the volume of test solution into a conical flask and titrate with 0.01M HCI using methyl red as an indicator.

Perform blank titration with water and the difference between the titration represents the volume of 0.01M HCl consumed by the test

iii. Arsenic test

This test is for glass containers intended for aqueous parenterals.

Procedure :

Wash the inner and outer surface of container with fresh distilled water for 5min. Prepare test solution as described in the test for hydrolytic resistance for an adequate number of samples to produce 50ml.

Pipette out 10 ml solution from combined contents of all ampoules to the flask. l'I Add 10 ml of HNO3 to dryness on the water bath and dry the residue in an oven at 130p C for 30 min cool and add 10 ml hydrazine molybdate reagent.

Swirl the solution till it is dissolved and heat under water bath and reflux for 25 min. Cool at room temperature and determine the absorbance at 840 nm. do d Determine the blank with only 10 ml hydrazine molybdate.

The absorbance of the test solution should not exceed the absorbance obtained by repeating the determination using 0.1 ml of arsenic standard solution (10ppm) in place of test solution

iv. Thermal shock test

Procedure :

Place the samples in upright position in a tray.

Immerse the tray into a hot water for a given time and transfers to cold water bath, temperature of both should be closely controlled.

Examine cracks or breaks before and after the test. The amount of thermal shock a bottle can withstand depends on its size, design and glass distribution.

Small bottles withstand a temp differential of 60 to 80p C and 1 point bottle 30 to 40p C.

A typical test uses 45p C temperature difference between hot and cold water.

v. Internal bursting pressure test

The most commonly used instrument for this test is American glass research increment pressure tester.

Procedure :

The test bottle is filled with water and placed inside the test chamber. A scaling head is applied and the internal pressure automatically rises by a series of increments each of which is held for a set of time. The bottle can be checked to a preselected pressure level and the test continues until the container finally bursts.

vi. Leakage test

Procedure :

Drug filled container is placed in a container filled with coloured solution (Containing dye e.g. Methylene blue), which is at high pressure as compared to the pressure inside the glass container Coloured solution enters the container, if any cracks or any breakage is present.

vii. Light transmission test (For coloured glass containers)

Procedure :

Break glass container with carborundum (very hard solid of Silicon carbide used as an 91abrasive) or diamond wheel. Select wall section and Put it in specimen holder of spectrometer with care.

Place test specimen in the spectrometer with its cylindrical axis parallel to the slit and in 16 such a way light beam is perpendicular to the section. Measure the transmission of specimen with reference to air in spectral region of the 290 450 nm continuously or with interval of 20 nm.

The observed light transmission for colored glass should be not more than 10% at any wavelength in the range of 290-450 nm, irrespective of the type and capacity of container.

TEST FOR METAL CONTAINERS

Procedure :

Select a sample of 50 tubes from the lot to be tested and clean each tube by vibration and/blowing.

Fill the tubes with a suitable molten ointment base, close the open end of each tube by a double fold and allow the filled tubes to cool overnight at a temperature of 15°C to 20°C.

Take a metal bacteriological filter with 4.25 cm filter paper of suitable porosity supported

on suitable perforated plate and heat it above the melting range of the ointment base.

Remove the caps and apply uniform pressure to the closed end of each tube in turn, in such a manner that the time taken to express as much of the base as possible through each nozzle is not less than 20 seconds.

Collect the extruded base from the 50 tubes on the heated filter by applying suction. Wash the walls of the filter and the filter paper with three successive quantities, each of 30 ml of chloroform, allow the filter paper to dry.

Examine the filter paper under oblique lighting with the aid of magnifying glass with a graticule of 1 mm squares, one of which should be sub-divided into 0.2 mm squares.

TEST FOR PLASTIC CONTAINERS

1.Leakage test :

Fill 10 containers with water, fit with intended closures and keep them inverted at room temperature for 24hr. The test is said to be passed if there is no signs of leakage from any container.

2. Collapsibility test

This test is applicable to the containers which are to be squeezed for removing the contents. A container by collapsing inward during use, yield at least 90% of its normal contents at the required rate of flow at ambient temperature.

3. Clarity of aqueous extract

Randomly select unlabelled, unmarked and non laminated portions from suitable containers. Cut these portions into strips, none of which has a total surface area of 20 sq.cm. Wash the strips and free it from extraneous matter by shaking them with at least two separate portions of distilled water for about 30sec and drain off the water thoroughly.

Thus processed sample is taken in to the flask, previously cleaned with chromic acid Stimixtures and rinsed with several portions of distilled water and added 250 ml distilled water. Cover the flask and autoclave at 121p C for 30min.Carry out the blank determination using 250 ml dist water. Cool and examine the extract, it should be colourless and free from turbidity.

4. Water vapour permeability test

Fill 5 containers with normal volume of water and heat seal the bottles with an aluminium foil. Weigh accurately each container and allowed to stand for 14 days at a relative humidity of 60±5% and a temperature between 20 and 25p C. Reweigh the containers. The loss in weight in each container is NMT 0.2%

5. Transparency test

Standard suspension preparation: 1gm hydrazine sulphate in 100ml water and set aside for 6hr.take 25ml of this solution and add 25ml of 10%w/v hexamine and stand for 24hr.

Test solution preparation: Sample is prepared by 16fold dilution of the standard suspension. Fill 5 containers cloudiness detectable when compared to water filled containers. Absorbance is measured at 640 nm and the range is within 0.37 to 0.43.

TEST FOR RUBBER CLOUSER

1Sterility test

visado nad to signtre how y Subject treated closures to sterilization at 64-66p C and a pressure of about 0.7 Kilo "Pascal for 24hrs. (It should not become tacky or soften).

2. Fragmentation test

A. For aqueous preparations

Place water corresponding to the nominal volume minus 4 ml in each of 12 clean vials. Close the vials with the 'prepared' closures & allow it to stand for 16 hours.

Using a hypodermic needle with an external diameter of 0.8 mm inject 1 ml of water into the vial and remove 1 ml of air.

Carry out this operation 4 times with new needle each time.

Pass the liquid in the vials through a filter with a pore size of 0.5 µm.

No. of fragments NMT 10 except in the case of butyl rubber closures where the total no. of fragments NMT 15

B. For dry preparation

Close 12 clean vials with the 'prepared' closures. .

Using a hypodermic needle with an external diameter of 0.8 mm inject 1 ml of water into the vial and remove 1 ml of air.

Carry out this operation 4 times with new needle each time.

Pass the liquid in the vials through a filter with a pore size of 0.5 µm.

No. of fragments NMT 10 except in the case of butyl rubber closures where the total no. of fragments NMT 15

3. Self- seal ability

Close the vials with the 'Prepared' closures.

For each closure, use a new hypodermic needle with an external diameter of 0.8 mm & pierce the closure 10 times, each time at a different site.

Immerse the vials upright in a 0.1% w/v solution of methylene blue & reduce the external pressure by 27KPa for 10 min.

Restore the atmospheric pressure and leave the vials immersed for 30 minutes.

Rinse the outside of the vials.

None of the vials contains any trace of coloured solution.

4. pH of aqueous extract

Take 20 ml of solution A, add 0.1 ml bromothymol blue.

Add small amount of 0.01M NaOH, after its addition colour changes from blue to yellow.

The volume of NaOH required to change the colour should not be more than 0.3ml and divif it is done with HCI, the volume of HCI needed should not be more than 0.8ml.

5. Light absorption test

It must be done within 4 hrs of preparing solution

Solution A is filtered through 0.5µ filter and its absorbance is measured at 220 to 360nm.

Similarly take absorbance of Blank without closures and absorbance should not be more than 2.0

CONTROL TESTS FOR SECONDARY PACKAGING MATERIALS (PAPER AND BOARD)

Before performing tests on pieces of paper & board, they are conditioned for the tests to be carried out in standard conditions.

- Those conditions are: Temperature -23°C ± 1°C & Relative humidity -50% ±2%

Name of the Test	Description
Moisture content	All the substances will be measured at temperature specified for test
Folding Endurance	Fold the test piece back & forth until rupture occurs
Density of paper & board	For rigid cellular materials
Method for determining air permeability	Expressed in μm $pa^{-1}s^{-1}$. It is important for using lightweight uncoated paper on machine having vacuum pick up system
Grammage or substance (g/m^2)	The weight of material per unit area of sample
Paper Caliper	Single sheet thickness between one surface and other
Tensile strength	The maximum tensile force per unit width that a paper or board will withstand before breaking
Tear strength	The mean force required to continue the tearing of an initial cut in a single sheet of paper
Burst strength	The maximum uniformly distributed pressure, applied at right angles to surface that a test piece of paper & board will stand under conditions of test. Hydraulic pressure is applied to diaphragm, bulging it until test piece bursts.
Puncture resistance	Energy required to make initial puncture
Stiffness of thick paper & boards	Degree of resistance offered by paper/board when it is bent
Creasibility of boards	Method to determine creasing quality of board within the range of 300-1000 μm
Cobb test(g/m^2)	Test for water absorbency

Rub resistance	This is resistance of printed test piece to withstand rubbing against another similar test piece
Pick test/IGT test	A specified amount of a special oil is added to the printing system & printed on to the test piece. The surface is then examined for signs of pick.
pH, chloride or sulphate	The acidity or alkality (pH) can help the life of the paper board
Roughness/smoothness	This is very important for 'printablity' of the paper.
Brightness	This is the reflectance factor measured at the effective wavelength of 457 nm
Opacity	This is ratio expressed as percentage of luminous reflectance factor of a single sheet of paper with a black backing to intrinsic luminous reflectance factor.
Dennison wax test	This is a older test and was replaced by the IGT test
Wet burst strength	It is used to determine wet bursting strength of any paper or board following immersion in water
Wet tensile strength	It is to determine wet tensile strength on immersion in water
Ash in paper & board	This is a method of determining the ash content in paper & board
Detection & estimation of nitrogenous agents in paper	It applies only to substances that have a strong affinity for acid dyes
Ink absorbency	The determination of ink absorbency of paper & board by K & N ink.

Unit 4

Compalints

DEFINITION

"Complaint is defined as statement that is something wrong or not good enough, which shows customer dissatisfaction about the company and the product".

- Complaint about product is an indicator of the Product quality, and also about the expectation of the consumer from the product.
- Any product complaint should always be considered as a feedback and this information should be used for improving the product quality and related manufacturing/operational systems.
- The full significance of complaints may only be appreciated by certain responsible persons and then possibly only with the knowledge of other related complaints.
- A procedure must therefore exist to channel complaint reports appropriately otherwise a complaint (reported product defect) or adverse event may lead to the need for recall.
- All complaints and other information concerning defective products must be carefully reviewed according to detailed written standard operating procedures and detailed records must be kept and used for further improvement and elimination of defect in product.

NEED FOR COMPLAINT HANDLING SYSTEM

- It gives the company an opportunity to improve the quality of the product.
- It is helpful to maintain cGMP.
- It maintains committed relationship between the customer and company.
- It is the regulatory obligation

EVALUATION OF COMPLAINTS

Regulatory literature provides following guidelines:

- A standard operating procedure should be available giving full details about how to handle products complaints and necessary records about complaints handled should be maintained.
- A person should be designated for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. This person should normally be from the quality management department, with sufficient knowledge and experience in related work.
- If a product defect is suspected in a batch, other batches should also be checked in order to determine whether they are also affected.
- All decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- A file regarding such drug products complaints shall be maintained at the factory site, where the drug product involved was manufactured, processed or packed.
- Written records involving a drug product shall be maintained for at least 1 year after the expiration date of the drug product or 1 year after the date that the complaint was received, whichever is longer.
- In case of certain O.T.C. products where expiration date is not given the records should be maintained for at least for 3 years after the complete distribution of the drug product

- Such written record shall include the following information, where known:

  a) Name and strength of the drug product.

  b) Lot/control/batch number.

  c) Name of the complainant.

  d) Nature of complaint

  e) Reply to the complainant.

  f) If investigation is made, it's complete report.

- Where an investigation is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.
- Complaint records shall be regularly reviewed for any indication of specific recurring problems requiring attention and possibly the recall of the marketed product.
- All decisions and measures taken as a result of a complaint should be recorded and referenced in the corresponding batch records.
- Trend analysis should be performed in an event to identify possible recurrent causes leading to a negative effect on a product.

RETURNED GOODS

Pharmaceutical products can be returned from market for various reasons e.g. Quality problems, accidental damage of goods etc.

Such products when returned from market should have the following action immediately taken on it:

i. Physically examine the condition of the goods returned. Also check all the relevant documents.

ii. Ask Q.C. department to evaluate the quality of the goods received and take a decision on whether these products can be reprocessed, recovered or needs to be destroyed.

iii. If it possible to reprocess and recover, then such products after reprocessing or retesting may be considered for relabeling, repacking and reselling the same.

iv. Q.C. department should evaluate all aspects of the received material.

v. Where even a slightest doubt arises about the quality of the product, it should not be considered suitable for reissue or reuse.

vi. Any action taken should be recorded.

CLASSIFICATION OF RETURNED GOODS

Returned goods received by the company at any of its warehouse may be classified in relation to the primary cause of necessitating their cause:

- Date expired products
- Damaged/Broken primary containers
- Leaky/Broken seals of closures of primary containers

- Smudged labels rendering the products unidentifiable as to their name/batch number Soiled labels rendering the product aesthetically un-presentable, but otherwise clearly identifiable.
- Products recalled voluntarily by the company
- Products recalled as per directives from drug control authorities

HANDLING OF RETURNED GOOD: (SOP)

- ✓ Purpose: To Lay down systematic procedure to establish handling of returned material/ products from market.
- ✓ Scope: This method is applicable for the handling of returned material/products from market.
- ✓ Responsibility: Production Head / Technical Director/ Head Quality Assurance.
- ✓ Accountability: Head Quality Assurance..

Procedure :

1. Any material or goods (Finished products &/or intermediates) returned from the market shall be stored in a separate area dedicated for storage of returned goods.

2. Record all the details in Returned Goods Record, as per the Product record Format (Table 12.1).

3. Inform the Quality Assurance department for evaluation of the returned goods.

4. The Quality Assurance chemist shall evaluate the returned goods for the following:

a. Check the Certificate of analysis and other documents with the returned consignment.

b. Condition of the Packaging, carton and container.

c. Labeling details.

5. If the returned material has exceeded the labeled expiry period or the condition of the packaging, carton, container and storage condition of the material before returning/ shipping are doubtful, and then destroy the material as per the SOP for control sample destruction.

6. If none of the above condition is apparent, then sample the material as per the SOP for sampling of the finished good.

7. Analyze the sample as per the current approved product specification. If the product meets appropriate product specification, then the returned material/ product may be considered for reprocessing as per the SOP for reprocessing, provided the subsequent product meet the specifications.

RECALLING

Definition of Recall: "Recall" means a firm's removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action.

OBJECTIVES OF RECALL

- Stop the distribution and sale of the affected product.
- Effectively notify Management, customers and regulatory authority.
- Efficiently remove the affected product from the marketplace, warehouse and/or distribution areas.
- Dispose and Conduct a root cause analysis and report the effectiveness and outcome the recall. • Implement a corrective action plan to prevent another recall.

RECALL CLASSIFICATION

FDA classified the product recall depending on the health hazard caused by the product.

Class I is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death."

Class II is a situation in which use of, or exposure to, a violative product may temporary or medically reversible adverse health consequences. cause

Class III is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

RECALL PROCEDURE

- Any employee becoming aware of such medicine or any adverse event related to it should immediately notify to higher authorities.
- Immediately quarantine existing in-house of relevant medicine Record the following information:
- The product name, strength, packs size, batch no., Mfg. and Expiry date.
- The total number of units released for sale.
- Date on which distribution commenced.
- Total number of units distributed.
- Number of units still in stock.
- Nature of reported violation.
- In the light of above information higher officials evaluates the health hazard presented by the violation medicine and documents it on "medicine recall control document".
- Formulating a proposed recall strategy. It specifies the nature of communication to be used (phone, fax, telegram, letters etc) as well as the level in the distribution chain to which recall is extended. (wholesalers, retailers, public, etc).
- Relevant records shall be submitted to regulatory authorities with proposed plan of action.
- After that final reconciliation a report of final reconciliation after 90 days is prepared and a copy submitted is for verification and Steps should be taken to prevent the re occurrence.
- Prior to completion of recall the following points should be considered:
- Method of destruction of the product
- A designed area to receive returned medicines.
- Inventory of medicine.
- Destruction authorization.
- The recall will be terminated when the GM, QA/QC Regulatory or GM manufacturing are assured that recall has been completed reasonably and a "medicine record status report" is completed.

WASTE DISPOSAL

- There should be a written authorized procedures for handling, destruction and disposal of all rejects, wastes generated during production/ handling of pharmaceutical products and printed packaging products
- All rejects/wastes should be collected in suitable closed containers, labeled appropriately and held in segregated space until taken for destruction.
- Destruction must be carried out by authorized persons under the supervision of responsible person.
- Quantities rejected and destroyed must be recorded and reconciled in relevant batch document.
- Appropriate safety precautions must be taken while carrying out destruction.
- Final disposal of residual solids/liquids should be consistent with regulatory requirements including environmental impact.

Document Maintenance in Pharmaceutical Industry

Definition of Document

"Document is any written statement or proof".

OR

"A piece of written, printed, or electronic matter that provides information or evidence or that serves as an official record."

OBJECTIVES OF DOCUMENTATION

- Define the manufacturers system of information and control.
- To minimize the risk of misinterpretation and errors inherent in oral or casual written communication.
- To provide unambiguous procedures to be followed. To provide confirmation of performance of a task.
- To allow calculations to be checked.
- And finally to allow tracing of the batch history of any product.

IMPORTANCE OF DOCUMENTATION

Good documentation is an essential part of the quality assurance system and as such should be related to all aspects of GMP

It defines the specification for all materials and methods of manufacture anD control.

It ensures that all personnel concerned with manufacture know, what to do? How to do? When to do? And why to do? etc..

It ensures that authorized persons have all the information necessary to decide, whether or not to release a batch of a drug for sale or distribution.

It provides an audit trail that will permit investigations of the history of any suspected defective batch.

BATCH FORMULA RECORD

- Batch formula record or Batch manufacturing record is a product and batch specific document designed to give a complete reliable picture of the manufacturing history of each batch of every product.
- It provides a detailed description of all processing operations and controls.
- Batch formula record or Batch manufacturing record is a recurring document. This gives complete history of the batch produced.
- It gives the actual process record of the batch produced and helps in maintaining the complete production and control history of the batch.

Contents of Batch formula record: .

i.Dates and times of all the activities, which are carried out regarding production and control of the batch.

ii. Identification of individual major equipment and lines used.

iii. Identification of specific rooms/locations preferably with unique identification numbers should also be included.

iv. Specific identification of each batch of components or in-process materials used.

v. Weights and measures of components used in the course of processing.

vi. In-process and laboratory control results.

vii. Inspection of packaging and labeling area before and after use.

viii. A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phase of processing.

ix. Complete labeling control record, including specimens or copies of all labeling used.

x. Description of drug product containers and closures.

xi. Any sampling performed, during the production and / packaging activities.

xii. Identification of persons performing and directly supervising or checking each significant step in the operation.

xiii.Any investigation made regarding any unexplained discrepancies including yield variation etc., or other deviations if any should be recorded and authorized.

xiv. Results of examinations.

MASTER FORMULA RECORD

Master formula record for each drug product shall describe all aspects of its manufacture, packaging and control.

To assure uniformity form batch to batch, master formula record shall be prepared for each batch size separately and should be dated and signed by one person and independently checked, dated and signed by at least second person.

Master formula record is a product specific document compiled, checked, authorized and approved by competent technical personnel from product development, production, packaging and quality control department.

For manufacturing and packaging operations, it is important to have master formula record for each batch size to eliminate the need for recalculations of quantities of components, packaging materials and in-process samples.

Master formula record should ir clude:

i. Name and strength of product.
ii. Its description of dosage form.
iii. Name and weight of each ingredient per unit of dosage form.
iv. A complete list of components designated by names and codes.
v. statement concerning any calculated excess of components (variation from theoretical value)
vi. A statement of theoretical and practical yields at different stages of manufacture with minimum and maximum limits
vii. Complete instructions of manufacturing, control, sampling, testing, procedures, specifications and precautions.
viii. Description of drug product containers, closures and packaging materials.

The master formula record should clearly identify:

i. Equipment to be utilized Designated by name and number).
ii. Stepwise manufacturing process with details of conditions such as temperature, time, speed, sequence of addition of ingredients etc.
iii. Critical in-process checks and controls with permissible limits.
iv. Precautions, hazardous conditions and safety measures.
v. Theoretical and actual yields.
vi. Signature and date of authorized person.

SOP (STANDARD OPERATING PROCEDURE)

INTRODUCTION

• **Definition:** "A Standard Operating Procedure (SOP) is a set of written instructions that document a routine or repetitive activity followed by an organization".

The development and use of SOPs are an integral part of a successful quality system as it provides individuals with the information to perform a job properly, and facilitates consistency in the quality and integrity of a product or end-result. .

Since each institute operates and functions differently depending on varying circumstances, and has its own ways of carrying out certain procedures, the SOPs in different factories will differ. However, the basic content, structure, and the concepts of SOPs will obviously be the same.

Contents of SOP :

1) Name & Address of the company.
2) SOP number and Date when the SOP was prepared/ reviewed.
3) Aim or Objective of the SOP.
4) Scope of the SOP (area which will be covered by the SOP).
5) Process/Steps to be carried out, in sequential order.
6) Whose responsibility it is to carry out the SOP.
7) Any other useful information.
8) Name and signature of the person/s who made/reviewed the SOPs, along with date of review.

BENEFITS OF SOP

The development and use of SOPs minimizes variation and promotes quality through consistent implementation of a process or procedure within the organization, even if there are temporary or permanent personnel changes.

When historical data are being evaluated for current use, SOPs can also be valuable for reconstructing project activities when no other references are available.

Ultimately, the benefits of a valid SOP are reduced work effort, along with improved comparability, credibility, and legal defensibility.

DISTRIBUTION RECORDS

Distribution records shall contain the name and strength of the product and description of dosage form, name and address of consignee, date and quantity shipped, lot number or control number of drug product.

The primary purpose of distribution record is to ensure that adequate data is available. to access trade customers should a recall be initiated.

The recording of batch number to each order will accomplish this purpose. This, coupled with recording of dates on which a specific lot of product commenced and ceased distribution may be used.

All customers receiving the product between these dates could be then contacted.

Distribution records include wide range of documentation such as invoices, bills of lading, customer's receipts, and internal warehouse storage and inventory records

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UNIT 5

INTRODUCTION, DEFINITION AND GENERAL PRINCIPLES OF CALIBRATION, QUALIFICATION AND VALIDATION

CALIBRATION

Definition: "Calibration of an instrument is the process of determining its accuracy. The process involves obtaining a reading from the instrument and measuring its variation from the reading obtained from a standard instrument."

- Calibration of an instrument also involves adjusting its precision and accuracy so that its readings come in accordance with the established standard.
- This is important for justifying the processes of Qualification and Validation
- . The instrument or equipment with the known accuracy is known as standards. All the other instruments are measured against this standard.
- It is important to know that the standards vary from one country to the other depending upon the type of industry
- Calibration Achieves Two Main Objectives:

    1. It checks the accuracy of an instrument.

    2. It determines the traceability of the measurement.

SCOPE/PURPOSE OF CALIBRATION

Calibration is primarily done to achieve 5 main purposes which are:

- To make sure that the readings of equipment or instruments are consistent with other measurements and display the correct readings every single time
- To determine the accuracy, precision, reliability and deviation of the measurements produced by all the instruments.
- To establish the reliability of the instrument being used and whether it can be trusted to deliver repeatable results each time.
- To map the 'drift' as documented. Instruments have a tendency to produce inaccurate measurements over a period of time, following repeated use.
- To ensure that the industry standards, quality assurance benchmarks such as current good manufacturing practice (cGMP) and government regulations are adhered to

Calibration Principles:

Calibration is the activity of checking, by comparison with a standard, the accuracy of a measuring instrument of any type. It may also include adjustment of the instrument to bring it into alignment with the standard.

IMPORTANCE OF CALIBRATION

- Calibration is responsible for defining the accuracy of any measurement and its quality that is recorded by any instrument
- . Calibration minimizes uncertainties by assuring the accuracy of the test equipment.
- Calibration helps in quantifying and controlling errors and uncertainties within various measurement processes to an acceptable level.

- It helps in improving the accuracy of the measuring device, which in turn improves the quality of the end product. Calibration allows pharmaceutical companies to have confidence in their results which
- they can record, monitor and control.

QUALIFICATION

Definition: "It is the action of proving and documenting that equipment or ancillary systems is properly installed, work correctly, and actually lead to the expected results".

- It refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly.
- It is the action of proving that any equipment or process works correctly and consistently and produces the expected results
- Qualification is part of validation, but the individual qualification steps alone do not
- constitute process validation
- Qualification of analytical instrumentation is essential for accurate and precise measurement of analytical data. If the instrumentation is not qualified, ensuring that the results indicated are trustworthy, all other work based upon the use of that instrumentation is suspect.
- Qualification of instruments is not a single, continuous process but instead results from many discrete activities.
- For convenience, these activities are grouped into 4 phases of qualification. These phases are described below:
    1) Design Qualification (DQ)
    2) Installation Qualification (IQ)
    3) Operational Qualification (OQ)
    4) Performance Qualification (PQ)

1. DESIGN QUALIFICATION (DQ

It is the documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

- DQ should be performed when new equipment is being purchased, or when existing equipment is being used for a new application.
- DQ serves as the precursor to defining the equipment Installation Qualification (IQ) and
- OQ protocols.
- The purpose is to ensure that all the requirements for the final systems have been clearly
- defined at the start.
- DQ Checklist includes:
    - GMPs and regulatory requirements
    - Performance criteria
    - Reliability and efficiency
    - Commissioning requirements
    - Construct ability and installation of equipment
    - Safety and environment impact
    - Description of the intended use of the equipment
    - Preliminary selection of the supplier
    - Final selection of the equipment

2. INSTALLATION QUALIFICATION (IQ)

- It is documented evidence that the premises, supporting utilities, the equipment have
- been built and installed in compliance with design specifications.
- It verifies that the equipment has been installed in accordance with manufacturer's recommendation in a proper manner and placed in an environment suitable for its intended purpose.
- It involves the co-ordinate efforts of the vendor, the operating department and theproject team.
- The purpose of IQ is to check the installation site/environment, confirms equipment specifications and verifies the condition of installed equipment; and also to ensure that all aspects (static attributes) of the facility or equipment are installed correctly and comply with the original design.
- IQ checklist includes:
    - Equipment design features
    - Installation conditions.
    - Calibration, preventative maintenance, cleaning schedules.
    - Safety features.
    - Supplier documentation, prints, drawings and manuals.
    - Software documented.
    - Spare parts list.
    - Environmental conditions
- Any problems identified in I.Q must be investigated and appropriate actions must be taken. All such actions must be documented and approved by higher authority.

3. OPERATIONAL QUALIFICATION (OQ)

- It refers to establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements.
- OQ is the process of demonstrating that an instrument will function according to its operational specification in the selected environment.
- The purpose is to ensure that all the dynamic attributes comply with the original design.
- Prior to implementing O.Q, check the system configuration, determine the items to be evaluated and record.
- OQ checklist includes:
    - Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
    - Software parameters.
    - Raw material specifications
    - Process operating procedures.
    - Material handling requirements.
    - Process change control.
    - Training.
    - Potential failure modes, action levels and worst-case conditions.
    - The use of statistically valid techniques such as screening experiments to optimize the process can be used during this phase.
- Any problems identified in O.Q must be investigated and appropriate actions must taken. All such actions must be documented and approved by higher authority.

PERFORMANCE QUALIFICATION

- After the IQ and OQ have been performed, the instruments continued suitability for itsintended use is proved through performance qualification.
- It refers to establishing by objective evidence that the process, under anticipatedLa conditions, consistently produces a product which meets all predetermined requiremen
- PQ should always be performed under conditions that are similar to routine sample analysis. PQ should be performed on a daily basis or whenever the equipment is being used.
- PQ considerations include:
    - Actual product and process parameters and procedures established in OQ.
    - Acceptability of the product.
    - Assurance of process capability as established in OQ.
    - Process repeatability, long term process stability.
- The objective of PQ is to ensure that the instrument is performing within specified limits.
- The PQ represents the final qualification of equipment or system.

VALIDATION

- Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified.
- A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved.
- Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.

DEFINITION OF VALIDATION

According to ISO: "Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled".

According to the USFDA: "To establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes".

According to European commission: "Action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results".

IMPORTANCE OF VALIDATION

- Assurance of quality.
- Process optimization.
- Reduction of quality cost.
- Minimal batch failures, improved efficiently and productivity.
- Reduction in rejections.
- Increased output.
- Fewer complaints about process related failures.
- Reduced testing in process and in finished goods
- More rapid and reliable start-up of new equipments.

- Easier maintenance of equipment.
- Improved employee awareness of processes.
- More rapid automation.
- Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products).

3. SCOPE OF VALIDATION

- Validation requires an appropriate and sufficient infrastructure including: organization documentation, personnel and finances.
- Validation requires Involvement of management and quality assurance personnel.
- Validation requires Personnel with appropriate qualifications and experience.
- Validation requires Extensive preparation and planning before validation is performed.
- Validation should be performed: for new premises, equipment, utilities and systems, and processes and procedures; at periodic intervals; and when major changes have been made.
- Validation should be done in accordance with written protocols and for over a period of time, e.g, at least three consecutive batches (full production scale) to demonstrate consistency.
- Significant changes like facilities, equipment, processes should be validated.
- Risk assessment approach should be used to determine the scope and extent of validation

TYPES OF VALIDATION

1. Prospective validation

- It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol.
- This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process.
- It is Performed on at least three successive production-sizes (Consecutive batches).
- The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials.
- Prospective validation should normally be completed prior to the distribution and sale of the medicinal product.
- In Prospective Validation, the validation protocol is executed before the process is put into commercial use.

2. Concurrent validation

- It is a process where current production batches are used to monitor processing parameters.
- Concurrent Validation means establishing documented evidence a process does what it is supposed to based on data generated during actual implementation of the process.
- It is important in these cases when the systems and equipment to be used have been fully validated previously.
- It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.
- This validation involves in-process monitoring of critical processing steps and product testing.
- This helps to generate and documented evidence to show that the production process is in a state of contrl

3. Retrospective validation

- It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information.
- This type of validation of a process is for a product already in distribution.
- Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment. .
- Validation of such processes should be based on historical data.
- For retrospective validation, generally data from ten to thirty consecutive batches should be examined to access process consistency, but fewer batches may be examined if justified.

VALIDATION MASTER PLAN

Definition "Validation master plan is an internally approved document that describes, in clear and concise wording, the general expectation, intentions, methods and approach to be used during the entire validation effort".

- The FDA inspectors during audit ask for VMP as a source document along with other important documents like site master file, calibration master plan etc. Hence, this document must always be updated and in presentable form.
- The main advantage of VMP is for people of organization, FDA and other auditors. easily:
- VMP give these peoples following information easily :
    - What activities are planned?
    - Who is going to authorize these activities?
    - Who is to actually carry out these activities?
    - Who is going to certify the satisfactory completion of the validation activities?
    - What re the protocols and reports?
    - When each planed activity is going to be started and finished? Etc.
- Following are the some of the aspects that one should know the physical aspects of this document (VMP):
    - VMP should be physically attractive, so that one would like to read it.
    - VMP should be typed on good quality white paper (A4 size) of not less than 80 GSM (Preferably 100-120 GSM bond paper)
    - This paper should be bordered from all sides (generally 25mm from left side and 15mm from all other side).
    - File it in presentable form.
    - It should have sufficient explanatory drawings, charts, tables etc. (Use coloured drawing)
    - Clearly divide the VMP in different sections like introduction, main body of the subject and appendices.
    - It must be dated and signed by authorized person.

GENERAL PRINCIPLES OF ANALYTICAL METHOD VALIDATION

Definition: Validation of Analytical method may be defined as "The process by, which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical application".

Typical analytical characteristics can be listed as follows:

1. Accuracy

2. Precision

3. Specificity

4. Limit of Detection

5. Limit of Quantitation

6. Linearity

7. Range

8. Ruggedness

9. Robustness

1. ACCURACY .

Definition: Accuracy of an analytical method may be defined as "The closeness of test results obtained by that method to the true value. This accuracy should be established across its range".

- Accuracy of an analytical method may be determined by the assay method used on a highly pure substance like reference standards and compared it with the same material with a known and established method.
- This can also be further evaluated by addition of known pure substance and assessing the recovery of the added substance.
- In case of quantitative analysis of impurities, accuracy should be assessed on samples of drug substance or product by spiking with known amounts of impurities.
- The L.C.H. Recommends that the accuracy should be assessed using a minimum of nine determinations over a minimum of 3 concentration levels, covering the specified range (i.e. 3 concentration and 3 replicates of each concentration).

2. PRECISION

Precision of an analytical method may be defined as "the degree of agreement among individual test results when the method is applied repeatedly to multiple sampling of a homogenous sample".

- The precision of an analytical method in usually expressed as the standard deviation or relative standard deviation (i.e. coefficient of variation) of a series of measurement
- Precision refers to degree of reproducibility of results. This can be within a single laboratory or between more than one laboratories.
- Precision can also be considered as repeatability of results, which refers to comparison of results of an analysis within a short time by the same analyst, in same laboratory and using the same equipment.
- The precision of an analytical method is determined by assessing sufficient number of aliquots of a homogenous sample to be able to calculate statistically valid estimates of standard deviation or relative standard deviation (ie. Coefficient of variation).
- The I.C.H. Documents recommend that repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure (i.e. 3 concentrations and 3 replicates of each concentration or using minimum of six determinations at 100% of test concentration).

3. SPECIFICITY

Definition: Specificity may be defined as "The ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities degradation products and matrix components".

- Specificity can be used for identification tests, purity tests, assays, etc.
- The ICH documents state that, when chromatographic procedures are used, representative chromatogram should be represented to demonstrate the degree of specificity (selectivity) and peaks should be appropriately labeled. Peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component.

4. LIMIT OF DETECTION

- **Definition**: The limit of Detection may be defined as "The lowest amount of analyte in a sample that can be detected, but not necessarily quantitated, under the stated experimental conditions".
- The L.O.D. is generally expressed as the concentration of the analyte sample (e.g. percentage or parts per million, etc).
- The I.C.H. documents describe a common approach, which is to compare measured signals from samples with known low concentrations of analytes with those of blank samples
- These detection limits should be subsequently validated by the analysis of a suitable number of samples of known to be near or prepared at the detection limit.

5. LIMIT OF QUANTIZATION

- **Definition**: L.O.Q. May be defined as "As characteristic of quantitative assays for low levels of compounds in sample matrices such as impurities in bulk substances and degradation products in finished pharmaceuticals. It is the lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions".
- The L.O.Q. is generally expressed as the concentration of the analyte in the sample (e.g. percentage or parts per million, etc).

WAREHOUSE

- A warehouse is a commercial building for storage of goods.
- Warehouses are used by manufacturers, importers, exporters, wholesalers, transport businesses, customs, etc.
- They are usually large plain buildings in industrial parks on the outskirts of cities, towns or villages.

WAREHOUSING

Warehousing refers to the process of holding and conservation of goods till they are dispatched to the customers.

GOOD WAREHOUSING PRACTICE

- Good Warehousing Practices (GWP) shall be established to ensure that products are stored and handled under sanitary conditions.
- Stocks Received From the factory should be received with proper documents detailing the names of products, batch number, number of units of final packs, the date of dispatch and the quality status of the batches.
- Finished products that are under test must be quarantined and segregated from passed stocks.

- Rejected stocks must be held in a secure place segregated from passed stocks and disposed off with the approval of QC manager.
- The stock control system must be such that only passed batches of products are issued for distribution.
- Stocks should be stored product-wise to enable quick identification and control of stock movement.
- Stock rotation should be on the 'First-in, First-out' basis, Stocks should therefore be A racked and stored in a manner that earlier stocks are more easily accessible than the later ones.
- Processing of orders vary often involves the dispatch of a variety of products in one consignment, to fulfil such orders there should be an arrangement of picking products and assembling them.
- The picking and assembling areas should be so arranged as to minimize the distance travelled by warehouse operators.
- Picking stock should be stored to facilitate stock security, stock rotation, order assembly and dispatch.
- Picking stock should be located on shelves at convenient heights and with proper labels which clearly identify the products.
- Picking and assembling of products according to orders should be done against, dated and serially numbered documents.
- Assembled products should be checked for accuracy of quantities and identities of products ordered. Batch details should be recorded in relevant documents.
- Finished products outer packs should be so prepared and packed for transport that only released products are dispatched.
- Adequate precautions are taken to prevent spillage, breakage or pilferage in transit and the unit product packs should not be contaminated by other products.

GWP INCLUDES FOLLOWING ASPECTS

1. Premises
2. Security
3. Temperature and humidity control
4. Equipment
5. Personnel
6. Sanitation
7. Receipt of incoming goods
8. Assembling orders and issuing goods
9. Packing for transportation
10. Transport
11. Records

1.PREMISES

- Premises should be of suitable size and construction to facilitate cleaning, maintenance oot and orderly segregated storage
- Storage areas must be designed to provide adequate:
  - Lightening
  - Ventilation
  - Temperatur
  - Sanitation
  - Humidity

  - Space
  - Equipment
  - Security conditions
- Medicinal products should be stored separate cross contamination.
- Incoming goods should be physically or electronically separated from goods awaiting distribution until approved by the responsible person.
- A segregated area must be provided for the holding and storage of returned and rejected goods prior to a decision on further action.
- A secure, segregated area must be provided for the storage of controlled drugs.
- A separate, designed area should be provided for the assembly of customer orders.

2. SECURITY

- Storage areas should be provided with security to prevent theft or unauthorised entry
- Maintain a control of who may enter the facilities.
- Establish system for controlling access to the facility (including all entrances and exits).

3. TEMPERATURE AND HUMIDITY CONTROL

- All drug products must be stored at appropriate conditions as stated on the label of the product.
- The temperature of all storage areas should be regularly monitored.
- Controlled temperature storage areas should be equipped with recorders and devices which indicate when the specific temperature range has not been maintained.
- A written procedure must specify the action to be taken when this occurs Control should be adequate to ensure that all parts of the storage area are kept within the specified temperature range.
- There Should always be a backup system in case main system fails.
- The humidity of all storage areas should be regularly monitored using recorders and devices which document the humidity measures.
- If the product space requires a specific humidity, a written procedure must specify the action to be taken when the specified humidity range has not been maintained.
- Establish a normal operating baseline of humidity if no specific value is required.
- Records of temperature and humidity in all storage areas should be reviewed and retained by a designated responsible person. .

4. EQUIPMENTS

- There should be a planned preventative maintenance programme in place.
- Recording and control equipment should be calibrated and checked at defined intervals by appropriate methods.
- Alarm set-points should be checked on periodic intervals.
- A computerised system used for stock control/distribution should be validated.

5. PERSON

- The organisation chart should be in place.
- There should be a sufficient number of staff.
- There should be clearly defined job description.
- Personnel should be trained in relation to good storage and distribution practice and to the duties assigned to them.
- The current records of training should be in place.
- The trainers should have established and approved qualification.

6. SANITATION

- A written sanitation program should be in place indicating the frequency and method of cleaning the facility.
- Storage areas should be cleaned and accumulated waste removed at regular intervals
- A pest control program should be in place.
- Smoking, eating and drinking should be permitted only in segregated areas, and not in those areas used for the storage and handling of final drug product.
- Spills involving drug products must be promptly cleaned-up and rendered safe in accordance with the relevant health and safety requirements for the product.
- Adequate toilet and changing facilities should be provided, and they should be segregated from the main storage and order assembly areas.

7. RECEIPT OF INCOMING GOODS

- It should be carried out according to approved adequate SOP:
    - Visually examine for identity against the relevant supplier's documentation.
    - Visually examine for damage.
    - Sub-divide according to batch numbers if more than one batch.
    - Reject product if damage or otherwise unfit for use.
    - Handle high security materials (control drug, high value items and products requiring a specific storage temp.)
    - Confirm with signature that receiving goods are as specified by supplier or if not provide adequate comments.

8. ASSEMBLING ORDERS AND ISSUING GOODS

- It should be carried out according to approved adequate SOP:
    - Pick up goods according to formal despatch documents.
    - Assemble complete order.
    - Visually examine for identity and completeness.
    - Visually examine for damage.
    - Confirm with signature properly assembled order.
    - Prepare adequate shipping package to protect any damage of goods, seal pack and provide relevant identification.
    - The heat sensitive drugs if not transported by appropriate specialised means should be provided isolated packing.

9. PACKING FOR TRANSPORTATION

- Products should be transportin such a way that :
  - The identification of the product is not lost.
  - The product does not contaminate and is not contaminated by other products or materials.
  - Adequate precautions are taken against spillage and breakage.
  - Products requiring controlled temperature storage should be provided with insulated packs
  - There should be in place documented evidence that the insulated packs ensured adequate transport conditions with regards to:
    - o Product quantity
    - o Ambient temperature
    - o Maximum delivery time

10. TRANSPORT

- Products should be transported in such a way that:
  - The safety, identity, strength, quality and purity of the product are not lost.
  - The product is not contaminated by other products or materials.
  - Adequate precautions are taken against spillage or breakage.
  - The product and its package are not subjected to unacceptable degrees of heat, cold, light, moisture or other adverse influences nor to attack by micro-organisms or pests.
  - Drug products requiring controlled temperature storage by appropriate specialised means, or should be packed with adequate insulation.

11. RECORDS

- Following records should be in place:
  - Receiving goods
  - Issuing goods
  - Training
  - Monitoring temperature and humidity
  - Cleaning operation
  - Pest control
  - Calibration
  - Preventative maintenance
  - Recall
  - Complaints
  - Inventory
  - Log of signature

MATERIALS MANAGEMENT

- Materials management is a scientific technique concerned with planning, organizing and control of flow of materials from their initial purchase to destination
- It is concerned with planning, organizing and controlling the flow of materials from their initial purchase through internal operations to the service point through distribution.
- Aim of materials management is:
  - To obtain Right quality
  - To obtain Right quantity

- At Right cost # At Right time and Place

1. PURPOSE OF MATERIALS MANAGEMENT

- To provide reasonable level of client services.
- To gain economy in purchasing.
- To satisfy the demand during the period of replenishment.
- To carry reverse stock to avoid stock out.
- To stabilize fluctuations in consumptions.

2. NEED OF MATERIALS MANAGEMENT

- To have adequate materials on hand when needed.
- At lowest possible prices, consistent with quality and value requirements for purchase of materials.
- To minimize the inventory investment.
- To operate efficiently.

3. PRINCIPLES OF MATERIALS MANAGEMENT

1. Planning: Planning in organizations and public policy is both the organizational process of creating and maintaining a plan; and the psychological process of thinking about the activities required to create a desired goal on same scale..

2. Organizing: Organizing is the function of management which follows planning. According to Chester Bernard, "Organizing is a function by which the concern is able to define the role positions, the jobs related and the co-ordination between authority and responsibility

3. Staffing: The managerial function of staffing involves managing the organizational structure through proper and effective selection, appraisal and development of the personnels to fill the roles assigned to the employers. According to Theo Haimann, "Staffing pertains to recruitment, selection, development and compensation of subordinates".

4. Directing: Directing is said to be a process in which the managers instruct, guide and oversee the performance of the workers to achieve predetermined goals. Directing is said to be the heart of management process or technique by which instructions can be issued and operations can be carried out as originally planned".

5. Controlling: Controlling consists of verifying whether everything occurs in conformities with the plans adopted, instructions issued and principles established. Controlling ensures that there is effective and efficient utilization of organizational resources so as to achieve the planned goals.

6. Budgeting: Budgeting is the key to financial management. The process of calculating the cost of a small business begins with a list of all necessary purchases including services, working capital and sources.