Concise Course in

PHARMACEUTICAL QUALITY ASSURANCE

Strictly As Per Syllabus Prescribed for B. Pharmacy, Semester-VI by Pharmacy Council of India, New Delhi

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SYLLABUS

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ICH Guidelines: Purpose, participants, process of harmonization, Brief overview of QSEM, with special emphasis on Q-series guidelines, ICH stability testing guidelines

Quality by Design (QbD): Definition, overview, elements of QbD program, tools.

ISO 9000 & ISO14000: Overview, Benefits, Elements, steps for registration.

NABL accreditation: Principles and procedures.

UNIT-II

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UNIT-V

Calibration and Validation: Introduction, definition and general principles of calibration, qualification and validation, importance and scope of validation, types of validation, validation master plan. Calibration of pH meter, Qualification of UV-Visible spectrophotometer, General principles of Analytical method Validation.

Warehousing: Good warehousing practice, materials management

UNIT-I

HIGHLIGHTS

CHAPTER 1

QUALITY ASSURANCE AND QUALITY MANAGEMENT CONCEPTS

In the present scenario the context of Quality has emerged as an important factor. 'Quality' is generally referred to a parameter which decides the inferiority or superiority of a product or service. It is a measure of goodness to understand how a product meets its specifications.

Quality management in pharmaceutical industries, is an important subject because the drugs/ or pharmaceutical products are directly delivered to the customers body system, thus identity, purity safety and ultimately appropriate quality of product are strongly essential. There are numerous guidelines worldwide that has made some sort of rules and specifications which must be followed by every pharmaceutical industry.

A quality management system (QMS) is defined as a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives. A QMS helps coordinate and direct an organization's activities to meet customer and regulatory requirements and improve its effectiveness and efficiency on a continuous basis.

1.1 ELEMENTS OF QUALITY MANAGEMENT SYSTEM

A quality management system typically consists of four facets

1. Quality planning: Process of translating quality policy into processes, procedures, and instructions to achieve measurable objectives and requirements.
2. Quality assurance: Planned and methodical activities executed as part of a quality system to provide confidence that process, product, or service requirements for quality are being satisfied.
3. Quality control: Act of monitoring, appraising, and correcting a process, product, or service to ensure requirements for quality are being satisfied.
4. Quality improvement: Process of analyzing performance and taking methodical, systemic actions to improve it.

Each element of a quality management system helps achieve the overall goals of meeting the customers' and organization's requirements. Quality management systems should address an organization's unique needs; however, elements all systems have in common include:

- The organization's quality policy and quality objectives
- Quality manual
- Procedures, instructions, and records
- Data management
- Internal processes

- Customer satisfaction from product quality
- Improvement opportunities
- Quality analysis

Quality management systems serve many purposes, including:

- Improving processes
- Reducing waste
- Lowering costs
- Facilitating and identifying training opportunities
- Engaging staff
- Setting organization-wide direction

1.2 QUALITY MANAGEMENT STANDARDS

To maintain quality in pharmaceutical products, Quality Management System is followed. Internationally harmonized guidance ICH Q10 governs the concept of current pharmaceutical quality management system for Registration of Pharmaceuticals for Human Use and USFDA and in final phases. ISO 9001:2015, the international standard specifying requirements for quality management systems, is the most prominent approach to quality management systems. While some use the term "QMS" to describe the ISO 9001 standard or the group of documents detailing the QMS, it actually refers to the entirety of the system.

ISO 9001:2015 is the most recognized and implemented quality management system standard in the world. ISO 9001:2015 specifies the requirements for a QMS that organizations can use to develop their own programs.

Other standards related to quality management systems include the rest of the ISO 9000 family (including ISO 9000 and ISO 9004), the ISO 14000 family (environmental management systems), ISO 13485 (quality management systems for medical devices), ISO 19011 (auditing management systems), and ISO/TS 16949 (quality management systems for automotive-related products).

1.3 DEFINITIONS

Quality assurance

According to WHO, quality assurance (QA) is a wide- ranging concept covering all matters that individually or collectively influence the quality of a product. With regard to pharmaceuticals, quality assurance can be divided into major areas: development, quality

control, production, distribution, and inspections. ISO 9000 defines QA as "part of quality management focused on providing confidence that quality requirements will be fulfilled"

Quality Control

ISO 9000 defines quality control as "A part of quality management focused on fulfilling quality requirements". It is that part of GMP concerned with sampling, specification & testing, documentation & release procedures which ensure that the necessary & relevant tests are performed & the product is released for use only after ascertaining it's quality.

Calibration

Calibration is defined as operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties (of the calibrated instrument or secondary standard) and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication.

Validation

Validation is a process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages. In Pharma Industry it is very important apart from final testing and compliance of product with standard that the process adapted to produce itself must assure that process will consistently produce the expected results.

Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

• Equipment validation •Facilities validation •HVAC system validation •Cleaning validation • Process Validation •Analytical method validation •Computer system validation •Packaging validation •Cold chain validation

Qualification

Qualification is defined as action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

1.4 DIFFERENCE BETWEEN QA AND QC

The major difference between quality assurance and quality control is that quality control is product oriented, while quality assurance is process oriented. The other differences are stated in table 1.

Table 1.1: Difference between QA and QC

Parameters	QA	QC
Definition	QA is a set of activities for ensuring quality in the processes by which products are developed.	QC is a set of activities for ensuring quality in products. The activities focus on identifying defects in the actual products produced.
Action	QA is a managerial tool	QC is a corrective tool
Aim	QA aims to prevent defects with a focus on the process used to make the product. It is a proactive quality process	QC aims to identify (and correct) defects in the finished product. Quality control, therefore, is a reactive process.
Goal	The goal of QA is to improve development and test processes so that defects do not arise when the product is being developed.	The goal of QC is to identify defects after a product is developed and before it's released.
What and how does it work	• Prevention of quality problems through planned and systematic activities including documentation. • Establish a good quality management system and the assessment of its adequacy. Periodic conformance audits of the operations of the system.	• The activities or techniques used to achieve and maintain the product quality, process and service. • Finding & eliminating sources of quality problems through tools & equipment so that customer's requirements are continually met.
Whose responsibility is it and what is the example of it?	• Everyone on the team involved in developing the product is responsible for quality assurance. • Verification is an example of QA.	• Quality control is usually the responsibility of a specific team that tests the product for defects. • Validation is an example of QC.

The following flow chart (figure 1) shows an example of process of quality assuarance for raw material and packaging material

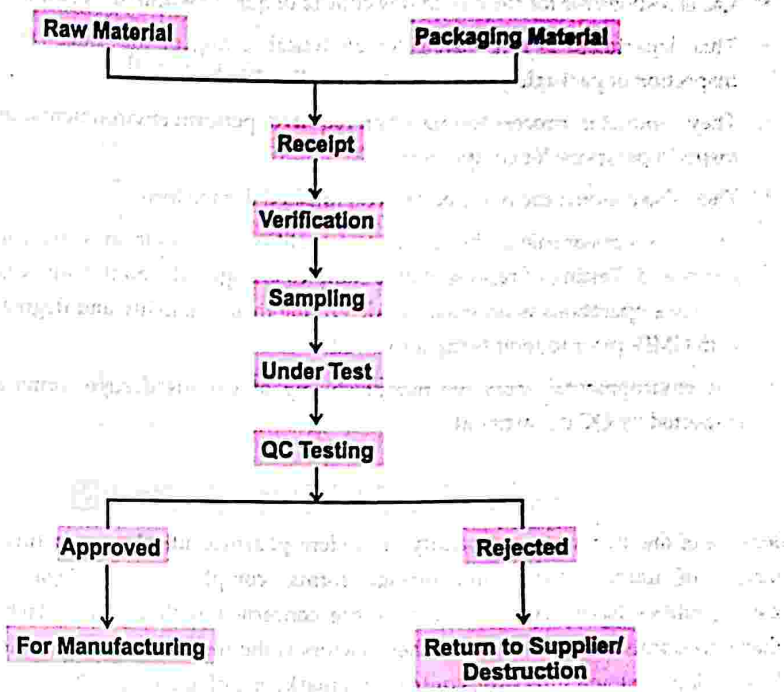

Fig.1.1: Flow chart for raw material and packaging material quality assurance.

1.5 RESPONSIBILITIES

Responsibilities of QA

- The QA department is responsible for ensuring that the quality policies adopted by a company are followed.
- It helps to identify and prepare the necessary SOPs relative to the control of quality.
- It must determine that the product meets all the applicable specifications and that it was manufactured according to the internal standards of GMP.
- QA also holds responsible for quality monitoring or audit function.

- QA functions to assess operations continually and to advise and guide them towards full compliance with all applicable internal and external regulations.

Responsibilities of QC

- QC is responsible for the day-to-day control of quality within the company.
- This department is responsible for analytical testing of incoming raw materials and inspection of packaging components, including labelling.
- They 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. Testing of representative samples is required, and in many cases, an audit of vendor's operations is necessary to determine their suitability and degree of compliance with GMPs prior to their being approved.
- The environmental areas for manufacturing of various dosage forms are tested and inspected by QC department.

1.6 SOURCES OF QUALITY VARIATION

Because of the increasing complexity of modern pharmaceutical manufacture arising from a variety of unique drugs and dosage forms, complex ethical, legal, and economic responsibilities have been placed on those concerned with the manufacture of modern pharmaceuticals. An awareness of these factors is the responsibility of all those involved in the development, manufacture, control, and marketing of quality products.

Following variables may affect ultimate quality of product: * Raw material * In process variations * Packaging material * Labeling * Finish product * Manual Error

1.7 CONTROL OF QUALITY VARIATION

1. Raw material control

- Good raw material specifications must be written in precise terminology, must be complete, must provide specific details of test methods, type of instruments, and manner of sampling must be properly identified.
- Each raw material is sampled according to standard sampling procedures and is sent to the quality control laboratory for testing according to written procedures. If acceptable, it is moved to the release storage area, after being properly stickered to indicate the item no., material name, lot no., release date, reassay date and sign of QA inspector.

- QA personnel should keep preservation samples of active raw materials that consists of atleast twice the necessary quantity to perform all tests required, to determine whether the material meets the established specifications. These preservation samples should be retained for atleast 7 years. Approved material should be rotated so that the oldest stock is used first. Raw materials may be classified into 2 groups:
- Active or therapeutic Inactive or inert

2. In-process Items Control

- The FDA-CGMP regulations emphasize environmental factors to minimize cross-contamination of products and errors, however, they do little to minimize within-batch and batch-to- batch variation. Therefore, it is important function of the IPQA program to ensure that the final produts have uniform purity and quality.

There are some critical steps to be followed in this:

- QA before start-up:

- Environmental and microbiologic control and sanitation
- Manufacturing Working Formula Procedures
- Raw Materials
- Manufacturing Equipment

- QA at start-up:

- Raw Material Processing
- Compounding
- Packaging Materials Control
- Labels Control
- Finished Product Control

3. Manufacturing Variation Control

- Monitoring environmental conditions under which products are manufactured/stored
- Monitoring of air and water systems to prevent contamination– Air Handling Units
- Monitoring of personnel
- Feedback and follow-up

1.8 QUALITY ASSURANCE MANAGEMENT PROCEDURE

1. How to write Standard Operating Procedure?

- SOP describes standard SOP format that you can use immediately for your quality procedure.
- SOP has instructions on how to write a formal operating procedure for your systems which your people can follow every day.

2. All Document-Classifications, Definitions and Approval Matrix

- In this SOP all type of quality and Technical/Master file documents to build up a good quality management system for manufacturing sites, definition of documents, their classification, approval requirements and retention requirements are described.
- This procedure has schematic diagrams for understanding of how different types of documents are prepared and stored in a typical documentation.

3. Quality Documentation Management and Change Control

- This SOP describes how to generate new quality documents or change control of existing documents, review of quality documents, satellite file management, role of document author, approver, document control officer and satellite file administrator.
- In this SOP numbering systems of different quality documents like audit files, SOP's, forms, manuals, training files, QA agreements, project files etc and their effective archiving system are described.

4. Documentation Rule for GMP Documents

- This SOP describes the principles to be followed in GMP documents, entry of data and information, signature requirements and correction technique of incorrectly entered data or information.

5. Quality Documentation- Tracking, Control and Distribution

- This SOP mainly describes the role of document control officer during the initiation, creation, circulation and approval of new quality related documents.
- It also describes the procedure of modification and review of existing document using a documentation database.
- Management of existing and superseded documents is also a art of this procedure.

6. Preparation, Maintenance and Change Control of Master Documents

- This SOP particularly focused on the management of master file documents like specifications, control methods, raw materials, finished goods and packaging

specification and test reports, formulation, stability files etc required to generate during the product registration in the market.

- This SOP gives instruction on their creation, change control, numbering system, approval requirements and maintenance in a simple master file database.
- All the forms referred during the instruction are attached at the end of the procedure.

7. Deviation Report System

- It is a regulatory requirement to capture all sorts of deviations evolves in your systems in order to maintain the continuous improvement to your processes and systems.
- This SOP describes how to categorize the deviations between production, audit, quality improvements, technical deviations, customer complaints and environmental, health and safety deviations.
- It describes the management responsibilities of initiating deviation, capture data, analysis, investigation, determination of assignable causes, generation of management report and initiatives to be taken on corrective and preventative actions.

8. Example- Checklist for Batch Documentation

- This SOP describes the identification of all documentation relevant to a production process in the form of "Batch Documentation Checklists" and to ensure their collection by completion of the checklists by Authorized Persons.
- This procedure is based on an example of tablet packaging process described in the 'Manufacturing' category.

9. Evaluation of Batch Documentation and Release of Sale

- This procedure describes the process of collection, evaluation and record of batch related document generated during the production of a batch before an authorized person can release the batch for sale.
- This procedure is based on an example of tablet packaging process described in the 'Manufacturing' category.

10. Raw Materials- Laboratory Testing and Documentation

- This SOP describes the procedure for sampling, location, pre-testing, testing and documentation of all raw materials and components subject to test, out of specification results, microbiological tests and release procedure for passed raw materials and components.

11. Finished Goods- Laboratory Testing and Documentation

- This SOP describes the procedure for sampling, location, pre-testing, testing and documentation of all finished products subject to test, reagents and standards to be used for analysis, management of out of specification results, microbiological tests and release procedure for passed finished goods.

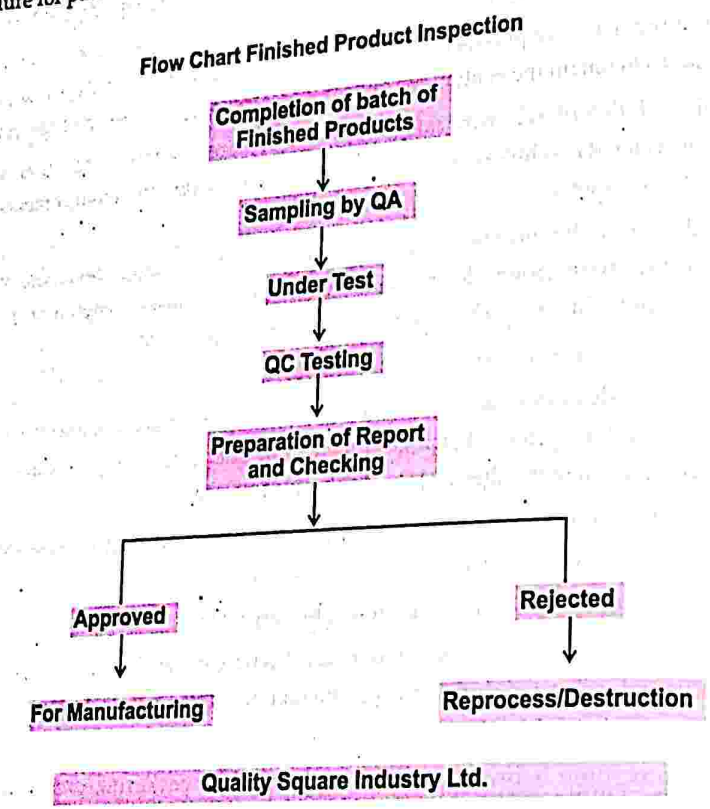

Fig 1.2: QA activity flow chart for finished product inspection

1.9 ROLE OF QA IN PHARMA INDUSTRIES

1. To establish Quality Audit

- Establish the quality management system to describe how the firm complies CGMPs and operates to maintain a state of control

- Keep current with good industry practices, and applicable to the mission of your operation.
- To audit compliance to the Quality System
- Audit for compliance to policies and procedures: on paper vs. practice
- Report on the performance of the quality system, including trends, that help decision making for targeted actions

2. To establish procedures and specifications

- Ensure that procedures and specifications are appropriate and followed.
- Ensure that the procedures and specifications of firms under contract are also appropriate and followed, i.e., maintain control and take responsibility for third-party services providers (contract manufacturers, contract laboratories, etc.)

3. To establish manufacturing controls

- Ensure that appropriate manufacturing in- process controls are implemented.
- Ensure in-process controls are performed during manufacturing operations and results are satisfactory

4. To perform laboratory tests

- Perform laboratory testing of components, containers, in-process materials, packaging materials and drug product using validated methods against scientifically-derived, fit-for-purpose specifications
- Approve or reject drug products manufactured, processed, packed, or held under contract by another company, i.e., final product release is not delegated to a contractor
- Perform retests or reexamine approved components, drug product containers and closures after long storage or exposure to adverse conditions.

5. To review and approve or reject

- Review and approve/reject any document that gives work instructions and set requirements such as procedures, protocols, test methods, and specifications—including changes to these documents
- Review and approve/reject reprocessing and rework procedures
- Review and approve/reject production batch records and make the final decision to release a product lot into commerce.

6. To ensure investigation of nonconformance

- Ensure investigation is conducted and root cause is eliminated for production and control record errors, discrepancies, and failure to meet specification, including quality attributes
- Review complaints to determine if it relates to a failure to meet specification, if so investigate and report to FDA if it is serious and unexpected

7. To keep management informed

- Report on product, process and system risks
- Report on outcome of regulatory inspections and ensure responses are complete and managed to verifiable closure

8. To describe responsibilities in writing

- Have a complete and compliant procedure that describes responsibilities. Follow the procedure

9. To remain independent

- Ensure there is no conflict of interest between regulatory responsibilities and actual daily activities
- Be independent reviewer and approver with respect to manufacturing and process/ product development units

1.10 CONTROL AND ASSURANCE OF MANUFACTURING PRACTICES

1. Personnel

Important parts for successful personnel are:

- Proper selection * Training * Motivation of Production * Packaging * Control
- It is essential that the qualified personnel be employed to supervise the formulation, Processing, Sampling, testing, packaging and labeling of the drug product, and that competent staff be placed in charge of the maintenance of machinery, equipment and sanitation.

2. Equipments and Buildings

- The building should provide adequate space for the orderly placement of materials and equipment to minimize any risks of mix-ups or cross-contamination between the drugs, excipients, packaging and labeling from the time the materials are received to the time the products are released.

- The desired characteristics of equipments for producing quality products are numerous, however, the equipment should be of suitable size, accuracy and reproducibility.

3. Control of records

- The records, such as Master Formula and Batch production records, should be prepared and maintained in accordance with established procedures.
- Control of Production Procedures
- To ensure that products have the intended characteristics of identity, strength, quality, and purity, production and the related in-process quality control procedures should be rigidly followed as required by the master formula record or batch production record.

4. Packaging Control

- A packaging record bearing an identification number is issued to the packaging section. This record specifies the packaging materials to be used, operations to be performed, and the quantity to be packaged.

5. Validation

- Validation of a process is the demonstration that controlling the critical steps of a process results in products of repeatable attributes or causes a reproducible event.

6. Control and Assurance of Finished Products

- Unless the testing procedures by which the product quality is finally measured are established on an equally sound basis, the entire system may be deficient.
- Product failures causing rejections or recalls after market introduction are serious and can be easily detected and minimized by an effectively administered quality testing program.
- Therefore, the testing of the finished products for compliance with the established standards prior to release of the material for distribution is a critical factor for quality control and assurance.

CHAPTER 2

TOTAL QUALITY MANAGEMENT

W. Edwards Deming, Armand V. Feigenbaum and Joseph M. Juran jointly developed the concept of TQM. Initially, TQM was originated in the manufacturing sector but it could be applied to all organizations. The concept of TQM states that every employee works towards the improvement success of the organization. TQM is a management approach for an organization, depending upon the participation of all its members (including its employees) and aiming for a long-term success of work culture, services, systems, processes and so on to ensure a continuing through customer satisfaction. This approach is beneficial to all members of the organization and to the society as well.

2.1 DEFINITION OF TQM

Total Quality Management is defined as a customer-oriented process and aims for continuous improvement of business operations. It ensures that all allied works (particularly work of employees) are toward the common goals of improving product quality or service quality, as well as enhancing the production process or process of rendering of services. However, the emphasis is put on fact-based decision making, with the use of performance metrics to monitor progress.

2.2 BACKGROUND

Concepts developed in Japan beginning in the late 1940's and 1950's, pioneered there by Americans Feigenbum, Juran and Deming set the foundations of TQM. The evolution of TQM happened in a few stages easily identified as Inspection, Quality Control, Quality Assurance and now Total Quality Management.

2.3 THE KEY ELEMENTS OF THE TQM APPROACH ARE

1. Focus on the customer: It is important to identify the organization's customers. External customers consume the organization's product or service. Internal customers are employees who receive the output of other employees.
2. Employee/Total Involvement: Since the quality is considered the job of all employees, employees should be involved in quality initiatives. Front line employees are likely to have the closest contact with external customers and thus can make the most valuable contribution to quality. Therefore, employees must have the authority to innovate and improve quality.
3. Continuous improvement: The quest for quality is a never-ending process in which people are continuously working to improve the performance, speed and number of features of the product or service. Continuous improvement means that small, incremental improvement that occurs on a regular basis will eventually add up to vast improvement in quality

2.4 THE KEY PRINCIPLES OF TOTAL QUALITY MANAGEMENT

The principles of the TQM are as follows and graphically represented in figure 2.1

Commitment from the management:

- Plan (drive, direct)
- Do (deploy, support, and participate)
- Check (review)
- Act (recognize, communicate, revise)

Employee Empowerment

- Training
- Excellence team
- Measurement and recognition
- Suggestion scheme

Continuous Improvement

- Systematic measurement
- Excellence teams
- Cross-functional process management
- Attain, maintain, improve standards

Customer Focus

- Partnership with Suppliers
- Service relationship with internal customers
- Customer-driven standards
- Never compromise quality

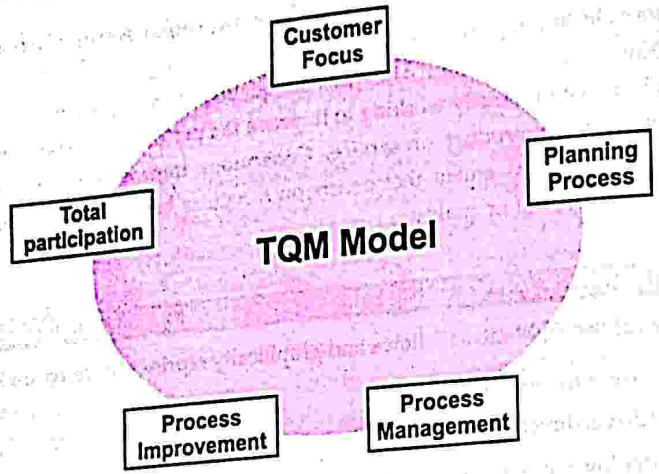

Fig.2.1: TQM in Pharma Industries

2.5 ADVANTAGES OF TQM

01. Improves reputation- faults and problems are spotted and sortedquicker.

02.Higher employee morale- workers motivated by extra responsibility,team work and involvement indecisions of TQM

03. Lower cost –decrease waste as fewer defective products and no needfor separate.

04.Quality control inspector

2.6 DISADVANTAGE OF TQM

01.Initial introduction cost.

02. Benefits may not be seen for several years.

03.Workers may be resistant to change

2.7 IMPORTANCE OF TQM IN PHARMA INDUSTRY

1. Handling:

- Containers should be opened carefully and subsequently resealed in an approved manner.
- Highly sensitising material such as penicillins and cephalosporins should be handled in separate production areas.

- Highly active or toxic API (e.g.certain steroids, cytostatic substances) should be manufactured in a dedicated area and using dedicated equipment.
- Pure and final API should be handled in an environment giving adequate protection against contamination.

2. Storage:

- Secure storage facilities should be designated for use to prevent damage or deterioration of materials.
- These should be kept clean and tidy and subject to appropriate pest control measures.
- Environmental conditions should be recorded.
- The condition of stored material should be assessed at appropriate intervals.
- Storage conditions for api should be based upon stability studies taking into account time, temperature, humidity, light etc

3. Packaging:

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

4. Facilities and equipment:

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

5. Sterile area

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

6. Labelling

- Each container should be identified by an appropriate label, showing at least the product identification and the assigned batch code, or any other easily understandable combination of both.
- Containers for external distribution may require additional labels.

7. Computerised systems

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

2.8 FUNCTIONS OF TQM

- Product quality criteria are established, and detailed specifications are written. Meticulous, written procedures must be prepared for production and control. Raw material must be characterised and then purchased from reputable, approved suppliers.
- Facilities must be designed, constructed, and controlled to provide the proper stable environment for protecting the integrity of products. Equipments must be selected that is efficient and can be cleaned readily and sanitised.
- Personnel must be trained properly. The directions they use must be in writing, approved by responsible individuals.
- Distribution departments are responsible for controlling the shipping and handling of products, using inventory-control systems.
- The marketing department must be sensitive to the costumers' needs and be responsive to complaints.
- QA is ever present and gives approval only after assessing and being assured that the entire production process has been completed satisfactorily and that all the aspects of the GMPs have been satisfied.

2.9 PHILOSOPHY OF TQM

'Individuals who have been identified as making a significant contribution to improving the quality of goods and services' are known as Quality Gurus. Famous quality gurus are

- Walter A. Shewhart

- W. Edwards Deming
- Joseph M. Juran
- Armand Feigenbaum
- Philip Crosby
- Genichi Taguchi
- Kaoru Ishikawa

Commonalities of Themes of Quality Gurus

- Inspection is never the answer to quality improvement, nor is "policing".
- Involvement of leadership and top management is essential to the necessary culture of commitment to quality
- A program for quality requires organization-wide efforts and long term commitment, accompanied by the necessary investment in training
- Quality is first and schedules are second

2.9.1 PHILIP CROSBY

Quality is defined as conformance to requirements, neither as 'goodness' nor 'Elegance'.

- There is no such thing as a quality problem.
- It is always cheaper to do it right first time.
- The only performance measurement is the cost of quality.
- The only performance standard is zero defects.

Crosby's five absolutes of quality:

1. Quality is defined as conformance to requirements, not as 'goodness' or 'elegance':
2. There is no such thing as a quality problem.
3. It is always cheaper to do it right first time.
4. The only performance measurement is the cost of quality.
5. The only performance standard is zero defects

Summarizing Crosby's perspective on quality, there appear to be three essential strands:

- A belief in quantification
- Management leadership
- Prevention rather than cure.

Quality is then considered by Crosby to be an inherent characteristic of the product not an added extra.

He considers that the workers must not be blamed for error, but rather, that management should take the lead and that the workers will then follow.

Crosby suggests that 80 per cent of quality problems are within the control of management

Methods for quality improvement:-

Step 1 Establish management commitment

Step 2 Form quality improvement teams

Step 3 Establish quality measurements

Step 4 Evaluate the cost of quality

Step 5. Raise quality awareness

Step 6 Take actions to correct problems

Step 7 Zero defects planning

Step 8 Train supervisors and managers

Step 9 Hold a 'Zero Defects' day to establish the attitude and expectation within the company.

Step 10 Encourage the setting of goals for improvement.

Step 11 Obstacle reporting

Step 12 Recognition for contributors

Step 13 Establish Quality Councils

Step 14 Do it all over again

2.9.2 ARMAND V. FEIGENBOUM

Quality is simply a way of managing a business organization.

Four steps to quality: Armand V. Feigenbaum

Step 1 Set quality standards.

Step 2 Appraise conformances to standards.

Step 3 Act when standards are not met.

Step 4 Plan to make improvements.

Advantage of Feigenbaum theory:

Feigenbaum 's approach has undoubtedly been successful and has been adopted in whole, or in part, by a number of organisations. Emphasis is given on the importance of management. Socio-technical systems thinking is taken into account; participation is promoted.

Weaknesses are:

- The work is systemic but not complementary;
- The breadth of management theory is recognised but not unified;
- The political or coercive context is not addressed.

Felgenbaum's 10 benchmarks for total quality success

1 Quality is a company-wide process.

2 Quality is what the customer says it is.

3 Quality and cost are a sum, not a difference.

4 Quality requires both individual and team zealotry.

5 Quality is a way of managing.

6 Quality and innovation are mutually dependent.

7 Quality is an ethic.

8 Quality requires continuous improvement.

9 Quality is the most cost-effective, least capital-intensive route to productivity.

10 Quality is implemented with a total system connected with customers and suppliers.

2.9.3 KAORO ISHIKAWA

He is a 'Father of Quality Circles' and as a founder of the Japanese quality movement

His approaches include:-

1. An atmosphere where employees are continuously looking to resolve problems;

2. Greater commercial awareness;

3. a change of shop floor attitude in aiming for ever increasing goals.

Methods:

Quality circle is a voluntary group of employees who work on similar tasks or share an area of responsibility. The group agrees to meet on a regular basis to discuss & solve problems related to work. The team operates on the principle that employee participation in decision-making and problem solving improves the quality of work.

1) The number of members range from 3-12 people.

2) The focus is on specific issues to resolve problems.

3) The team generally meets once a week to analyze work related problems and proposes solutions to Management and where possible implements those solutions.

4) Members also tend to generate a mutual respect and trust as they work on solutions, which is conducive for collaborating as a team.

The following basic elements constitute the structure of the quality circle:

i) Top Management

ii) Steering committee
iii) Co-coordinator
iv) Facilitator
v) Leader
vi) Members
vii) Non-members

Table 2.1: Seven tools of quality control: kaoru is hikawa

Tool	Type	Use
TOOL 1	Pareto charts	Used to identify the principal causes of problems.
TOOL 2	Ishikawa/fishbone diagrams	Charts of cause and effect in processes
TOOL 3	Stratification Layer charts	charts which place each set of data successively on top of the previous one.
TOOL 4	Check sheets	To provide a record of quality
TOOL 5	Histograms Graphs	used to display frequency of various ranges of values of a quality.
TOOL 6	Scatter Graphs	Used to help determine whether there is a correlation between two factors
TOOL 7	Control charts	Used as a device in statistical Process Cont

CHAPTER 3

INTERNATIONAL COUNCIL FOR HARMONISATION

The International Council for Harmonisation (ICH) is a technical requirement for pharmaceuticals for Human Use (ICH). It is a unique step to bring together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug evelopment. The International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation (ICH) held the inaugural Assembly meetings on 23 October 2015 establishing ICH as an international association, a legal entity under Swiss law.

ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

3.1 PURPOSE

- To make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration and the maintenance of such registrations;
- To maintain a forum for a constructive dialogue on scientific issues between regulatory authorities and the pharmaceutical industry on the harmonisation of the technical requirements for pharmaceutical products;
- To contribute to the protection of public health in the interest of patients from an international perspective;
- To monitor and update harmonised technical requirements leading to a greater mutual acceptance of research and development data;
- To avoid divergent future requirements through harmonisation of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products;
- To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices;

- To encourage the implementation and integration of common standards through the dissemination of, the communication of information about and coordination of training on, harmonised guidelines and their use;
- And to develop policy for the ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA) whilst ensuring the scientific and technical maintenance, development and dissemination of MedDRA as a standardised dictionary which facilitates the sharing of regulatory information internationally for medicinal products used by humans.

3.2 PROCESS OF HARMONISATION

ICH harmonisation activities fall into 4 categories: Formal ICH Procedure, Q&A Procedure, Revision Procedure and Maintenance Procedure, depending on the activity to be undertaken (as shown in figure 3.1).

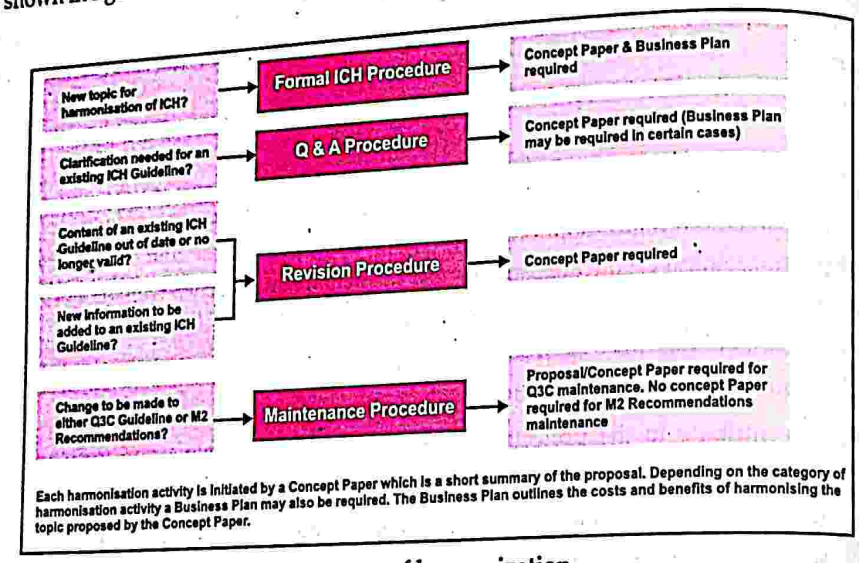

Fig. 3.1: Process of harmonization

Each harmonisation activity is initiated by a Concept Paper which is a short summary of the proposal. Depending on the category of harmonisation activity a Business Plan may also be required. The Business Plan outlines the costs and benefits of harmonising the topic proposed by the Concept Paper.

3.3 CATEGORIES OF ICH TOPICS

The ICH topics are divided into four categories.

1. **Quality Guidelines**

   Harmonisation 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.

2. **Safety Guidelines**

   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.

3. **Efficacy Guidelines**

   The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, 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.

4. **Multidisciplinary Guidelines**

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

3.4 BRIEF OVER VIEW OF QSEM GUIDELINES

Quality Guidelines (Q series)

Harmonisation 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. Q series guidelines are:

- Q1A - Q1F Stability
- Q2 Analytical Validation
- Q3A - Q3D Impurities
- Q4 - Q4B Pharmacopoeias

- Q5A - Q5E Quality of Biotechnological Products
- Q6A- Q6B Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System
- Q11 Development and Manufacture of Drug Substances
- Q12 Lifecycle Management
- Q13 Continuous Manufacturing of Drug Substances and Drug Products
- Q14 Analytical Procedure Development

Safety Guidelines (S series)

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.S series guidelines are:

- S1A - S1C Carcinogenicity Studies
- S2 Genotoxicity Studies
- S3A - S3B Toxicokinetics and Pharmacokinetics
- S4 Toxicity Testing
- S5 Reproductive Toxicology
- S6 Biotechnological Products
- S7A - S7B Pharmacology Studies
- S8 Immunotoxicology Studies
- S9 Nonclinical Evaluation for Anticancer Pharmaceuticals
- S10 Photosafety Evaluation
- S11 Nonclinical Paediatric Safety

Efficacy Guidelines (E series)

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

- E1 Clinical Safety for Drugs used in Long-Term Treatment
- E2A - E2F Pharmacovigilance
- E3 Clinical Study Reports

- E4 Dose-Response Studies
- E5 Ethnic Factors
- E6 Good Clinical Practice
- E7 Clinical Trials in Geriatric Population
- E8 General Considerations for Clinical Trials
- E9 Statistical Principles for Clinical Trials
- E10 Choice of Control Group in Clinical Trials
- E11 - E11A Clinical Trials in Pediatric Population
- E12 Clinical Evaluation by Therapeutic Category
- E14 Clinical Evaluation of QT
- E15 Definitions in Pharmacogenetics / Pharmacogenomics
- E16 Qualification of Genomic Biomarkers
- E17 Multi-Regional Clinical Trials
- E18 Genomic Sampling
- E19 Safety Data Collection

Multidisciplinary Guidelines (M series)

M series guidelines are:

- M1 MedDRA Terminology
- M2 Electronic Standards
- M3 Nonclinical Safety Studies
- M4 Common Technical Document
- M5 Data Elements and Standards for Drug Dictionaries
- M6 Gene Therapy
- M7 Mutagenic impurities
- M8 Electronic Common Technical Document (eCTD)
- M9 Biopharmaceutics Classification System-based Biowaivers
- M10 Bioanalytical Method Validation
- M11 Clinical electronic Structured Harmonised Protocol (CeSHarP)

3.5. Q SERIES GUIDELINES

Harmonisation 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.

Q1-A (R2): STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

The guideline addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc. The details of this test guideline is described in the last section.

Q1-B: STABILITY TESTING: PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected as described under Selection of Batches in the Parent Guideline. Under some circumstances these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging).

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as:

i) Tests on the drug substance;

ii) Tests on the exposed drug product outside of the immediate pack; and if necessary ;

iii) Tests on the drug product in the immediate pack; and if necessary ;

iv) Tests on the drug product in the marketing pack.

The details of this test guideline are described in the last section.

Q1-C: STABILITY TESTING FOR NEW DOSAGE FORMS

NEW DOSAGE FORMS A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority. Such pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension). Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (e.g., 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases.

Q1-D: BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved.

Any reduced design should have the ability to adequately predict the retest period or shelf life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter retest period or shelf life than could be derived from a full design due to the reduced amount of data collected. During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if a justification is provided and the principles of full designs and reduced designs are followed. However, proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change. Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

Bracketing

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the strengths or container sizes and/or fills selected for testing are indeed the extremes.

An example of a bracketing design is based on a product available in three strengths and three container sizes. In this example, it should be demonstrated that the 15 ml and 500 ml high-density polyethylene container sizes truly represent the extremes. The batches for each selected combination should be tested at each time point as in a full design.

Matrixing

As defined in the glossary of the parent guideline, matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as,

for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

Potential Risk

Due to the reduced amount of data collected, a matrixing design on factors other than time points generally has less precision in shelf life estimation and yields a shorter shelf life than the corresponding full design. In addition, such a matrixing design may have insufficient power to detect certain main or interaction effects, thus leading to incorrect pooling of data from different design factors during shelf life estimation. If there is an excessive reduction in the number of factor combinations tested and data from the tested factor combinations cannot be pooled to establish a single shelf life, it may be impossible to estimate the shelf lives for the missing factor combinations.

Q1E: EVALUATION OF STABILITY DATA

A systematic approach should be adopted in the presentation and evaluation of the stability information. The stability information should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms). The adequacy of the mass balance should be assessed.

Factors that can cause an apparent lack of mass balance should be considered, including, for example, the mechanisms of degradation and the stability-indicating capability and inherent variability of the analytical procedures. The basic concepts of stability data evaluation are the same for single- versus multifactor studies and for full- versus reduced-design studies. Data from formal stability studies and, as appropriate, supporting data should be evaluated to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately, and an overall assessment should be made of the findings for the purpose of proposing a retest period or shelf life. The retest period or shelf life proposed should not exceed that predicted for any single attribute.

Q1F: STABILITY DATA PACKAGE FOR REGISTRATION APPLICATIONS IN CLIMATIC ZONES III AND IV

ICH Q1 F Stability Data Package for Registration Applications in Climatic Zones III and IV defined storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IV (hot and humid), i.e. countries not located in the ICH regions and not

covered by ICH Q1 A (R2) Stability Testing for New Drug Substances and Drug Products. ICH Q1 F described harmonised global stability testing requirements in order to facilitate access to medicines by reducing the number of different storage conditions. In the course of the discussions which led to the development of the guideline, WHO conducted a survey amongst their member states to find consensus on 30°C/65% RH as the long-term storage conditions for hot and humid regions. As no significant objections were raised in this survey, 30°C/65% RH was defined as the long-term storage condition for Climatic Zone III/IV countries in ICH Q1F. The document was adopted by the ICH Steering Committee in February 2003 and subsequently implemented in the ICH regions.

Q2: ANALYTICAL VALIDATION

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

Types of Analytical Procedures to be Validated

The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests;
- Quantitative tests for impurities' content;
- Limit tests for the control of impurities;
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures.

Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

1. Accuracy
2. Precision

3. Repeatability
4. Intermediate Precision
5. Specificity
6. Detection Limit
7. Quantitation Limit
8. Linearity
9. Range

The details of analytical validation are described in unit 5.

Q3A - Q3D: IMPURITIES

Impurities in new drug substances are addressed from two perspectives:

Chemistry Aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures; and

Safety Aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

Classification of impurities

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts

- Other materials (e.g., filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are Impurities in New Drug Substances generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Guideline Q3C on Residual Solvents).

Excluded from this document are: (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as Good Manufacturing Practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

Other impurity guidelines of ICH are as follows:

- Q3A(R2)Impurities in New Drug Substances
- Q3B(R2)Impurities in New Drug Products
- Q3C(R7)Impurities: Guideline for Residual Solvents
- Q3C(R8)Impurities: Guideline for Residual Solvents
- Q3DGuideline for Elemental Impurities
- Q3D(R1)Revision of Q3D Cadmium Inhalation PDE
- Q3D(R2)Revision of Q3D for cutaneous and transdermal products
- Q3D training Implementation of Guideline for Elemental Impurities

Q4 - Q4B: PHARMACOPOEIAS

- Q4Pharmacopoeias
- Q4APharmacopoeial Harmonisation
- Q4BEvaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
- Q4B Annex 1R1Residue on Ignition/Sulphated Ash General Chapter
- Q4B Annex 2R1Test for Extractable Volume of Parenteral Preparations General Chapter
- Q4B Annex 3R1Test for Particulate Contamination: Sub-Visible Particles General Chapter
- Q4B Annex 4AR1Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter
- Q4B Annex 4BR1Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms General Chapter

- Q4B Annex 4CR1Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter
- Q4B Annex 5R1Disintegration Test General Chapter
- Q4B Annex 6Uniformity of Dosage Units General Chapter
- Q4B Annex 7R2Dissolution Test General Chapter
- Q4B Annex 8R1Sterility Test General Chapter
- Q4B Annex 9R1Tablet Friability General Chapter
- Q4B Annex 10R1Polyacrylamide Gel Electrophoresis General Chapter
- Q4B Annex 11Capillary Electrophoresis General Chapter
- Q4B Annex 12Analytical Sieving General Chapter
- Q4B Annex 13Bulk Density and Tapped Density of Powders General Chapter
- Q4B Annex 14Bacterial Endotoxins Test General Chapter
- Q4B FAQsFrequently Asked Questions

Q5A - Q5E: QUALITY OF BIOTECHNOLOGICAL PRODUCTS

- Q5A(R1)Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal OriginQ5A
- Q5BAnalysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
- Q5CStability Testing of Biotechnological/Biological Products
- Q5DDerivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
- Q5EComparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

Q6A- Q6B: SPECIFICATIONS

- Q6ASpecifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- Q6BSpecifications : Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products

Q7: GOOD MANUFACTURING PRACTICE

This document is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an

appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

Application of this Guide to API Manufacturing. The following figure 3.2 shows the good manufacturing practice carried at different steps (shaded) involved in control of API derived from various sources.

Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plants	Cutting, and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing and packaging
Herbal extracts used as API	Collection of plants	Cutting, and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging

Fig.3.2: Good manufacturing practice carried at different steps (shaded) involved for control of API derived from various sources.

Q8 :PHARMACEUTICAL DEVELOPMENT

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The

information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space*, specifications, and manufacturing controls. Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality* cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful.

Q9: QUALITY RISK MANAGEMENT

Quality Risk Management: A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. Quality System: The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Principles

Two primary principles of quality risk management are: • The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and • The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Process

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensur.

Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;

- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable.

Quality Risk Management

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk analysis is the estimation of the risk associated with the identified hazards. Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions

Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Q10: PHARMACEUTICAL QUALITY SYSTEM

It is a management system to direct and control a pharmaceutical company with regard to quality. ICH Q10 is based upon ISO 9000:2005.

Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards and ICH Q7 Regional GMP requirements, the ICH Q7 Guideline, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", and ISO quality management system guideline form the foundation for ICH Q10. To meet the objectives described below, ICH Q1 augments GMPs by describing specific quality system elements and manageme responsibilities. ICH Q10 provides a harmonised model for a pharmaceutical quality syst throughout the lifecycle of a product and is intended to be used together with regional G requirements. The regional GMPs do not explicitly address all stages of the product lifec

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- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;

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- Identify a leader and necessary resources;
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(e.g., Development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science and risk based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

Q11: DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES

It addresses aspects of development and manufacture that pertain to drug substance, including the presence of steps designed to reduce impurities. In addition, ICH Q11 provides further clarification on the principles and concepts described in ICH Guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) as they pertain to the development and manufacture of drug substance. A company can choose to follow different approaches in developing a drug substance.

For the purpose of this guideline, the terms "traditional" and "enhanced" are used to differentiate two possible approaches. In a traditional approach, set points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and develop appropriate control strategies applicable over the lifecycle of the drug substance which may include the establishment of design space(s).

Q12: LIFECYCLE MANAGEMENT

The PLCM document outlines the specific plan for product lifecycle management that is proposed by the MAH, includes key elements of the control strategy, the ECs, proposed reporting categories for changes to ECs, PACMPs (if used) and any post approval CMC commitments. This will encourage prospective lifecycle management planning by the MAH and facilitate regulatory assessment and inspection. The PLCM document should be updated throughout the product lifecycle as needed.

Q13: CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

There is a general consensus that continuous manufacturing (CM) has potential for improving the efficiency, agility, and flexibility of drug substance and drug product manufacturing. Regulatory agencies have seen more companies engaged in the development and implementation of CM in recent years than in the past. Although current regulatory

frameworks allow for commercialization of products using CM technology, a lack of regulatory guidelines can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally. An ICH guideline would facilitate international harmonisation and could reduce barriers to the adoption of CM technology.

Q14: ANALYTICAL PROCEDURE DEVELOPMENT

It is proposed to develop a new quality guideline on Analytical Procedure Development and to revise the ICH Q2(R1) Guideline on Validation of Analytical Procedures: Text and Methodology. The new guideline is proposed for harmonising the scientific approaches of Analytical Procedure Development, and providing the principles relating to the description of Analytical Procedure Development process.

Applying this guideline will improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures. Q2(R1) Revision The scope of the revision will include validation principles that cover analytical use of spectroscopic or spectrometry data (e.g., NIR, Raman, NMR or MS) some of which often require multivariate statistical analyses.

3.5 STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A (R2)

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 and recommended storage conditions.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guideline addresses climatic zones I and II.

Stress testing

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The

nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. It should include

- The effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance.
- The susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.
- Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions. Results from these studies will form an integral part of the information provided to regulatory authorities.

FREQUENCY OF TESTING

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed re-test period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

STORAGE CONDITIONS

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

General case

The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period. Condition is as follows:

- Long term*(12 months): 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH
- Intermediate** (6 months): 30°C ± 2°C/65% RH ± 5% RH
- Accelerated (6 months): 40°C ± 2°C/75% RH ± 5% RH

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

"Significant change" for a drug substance is defined as failure to meet its specification.

Drug substances intended for storage in a refrigerator

Study storage condition in a refrigerator is follows:

Long term 5°C ± 3°C 12 months

Accelerated 25°C ± 2°C/60% RH ± 5% RH 6 months

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling.

Drug substances intended for storage in a freezer

Condition is as follows: Long term - 20°C ± 5°C 12 months

Drug substances intended for storage below -20°C

Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

Evaluation

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate.

Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided.

A re-test period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

3.6 PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (Q1B)

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate.

SELECTION OF BATCHES

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing.

CONTAINER CLOSURE SYSTEM

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

TESTING FREQUENCY

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

- At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended.
- Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.
- When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.
- Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

LIGHT SOURCES

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified. For both options 1 and 2, a pharmaceutical manufacturer/applicant may rely on the spectral distribution specification of the light source manufacturer.

Option 1

Any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter(s) may be fitted to eliminate such radiation.

Option 2

For option 2 the same sample should be exposed to both the cool white fluorescent and near ultraviolet lamp. 1. A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977(1993) ; and 2. A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm.

PROCEDURE

- For confirmatory studies, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter to allow direct comparisons to be made between the drug substance and drug product.
- Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters.
- If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, these should be placed alongside the authentic sample.

STORAGE CONDITIONS

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested.

General case

Condition is as follows:

- Long term* (12 months): 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH
- Intermediate**(6 months): 30°C ± 2°C/65% RH ± 5% RH
- Accelerated (6 months): 40°C ± 2°C/75% RH ± 5% RH

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, "significant change" for a drug product is defined as:

- A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
- Any degradation product's exceeding its acceptance criterion;
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions; and, as appropriate for the dosage form:
- Failure to meet the acceptance criterion for pH; or
- Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Drug products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

Drug products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Drug products intended for storage in a refrigerator

Condition is as follows:

- Long term 5°C ± 3°C 12 months
- Accelerated 25°C ± 2°C/60% RH ± 5% RH 6 months

If the drug product is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

Drug products intended for storage in a freezer

Condition is as follows: Long term - 20°C ± 5°C 12 months

Drug products intended for storage below -20°C

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

EVALUATION

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

3.7 GLOSSARY

The following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Climatic zones

The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions. This is based on the concept described by W. Grimm (Drugs Made in Germany, 28:196-202, 1985 and 29:39-47, 1986).

Formal stability studies

Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Intermediate testing

Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

Long term testing

Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be

identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

New molecular entity

An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot scale batch

A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Stress testing (drug substance)

Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product)

Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

CHAPTER 4

QUALITY BY DESIGN

The pharmaceutical Quality by Design (QbD) is 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. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance.

4.1 THE GOALS OF PHARMACEUTICAL QBD

May include the following:

1. To achieve meaningful product quality specifications that are based on clinical performance
2. To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control
3. To increase product development and manufacturing efficiencies
4. To enhance root cause analysis and postapproval change management

Table 4.1: Traditional Approach & Enhanced QbD Approach

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

4.2 ADVANTAGES OF QBD

Benefits for Industry:

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.

Additional opportunities:

- An enhance QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches. Ex: Manufacturing changes within the approved design space without further regulatory review.
- Reduction of post-approval submissions.
- Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.
- More efficient technology transfer to manufacturing.
- Greater regulator confidence of robust products.
- Risk-based approach and identification.
- Innovative process validation approaches.
- Less intense regulatory oversight and less post-approval submissions.
- For the consumer, greater drug consistency.
- More drug availability and less recall.
- Improved yields, lower cost, less investigations, reduced testing, etc.
- Time to market reductions: from 12 to 6 years realized by amongst others.
- First time right: lean assets management.
- Continuous improvement over the total product life cycle (i.e. controlled, patient guided variability).
- Absence of design freeze (no variation issues).
- Less validation burden.
- Real time controls (less batch controls).
- Realistic risk perceptions.
- Contributes substantially to realize the better, cheaper and safer mandate.

4.3 QBD ACTIVITIES WITHIN FDA

Specifically, the following activities are guiding the overall implementation of QbD:

- In FDA's Office of New Drug Quality Assessment (ONDQA), a new risk-based pharmaceutical quality assessment system (PQAS) was established based on the application of product and process understanding.
- Implementation of a pilot program to allow manufacturers in the pharmaceutical industry to submit information for a new drug application demonstrating use of QbD principles, product knowledge, and process understanding. In 2006, Merck & Co.'s Januvia became the first product approved based upon such an application.
- Implementation of a Question-based Review (QbR) Process has occurred in CDER's Office of Generic Drugs.
- CDER's Office of Compliance has played an active role in complementing the QbD initiative by optimizing pre-approval inspectional processes to evaluate commercial process feasibility and determining if a state of process control is maintained throughout the lifecycle, in accord with the ICH Q10 lifecycle Quality System.
- Implementation of QbD for a Biologic License Application (BLA) is progressing.

While QbD will provide better design predictions, there is also a strong recognition that industrial scale-up and comercial manufacturing experience provides new and very important knowledge about the process and the raw materials used therein. FDA is aware that knowledge is not static and builds throughout the manufacturing lifecycle.

FDA's release of the Process Validation guidance in January 2011 notes the need for companies to continue benefiting from knowledge gained, and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are quickly corrected. This vigilant and nimble approach is explained by FDA to be essential to best protect the consumer (patient).

4.4 ELEMENTS OF QBD

There are five elements of QbD. They are listed below.

1. Quality Target Product Profile (QTPP) and Define Critical Quality Attributes (CQAs)
2. Product Design and Understanding including the identification of critical material attributes (CMAs)
3. Link raw material attributes and process parameters to CQAs
4. Design and implement a control strategy
5. Manage product lifecycle, including continuous improvement

4.4.1. QUALITY TARGET PRODUCT PROFILE THAT IDENTIFIES THE CRITICAL QUALITY ATTRIBUTES OF THE DRUG PRODUCT

Intended use in a QTPP 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. QTPP forms the basis of design for the development of the product. Considerations for inclusion in the QTPP could include the following:

- clinical setting, route of administration, dosage form, and delivery system(s)
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed
- Drug product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product

Identification of the CQAs of the drug product is the next step in drug product development. A CQA is a physical, chemical, biological, or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality. The quality attributes of a drug product may include identity, assay, content uniformity, degradation products, residual solvents, drug release or dissolution, moisture content, microbial limits, and physical attributes such as color, shape, size, odor, score configuration, and friability. These attributes can be critical or not critical. Criticality of an attribute is primarily based upon the severity of harm to the patient should the product fall outside the acceptable range for that attribute. Probability of occurrence, detectability, or controllability does not impact criticality of an attribute.

It seems obvious that a new product should be adequately defined before any development work commences. However, over the years, the value of predefining the target characteristics of the drug product is often underestimated. Consequently, the lack of a well-defined QTPP has resulted in wasted time and valuable resources. A recent paper by Raw et al. illustrates the significance of defining the correct QTPP before conducting any development. Also, QbD examples exemplify the identification and use of QTPPs.

4.4.2. PRODUCT DESIGN AND UNDERSTANDING

Over the years, QbD's focus has been on the process design, understanding, and control, as discussed in the ICH Q8 (R2) guidance. It should be emphasized that product design,

understanding, and control are equally important. Product design determines whether the product is able to meet patients' needs, which is confirmed with clinical studies. Product design also determines whether the product is able to maintain its performance through its shelf life, which is confirmed with stability studies. This type of product understanding could have prevented some historical stability failures.

The key objective of product design and understanding is to develop a robust product that can deliver the desired QTPP over the product shelf life. Product design is open-ended and may allow for many design pathways. Key elements of product design and understanding include the following:

- Physical, chemical, and biological characterization of the drug substance(s)
- Identification and selection of excipient type and grade, and knowledge of intrinsic excipient variability
- Interactions of drug and excipients
- Optimization of formulation and identification of CMAs of both excipients and drug substance

To design and develop a robust drug product that has the intended CQAs, a product development scientist must give serious consideration to the physical, chemical, and biological properties of the drug substance. Physical properties include physical description (particle size distribution and particle morphology), polymorphism and form transformation, aqueous solubility as a function of pH, intrinsic dissolution rate, hygroscopicity, and melting point(s). Pharmaceutical solid polymorphism, for example, has received much attention recently since it can impact solubility, dissolution, stability, and manufacturability. Chemical properties include pKa, chemical stability in solid state and in solution, as well as photolytic and oxidative stability. Biological properties include partition coefficient, membrane permeability, and bioavailability.

Pharmaceutical excipients are components of a drug product other than the active pharmaceutical ingredient. Excipients can

(1) aid in the processing of the dosage form during its manufacture;

(2) protect, support, or enhance stability, bioavailability, or patient acceptability;

(3) assist in product identification; or

(4) enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use.

They are classified by the functions they perform in a pharmaceutical dosage form. Among 42 functional excipient categories listed in USP/NF, commonly used excipients include

binders, disintegrants, fillers (diluents), lubricants, glidants (flow enhancers), compression aids, colors, sweeteners, preservatives, suspending/dispersing agents, pH modifiers/ buffers, tonicity agents, film formers/coatings, flavors, and printing inks. The FDA's inactive ingredients database lists the safety limits of excipients based on prior use in FDA-approved drug products.

It is well recognized that excipients can be a major source of variability. Despite the fact that excipients can alter the stability, manufacturability, and bioavailability of drug products, the general principles of excipient selection are not well-defined, and excipients are often selected ad hoc without systematic drug-excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 (R2) recommends drug-excipient compatibility studies to facilitate the early prediction of compatibility. Systematic drug-excipient compatibility studies offer several advantages as follows: minimizing unexpected stability failures which usually lead to increased development time and cost, maximizing the stability of a formulation and hence the shelf life of the drug product, and enhancing the understanding of drug-excipient interactions that can help with root cause analysis should stability problems occur.

Formulation optimization studies are essential in developing a robust formulation that is not on the edge of failure. Without optimization studies, a formulation is more likely to be high risk because it is unknown whether any changes in the formulation itself or in the raw material properties would significantly impact the quality and performance of the drug product, as shown in recent examples. Formulation optimization studies provide important information on the following:

- Robustness of the formulation including establishing functional relationships between CQAs and CMAs
- Identification of CMAs of drug substance, excipients, and in-process materials
- Development of control strategies for drug substance and excipients

In a QbD approach, it is not the number of optimization studies conducted but rather the relevance of the studies and the utility of the knowledge gained for designing a quality drug product that is paramount. As such, the QbD does not equal design of experiments (DoE), but the latter could be an important component of QbD.

Since there are many attributes of the drug substance and excipients that could potentially impact the CQAs of the intermediates and finished drug product, it is unrealistic that a formulation scientist investigate all the identified material attributes during the formulation optimization studies. Therefore, a risk assessment would be valuable in prioritizing which material attributes warrant further study. The assessment should leverage common scientific

knowledge and the formulator's expertise. A material attribute is critical when a realistic change in that material attribute can have a significant impact on the quality of the output material. Product understanding includes the ability to link input CMAs to output CQAs. The steps taken to gain product understanding may include the following:

1. Identify all possible known input material attributes that could impact the performance of the product
2. Use risk assessment and scientific knowledge to identify potentially high risk attributes
3. Establish levels or ranges of these potentially high-risk material attributes
4. Design and conduct experiments, using DoE when appropriate
5. Analyze the experimental data and, when possible, apply first principle models to determine if an attribute is critical
6. Develop a control strategy. For critical material attributes, define acceptable ranges. For noncritical material attributes, the acceptable range is the range investigated. When more than one excipient is involved, these defined acceptable ranges may be termed formulation design space

4.4.3. PROCESS DESIGN AND UNDERSTANDING

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. Unit operations may be executed in batch mode or in a continuous manufacturing process. A unit operation is a discrete activity that involves physical or chemical changes, such as mixing, milling, granulation, drying, compression, and coating. A process is generally considered well-understood when

(1) all critical sources of variability are identified and explained,

(2) variability is managed by the process, and

(3) product quality attributes can be accurately and reliably predicted.

Process parameters are referred to as the input operating parameters (e.g., speed and flow rate) or process state variables (e.g., temperature and pressure) of a process step or unit operation. A process parameter is critical when its variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials.

4.4.4. CONTROL STRATEGY

The knowledge gained through appropriately designed development studies culminates in the establishment of a control strategy. As shown in Fig. 4.1, control strategy could include three levels of controls as follows:

- Level 1 utilizes automatic engineering control to monitor the CQAs of the output materials in real time. This level of control is the most adaptive. Input material attributes are monitored and process parameters are automatically adjusted to assure that CQAs consistently conform to the established acceptance criteria. Level 1 control can enable real-time release testing and provides an increased level of quality assurance compared to traditional end-product testing.
- Level 2 consists of pharmaceutical control with reduced end-product testing and flexible material attributes and process parameters within the established design space. QbD fosters product and process understanding and facilitates identification of the sources of variability that impact product quality.
- Level 3 is the level of control traditionally used in the pharmaceutical industry. This control strategy relies on extensive end-product testing and tightly constrained material attributes and process parameters.
- In reality, a hybrid approach combining levels 1 and 2 can be used. ICH Q8 (R2) defines a control strategy as a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. A control strategy can include, but is not limited to, the following:
  - Control of input material attributes (e.g., drug substance, excipient, in process material, and primary packaging material) based on an understanding of their impact on processability or product quality
  - Product specification(s)
  - Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation and particle size distribution of the granulate on dissolution)
  - In-process or real-time release testing in lieu of end-product testing (e.g., measurement and control of CQAs during processing)

- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models

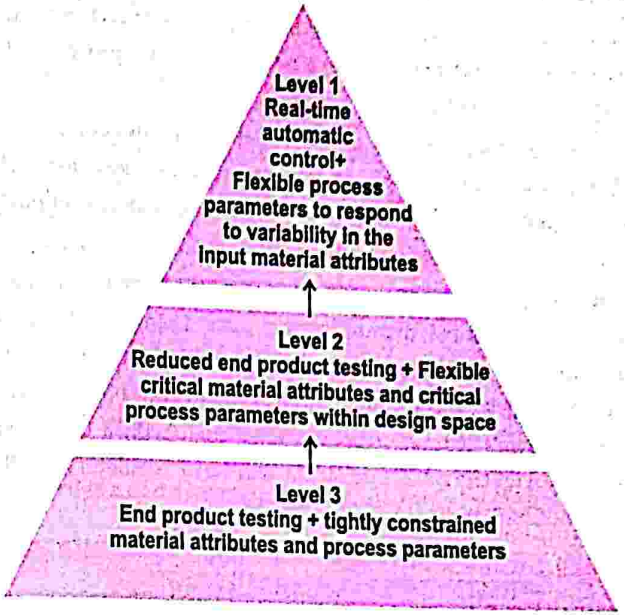

Fig. 4.1: Levels of Control Strategy

4.4.5. PROCESS CAPABILITY AND CONTINUAL IMPROVEMENT

Process capability measures the inherent variability of a stable process that is in a state of statistical control in relation to the established acceptance criteria. When the process has not been demonstrated to be in a state of statistical control, the calculation needs to be based on sample standard deviation of all individual (observed) samples taken over a longer period of time; the result is a process performance index (P_p and P_{pk}). A state of statistical control is achieved when the process exhibits no detectable patterns or trends, such that the variation seen in the data is believed to be random and inherent to the process.

Continuous improvement is a set of activities that the applicant carries out in order to enhance its ability to meet requirements. Continual improvements typically have five phases as follows:

- Define the problem and the project goals, specifically

- Measure key aspects of the current process and collect relevant data
- Analyze the data to investigate and verify cause-and-effect relationships. Determine what the relationships are, and attempt to ensure that all factors have been considered. Seek out root cause of the defect if any.
- Improve or optimize the current process based upon data analysis using techniques such as design of experiments to create a new, future state process. Set up pilot runs to establish process capability.
- Control the future state process to ensure that any deviations from target are corrected before they result in defects. Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process.

In addition, continuous improvement can apply to legacy products. Legacy products usually have a large amount of historical manufacturing data. Using multivariate analysis to examine the data could uncover major disturbances in the form of variability in raw materials and process parameters. Continuous improvement could be achieved by reducing and controlling this variability. Newer processes associated with a design space facilitate continuous process improvement since applicants will have regulatory flexibility to move within the design space (ICH Q8).

4.5 QUALITY BY DESIGN TOOLS

Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. They are not check-box requirements.

4.5.1 DESIGN OF EXPERIMENTS (DOE)

Design of Experiments (DOE) Structured, organized method for determining the relationship between factors affecting a process and the response of that process. DOE Methodology

- Choose experimental design (e.g., full factorial, d-optimal)
- Conduct randomized experiments
- Analyze data
- Create multidimensional surface model

The DoE also reveals relationships between input factors and output responses. A series of structured tests are designed in which planned changes are made to the input variables of a process or system. The effects of these changes on a predefined output are then assessed. The

strength of DoE over the traditional univariate approach to development studies is the ability to properly uncover how factors jointly affect the output responses. DoE also allows us to quantify the interaction terms of the variables. DoE is important as a formal way of maximizing information gained while minimizing the resources required. DoE studies may be integrated with mechanism-based studies to maximize product and process understanding.

When DoE is applied to formulation or process development, input variables include the material attributes (e.g., particle size) of raw material or excipients and process parameters (e.g., press speed or spray rate), while outputs are the critical quality attributes of the in-process materials or final drug product (e.g., blend uniformity, particle size or particle size distribution of the granules, tablet assay, content uniformity, or drug release). DoE can help identify optimal conditions, CMAs, CPPs, and, ultimately, the design space. FDA scientists have shown the use of DoE in product and process design in recent publications.

4.5.2. RISK ASSESSMENT

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. Risk Assessment – A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

4.5.3. PROCESS ANALYTICAL TECHNOLOGY(PAT)

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in process materials and processes with the goal of ensuring final product quality. The term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

Example:

Current Tablet Production:

Example: Current Tablet Production Current Tablet Production Raw Material Dispensing Blending Compression Identification Tests (Chemical Only) Test Product Quality for Release (Active Only) No Tests (Time Based) End-Product Focused Testing to Document Quality Process at Risk.

PAT Tablet Production:

- PAT Tablet Production:
- Compression Functional Tests (Chemical and Physical)
- Validate Process Control
- Control Blending (Particle Size & Disintegrant Distribution)
- Process Focused Mitigate the Process
- Risk Predictive Models

The application of PAT may be part of the control strategy. ICH Q8 (R2) identifies the use of PAT to ensure that the process remains within an established design space. PAT can provide continuous monitoring of CPPs, CMAs, or CQAs to make go/no go decisions and to demonstrate that the process is maintained in the design space. In-process testing, CMAs, or CQAs can also be measured online or in line with PAT. Both of these applications of PAT are more effective at detecting failures than end-product testing alone. In a more robust process, PAT can enable active control of CMAs and/or CPPs, and timely adjustment of the operating parameters if a variation in the environment or input materials that would adversely impact the drug product quality is detected.

Application of PAT involves four key components as follows:

- Multivariate data acquisition and analysis
- Process analytical chemistry tools
- Process monitoring and control
- Continuous process optimization and knowledge management

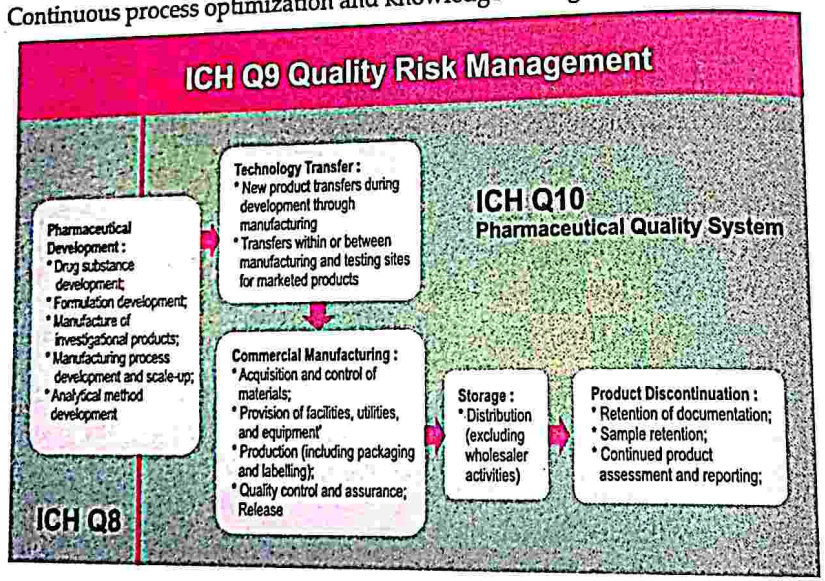

Fig. 4.2: Guideline to implement QbD by FDA in 2002

4.6 APPLICATIONS OF QUALITY BY DESIGN (QBD)

- Quality by design (QBD) – A comprehensive systematic approach to pharmaceutical development and manufacturing advancement in the pharmaceutical development and manufacturing by qbd can be explained against traditional approach
- In pharmaceutical development
- To design a quality product and a manufacturing process to consistently deliver the intended performance of the product
- In life cycle management
- Continual improvement enabled within design space.

CHAPTER 5

INTERNATIONAL STANDARD ORGANIZATION (ISO)

5.1 ISO INTRODUCTION

- ISO is a name used for the International standard organization is the world's largest developer and publisher of International Standards.
- Formed in 1947 in Geneva, Switzerland
- It is federation of national standards bodies of 143 countries.
- ISO is a network of the national standards institutes of 159 countries, one member per country, with a Central Secretariat in Geneva, Switzerland, that coordinates the system.
- Non-governmental organization.
- To increase quality awareness.

Concept: determine characteristics of the management practices that must be standardized.

Main objective: total quality improvement

Difficulties: many countries initiated and implemented their own National Quality Policies.

Two main features:

1. Internal Quality Audit at predetermined interval
2. Continuous monitoring of Quality system

5.2 ISO SERIES

There are five series of ISO. They are as follows

ISO 9000: It is a guide.

ISO 9001: It is a set of requirements for the quality system of the supplier.

ISO 9002: it is a set of standards for product.

ISO 9003: It is a set for final inspection and testing.

ISO 9004: It is a guidelines for developing and implementing quality system principles, structure, auditing and review.

5.3 PROCESS FOR ISO REGISTRATION

Steps required for ISO registration are discussed below in figure 5.1

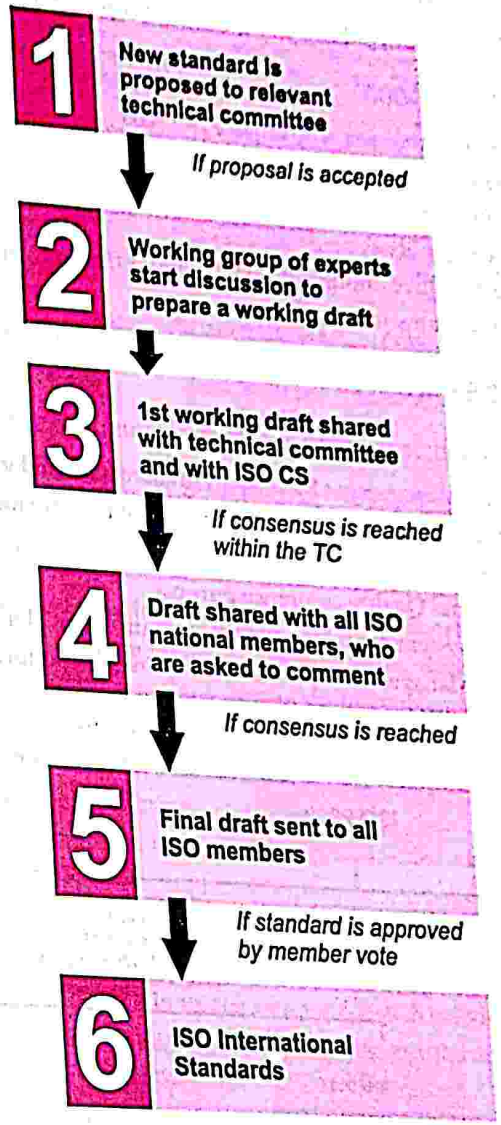

Fig. 5.1 Steps for ISO registration

5.4 ISO 9000

5.4.1 DEFINITION

ISO 9000 is a series of standards, development & published by the ISO that define , establish & maintain an effective QA system for manufacturing & service industries.

5.4.2 PURPOSE OF ISO 9000

- To comply with customers who require ISO 9000
- To sell in the European Union market
- To compete in domestic markets
- To improve the quality system
- To minimize repetitive auditing by similar and different customers
- To improve subcontractors' performance

5.4.3 THE ISO 9000 SERIES

ISO 9000 categories and description is shown in figure 5.2 and 5.3

- ISO 9000 Quality Management Systems – Fundamentals and vocabulary
- ISO 9001 Quality Management Systems – Requirements(demonstration of suppliers capability to design and supply the product)
- ISO 9002 for external Quality assurance purpose
- ISO 9003 Quality system model for quality assurance in final inspection and test
- ISO 9004 Quality Management Systems – Guidelines for performance improvement

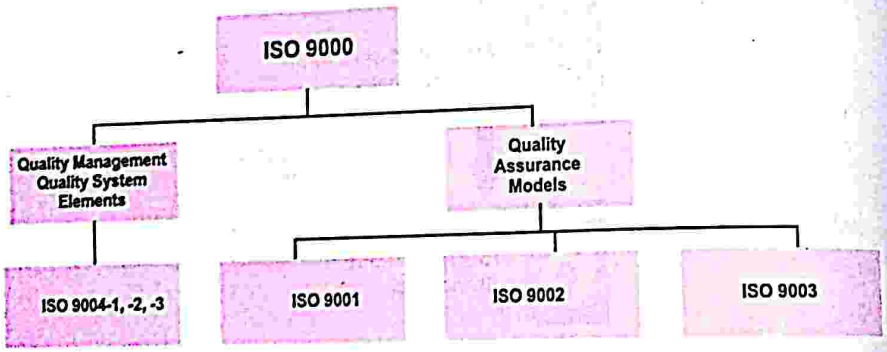

Fig. 5.2 ISO 9000 categories

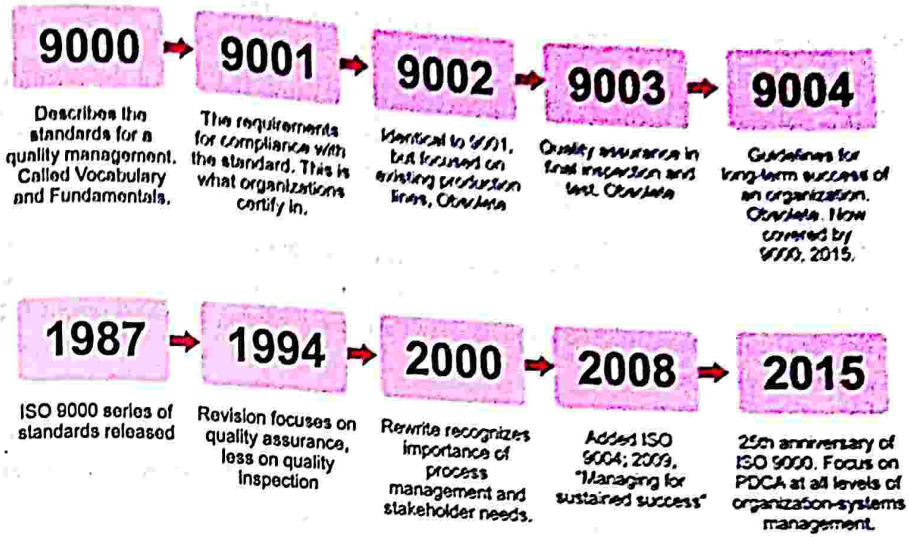

Fig. 5.3 At a glance ISO description

5.4.4 BENEFITS OF THE ISO 9000 SERIES OF STANDARDS

1. Improved controls, discipline (e.g. prevents the use of short cuts and duplication of activities), procedures, documentation, communication, dissemination and customer satisfaction, quicker identification and resolution of problems, greater consistency (i.e. the job is done the same way, time after time and best practices are shared).
2. A reduction in errors, customer complaints and non-conforming products, services and costs and the retention of customers.
3. Assistance with the liberalization of trade through common rules and language.
4. Responsibility for quality issues is placed firmly where it belongs, with the supplier and not the customer.
5. Reduction in the number of customer audits and assessments and also a reduction in the time taken, leading to a saving in resources need for such activities.
6. Identification of ineffective and surplus procedures and documents and other forms of waste.
7. A better working environment.

5.4.5 LIMITATIONS OF THE ISO 9000 SERIES OF STANDARDS

1. **Cost**
   It is not cheap to become an ISO 9000-certified company. The cost of the certification process depends greatly on the type of business, the size of the business and other factors that are different for every type of business

2. **ISO Certification Process**
   The ISO 9000 certification process does not end with the final implementation of the initial certification. It must be maintained throughout the life of the company, or at least the life span of the company as it pertains to the company being ISO 9000 certified. This can lead to expenses

3. **Employee Buy-in**
   If the employees are not interested in or capable of understanding and completing the policies and procedures required to maintain the ISO 9000 status, then the certification process will quickly break down and become meaningless.

4. **Competitive Disadvantage**
   People who don't understand what ISO 9000 is may not be impressed with the ISO 9000 certification and may choose to do business with cheaper competitors who are not ISO 9000 certified and who can operate less expensively as a result.

5.4.6 DIFFERENCES BETWEEN STANDARDS AND REQUIREMENTS

Standards are defined levels of quality, and requirements are what is needed to make something else happen. For the purposes of ISO, standards include requirements, guidelines, and specifications to point the way to quality output. In the ISO 9000 series, different standards exist; we refer to these standards as a family of standards.

5.4.7 ISO 9000 VS. ISO 9001

ISO 9000 is a family of standards encompassing a handful of documents. ISO 9000 is also the name of the document that details the fundamentals and vocabulary of what constitutes a quality system. "It's a primer for us all to understand the same technical language," says veteran quality management consultant René French.

ISO 9001 represents specific requirements to improve processes, and is considered the most essential certification of the ISO 9000 family.

5.4.8 REQUIREMENTS OF ISO 9001

- **Customer Focus:** By making the customer the center of the business, organizations can understand needs and generate customer loyalty.
- **Engagement of People:** As with total quality management (TQM), Kaizen, andLean, this principle should include all employees. In this way, people with a vested interest will be more committed to the venture's success.
- **Leadership:** Good leaders create an environment that focuses on customers and involves all employees.
- **Process Approach to Quality Management:** When you view the goals and activities of a company through the lens of processes, the big picture becomes clear. Rather than focusing on silos or inspection at the finish, the process reveals issues and concerns on the way to product delivery.
- **Continual Improvement:** Organizations must regularly seek improvement beyond the changes they make to gain certification.
- **Evidence-Based Decision Making:** You should make data-driven decisions to provide a foundation for comparing results and build organizational confidence.
- **Relationship Management:** Actively managing all relationships with suppliers, partners, and others is critical to the success of your organization. This includes understanding their needs and providing feedback on services.

5.5 ISO 14000

5.5.1 DEFINITION

ISO 14000 is a family of standards related to environmental management that exists to help organizations. It is an International Voluntary Standards for providing common framework for managing environmental issues. ISO 14000 is Product and Process oriented. Determines environmental impacts of products and services; establish, maintain and evaluate EMS. ISO 14000 is a process but not a performance standard. ISO 14000 is similar to ISO 9000 quality management. The requirements of ISO 14000 are an integral part of the European Union's Eco- Management and Audit Scheme (EMAS).

5.5.2 FEATURES

- Better Environment management
- Flexible and applicable to all nations
- Scientific
- Practical & useful

5.5.3 OBJECT

- Minimize operations which negatively affect the environment
- Comply with applicable laws, regulations, and other environmentally oriented requirements
- Continually improve in the above.

5.5.4 HISTORY

It evolved in the early nineties. In 1972 UN organized a Conference in which United Nations Environment Program (UNEP) was launched. In 1992, Earth Summit was held. Same year, BSI Group published the environmental management systems standard, BS 7750. Then in 1996, ISO 14000 series was launched by the International Organization for Standardization. It is spread over 2,23, 149 organizations in 159 countries and economies

5.5.5 ISO 14000 ENTAILS FIVE ASPECTS

- Environmental Management System
- Environmental Auditing and related investigations
- Environmental Labels and Declarations
- Environmental Performance Evaluation
- Life Cycle Analysis & Terms and Definitions.
- ISO 14000 / EMAS / BS 7750 are all standards of implementation of EMS.

(An environmental management system (EMS) is a management structure that allows an organization to assess and control the environmental impact of its activities, products or services).

5.5.6 IMPORTANCE OF ISO 14000

- Reduces environmental liability
- Enhances public image and reputation
- Assures customers
- Satisfies investor criteria
- Meets your clients' registration requirements
- Reduces your consumption of materials and energy
- Facilitates permits & authorizations
- Reduces the cost
- Improve industry-government relations

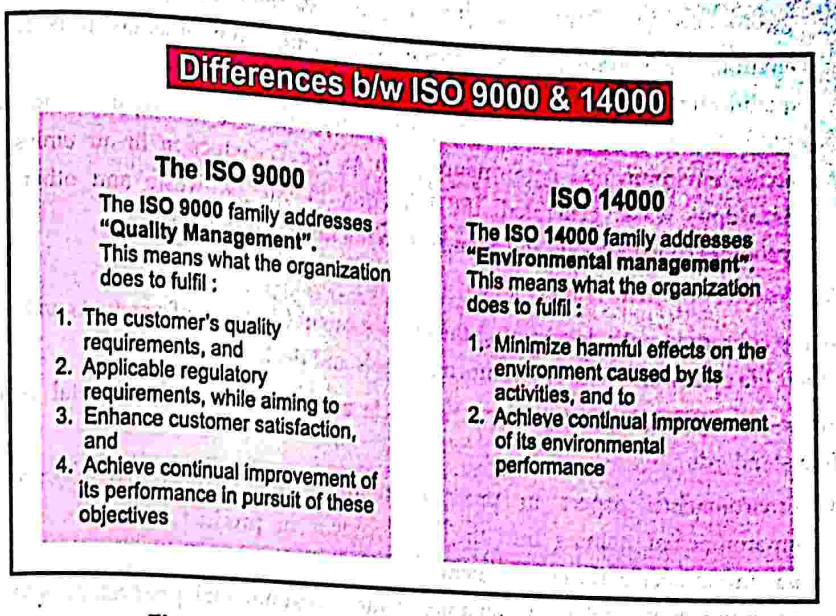

Fig. 5.4: Difference between ISO 9000 and ISO 14000

5.5.7 AREA OF ISO 14000

The series is divided into two separate areas :

1. Organizational evaluation standards
2. Product standards evaluation

5.5.7.1. Organizational evaluation standards:

The organization-oriented standards provide comprehensive guidance for establishing, maintaining and evaluating an environmental management system (EMS).

It covers –

a. Environmental management systems,

b. Environmental auditing,

c. Environmental performance evaluation

1. Environmental Management System (EMS) • It is systematic way of managing an organisation's environmental affairs • Addresses immediate and long term impact of an organizations products, services and processes of the environment.

2. Environmental auditing • This section describes the general principles of environmental auditing, procedures for conducting environmental audits & auditor qualifications.
3. Environmental performance level • Co. must developed measures and goals to access environmental performance such as the % reduction in air emission, the hazardous waste generated, the reduction in energy, waste and other natural resources consumptions and reduction in the fines and penalties .

5.5.7.2. Product-oriented standards:

These are concerned with determining the environmental impacts of products and services over their life cycles, and with environmental labels and declarations.

It covers:- a. environmental labeling b. life-cycle assessment c. environmental aspects in product standards

1. Environmental aspect in product standard- Its purpose is to incorporate environmental training into the development of product standards to prevent adverse impact on the environment.
2. Environmental labeling- Companies using environmental product advertising or making environmental claims for products would have to do so as per ISO Standards.
3. Life cycle assessment- The principles and guidelines used to determine the impact of a product on the environment from the design state through to disposal.

5.6. ISO 14001

- The ISO 14001 standard is the most important standard within the ISO 14000 series.
- ISO 14001 is an international standard against which your company's environmental management system can be measured.
- Does NOT mean that products are more environmentally friendly, Does mean have a documented EMS that is fully implemented and consistently followed.
- It is the only standard in the ISO 14000 family that can be used for certification by third party. all the other standards are for guidance.
- They are not product standards and sevice standards rather process standards. ISO 14001 gives the requirements for what the organization must do to manage processes affecting the impact of its activities on the environment.
- ISO 14001:2004 is the latest, improved version. It replaces the old ISO 14001-1996 standard.
- ISO 14001 is for environmental management. This means what the organization does to minimize harmful effects on the environment caused by its activities, to conform to

applicable regulatory requirements, and to achieve continual improvement of its environmental performance.

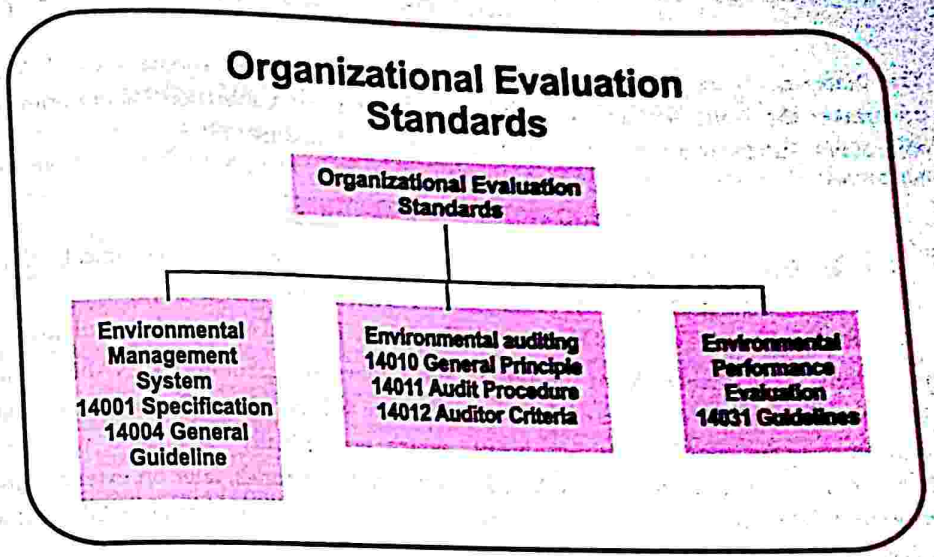

Fig. 5.5 Organizational evaluation standards

CHAPTER 6

NATIONAL ACCREDITATION BOARD FOR TESTING AND CALIBRATION LABORATORIES (NABL)

The National Accreditation Board for Testing and Calibration Laboratories (NABL) undertakes the assessment and accreditation of Testing and Calibration Laboratories, in accordance with the international standard ISO / IEC 17025 and ISO 15189.

6.1 ACCREDITATION AREAS

- Testing: Biological, Chemical, Electrical, Electronics, Fluid-Flow, Mechanical, Non-Destructive Testing, Photometry, Radiological, Thermal, Forensic, Medical
- Calibration: Electro-Technical, Mechanical, Fluid flow, Thermal & Optical, Radiological

The National Accreditation Board for Testing and Calibration Laboratories (NABL) is an autonomous body under the aegis of the Dept. of Science & Technology, Govt. of India, and is registered under the Societies Act. NABL, which was initially established with the objective to provide accreditation to testing & calibration laboratories, later on extended its services to the clinical laboratories in our country. Govt. of India has authorized NABL as the sole accreditation body for testing and calibration laboratories.

The objective of NABL is to provide third party assessment of quality and technical competence. Four years ago NABL established links with international bodies - Asia Pacific Laboratory Accreditation . Cooperation and International Laboratory Accreditation Cooperation. This has imparted international recognition to NABL accredited laboratories. The international standard currently followed by NABL is ISO 15189, specific for medical laboratories.

6.2 AIMS AND OBJECTIVES

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 has been 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.

In order to achieve this objective, NABL provides laboratory accreditation services to laboratories that are performing tests / calibrations in accordance with NABL criteria based

on internationally accepted standard for laboratory accreditation ISO/IEC 17025. These services are offered in a non-discriminatory manner and are accessible to all testing and calibration laboratories in India and abroad, regardless of their ownership, legal status, size and degree of independence.

6.3 IMPORTANCE OF LABORATORY 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 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. The globalization of Indian economy and the liberalization policies initiated by the Government in reducing trade barriers and providing greater thrust to exports makes it imperative for Accredited Laboratories to be at international level of competence.

6.4 BENEFITS OF ACCREDITATION

1. Potential increase in business due to enhanced customer confidence and satisfaction.
2. Savings in terms of time and money due to reduction or elimination of the need for re-testing of products.
3. Better control of laboratory operations and feedback to laboratories as to whether they have sound Quality Assurance System and are technically competent.
4. Increase of confidence in Testing / Calibration data and personnel performing work.
5. Customers can search and identify the laboratories accredited by NABL for their specific requirements from the directory of Accredited Laboratories.
6. Users of accredited laboratories will enjoy greater access for their products, in both domestic and international markets, when tested by accredited laboratories.

6.5 TYPES OF LABORATORIES SEEK FOR ACCREDITATION

The laboratories should be legally identifiable & appropriately registered. They can be a part of a big organization or an independent entity. NABL can provide accreditation to

Laboratories undertaking any sort of testing or calibration in the specified fields. Private or government laboratories. Small operations to large multi-field laboratories. Site facilities, temporary field operations and mobile laboratories.

NABL Accreditation is currently given in the following fields:

- Testing laboratories
- Calibration laboratories
- Medical laboratories

6.6 ACCREDITATION PROCESS

1. An applicant laboratory is expected to submit to NABL 5 copies of the application and 5 copies of Quality Manual.
2. The Quality Manual will be forwarded by NABL to a Lead Assessor to judge the adequacy of the Quality Manual as to whether it is in compliance with ISO 15189 standards.
3. Thereafter the Lead Assessor will conduct a PreAssessment of the laboratory for one day. Based on the Pre-Assessment report the laboratory may have to take certain corrective actions, so as to be fully prepared for the final assessment.
4. It is essential for the applicant as well as accredited laboratories to satisfactorily participate in Proficiency testing/ Interlaboratory comparisons/External quality assessment programme as Asia Pacific Laboratory Accreditation Cooperation (APLAC) Mutual Recognition Arrangement calls for mandatory participation in such programmes.
5. Finally when the laboratory is ready, the Lead Assessor and a team of technical assessors will conduct the final assessment. The number of technical assessors will depend on the number of disciplines applied for.
6. The accreditation process involves a thorough assessment of all the elements of the laboratory that contribute to the production of accurate and reliable test data. These elements include staffing, training, supervision, quality control, equipment, recording and reporting of test results and the environment in which the laboratory operates.
7. The laboratory may have to take certain corrective actions, after the final assessment. After satisfactory corrective actions are taken by the laboratory (within a period of 3 months), the Accreditation Committee will examine the report and if satisfied recommend accreditation.

8. The time required for the process of accreditation will depend upon the preparedness of the laboratory and its response to the non - conformances raised during the pre-assessment and final assessment. The total duration ranges between 6 and 8 months.
9. Surveillance and Re-Assessment Accreditation to a laboratory shall be valid for a period of three years. NABL shall conduct annual surveillance of the accredited laboratories. The laboratories may enhance or reduce the scope of accreditation during surveillance.
10. The laboratories need to apply for renewal of accreditation, at least six months before the expiry of validity of accreditation for which a re-assessment shall be conducted.

REVIEW QUESTIONS

SHORT ANSWER TYPE QUESTIONS

Q.1. Define QMS.

Ans. A quality management system (QMS) is defined as a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives.

Q.2. Write down the elements of quality management system.

Ans. A quality management system typically consists of four facts

a) Quality planning, b) Quality assurance, c) Quality control, d) Quality improvement.

Q.3. What are the purposes of QMS?

Ans. Quality management systems serve many purposes, including:

- Improving processes
- Reducing waste
- Lowering costs
- Facilitating and identifying training opportunities
- Engaging staff
- Setting organization-wide direction

Q.4. What is ICH Q10?

Ans. ICH Q10 governs the concept of current pharmaceutical quality management system for Registration of Pharmaceuticals for Human Use and USFDA and in final phases.

Q.5. What is the difference between calibration and validation?

Ans Calibration is defined as operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties (of the calibrated instrument or secondary standard) and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication. Whereas, validation is a process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages.

Q.6. What do you mean by qualification?

Ans Qualification is defined as action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results.

Q.7. What are the different sources of quality variation?

Ans * Raw material * In process variations * Packaging material * Labeling * Finish product * Manual Error

Q.8. What are the stages of QA before start-up ?

Ans Environmental and microbiologic control and sanitation, establishing manufacturing Working Formula Procedures, design of formula for raw materials and manufacturing equipment.

Q.9. What is TQM?

Ans Total Quality Management is defined as a customer-oriented process and aims for continuous improvement of business operations. It ensures that all allied works (particularly work of employees) are toward the common goals of improving product quality or service quality, as well as enhancing the production process or process of rendering of services

Q.10. Write the name of famous quality philosopher (guru).

Ans Famous quality gurus are

Walter A. Shewhart

W. Edwards Deming

Joseph M. Juran

Armand Feigenbaum

Philip Crosby

Genichi Taguchi

Q.11. What are the seven tools of quality control?

Ans

Pareto charts	Used to identify the principal causes of problems.
Ishikawa/fishbone diagrams	Charts of cause and effect in processes
Stratification Layer charts	charts which place each set of data successively on top of the previous one.
Check sheets	To provide a record of quality
Histograms Graphs	Used to display frequency of various ranges of values of a quality.
Scatter Graphs	Used to help determine whether there is a correlation between two factors
Control charts	Used as a device in statistical Process Cont

Q.12. What is QbD?

Ans. The pharmaceutical Quality by Design (QbD) is 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.

Q.13. What are the elements of QbD?

Ans. Elements of QbD

There are five elements of QbD. They are listed below.

1. Quality Target Product Profile (QTPP) and Define Critical Quality Attributes (CQAs)
2. Product Design and Understanding including the identification of critical material attributes (CMAs)
3. Link raw material attributes and process parameters to CQAs
4. Design and implement a control strategy
5. Manage product lifecycle, including continuous improvement

9. The objective of ISO-9000 family of Quality management is
   a. Customer satisfaction
   b. Employee satisfaction
   c. Skill enhancement
   d. Environmental issues .

10. Total Quality Management (TQM) focuses on
   a. Employee
   b. Customer
   c. Both (a) and (b)
   d. None of the above

11. Which of the following is responsible for quality objective?
   a. Top level management
   b. Middle level management
   c. Frontline management
   d. All of the above

12. TQM & ISO both focuses on
   a. Customer
   b. Employee
   c. Supplier
   d. All of the above

13. Match The Following

A. TQM promotes	1. Small change
B. Kaizen is	2. Continuous improvement
C. Quality circle can solve problem related to	3. Employee participation
D. Quality circle benefit to	4. Employee

The correct order is
   a. A-3, B-1, C-2, D-4
   b. A-1, B-3, C-2, D-4
   c. A-3, B-1, C-4, D-2
   d. A-3, B-2, C-1, D-4

14. Which of the following is for Environment management?
   a. ISO-9000
   b. ISO-14000
   c. ISO-20000
   d. ISO-31000

15. What is ISO?
   a. International organization for standard
   b. None of the above
   c. Indian organization for standard
   d. Internal organization for standard

16. EMS stands for
   a. Environmental management system
   b. Employees management system
   c. Engineering management system
   d. Equipment management system

17. Match The Following

A. Bureaucratic	1. Satisfy all customer need
B. Leadership from top	2. Working together for excellence
C. Excellence mean	3. Provide consistent vision direction
D. Team work mean	4. Unlimited thinking

The correct order is
A-2, B-1, C-3, D-4
   a. A-2, B-3, C-1, D-4
   b. A-2, B-3, C-4, D-1
   c. A-4, B-3, C-1, D-2

18. Match the following

A. Dr. Deming believes	1. Common causes
B. Ishikawa development	2. To prevent defect
C. Type of variation is due to	3. Cause & effect diagram
D. Crosby's objective of quality	4. Histogram

CHAPTER 7

ORGANIZATION AND PERSONNEL

This chapter is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess. Here "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and the related controls. This content is reproduced from Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH-Q7 guidelines).

7.1 ORGANIZATION AND PERSONNEL

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicinal 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.

7.2 RESPONSIBILITIES OF PERSONNEL

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

7.2.1 ORGANIZATION CHART

The manufacturer must have an organization chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities.

There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice

There are mainly three key personnel which control the overall management.

They are including:

- The head of Production
- The head of Quality Assurance
- The head of Quality Control

7.2.2 RESPONSIBILITY OF THE HEAD OF THE PRODUCTION DEPARTMENT

- To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality
- To approve the instructions relating to production operations and to ensure their strict implementation
- To ensure that the production records are evaluated and signed by an authorized person before they are sent to the Quality Control Department
- To check the maintenance of his department, premises and equipment
- To ensure that the appropriate validations are done
- To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

7.2.3 RESPONSIBILITIES OF THE HEAD OF QUALITY CONTROL DEPARTMENT

- To approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products
- To evaluate batch records
- To ensure that all necessary testing is carried out
- To approve specifications, sampling instructions, test methods and other Quality Control procedures
- To approve and monitor any contract analysts[1]
- To check the maintenance of his department, premises and equipment
- To ensure that the appropriate validations [2]are done
- To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

1They are basically analysts working either as contract employee or working for any particular contract or project

2Validation is the process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in testing and then production maintains the desired level of compliance at all stages. In the pharmaceutical industry, it is very important that in addition to final testing and compliance of products, it is also assured that the process will consistently produce the expected results

7.2.4 JOINT RESPONSIBILITY

- The authorization of written procedures and other documents, including amendments
- The monitoring and control of the manufacturing environment
- Plant hygiene
- Process validation
- Training
- The approval and monitoring of suppliers of materials
- The approval and monitoring of contract manufacturers
- The designation and monitoring of storage conditions for materials and products
- The retention of records
- The monitoring of compliance with the requirements of Good Manufacturing Practice
- The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

7.2.5 PERSONNEL TRAINING

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

Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

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.

Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

7.2.6 PERSONNEL HYGIENE

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. 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.

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.

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

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

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 • In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected, should be forbidden.

Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

Personnel should be instructed to use the hand-washing facilities.

Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

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CHAPTER 8

BUILDINGS AND FACILITIES (PREMISES)

8.1 DESIGN AND CONSTRUCTION

Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture.

Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors. The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
- Quarantine before release or rejection of intermediates and APIs;
- Sampling of intermediates and APIs;
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction);
- Storage of released materials;
- Production operations;
- Packaging and labelling operations; and
- Laboratory operations.

8.1.1 TOILETS AND WASHING

Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

8.1.2 UTILITIES

- All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.
- Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment. If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.
- Permanently installed pipe work should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipe work should be located to avoid risks of contamination of the intermediate or API. Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

8.1.3 WATER

Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use. Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality. If drinking (potable) water is insufficient to assure API quality and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established. Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits. Where the manufacturer of a non-sterile API either

intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

8.1.4 CONTAINMENT

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins. Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained. Appropriate measures should be established and implemented to prevent cross contamination from personnel, materials, etc. moving from one dedicated area to another. Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

8.1.5 LIGHTING

Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

8.1.6 SEWAGE AND REFUSE

Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

8.1.7 SANITATION AND MAINTENANCE

Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition. Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities. When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the

contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.

8.2 ENVIRONMENT CONTROL

Clean areas should be ventilated with air passed through an appropriate filter, e.g. a high-efficiency particulate air (HEPA) filter, to maintain air quality in the areas and pressure difference between areas at acceptable levels.

Temperature and relative humidity in clean areas should be controlled within the limits compatible with properties of materials and products being handled therein and also should be set at levels suitable for microbiological control. Environmental temperature and relative humidity should be controlled within specified limits and, wherever feasible, monitored continuously.

The pressure difference should be monitored to maintain the difference constant throughout operations. Air pressure in clean areas should be maintained higher than that in adjacent areas of lower cleanliness levels. Areas provided with the closed ventilation scheme should be designed to be capable of adjusting air pressure effective in preventing proliferation of particulate matters to adjacent areas as well as maintaining the cleanliness at the required level.

Airflow patterns in filling and sealing areas, if their cleanliness levels are specified as Grade A, should be controlled to meet sterility requirements for the prevention of the surfaces of pharmaceutical products and critical points in the areas from contamination.

Direct support areas should be separated from adjacent areas by airlocks, if their cleanliness levels are different. If the levels are the same for the two areas, the installation of airlock system should be considered depending on the type of operations to be performed in the areas.

Spaces located between direct support areas and adjacent areas should be equipped with pass-through rooms and/or pass-through boxes for the transfer of sterilized materials. Further, pass-through rooms and pass-through boxes should be designed to be capable of decontaminating outer packages of sterilized materials or the materials difficult to sterilize (including measurement instruments), as the situation may require.

Airlock doors should be equipped with systems that prevent simultaneous opening of both doors (e.g. mechanical and electrical interlocking systems and visual and audible alarm systems).

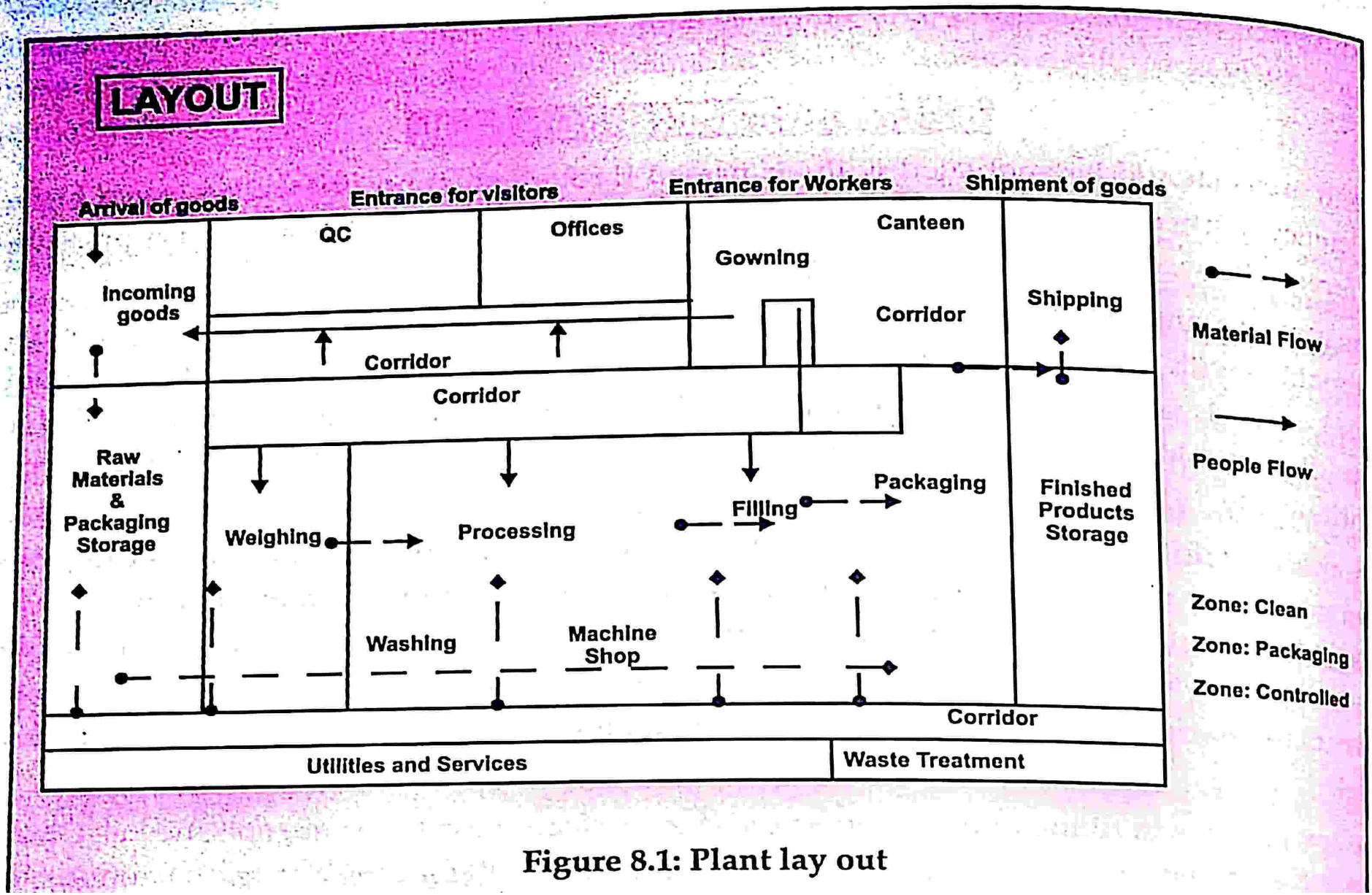

Figure 8.1: Plant lay out

Table 8.1. Classification of Clean Areas

Air cleanliness Note (1)	Maximum number of airborne particles (/m³)			
	Count under non-operating coditions		Count under operating coditions	
	≥ 0.5 µm	≥ 5.0 µm	≥ 0.5 µm	≥ 5.0 µm
Grade A (ISO 5)	3,520	20	3,520	20
Grade B (ISO 7)	3,520	29	352,000	2,900
Grade C (ISO 8)	352,000	2,900	3,520,000	29,000
Grade D	3,520,000	29,000	Dependent on process attributes Note (2)	Dependent on process attributes Note (2)

Note 1) The ISO class designation in parenthesis refers to the count during operation.

Note 2) There are cases where maximum allowable number may not be specified.

Direct Support Areas

- Direct support area is defined as a supporting area of filling and sealing areas.
- The cleanliness of the direct support area should be Grade C or higher, and the grade of each area should be defined by taking into account the level of potential risk of contamination.
- The count of airborne particles and microorganisms should be regularly monitored by suitable methods in the direct support area. The frequency and method of monitoring should be carefully selected based on evaluation results of product contamination risks in the filling and sealing areas.

Other Support Areas

- Other direct support areas comprise areas for preparing pharmaceutical solutions prior to sterilization and areas for washing and cleaning manufacturing equipment and apparatuses.
- The cleanliness of other direct support areas should be controlled by establishing specifications for acceptable airborne particle count by taking into account the required level of contamination control and type of work performed in the area.
- Weighing and preparation processes of pharmaceutical solution, etc. are usually conducted in Grade C areas. If certain contamination-preventive measures are implemented by, for example, processing in closed systems, the preparation of pharmaceutical solution may be performed in Grade D area.

- Heating, Ventilating and Air Conditioning Systems: Air in clean areas should be controlled by designing, instituting, and managing suitable heating, ventilation, and air conditioning (HVAC) systems to maintain atmospheric conditions at appropriate levels. The systems should be managed to ensure constant and secure operations against not only temporal variations due to operational activities, such as door opening and closing and facility equipment operation, but also sustained variations due to non-operational activities, such as seasonal changes in outdoor conditions and deterioration of equipment and apparatuses over time. The HVAC systems and their management programs are comprised of the following basic elements: temperature, relative humidity, air flow volume, air exchange rate, unidirectional air flow, pressure difference relative to adjacent rooms, integrity of HEPA filter, airborne particle count, and microbial count.

8.3.2 TEMPERATURE AND RELATIVE HUMIDITY

Temperature and relative humidity can have direct impact on materials and products, comfort of personnel, and potential for microbial contamination in processing areas; therefore, the level of temperature and relative humidity should be appropriately established, controlled, monitored, and maintained throughout processing.

8.3.3 AIR

- It is critical to secure constant airflow from an area of higher cleanliness level to an area of lower cleanliness level in order to maintain the environmental conditions of clean areas at appropriate levels.
- Pressure difference between areas of different cleanliness levels should be adequately defined, monitored, and controlled.
- When pressure difference is one of the most important factors for controlling bioburden before sterilization, it is recommended to continuously monitor pressure difference between areas and install an alarm system to enable prompt detection of abnormal pressure difference.
- In the case that areas of different cleanliness levels (e.g. Grades A and B) are located in a facility, the air control measure should, as a rule, meet the applicable requirements specified in the Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing.

8.3.4 CLEANING AND DISINFECTION

This area should be cleaned and disinfected in accordance with applicable SOPs, and the performance of such activities should be recorded in writing and retained in archive.

Cleaning Agents and Disinfectants

- Cleaning agents and disinfectants should be evaluated and confirmed by the quality unit prior to use to be suitable and reliable in removing contaminants. The efficacy of disinfectants should be assessed and validated based on the type and count of microorganisms characterized by periodic environmental monitoring.
- SOPs should be established for the application of cleaning agents and disinfectants, cleaning and disinfection schedules, cleaning following disinfection where necessary, precautions for cleaning staff to ensure their safety as well as for caring and storage of cleaning tools.
- Cleaning agents and disinfectants used in Grade A or B areas should be filtered or treated by some other means before use to ensure their sterility and controlled to prevent internal microbial contamination until use.
- Cleaning agents and disinfectants, when prepared in-house, should be prepared in accordance with applicable SOPs, and records of preparation should be produced and retained. When commercial cleaning agents and disinfectants are used after dilution, details of the dilution procedure □such as diluents, dilution ratio, expiration date, storage conditions, and, if applicable, sterilization methods □should be recorded in writing.
- When cleaned or disinfected, the surfaces of facilities and equipment that may come into direct contact with pharmaceutical products should be verified to be free of cleaning agents or disinfectants by appropriate methods after the completion of cleaning or disinfection procedures.
- Reasonable expiration dates should be established for individual disinfectants, and the agents should be only used before such dates.
- The disinfection of the manufacturing environment should not precede the cleaning procedure, as a rule. If there are any locations in the environment where cleaning agents may reside after cleaning, it should be verified that the cleaning agents do not impair the efficiency of disinfectants.
- Disinfectant containers should not be refilled with disinfectants. The following matters should be taken into account in the selection and use of disinfectants:
  - The storage and usage of disinfectants should be in accordance with the supplier's instructions.
  - The selection of disinfectants and disinfection procedures should be primarily based on the safety of the personnel engaged in disinfection work.
  - If the selected disinfectants are suspected of being ineffective against microorganisms isolated from the environment, the efficacy of the agents should be reevaluated and the replacement or alternate use of different disinfectants should be considered and implemented, as appropriate.
  - If environmental monitoring data indicate or suggest the presence of spore-forming bacteria or fungi, effective sporicides or fungicides should be selected for disinfection, as required.
  - The directions for use of disinfectants should include the method of disinfection, application sites, and duration of use required for obtaining anticipated effects.
  - The chemical properties of cleaning agents and disinfectants, in terms of their effects (e.g. corrosiveness) on facility and equipment surfaces, should be assessed prior to the selection of the agents.
- If sporicides or fungicides (including fumigating agents) are likely to be used in irregular manners in areas for processing sterile pharmaceutical products by terminal sterilization procedures, the type, concentrations, usage, and procedures for efficacy confirmation of the agents should be predetermined and specified in writing.
- Cleaning agents, disinfectants, and cleaning utensils should not be stored in critical areas. Materials necessary for operations in the critical area such as hand sprays to sanitize gloves may be stored in critical areas, if well controlled. If cleaning agents and disinfectants are stored in critical areas, control procedures for their storage in critical areas should be defined in writing.

8.3.5 MONITORING OF ADEQUACY AND EFFICACY OF CLEANING AND DISINFECTION PROCEDURES

- The adequacy and efficacy of cleaning and disinfection processes should be established through the overall environmental monitoring program.
- Microorganism counts on the surfaces of equipment and instruments should be periodically obtained by environmental monitoring and analyzed to detect trends in occurrence and proliferation. A full investigation is mandatory to determine causes of abnormalities when the microbial count exceeds the action level, when the species ratio of microorganisms is obviously different from that routinely reported, or when abnormalities in the count or species ratio continue for an extended period of time. Corrective and preventive measures should be implemented, as appropriate whenever considered necessary.

- If the established disinfection procedure is not found to be effective for certain types or concentrations of disinfectants used, the reliability of such disinfectants should be reevaluated by, for example, using different disinfectants interchangeably or replacing with other disinfectants, as appropriate.

8.4 ENVIRONMENTAL MONITORING

The primary objectives of environmental monitoring of areas for processing sterile pharmaceutical products by terminal sterilization procedures are to control the levels of microorganisms and airborne particles within specified limits, predict the damage to the environment, and continuously evaluate the efficiency of cleaning, disinfection, and decontamination procedures in the filling and sealing areas as well as in other support areas, where the risk of microbial and particulate contamination is high, in order to maintain the required cleanliness level of the pharmaceutical manufacturing environment. The purpose of environmental monitoring can be classified into two categories: microbiological control and particle control. Microbiological control is intended to allow the scientific identification and characterization of bioburden organisms residing in the manufacturing environment in order to ensure that the manufacture of sterile pharmaceutical products has been conducted in an appropriately controlled environment and institute the measures (e.g. disinfection procedures) necessary to maintain the environment under the predefined conditions.

8.4.1 ENVIRONMENTAL MONITORING PROGRAMS

SOPs for implementing environmental monitoring programs should be established, and the outcome of the implementation should be adequately recorded. The programs should be developed by assessing and examining properties of substances monitored, frequency of monitoring, sampling locations, and action levels in order to appropriately estimate environmental contamination risks.

Targets for monitoring

Monitoring targets are microorganisms and airborne particles.

- Target airborne particles are those ≧ 0.5 μm in diameter. Particles of other diameter (e.g. - 30 -≧ 5.0 μm) should be measured as required by a need of environmental monitoring for better environmental control on an as-needed basis.
- Target microorganisms are bacteria and fungi.
- Target microorganisms should include not only airborne microorganisms but also those on the surface of walls, floors, fixtures, equipment, gowns, etc.

Preparation of environmental monitoring programs

Environmental monitoring programs should be drawn up prior to performance qualification (PQ). The programs should be reevaluated based on PQ subsequently performed and included in the routine control program for routine practices. Since PQ includes performance testing of the worst-case scenario, the number of sampling locations and frequency of measurement tend to be larger. The number of sampling locations may be reduced by, for example, setting up representative locations for analysis if the monitoring programs are included in the routine control program based on PQ-based reevaluation. Procedures for bacterial monitoring may be simplified by implementing adequate inspection, maintenance, and supervision of facilities and equipment on regular or occasional basis, if the facilities and equipment are provided with isolators, RABS, a blow-fill-seal system, or other devices that prove it sufficiently robust to prevent bacterial contamination.

Monitoring targets and locations

Environmental monitoring targets should include air that comes in contact with working areas, manufacturing equipment (and process control equipment, where appropriate), and aseptic environments; air for maintaining the aseptic environment clean; and compressed air or gas that comes in contact with the environment and equipment. The monitoring frequency of compressed air and gas supplied for manufacturing equipment or used during manufacturing processes may be separately set, provided the cleanliness level can be maintained by filter integrity test or other suitable tests.

8.4.2 SAMPLING FREQUENCY FOR ENVIRONMENTAL MONITORING

Sampling frequency should be determined in accordance with air cleanliness levels for working areas separately under operating and non-operating conditions. The sampling procedures should include the frequency of sample collection from gown and other clothing of personnel.

Monitoring methods:- sampling and testing procedures

- Optimal number and locations of monitoring points should be determined for individual processing areas by taking into account the size of working area, scope of operations, and process flows of materials and products. The monitoring points considered to be

necessary for assessing potential product contamination should be added, as appropriate.

- Devices for collecting and counting airborne particles should be used only after validated calibration. For the evaluation of particle counts obtained, the counts should be converted to the count per-cubic-meter of atmosphere.
- Samples of airborne microorganisms should be collected by one or more suitable procedures including the settle plate, impact, and filtration methods, and microorganisms on the surface should be collected by one or more suitable procedures including the contact plate and swabbing methods. The size of the area to be sampled should be determined based on the shape and surface condition of monitoring targets and locations. In principle, the recommended size of sampling area of equipment and apparatuses is 24 to 30 cm2. Air volume to be sampled for airborne microorganism monitoring should be decided by general considerations and upon discussion of factors involved, such as cleanliness of the target area and routine monitoring frequency. If the cleanliness level of a target area is Grade A, air volume to be sampled should be at least 1 m3 each time. Microbial count monitoring should usually use a circular flat plate of 90 cm in diameter and a maximum exposure time of 4 hours.
- Culture medium used for the monitoring should be tested in advance for the absence of cell growth inhibitory substances for selection of a competent medium suitable for the microbial monitoring. The objective of this testing is to ensure that the collection and growth of microorganisms would not be affected by the presence of alcohol, antibiotics, etc. during microorganism collection and culturing processes. The incubation temperature of the medium should be suitable for the growth of target microorganisms.
- Alert and action level specifications

  Alert and action levels should be specified for individual target substances and locations to be monitored.

  - Alert level specifications should be established based on results of PQ tests.
  - The monitoring program should include the actions and measures to be taken, such as identification of causes of non-compliance and suspension of manufacturing, when alert or action level specifications are met.

Test	Frequency
I. Particle Monitoring in air	6 monthly
II. HEPA Filter Integrity Testing	Yearly
III. Air Changes Rate Calculationn	6 monthly
IV. Air Pressure Differentials	Daily
V. Temperature and Humidity	Daily
VI. Microbiological monitoring by settle plates and/or swabs in other aseptic areas	Daily, and at decreased frequency in areas

Figure 8.2: Testing frequency for environmental monitoring

8.4.3 REQUIREMENTS FOR MONITORING AND CONTROL OF ROUTINE OPERATING CYCLES

1. Implementation of the monitoring program

Microorganisms and particulate matters should be routinely monitored in accordance with the monitoring program.

2. Microbiological control

The microbiological environmental monitoring program should include periodic investigation of the characteristics of environmental flora and isolates for the assessment of contamination risks to pharmaceutical products.

3. Sample collection

Sampling of surfaces that come in contact, prior to sterilization process, with pharmaceutical products and other materials in filling and sealing areas should be performed immediately after the completion of filling and other processing operations.

4. Gases for manufacturing

Gases that may directly contact pharmaceutical products, primary containers, and surfaces that directly come in contact with pharmaceutical products should be periodically inspected and controlled to ensure the absence of microorganisms. The frequency of monitoring

should be separately specified if the sterility of gas supplied needs to be ensured by, for example, the integrity test of filters.

5.Routine analyses

For the adequate maintenance of the manufacturing environment, monitoring data routinely obtained should be analyzed to detect any trends in changes in the environmental conditions and establish specific limits for trend analysis. Even if changes in environmental conditions do not deviate from the specific limits (alert limits), any trends suggesting variations from normal conditions (trend analysis levels) should be predicted and the causes investigated to maintain the quality of the environment at an appropriate level. Trend analysis results should also be utilized for the maintenance of equipment for environmental control, such as the HVAC system, and for optimization of sterilization and disinfection/cleaning procedures.

8.5 CONTROL OF CONTAMINATION

The presence of unwanted materials such as dust and particles during the manufacturing and transportation time is called contamination. The term contaminants includes any unwanted matter that is found in the product.

8.5.1.TYPES OF CONTAMINATIONS

Contaminations are classified in two general types i.e. functional and nuisance.

1. Functional Contamination - Contamination which has a detrimental effect on product or processes.
2. Nuisance Contamination - Contamination which does not have a functional affect on product or processes, but which interferes with the discovery of functional contamination or interferes with the orderly management of the cleanroom.

Five major classes of contaminants which usually found in pharma industries are particles, metallic ions, chemicals, bacteria, airborne molecular contaminants (AMCs).

8.5.2 CONTAMINATION SOURCES

There are seven sources of contamination like air, production facility, cleanroom personnel, process water, process chemicals, process gasses, static charge.

1. Air

Normal air contains contaminants. It must be treated before entering a cleanroom. Major contaminant is airborne particles; particulates or aerosols. They float and remain in air for

long period of time. Air cleanliness or levels of cleanroom is determined by the particulate diameters and their number in air.

As per Federal standard 209E class: Number of particles 0.5µm or larger in a cubic foot of air is allowed. In normal city with smoke, smog and fumes can contains up to 5 million particles per cubic foot.

Clean air strategies 1. Clean workstation 2. Tunnel design 3. Total cleanroom 4. Mini-environments

2. Production facility

2.1 Clean room strategy

Fabrication area consists of a large room with workstations (called hoods) arranged in rows so that the wafers could move sequentially through the process without being exposed to dirty air. To maintain clean room high-efficiency particulate attenuation (HEPA) filters and ultra-low-particle (ULPA) filters are used. There should be low passage of large volumes of air at low velocity. Low velocity contributes to the cleanliness of the hood by not causing air currents, and also for operators comfort. There should be slight positive pressure inside in the station to prevent airborne dirt from operators and from aisle area.

Criteria of air filters:

- HEPA and ULPA filters efficiency should be 99.9999+ % at 0.12micron particle size
- Typical flow rate should be 90-100 ft/min
- They should be mounted on a clean hood.
- Two types of air flow are obtained from these filters.
  - Vertical laminar flow (VLF) → air leave the system in a laminar pattern, and at the work surface, it turns and exits the hood
  - Horizontal laminar flow (HLF) → HEPA filter is placed in the back of the work surface
- Both VLF and HLF stations keep the wafer cleans:

2.2 Clean room construction

• Primary design is to produce a sealed room that is supplied with clean air, build with materials that are non contaminating, and includes the system to prevent accidental contamination from the outside or from operators. All materials must be non-shedding including wall covering, process station materials and floors coverings. All piping holes are sealed and all light fixtures must have solid covers. Design should minimize flat surfaces that can collect dust. Stainless steel is favourable for process stations and work surfaces

2.3 Clean room elements:

1. Adhesive floor mats – These floor mats are placed at every entrance to pull off and holds dirt adhered at the bottom of the shoes
2. Gowning area – It is a buffer between cleanroom and the plant. It is always supplied with filtered air from ceiling HEPA filters. It is a storage area of cleanroom apparel garments.
3. Air pressure – Highest pressure is maintained in cleanroom, second highest in gowning area and the lowest in factory hallways. Higher pressure in cleanroom causes a low flow of air out of the doors and blow airborne particle back into the dirtier hall way
4. Air showers - Air shower is located between the governing room and the cleanroom. High velocity air jets blow off particles from the outside of the garments. Air shower possesses interlocking system to prevent both doors from being opened at the same time.
5. Service bay – It is a semi-clean area for storage materials and supplies. Service bay has Class 1000 or class 10 000. Bay area contains process chemical pipes, electrical power lines and cleanroom materials. Critical process machines are backed up to the wall dividing the cleanroom and the bay → allows technician to service the equipment from the back without entering the cleanroom
6. Double-door-pass-through - Simple double-door boxes or may have a supply of positive-pressure filtered air with interlocking devices to prevent both doors from being opened at the same time. It is often fitted with HEPA filters
7. Static control

2.4 Clean room personnel

Even after shower and sitting 100000 -1000000 particles/minute are found in air. This number increase dramatically when moving e.g. generate 5 million particles/min with movement of 2 miles/hr . Example of human contaminants is listed below:

- Flakes of dead hair
- Normal skin flaking
- Hair sprays
- Cosmetics
- Facial hair
- Exposed clothing

2.5 Process water

Unacceptable contaminants are found in normal city water. These are including dissolves minerals, particles, bacteria, organics, dissolved oxygen and silica. Dissolve minerals comes from salt in normal water like Na+, Cl-. They can be removed by reverse osmosis (RO) and ion exchange systems. It is must to monitor resistivity of all process water in the fabrication area between 15-18 MΩ. Solid particles can be removed by sand filtration, earth filtration,

membrane Bacteria can be removed by sterilize using UV radiation and filter out the particles. Organics like plant & fecal materials are separated by carbon bed filtration, force draft decarbonators and vacuum degasifies.

2.6 Process chemicals

Highest purity of acids, bases and solvents are used for etching and cleaning wafers and equipment. Chemical are found of different grades like commercial, reagent, electronic, semiconductor.

Main concerns: metallic mobile ionic contaminants (MIC) must be < 1 ppm. Generally chemicals with 1ppb MIC are widely available. Chemical should be of 99.9% purity. Other steps which should be followed are :

- Clean inside containers
- Use containers that do not dissolve
- Use particulate free labels
- Place clean bottles in bags before shipping

2.7 Process gasses

Many manufacturing unit uses different processed gases which may cause contamination. Semiconductor fabrication uses gases like air separation gases: O2, N2, H2; specialty gases: arsine and carbon tetrafluoride etc. Semicnductor fabrication requires extremely high purity process gasses for oxidation, sputtering, and plasma etc, chemical vapour deposition (CVD), reactive ion gas, ion implantation and diffusion. If gas is contaminated, wafer properties could be altered due to chemical reaction • Gas quality is also shown in assay no; 99.99-99.999999. The highest quality is called "six 9s pure".

2.8 Static charge

Static charge attracts smaller particles to the wafer. The static charge may build up on wafers, storage boxes, work surfaces and equipment. It may generate up to 50 000V. Static charge attracts aerosols out of the air and personal garment. Particles held by static charge are hard to remove using a standard brush or wet cleaning system. Most static charge is produced by tribo electric charging. In this phenomenon two materials initially in contact are separated. After this one surface possesses positive charge because it losses electron and one surface becomes negative because it gains electron

Electrostatic Discharge (ESD): Rapid transfer of electrostatic charge between two objects, usually resulting when two objects at different potentials come into direct contact with each other. ESD can also occur when a high electrostatic field develops between two objects in close proximity.

Control of static charge

- Use antistatic materials in garments and in-process storage boxes
- Apply antistatic solution on certain walls to prevent charge build up. This should not be used in critical station due to possible contamination. Use discharge technique for those places.
- Use ionisers and grounded static-discharge

How to eliminate static charge?

- Use air ioniser – It neutralise nonconductive materials
- Grounding of conducting surfaces
- Increasing conductivity of materials
- Humidity control
- Surface treatment with topical antistatic solutions

8.5.3 THE OPPORTUNITY TO CONTAMINATE

1. Toxicity
2. Quantity of active ingredient used per batch
3. Process train used in product manufacture
4. Level of containment and energies used in processing
5. Proximity to other products and the use of shared equipment
6. Opportunity to contaminate
7. Dosing regime of the product and in particular the number of daily doses contained in a batch
8. Frequency of the ingredients or product's manufacture
9. Any other products manufactured that might be contraindicated for users of the target drug

8.5.4 PREVENTION FOR EFFECTIVE CONTAMINATION CONTROL IN PHARMACEUTICAL FACILITIES

Contamination control has long been one of the main challenges in pharmaceutical production as nothing is a greater liability to the safety of patients.

As per FDA, GMP Regulations 1978:

"There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups"

As per EMA, GMP Regulations:

"In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular medicinal products"

70% to 80% of all contamination entering a room is carried in on wheels or feet (UK Department of the Environment)

1. Contamination on unprotected floors will rise to shoulder level and above on air particle movement created by vortices
2. Installation of a contamination control system at floor level is the most cost effective solution to the removal of the majority of contamination
3. By removing 80% for small cost compared with the expense of trying to cope with the 20% (air handling systems, gowns, hats, gloves, physical barriers, clean, controlled, critical facility costs!!)

8.5.4.1 Preventative Measures

1) Filters
2) Specialist Cleaning
3) Containment
4) Implementation of Barrier Technology
5) Controlling Personnel Habits
6) Restricting foreign materials (Cardboard,Packaging, Feed etc)
7) Contamination Control Flooring/Mats

8.5.4.2 Benefits of contamination prevention

1) Reduced chance of Animal study failure costing considerable sums and even threatening the viability of the facility
2) The animals have a degree of protection which can counter premature death
3) Staff and other stakeholders see you are serious about the running of the facility and the importance of controls
4) Less time and money spent in trying to identify rogue organisms and sources of contamination

CHAPTER 9

PROCESS EQUIPMENT AND RAW MATERIALS

9.1 PROCESS EQUIPMENT

Equipment may be defined as a physical entity which is used to carry out a general or specific activity in the plant. Equipment is the major inputs in the manufacture of the pharmaceutical products, in the regulatory literature on GMP in various countries gives the importance & hence provide guidelines on the management of equipment in pharmaceutical plants.

Equipment may be : Single system or piece, Integrated system.

9.1.1 EQUIPMENT SELECTION

Selection of equipment has both strategic and financial impact on the companies. It is an essential for any company because it has direct influence on the success of the product facilities by optimum cost, improving quality, safety and reducing environmental hazards.

Factor that affect selection of equipment a) Operating criteria, b) Availability of spares and servicing c) Maintenance, d) Environmental issues, e) Availability of design & maintenance manuals, f) Cost.

9.1.2. DESIGN AND CONSTRUCTION

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications. Production equipment should only be used within its qualified operating range.

Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality

beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

9.1.3. EQUIPMENT CLEANING

Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment;
- Cleaning schedules, including, where appropriate, sanitizing schedules;
- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
- Instructions for the removal or obliteration of previous batch identification;
- Instructions for the protection of clean equipment from contamination prior to use;
- Inspection of equipment for cleanliness immediately before use, if practical; and
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

Non-dedicated equipment should be cleaned between productions of different materials to prevent cross-contamination.

Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

Equipment should be identified as to its contents and its cleanliness status by appropriate means.

9.1.4 CALIBRATION

Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

Equipment calibrations should be performed using standards traceable to certified standards, if existing.

Records of these calibrations should be maintained.

The current calibration status of critical equipment should be known and verifiable.

Instruments that do not meet calibration criteria should not be used.

Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

Computerized Systems: GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application. Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks. Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available. If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems. Data can be recorded by a second means in addition to the computer system.

9.1.5 EQUIPMENT MAINTENANCE

It is defined as facilities maintain to some desired level of efficiency to keep assets in a satisfactory condition.

Types of Maintenance:

Four types of maintenance are there.

1). Breakdown maintenance :- It means that people waits until equipment fails and repair it. Such a thing could be used when the equipment failure does not significantly affect the operation or production or generate any significant loss other than repair cost.

2). Corrective maintenance :- It improves equipment and its components so that preventive maintenance can be carried out reliably. Equipment with design weakness must be redesigned to improve reliability or improving maintainability.

3). Maintenance prevention:- It indicates the design of a new equipment. Weakness of current machines is sufficiently studied and is incorporated before commissioning new equipment.

4). Preventive maintenance: - It is a daily maintenance (cleaning, inspection, oiling and re-tightening), design to retain the healthy condition of equipment and prevent failure through the prevention of deterioration, periodic inspection or equipment condition diagnosis, to measure deterioration. It is further divided into periodic maintenance and predictive maintenance.

- Periodic maintenance (Time based maintenance - TBM) : Time based maintenance consists of periodically inspecting, servicing and cleaning equipment and replacing parts to prevent sudden failure and process problems.
- Predictive maintenance: - This is a method in which the service life of important part is predicted based on inspection or diagnosis, in order to use the parts to the limit of their service life. Compared to periodic maintenance, predictive maintenance is condition based maintenance.

9.2. RAW MATERIALS

All materials that used into the manufacturing of a finished bulk (even though it may not be present in final product e.g. certain solvents etc.) and which are consumed by person using it are called as raw materials. Raw materials can be either active drug or inactive substances. eg. Hard gelatin capsules: even though it is used to fill the blend of medicine, it is not considered as package materials because it is consumed by person using medicines.

9.2.1. PROCEDURE OF RAW MATERIAL MANAGEMENT

Steps involved in raw material managements are including purchasing, receipt and quarantine, Sampling and Testing of Incoming Production Materials, storage and reevaluation.

1. Purchasing

Purchasing is an activity directed towards procuring the materials, supplies, equipments and services required in the operations of an enterprise. There are six purchase objectives including: Source, Quality, Quantity, Price, Time and Place.

Purchase department: The organizational setup of a purchase department depends on the size of the company. Purchase Manager is responsible for the effective, efficient and economic operation of the department.

Types of purchasing

- **Centralised**[3]: When different branches of a company require similar type of raw materials, then centralised purchasing is preferred.
- **Decentralised**[4]: When different branches of a large organisation, require different types of materials, decentralised purchasing is adopted.

Steps Involved In Purchase Procedure

- Recognition of need and receipt of requisition
- Selection of potential sources of supply
- Inviting quotations
- Receipt and analysis of quotations
- Issuing the purchase order
- Receiving the material and inspecting it
- Checking of invoice and recording of bills
- Releasing the payment to the supplier

Selection of vendors

Selection of venders is carried out in four stages:

- First stage (Survey stage): Identifying potential sources of suppliers
- Second stage (Enquiry stage): Analysis of information in standard enquiry format

3 A centralised system is one in which a central controller exercises control over the lower-level components of the system

4 A decentralized system is one which requires multiple parties to make their own independent decisions.

- Third stage (Negotiations and selection stage): Quality control specifications, clarification, credit, quantity discounts
- Fourth stage (Experience and evaluation stage): Performance appraisal

2. Receipt and Quarantine

Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

3. Sampling and Testing of Incoming Production Materials

At least one test to verify the identity of each batch of material should be conducted. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis.

Reliability of Certificates of Analysis should be checked at regular intervals.

Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis. Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials. Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

4. Storage

Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination. Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection. Materials should be stored under conditions and for a period that have no adverse affect on their quality, and should normally be controlled so that the oldest stock is used first.

Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

5. Re-evaluation

Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

9.2.2 MAINTENANCE OF STORES

Location of stores: The stores should be located adjacent to the manufacturing area. The location depends upon the nature and value of items to be stored and the frequency with which items are received and issued. Objectives of store location:

- Minimum wastage of space
- Maximum ease of operations
- Minimum handling costs
- Minimum other operating costs.

Facilities

* Inspection centre * Space for storing retained samples for quality control * Centralised weighing room * Washing room * Quarantine room

* Storage conditions:

- Room temperature should be 30° C and R. H. 60%
- A.C storage (25± 2 ° C & R.H. 45 – 55%)
- Low temperature storage 2 – 8 ° C
- Light sensitive material in amber color container

* Labeling of material in storage area:

- Designated name of product and internal code reference
- Batch no. given by supplier
- Status of Content
- Expiry date or date beyond which retesting is necessary

REVIEW QUESTIONS

SHORT ANSWER TYPE QUESTIONS

Q.1. Grade B area comes under which ISO standard?

Ans. Grade B area comes under ISO- 7 standard.

Q.2. What is cross-contamination?

Ans. It is a process by which bacteria or other microorganisms are unintentionally transferred from one substance or object to another, with harmful effect.

Q.3. What is in-house testing?

Ans. In-house refers to conducting an activity or operation within a company, instead of relying on outsourcing.

Q.4. What is Quarantine?

Ans. It is simply an area where under process product is kept if due to some reason manufacturing process of that particular product is at halt. The quarantine process helps to ensure that less (or no) defective product reaches the consumer.

Q.5. What is Calibration?

Ans. Calibration is the process of configuring an instrument to provide a result for a sample within an acceptable range.

Q.6. What is Bioburden?

Ans. Bioburden is normally defined as the number of bacteria living on a surface that has not been sterilized.

Q.7. What is HVAC?

Ans. Heating, ventilation, and air conditioning (HVAC) system.

Q.8. Write down the factors affecting selection of equipment.

Ans. a) Operating criteria, b) Availability of spares and servicing c) Maintenance, d) Environmental issues, e) Availability of design & maintenance manuals, f) Cost.

Q.9. How static charge is controlled?

Ans. • Use antistatic materials in garments and in-process storage boxes.

• Apply antistatic solution on certain walls to prevent charge build up. This should not be used in critical station due to possible contamination. Use discharge technique for those places.

• Use ionisers and grounded static-discharge

CHAPTER 10

QUALITY CONTROL OF P...

Packaging of materials is an integral part of any pharmaceutical industry. Packaging affects the quality stability and identification of drug product. Packaging provide an adequate degree of protection, minimize the loss of constituents and should not interact physically or chemically with the contents in a way that will alter their quality to an extent beyond the limits given in the individual monograph, or present a risk of toxicity.

Pharmaceutical packaging is the means of providing protection, presentation, identification, information and convenience to encourage compliance with a course of therapy. The commonly used packaging materials are Container, Closure, Carton or Outer and Box. The containers may be made of glass, plastic, metal or paper. The material for closure may include Cork, Glass, Plastic, Metal or rubber.

There are various tests for determination of quality, integrity and compatibility of packaging materials. The specification and requirement of quality testing depends on type of pharmaceutical materials used. The requirement of packaging material testing is set according to specification of regulatory agencies like WHO, GMP, USFDA and ICH guidelines.

Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

10.1 TYPES OF PACKAGING

1) Primary packaging- is the material that first envelops the product and hold it. This usually is the smallest unit of distribution or use. Ex. Aerosol spray can, blister packs, bottle ampoules, vials, polymer-coated foils.

Fig. 10.1: Primary packaging

2) Secondary packaging - Is outside the primary packaging perhaps used to group primary package together. Ex. Boxes, cartons,labels, leaflets
3) Tertiary packaging- is used to bulk handling and shipping. Ex. Barrel, container, edge protector

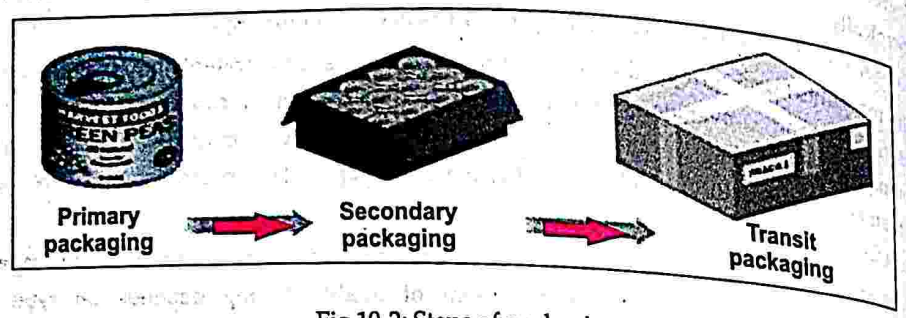

Fig.10.2: Steps of packaging

The choice of packaging material will depend upon:

- The degree of protection required
- Compatibility with the dosage form
- Customer convenience e.g. size, weight of dosage form,
- Filling method
- Sterilization method to be employed and cost

Composition of package:

(a) Container

(b) Closure

(c) Carton or Outer

(d) Box

10.2 TYPES OF PACKAGING MATERIALS USED FOR PHARMACEUTICAL PACKAGING

Packaging materials used in pharmaceuticals are * Glass * Plastics * Rubbers * Paper/card boards * Metals. They are discussed below.

10.2.1 GLASS

Glass has been widely used as a drug packaging material.

Advantages

- They are transparent.
- They have good protection power.
- They can be easily labeled.
- Economical
- Variety of sizes and shapes

Disadvantages

- Glass is fragile so easily broken.
- Release alkali to aqueous preparation

Composition of glass

- Sand (silicon dioxide) Soda ash (sodium carbonate) Limestone (calcium carbonate) Cullet (broken glass) - aluminium, boron, potassium, magnesium, zinc, barium,
- Amber: light yellowish to deep reddish brown, carbon and sulphur or iron and manganese dioxide
- Yellow: Compounds of cadmium and sulphur
- Blue: Various shades of blue, cobalt oxide or occasionally copper (cupric) oxide
- Green: iron oxide, manganese dioxide and chromium dioxide

Manufacturing of glass:

The four basic processes used in the production of glass are:

- Blowing uses compressed air form the molten glass in the cavity of metal mold.
- In drawing , molten glass is pulled through dies or rollers that shape the soft glass.
- In pressing mechanical force is used to press the molten glass against the side of a mold.

- Casting uses gravity or centrifugal force to cause molten glass to form in the cavity of mold.

Types of glass

- Type I—Highly resistant borosilicate glass
- Type II—Treated soda lime glass
- Type III—soda lime glass
- NP—soda glass (non parenteral usage)

Type I-borosilicate glass

Alkalinity is removed by using boric oxide to neutralized the oxide of potassium and sodium It is highly resistant glass. It has high melting point so can with stand high temperatures. It is more chemically inert than the soda lime glass. It can resist strong acids, alkalies and all types of solvents. It has reduced leaching action.

Uses: Laboratory glass apparatus for injection and water for injection.

Type II-treated soda lime glass

Type II containers are made of commercial soda lime glass that has been dealkalized or treated to remove surface alkali. The de-alkalizing process is known as sulphur treatment. Sulfur treatment neutralizes the alkaline oxides on the surface, rendering the glass more chemically resistant. Uses: Used for alkali sensitive products, infusion fluids, blood and plasma, large volume container.

10.2.2 PLASTIC

- Plastics may be defined as any group of substances, of natural or synthetic origins, consisting chiefly of polymers of high molecular weight that can be moulded into a shape or form by heat and pressure.

Advantages

- Less weight than glass,
- Flexible
- Variety of sizes and shapes
- Essentially chemically inert, strong, rigid Safety use, high quality, various designs
- Extremely resistant to breakage

Disadvantages

- Absorption permeable to moisture
- Poor printing, thermostatic charge

Types of plastics

- Thermosetting type – When heated they may become flexible but they do not become liquid e.g. Urea formaldehyde (UF),Phenol formaldehyde ,Melamine formaldehyde (MF), Epoxy resins (epoxides), Polyurethanes (PURs).
- Thermoplastics type- On heating they are softened to viscous fluid which harden again on cooling. e.g. Polyethylene(HDPE – LDPE), Polyvinylchloride(PVC), Polystyrene Polypropylene, Nylon(PA), Polyethylene terepthalate(PET), Polyvinylidene chloride (PVdC), Polycarbonate Acrylonitrile butadiene styrene(ABS)

10.2.3 METALS

Metals are used for construction of containers. The metals commonly used for this purpose are aluminum, tin plated steel, stainless steel, tin and lead.

Advantages:

- They are impermeable to light, moisture and gases.
- They are made into rigid unbreakable containers by impact extrusion.
- They are light in weight compared to glass containers.
- Labels can printed directly on to their surface.

Disadvantages:

- They are expensive.
- They react with certain chemicals

Collapsible tubes metal

- The collapsible metal tube is an attractive container that permits controlled amounts to be dispensed easily, with good reclosure, and adequate protection of the product.
- It is light in weight and unbreakable and lends itself to high speed automatic filling operations. Most commonly used are tin, aluminium and lead.

Tin:

- .Tin containers are preferred for food, pharmaceuticals and any product for which purity is considered.
- Tin is the most chemically inert of all collapsible metal tubes .

Aluminium:

- Aluminium tubes offer significant savings in product shipping costs because of their light weight.

- They are attractive in nature Lead:
- Lead has the lowest cost of all tube metals and is widely used for non food products such as adhesives, inks. paints and lubricants.
- Lead should never be used alone for anything taken internally because of the risk lead poison.
- With internal linings, lead tubes are used for products such as chloride tooth paste.

10.2.4 RUBBER

Rubber is used mainly for the construction of closure meant for vials, transfusion fluid bottles, dropping bottles and as washers in many other types of product. Widely used rubbers are

Butyl rubber: Advantages:

- Permeability to water vapour .
- Water absorption is very low.
- They are relatively cheaper compared to other synthetic rubbers.

Disadvantages:

- Slow decomposition takes place above 130 °C.
- Oil and solvent resistance is not very good.

Nitrile rubber: Advantages : Oil resistant due to polar nitrile group, heat resistant.

Disadvantages: Absorption of bactericide and leaching of extractives are considerable.

Chloroprene rubbers : Advantages: Oil resistant. Heat stability is good.

Silicon rubbers: Advantages: Heat resistance. Extremely low absorption and permeability of water. excellent aging characteristic.

Disadvantages: They are very expensive.

10.3 TAMPER RESISTANT PACKAGING

The requirement for tamper resistant packaging is now one of the major considerations in the development of packaging for pharmaceutical products. Tamper resistant package is one having an indicator to entry in which, if missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. FDA approves the following configurations as tamper resistant packaging: Film wrappers, Blister package, Strip package, Bubble pack, Shrink seals, and bands Oil, paper, plastic pouches, Bottle seals, Tape seals, Breakable caps, Aerosol containers.

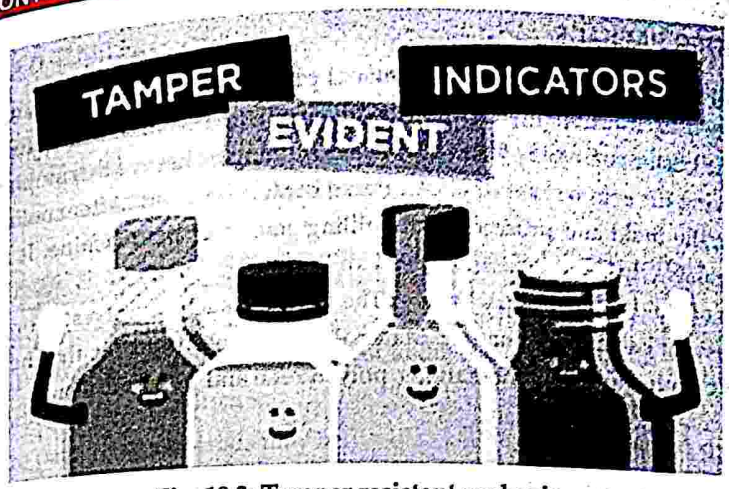

Fig. 10.3: Tamper resistant packaging

10.3.1. FILM WRAPPER

Film wrapping has been used extensively over the years for products requiring package integrity or environmental protection. It is categorizes into following types:

- End folded wrapper
- Fin seal wrapper
- Shrink wrapper

The end folded wrapper is formed by passing the product into a sheet of over wrapping film, which forms the film around the product and folds the edges in a gift wrap fashion. The folded areas are sealed by pressing against a heated bar. The materials commonly used for this purpose are cellophane and polypropylene.

Fin seal wrapper: The seals are formed by crimping the film together and sealing together the two inside surfaces of the film, producing a fin seal. Fin sealing is superior than end folded wrapper. With good seal integrity the over wrap can removed or opened by tearing the wrapper

Shrink wrapper: The shrink wrap concept involves the packaging of the product in a thermoplastic film that has been stretched and oriented during its manufacture. An L shaped sealer seals the over wrap. The major advantage of this type of wrapper is the flexibility and low cost of packaging equipment.

10.3.2. BLISTER PACKAGE

Blister package provides excellent environmental protection, and efficacious appearance. It also provides user functionality in terms of convenience , child resistance and tamper resistance The blister package is formed by heat softening a sheet of thermoplastic resin and vacuum drawing the soften sheet of plastic into a contoured mold .After cooling the sheet is released from the mold and proceeds to the filling station of the machine. It is then lidded with heat sealable backing material. Peel able backing material is used to meet the requirements of child resistance packaging. The material such as polyester or paper is used as a component of backing lamination. Materials commonly used for the thermo formable blister are PVC, polyethylene combinations, polystyrene and polypropylene.

10.3.3. STRIP PACKAGE

A strip package is a form of unit dose packaging that is commonly used for the packaging of tablets and capsule. A strip package is formed by feeding two webs of a heat sealable flexible through heated crimping roller. The product is dropped into the pocket formed prior to forming the final set of seals. A continuous strip of packets is formed in general. The strip of packets is cut into desired number of packets. Different packaging materials used are: paper/polyethylene/foil/PVC.

10.3.4. BOTTLE SEALS

A bottle may be made tamper resistant by bonding and inner seal to the rim of the bottle in such a way that the product can only be attained by destroying the seal. Typically glassine liners are two ply laminations use in two sheet of glassine paper bounded together with wax or adhesive. For pressure sensitive inner seals pressure sensitive adhesive is coated on the surface of the inner seal as an encapsulated adhesive.

10.3.5. TAPE SEALS

It involves the application of glued or pressure sensitive tape or label around or over the closure of the package which is to be destroyed to obtain the product. The paper used must often is a high density light weight paper with poor tear strength.

10.3.6. BREAKABLE CAPS

Breakable closures come in many different designs. The roll-on cap design of aluminium shell is used for carbonated beverages. The bottom portion of the cap is rolled around the bottle neck finish. The lower portion of the cap blank is usually perforated so that it breaks away when the cap is unscrewed. The bottom portion of the closure has a tear away strip.

10.3.7. SEALED TUBES

Collapsible tubes used for packaging are constructed of metal, plastic or lamination of foil, paper and plastic. Metal tubes are still used for products that required high degree of barrier protection. Most of these are made of aluminum. Extruded plastic tubes are widely used for products that are compactable and limited protection of plastic.

10.4. QUALITY CONTROL TESTING & STANDARDS

The testing procedures may be divided into two groups according to whether the test is applied to the packaging material in isolation or to the entire package.

I. Testing of material or components:

Tests applied to packaging materials may be:

- Chemical - The pH value of materials chloride and sulphate in paper or board, alkalinity of glass, compatibility test with chemicals or medicaments are typical of the chemical tests.
- Mechanical-Standard tests are available for the effect of creasing, folding and so on.
- Environmental-Materials may be tested by standard methods for absorption of water, permeability to water vapour, gases, oils, odours etc. and for characteristics such as light transmission.

II. Testing of final packages:

- Mechanical – Mechanical tests are applied mainly to outer packaging for protection from transportation hazards. They consist of the use of a standardized test procedure to compare the effect of different protective materials to prevent damage to the contents.
- Environmental- Packages are subjected to conditions that reproduce the environment and some evaluation is made at suitable intervals. Such procedures may be applied to testing closures for water vapour transmission.

  Quality control of a packaging component starts at design stage. All the aspects of a pack development may give rise to quality problems. It must be identified & minimized by performing quality control tests.

10.4.1 QUALITY CONTROL OF PRIMARY COMPONENTS

10.4.1.1. COMPONENT SPECIFICATIONS

Every detail concerning a component specification must be communicated to and agreed upon with the manufacture, including packaging, transportation, and labeling requirements. If any of the details are missing confusion or mistakes may occur.

The main specifications requirements are the component drawing, artwork (printed components only) and the quality control testing and standards.

There are two classes of components:-

1. Primary – in contact with the product, e.g., ampules, vials, plastic bottles, polymer coated foils

2. Secondary – not in contact with the product, e.g., cartons, labels, leaflets

The critical parameters are for setting standard are:-

- Appearance
- Dimensions
- Compatibility and costumer usability
- Chemical testing

1. Appearance – This can split into three categories:

- **Critical** – unacceptable at any level, e.g., rogue printed items in a delivery, incorrect printing of data such as the product name or concentration, insects in the bottle etc.
- **Major-** acceptable at a low level, the standard is decided by the pharmaceutical company. Examples of major appearance defects are missing print, making read text difficult, flashing on molded components and other defects.
- **Minor-** acceptable at a higher level than the major appearance defects. These will detract from perfection and include marked components, slight colour variations, slight smudging etc.

2. Dimensions – The dimensions of a component can be separated into two types:

- **Critical** – requiring close control to ensure that the component functions correctly and can be used satisfactorily by packaging equipment.
- **Noncritical** – necessary to maintain the component shape but not requiring close control for satisfactory function of the component.

The critical dimensions for each of these components are as follows:-

- Vial – flange depth , flange diameter , bore diameter , vial height , body diameter , wall thickness, base thickness , concentricity and verticality
- Rubber plug - flange depth, flange diameter and plug diameter
- Aluminum overseal- internal skirt depth, external diameter, and aluminum thickness.

3. Compatibility and costumer usability- This involves checking that each component forming a pack fits together and functions correctly. Example – eye dropper pack

- The nozzle must have a good interference fit into the bottle and allow one drop at a time deliver through the hole in the nozzle when inverted, but must not leak from the fitted position.
- The cap must screw into position, and leakage must not occur when the bottle is squeezed into the inverted position, i.e., a sterile seal is maintained.

Table 10.1: Critical dimension and defects of packaging material

CRITICAL DIMENSION	DEFECTS	EFFECTS
Flange depth	Variation in flange depth	Improper tucking of Aluminium skirt.
Flange diameters	Too large a diameter	Aluminium overseal could not fit over the flange
	Too small diameter	Overseal skirt would not tuck under the viral flange
Bore diameter	Too large a bore	Rubber plug would have loose fit.
	Too small a bore	The plug could not be inserted.
Viral height	The height of vial varies	Sealing mechanism will not operate satisfactory
	A high vial	May even by crushed by the filling machine sealing mechanism.
Body diameters	Vial with too large diameter Small diameter	Cannot travel down the conveyor track May not align to sealing mechanism correctly
Wall thickness & base thickness	Too thin wall	May crack or break during washing, sterilizing or frilling.
	Too thick wall	Vials may be too hot when they exit tunnel resulting in rapid cooling with the possibility of cracking.
Concentricity	Amount of flange movement when vial is rotated about center	Results in misalignment of flange with sealing mechanism. Preventing plug insertion & oversealing.
Verticality	Max angle of lean measured from base when vial is placed in horizontal surface & rotated about its center.	Misalignment of flange on sealing mechanism. Prevents plug insertion & oversealing.

4. Chemical testing

Chemical testing is depends on individual material for packaging.

10.4.1.2 CHEMICAL TESTING

Chemical testing glass container

Important chemical tests for glass container are

- Hydrolytic resistance test.
- Water attack test.
- Powdered glass test.
- Light transmission test.
- Arsenic test

1). Hydrolytic resistance test:- Determine average overflow volume. Auto clave at 121 ° C for 60 minutes. Combine the liquid from container being examined. To 50ml liquid add 0.15 ml methyl red solution and titrate to 0.01 M HCL. Repeat the same with freshly prepared distilled water. The difference between the two represents 0.01M HCL required by test solutions.

Table 10.2: Hydrolytic resistance test

Capacity of container corresponding to 90% of average overflow volume (ml)	Volume of 0.01M Type I/II	HCl/100ml Type III
NMT 1	2.0	20.0
More than 1 but NMT 2	1.8	17.6
More than 2 but NMT 5	1.3	13.2
More than 5 but NMT 10	1.0	10.2
More than 10 but NMT 20	0.8	8.1
More than 20 but NMT 50	0.6	6.1
More than 50 but NMT 100	0.5	4.8
More than 100 but NMT 200	0.4	3.8
More than 200 but NMT 500	0.3	2.9
More than 500	0.2	2.2

2). Powdered Glass Test

From the glass containers, alkaline constituents (oxides of sodium, potassium, calcium, aluminum, etc.) are leached into purified water under conditions of elevated temperatures. When the glass is powdered the leaching of alkali can be enhanced in the powdered is critical. The principle involved in the powdered glass test in estimate the amount of alkali leached form the glass powder. The amount of acid that is necessary to neutralize the released alkali (a specified limit) is specified in the pharmacopoeia. The basic analysis is acid-base titration using methyl red indicator.

3). Water Attack Test

This test is used only with containers that have been exposed to sulphur dioxide fumes under controlled humidity conditions. Such a treatment neutralizes the surface alkali. Now the glass becomes chemically more resistant. The principle involved in the water attack test is to determine whether the alkali leached form the surface of a container is within the specified limits or not. Since the inner surface is under test entire container (ampoule) has to be used. The amount of acid that is necessary to neutralize the released alkali from the surface is estimated, the leaching of alkali is accelerated using elevated temperature for a specified time. Methyl red indicator is used to determine the end point. The basic is acid-base titration.

4). Light transmission test:- Measure the transmission in reference to air at spectral region of 290nm to 450nm. The observed light transmission for colored glass containers for preparation not for parental use does not exceed 10% at any wavelength. Observed light transmission for colored glass containers for parental preparation does not exceed the limit in the table.

Result is not greater than value stated in table.

Table 10.3: Value for light transmission test

No. of containers used	Max percentage of LT at any wavelength between 290nm and 460nm	
	Flame sealed containers	Containers in closures
Upto 1	50	25
Above 1 & upto 2	45	20
Above 2 & upto 5	40	15
Above 5 & upto 10	35	13
Above 10 & upto 20	30	12
Above 20	15	10

5). Test for arsenic:- The absorbance of test solution does not exceed the absorbance obtained by repeating the same with 0.1ml arsenic standard solution (10ppm) in place of test solution (0.1ppm).

6). Other important test for glass container

Thermal shock test:- The samples are placed in an upright position in a tray which is immersed into hot water for given time, then transferred to cold water bath. Samples are examined before & after the tests for outside surface cracks or breakage.

Internal bursting pressure test:- The test bottle is filled with water & then placed inside the test chamber. A sealing head is applied & the internal pressure automatically raised by series of increments. Each increment is held for a set time. The bottle can either be checked to a pre-selected pressure level or the test continued until the container finally bursts.

Annealing test:- Annealing of glass is a process of slowly cooling hot glass objects after they have been formed, to relieve residual internal stresses introduced during manufacture. The sample is examined by polarized light in either a polariscope or strain viewer. The strain pattern is compared against standard discs or limit samples.

Vertical load test:- The bottle is placed between a fixed platform & a hydraulic ramp platform which is gradually raised so that a vertical load is applied. The load is registered on pressure gauge.

Autoclaving (121 ° C for 60 min):- Ability of a filled or empty container to withstand autoclaving may be checked.

6). Ampoules: – Testing of Ampoules sealing:

- Appearance
- Head space oxygen
- Sealed Ampoules length
- Quality of seal

Chemical testing for plastic containers

Plastic containers can be mainly categorized as:-

- Thermosetting plastics (cannot be remelted)
- Thermoplastics (can be reprocessed)

1). Infusion and Injections

- Physicochemical on aqueous extracts
- Nonvolatile residue, heavy metals, buffering capacity, reducing substances
- Biological invivo
- Acute systemic toxicity in mice
- Intra cutaneous test (rabbits), cardiovascular (cat) toxicity infusions
- Biological invitro
- Hemolytic effect of aqueous extracts

2). Aqueous ophthalmic preparation

- Physicochemical on aqueous extracts
- Non volatile residue, buffering capacity, reducing substances
- Biological test on aqueous extracts
- Eye irritation in rabbits on repeated instillation (Draize test)

3). Physicochemical test on aqueous extract

- Appearance
- Light absorption
- pH
- Non-volatile matter
- Residue on ignition
- Heavy metals
- Buffering Capacity
- Oxidizable substances

4). Biological tests:

4.1 Systemic injection test:- Test animal:- Albino Mice

Inject each of 5 mice in test group with sample or blank observe the animals immediately, again after 4hr & then at 24, 48, 72hrs. If none of animals shows significant greater biological reactivity than the blank the sample meets the requirements. If abnormal behavior such as Convulsion or Prostration occurs or if body weight loss is greater than 2g, the sample does not meet the requirements.

4.2 Intra cutaneous test:- Test animal:- Rabbit

Examine the sites of for any tissue reaction like erythema, edema, neurosis at 24, 48, 72 hours after injection.

- **Limit:-** difference between the scores of sample and blank should be lesser than 1.0.

4.3 Eye irritation test on rabbits:- Test animal:- albino rabbits

- **Limit:-** Sample extract shows no significant irritant response during the observation period with blank extract.

10.4.1.3. QUALITY CONTROL OF CLOSURES

The closure is normally the most vulnerable and critical component of a container as far as stability and compatibility with the product is concerned. Suitable closing of the container is necessary because

- It prevents loss of material by spilling or volatilization.
- It prevents the deterioration of product from the effects of environment such as moisture, oxygen, or carbon dioxide.
- It avoids contamination of the product from dirt, microorganism or insects.

Types of closures: (figure 10.4)

- Thread screw cap
- Lug cap
- Crown cap
- Pilfer proof closures

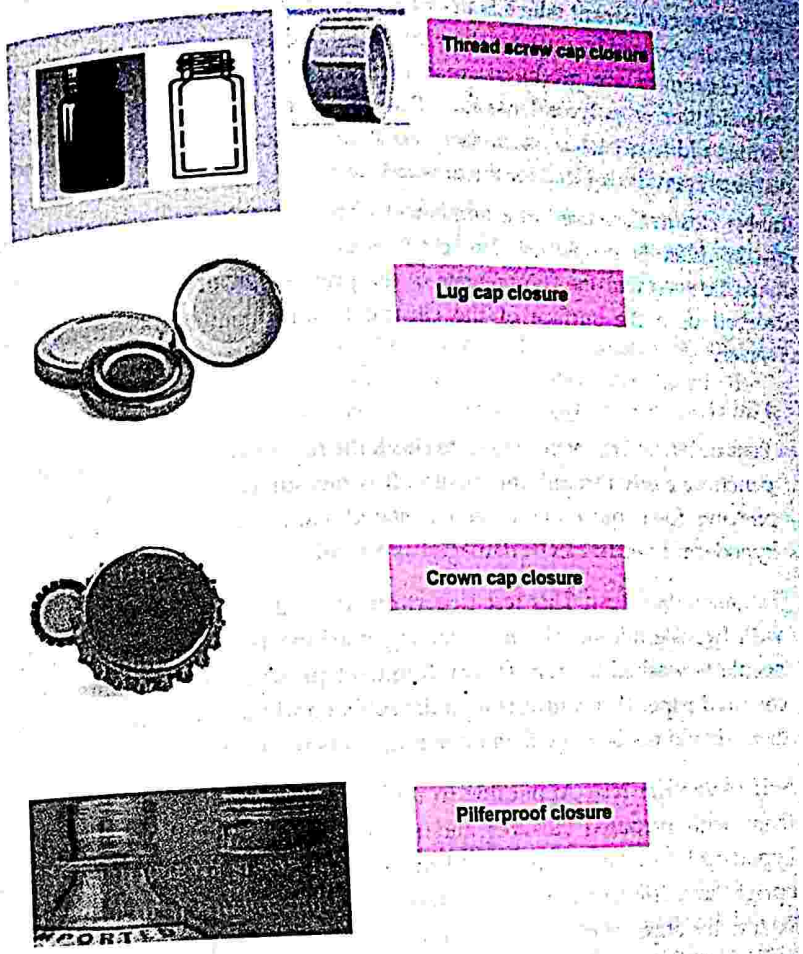

Figure 10.4 Different types of closures

Materials used for making closures:

- Cork
- Glass
- Plastic
- Metal
- rubber

A closure for a container for an aqueous parenteral preparation or for a sterile powder is a packaging component which is in direct contact with the drug. A rubber closure is made of materials obtained by vulcanization (cross-linking) of elastomers with appropriate additives. The elastomers are produced from natural or synthetic substances by polymerization, polyaddition or polycondensation. The nature of the principal components and of the various additives such as vulcanisers, accelerators, stabilizing agents, pigments, etc. depends on the properties required for the finished closure.

Rubber closures are used in a number of formulations and consequently different closures possess different properties. The closures chosen for use with a particular preparation should be such that the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure to an extent sufficient to affect the product adversely.

Test for closures:-

1. **Penetrability:** This is measured to check the force required to make a hypodermic needle penetrate easily through the closure. It is measured by using the piercing machine. The piercing force must not exceed a stated value. If it exceeds that stated value, the hypodermic needle can be damaged as a result of undesirable hardness of the closures.

2. **Fragmentation test:** This test is performed on 20 closures. Each closure is penetrated with hypodermic needle in a piercing machine five times within a limited area and needle is washed to transfer any fragment present. The contents are filtered through coloured paper that contrasts with the rubber and the fragments counted. On an average there should not be more than three fragments per unit.

3. **Self sealability test:** Applicable to multidose containers fill 10 vials with water close them with prepared closures and secure with a cap. For each closure use a new hypodermic needle and pierce 10 times each time at different site immerse the vials upright in methylene blue (0.1%) solution and reduce external pressure for 10 minutes. 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. **Extractive test:** In this test, the closure is boiled with water for four hours under reflux and the water evaporated to dryness. The residue must not exceed the specified amount.

5. **Compatibility test:** This test is performed to check the compatibility of the rubber closures with various types of the substances, since it is necessary to ensure that there is no interaction between the contents of the bottle and the closure.

6. **Light absorption:** Filter solution through membrane filter. Measure the light absorbance of filtrate in the range 220 to 360 nm using a blank solution (prepared in the same manner as solution A). The absorbance is not more than2.

10.4.1.4. QC TEST FOR COLLAPSIBLE TUBES

1. Leakage Test- Water was filled in the tube and tightly closed. External surface was wiped off and tube is kept inverted on filter paper at base. Allow to stand for 1hr.Filterpaper shows absorption at any time during test period
2. Lacquer Curing Test
   A) Power of adhesion: o Tube was spitted along the length and flattened. Cotton wool soaked in acetone was rubbed over lacquer surface for 20min.Lacquer should not lift from surface and cotton wool shall remain colorless.
   B) Flexibility test: o The tube was folded in such a manner that internal lacquer surface is outside. The lacquer coating should not be peeled off when the folded position is rubbed with finger.
3. Lacquer Compatibility test: 1 0 tubes are taken for the test. Product was filled and crimped subjected to 45:C for 72hr.Tubes were allowed to cool and cut lengthwise Lacquer compatibility test: Lifting or peeling of lacquer is checked. Product Compatibility-Content should not show any discolorations or change in colour or gas formation.

10.4.1.5. QUALITY CONTROL FOR METALLIC TINS

Protocols of test:

1) **Dimensions:-**
2) **Limit:-** Specimen metallic tins with tolerance 170mm ± 10mm.
3) **Diameter:-**
4) **Inner diameter:-** Limit:- It should not be less than 98mm.
5) **Outer diameter:-** Limit:- NMT 105mm.

10.4.1.6. QUALITY CONTROL TEST FOR STRIP & BLISTER PACKAGING

The strips & blisters were placed inside the desiccators & vacuum was applied. After sometime vacuum was released & strips, blisters were taken out. The water present over the outer surface of the packages was wiped off with tissue paper. The contents of strips & blister packages were removed & the presence of moisture was checked. If there is no leakage, the contents will not be wetted. This indicates the perfect sealing of packages.

10.4.2 QUALITY CONTROL OF SECONDARY COMPONENTS

10.4.2.1. Testing of Paper & Board

The test pieces for paper & board are conditioned for the tests to be carried out in standard conditions. Those conditions are Temperature – 23 ° C ± 1 ° C, Relative humidity – 50% ± 2% Figure 3 describes different QC tests for paper and boards.

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 'printability' 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.

Table 10.4: QC tests for paper and boards

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 $\mu m\ pa^{-1}s^{-1}$. 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 paper
Burst strength	The maximum uniformity 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 7 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 300-1000μm
Cobb test (g/m^2)	Test for water absorbency

10.4.2.2. Test for cartons

- *Compression:-* This method is used to assess the strength of erected package.
- *Carton opening force:-* The method is used to hold the flat carton as delivered, by its creases between thumb & first finger press.
- *Coefficient of friction:-* Both static & kinetic coefficients of friction are determined by sliding the specimen over itself under specific test conditions.
- *Crease stiffness:-* This involves testing a carton board piece & folding it through 90°. It will then try to recover its former position when bending force is removed.
- *Joint shear strength:-* This is a method of testing the glued lap seam on the side of a carton for strength of the adhesive using a tensile testing machine.

CHAPTER 11

GOOD LABORATORY PRACTICES

The formal, regulatory, concept of "Good Laboratory Practice" (GLP) originated in the USA in the 1970s due to the concerns about the validity of non-clinical5 safety data submitted to the Food and Drug Administration (FDA) in the context of New Drug Applications (NDA). The inspection of studies and test facilities revealed instances of inadequate planning and incompetent execution of studies, insufficient documentation of methods and results, and even cases of fraud. For example, replacing animals which had died during a study with new ones (which had not been treated appropriately with the test compound) without documenting this fact; taking haematology data for control animals from control groups not connected with the study; deleting gross necropsy observations because the histopathologist received no specimens of these lesions; and retrospectively changing raw data in order to "fit the result tables" in the final report. These deficiencies were made public in the Kennedy-Hearings of the US Congress, and the political outcome of these hearings led to the FDA's publication of Proposed Regulations on GLP in 1976, with the establishment of the Final Rule in June 1979 (**21 CFR 58**). The GLP regulations provided the basis for assurance that reports on studies submitted to FDA would reflect faithfully and completely the experimental work carried out. In the chemical and pesticide field, the US Environmental Protection Agency (EPA) had also encountered similar problems with study quality. Accordingly, it issued its own draft GLP regulations in 1979 and 1980, publishing the Final Rules in two separate parts (40 CFR 160 and 40 CFR 792, reflecting their different legal bases) in 1983.

11.1 DEFINITION

Good Laboratory Practice is defined in the OECD6 principles as "a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported."

5 Non-clinical study means an experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities.

6 The Organisation for Economic Co-operation and Development(OECD) is an intergovernmental economic organisation with 36 member countries, founded in 1961 to stimulate economic progress and world trade

11.2 PRINCIPLES OF GOOD LABORATORY PRACTICE

- It is to promote the development of quality test data and provide a tool to ensure a sound approach to the management of laboratory studies, including conduct, reporting and archiving.
- The principles may be considered as a set of standards for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data.
- The principles require institutions to assign roles and responsibilities to staff in order to ensure good operational management of each study and to focus on those aspects of study execution (planning, monitoring, recording, reporting, archiving) that are of special importance for the reconstruction of the whole study. Since all these aspects are of equal importance for compliance with GLP Principles.
- As far as pharmaceutical development is concerned, the GLP Principles, in their regulatory sense, apply only to studies which are non-clinical, i.e. mostly studies on animals or in vitro, including the analytical aspects of such studies; are designed to obtain data on the properties and/or the safety of items with respect to human health and/or the environment; are intended to be submitted to a national registration authority with the purpose of registering or licensing the tested substance or any product derived from it.

Depending on national legal situations, the GLP requirements for non-clinical laboratory studies conducted to evaluate drug safety cover the following classes of studies:

- Single dose toxicity
- Repeated dose toxicity (sub-acute and chronic)
- Reproductive toxicity (fertility, embryo-fetal toxicity, and teratogenicity, peri-/post-natal toxicity)
- Mutagenic potential
- Carcinogenic potential
- Toxicokinetics (pharmacokinetic studies which provide systemic exposure data for the above studies)
- Pharmacodynamic studies designed to test the potential for adverse effects (Safety pharmacology)
- Local tolerance studies, including phototoxicity, irritation and sensitization studies,

GLP Principles are independent of the site where studies are performed. They apply to studies planned and conducted in a manufacturer's laboratory, at a contract or subcontract facility, or in a university or public sector laboratory. The adherence to GLP removes many sources of error and uncertainty, adding to the overall credibility of the study. Through the

application of technically valid and approved Standard Operating Procedures many sources of systematic error and artifacts are avoided. The requirement to formulate a study plan[7] with a defined scientific purpose for the study will prevent false start and diminish the incidence of incomplete or inconclusive studies. GLP principles thus indirectly optimize the scientific yield of studies.

11.3 ORGANIZATION AND PERSONNEL

GLP regulations require clear definitions of the structure of the research organization and the responsibilities of the research personnel. This means that the organizational chart should reflect the reality of the institution and should be kept up to date. Organizational charts and job descriptions give an immediate idea of the way in which the laboratory functions and the relationships between the different departments and posts. GLP also stresses that the number of personnel available must be sufficient to perform the tasks required in a timely and GLP-compliant way. The responsibilities of all personnel should be defined and recorded in job descriptions and their qualifications and competence defined in education and training records. To maintain adequate levels of competence, GLP attaches considerable importance to the qualifications of staff, and to both internal and external training given to personnel. A point of major importance in GLP is the position of the Study Director who is the pivotal point of control for the whole study. This person is appointed by the test facility management and will assume full responsibility for the GLP compliance of all activities within the study. He/she is responsible for the adequacy of the study protocol and for the GLP compliant conduct of the study. He/she will assert this at the end of the study in his/her dated and signed GLP Compliance Statement which is included in the study report. The Study Director must therefore be aware of all events that may influence the quality and integrity of the study, evaluate their impact and institute corrective actions as necessary. Even when certain phases or parts of the study are delegated to other test sites (as in the case of multisite studies), the Study Director retains overall responsibility for the entire study, including the parts delegated, and for the global interpretation of the study data.

11.4 PERSONNEL

The managerial and organizational requirements of GLP account for about 15% of GLP regulations but, unfortunately, are still seen by regulators and QA as one of the principal

7 Study plan means a document which defines the objectives and experimental design for the conduct of the study, and includes any amendments.

sources of non-compliance. Without full management commitment and formal involvement of all personnel, GLP systems lack credibility and will not function as they should. Personnel are, therefore, a critical element when implementing GLP and maintaining compliance in a laboratory. It is clear that the manager of a test facility has overall responsibility for the implementation of both good science and good organization, including compliance with GLP.

Good Science means the careful definition of experimental design and parameters, the performance of experiments based on valid scientific procedures, control and documentation of experimental and environmental variables, careful, complete evaluation and reporting of results, assuring that results become part of accepted scientific knowledge.

Good Organisation means the provision of adequate physical facilities and qualified staff, planning of studies and allocation of resources, the definition of staff responsibilities and training of staff, good record keeping and organized archives, implementation of a process for the verification of results, compliance with GLP.

11.5 FACILITIES: BUILDINGS AND EQUIPMENT

Buildings

Test facilities should be of suitable size, construction and location to meet the requirements of the study and to minimize disturbances that could interfere with the study. They should be designed to provide an adequate degree of separation of the diverse elements of the study. The purpose of these requirements is to ensure that the study is not compromised because of inadequate facilities. It is important to remember that fulfilling the requirements of the study does not necessarily mean providing "state of the art" constructions, but carefully considering whether the objectives of the study can be achieved using the facilities available.

Separation ensures that disturbances are minimised and that different activities do not interfere with one another or adversely affect the study. This can be achieved by: Physical Separation; e.g. walls, doors, filters or separate cabinets or isolators. In new buildings, or those recently renovated, separation will be part of the design. Organisational Separation; e.g. carrying out different activities in the same area but at different times, allowing for cleaning and preparation between operations, maintaining separation of staff, or by establishing defined work areas within a laboratory. As an illustration of the principles involved we shall consider: Pharmacy and Dose Mixing Areas: concerned with test material control and mixing with vehicles (although the same considerations would apply to other areas such as analytical or histopathology laboratories).

Animal facilities.

The Pharmacy and Dose Mixing area is a laboratory zone dealing with test item8 work flow: receipt, storage, dispensing, weighing, mixing, dispatch to the animal house and waste disposal.

The area should be big enough to accommodate the number of staff working in it, and allow them to carry on their work without risk of getting in one another's way or of mixing up different materials. Each operator should have a workstation sufficiently large to enable him/her to carry out the operation efficiently. To reduce the chance of mix-up of materials or of cross-contamination, there should also be a degree of physical separation between the workstations The pharmacy is a sensitive area, and access to such facilities should be restricted so as to limit the possible contamination of one study or compound by another.

Construction

The zone must be built of materials that allow easy cleaning and that are not likely to allow test materials to accumulate and contaminate one another. There should be a ventilation system that provides air-flow away from the operator through filters which protect both personnel and prevent cross-contamination. Most modern dose mix areas are now designed in a "box" fashion, each box having an independent air system.

Arrangement

There should be separate areas for:

- Storage of test items under different conditions.
- Storage of control items.
- Handling of volatile materials.
- Weighing.
- Mixing of different dose formulations, e.g. in the diet or as solutions or suspensions.
- Storage of prepared dose formulations.
- Cleaning equipment.
- Offices and refreshment rooms.
- Changing rooms.

Animal facility

The facility should be designed and operated in order to minimize the effects of environmental variables on the animal. Consideration should also be given to measures

8 Test item means an article that is the subject of a study.

which prevent the animal from coming into contact with the disease, or with a test item other than the one under investigation. Requirements will differ depending on the nature and duration of the studies being performed. The risks of contamination c an be reduced by a "barrier" system, where all supplies, staff, and services cross the barrier in a controlled way, as well as by providing "clean" and "dirty" corridors for the movement of new and used supplies. A well-designed animal house would maintain separation by providing areas for:

- Different species.
- Different studies.
- Quarantine.
- Changing rooms.
- Receipt of materials.
- Storage, bedding and diet,- test doses,- cages.
- Cleaning equipment.
- Necropsy.
- Laboratory procedures.
- Utilities.
- Waste disposal.

The building and its rooms should provide enough space for animals and studies to be separated and to allow the operators to work efficiently. The environment and control system should maintain the temperature, humidity, and airflow at the defined levels depending on the species concerned.

The surfaces of walls, doors, floors, and ceilings should be constructed to allow for easy and complete cleaning, and there should be no gaps or ledges where dirt and dust can build up, or where water will collect, for instance on uneven floors. Whatever the capabilities or needs of the laboratory, sensible working procedures will reduce potential danger to the study from outside influences and will maintain a degree of separation between activities.

11.6 EQUIPMENT

For the proper conduct of the study, appropriate equipment of adequate capacity must be available. All equipment should be suitable for its intended use, and it should be properly calibrated and maintained to ensure reliable and accurate performance. Records of repairs and routine maintenance and of any non-routine work should be retained. Remember that

the purpose of these GLP requirements is to ensure the reliability of data generated and to ensure that data are not invalidated or lost as a result of inaccurate, inadequate or faulty equipment.

Suitability: can only be assessed by considering the tasks that the equipment is expected to perform: there is no need to have a balance capable of weighing to decimals of a milligram to obtain the weekly weight of a rat, but a balance of this precision may well be required in the analytical laboratory. Deciding on the suitability of equipment is a scientific responsibility and is usually defined in SOPs.

Calibration: All equipment, whether it is used to generate data (e.g. analytical equipment or balances), or to maintain standard conditions (e.g. refrigerators or air conditioning equipment), should work to fixed specifications. Proof that specifications are being met will generally be furnished by periodic checking. In the case of measuring equipment, this is likely to involve the use of standards. For example, a balance will be calibrated by the use of known standard weights. In the case of analytical equipment, a sample of known concentration will be used to ensure that the equipment is functioning as expected, as well as providing a basis for the calculation of the final result. Other equipment, such as air conditioning systems for animal facilities or constant temperature storage rooms, will be checked periodically by the use of calibrated instruments (probes, thermometers...). Verifications should be performed at a frequency that allows the action to be taken in time to prevent any adverse effect on the study should it be discovered that the equipment is not operating within specifications.

Maintenance: The requirement that equipment is properly maintained is based on the assertion that this ensures the constant performance of equipment to specifications and that it reduces the likelihood of an unexpected breakdown and consequent loss of data. Maintenance may be carried out in two quite distinct ways:

Preventive maintenance; when parts are changed regularly based upon the expected life of the part concerned. Planned maintenance of this type may be a useful precaution for large items of equipment or items that do not possess suitable backup or alternatives. Regular preventive maintenance, therefore, reduces the risk of breakdown.

Curative maintenance; when repairs are made in the case of a fault being detected. This approach particularly applies to equipment such as modern computer-driven analyzers or electronic balances that do not easily lend themselves to preventive maintenance. It is good practice to adopt contingency plans in case of failure; these may include having equipment duplicated or assuring that there is immediate access to a maintenance technician or an engineer. Back up for vital equipment should be available whenever possible as well as back up in the event of service failures, such as power cuts. A laboratory should have the ability

to continue with essential services to prevent animals or data being lost, and studies irretrievably affected. For example, a laboratory carrying out animal studies may, as a minimum, need a stand-by generator capable of maintaining the animal room environment, even if it does not allow the laboratory to function completely as normal; for example, test item analysis could wait until power is restored. Early warning that equipment is malfunctioning is important; hence the checking interval should be assigned to assure this. Alarms are very valuable, particularly if a problem occurs at a time when staff is not present in the laboratory.

11.7 DOCUMENTATION

Routine maintenance should be documented in such a way that users of equipment can be assured that it is reliable and not outside its service interval. A label attached to equipment or the provision of a clear service plan may ensure this. Records of equipment calibration, checking and maintenance demonstrates that the respective SOPs have been followed and that equipment used was adequate for the task and operating within its specifications. The records should also demonstrate that the required action was taken as a result of the checks that had been made, for example when parameters exceeded acceptable limits staff were aware of this and took appropriate remedial action.

11.8 TESTING FACILITIES OPERATION

Standard operating procedures shall be established for: Animal room preparation, Animal care, Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles, Test system9 observations, Laboratory tests, Handling of animals found moribund or dead during study, Necropsy of animals or post mortem examination of animals, Collection and identification of specimens, Histopathology, Data handling, storage, and retrieval, Maintenance and calibration of equipment, Transfer, proper placement, and identification of animals.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

The identity, activity, stability, and bioavailability of the test item are central to the validity of the study. To validate the study you must be able to show that the test system (often an animal) has received the correct amount of test item (often a chemical formulation). This is assured by proper control of the test item at all stages of its use, and by the accompanying

9 Test system means any biological, chemical or physical system or a combination thereof used in a study.

records and documents. The test item is supplied by the manufacturer/study sponsor. The supplier may be a department within the same test facility or a separate organization altogether. In either case and irrespective of the size of the test facility and the number of studies being conducted, a formal procedure must exist for test item receipt, storage and control. Staff must be designated to be responsible for receipt and handling of the test item. In a large laboratory the designated staff comprise a central group who record the receipt, identity, issue, retention and final disposal of the test item, but in small facilities the designated person may be an authorised technician or the Study Director. The assignment of responsibility should be documented in an SOP or other document.

The responsible person should be informed in advance about the arrival of test item to ensure correct handling and storage conditions. In the case of a study conducted by a Contract Research Organisation (CRO), the sponsor should provide test item information to enable safe handling and storage as well as other details which may help in the preparation of the dose formulation. A standard form for the sponsor to record this information is helpful. The sponsor will either supply, or indicate that he has obtained or will obtain, the necessary data on chemical characterisation and stability of the test material. The manufacturer, meanwhile, will archive and store batch records. The test item container should be robust enough to withstand transfer between facilities. Packaging of the test item is very important. The sponsor should keep in mind the method of transport and the duration of the journey. Each container should be clearly labelled with sufficient information for identification, enabling the test facility to confirm its contents. Ideally, labels should contain the following information:

- Test item name.
- Batch number.
- Expiry date.
- Storage conditions.
- Container number.
- Tare weight.
- Initial gross weight.

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

- There is proper storage.
- Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

- Proper identification is maintained throughout the distribution process.
- The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

Study Director should be informed of the arrival of the test item.Test facility's documentation about the arrival of test item normally includes the following information:Test item name;Batch number(s); Description of the test item on arrival at the laboratory; which should be compared to the description supplied by the sponsor. This ensures that any concern about the identity of the material can be sorted out at an early stage.

- Container number, to allow identification of the container in use.
- Container type.
- Net weight of the contents and container tare weight.
- Storage conditions and location of the container.
- Initials of the person receiving the container.
- Date of arrival of the container at the laboratory.
- Condition of goods on arrival.

11.9 PROTOCOL FOR CONDUCT OF A NON-CLINICAL LABORATORY STUDY

Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study.The protocol shall contain:

- A descriptive title and statement of the purpose of the study.
- Identification of the test and control articles by name, chemical abstract number, or code number.
- The name of the sponsor and address of the testing facility
- The number, body weight range, sex, the source of supply, species, strain, sub strain, and age of the test system.
- The procedure for the identification of the system.
- A description of the experimental design, including the methods for the control bias.
- Each dosage level to be administered and the method and frequency of administration.
- The records to be maintained.

The non-clinical laboratory study shall be conducted in accordance with the protocol. The systems shall be monitored in conformity with the protocol. Specimens shall be identified by the test system, study, nature, and date of collection. Records of gross findings for a specimen from post-mortem observations should be available to a pathologist when examining that specimen histopathologically. Any change in these entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change

11.10 RECORDS AND REPORT

A final report shall be prepared for each non-clinical laboratory study and shall include

- Name and address of the facility performing the study and the dates
- Statistical methods employed for analyzing data.
- The test and control articles identified by name, code number, strength, purity, and composition or other characteristics.
- Stability of the test and control articles under the conditions of administration.
- A description of the methods used.
- A description of the test system used.
- A description of the dosage, dosage regimen, route of administration, and duration.
- The name of the study director, other scientists, supervisory personnel involved in the study.
- A description of the transformations, calculations, or operations performed on the data, a summary, and analysis of the data, and a statement of the conclusions drawn from the analysis.
- The locations where all specimens, raw data, and the final report are to be stored.
- The statement prepared and signed by the quality assurance Unit.
- The final report shall be signed and dated by the study director.
- Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

11.11 STORAGE AND RETRIEVAL OF RECORDS AND DATA

All raw data, documentation, protocols, final reports, and generated as a result of a non-clinical laboratory study shall be retained. There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. An individual shall be identified as being responsible for the archives. Only authorized personnel shall enter the archives. Material retained or referred to in the archives shall be indexed to permit expedient retrieval.

11.12 DISQUALIFICATION OF A FACILITY

Before a workplace can experience the consequences of noncompliance, an explanation of disqualification is needed. The FDA states the purpose of disqualification as the exclusion of a testing facility from completing laboratory studies or starting any new studies due to not following the standards of compliance set by the Good Laboratory Practice manual.

Possible Violations can be (1) Failure to prepare, retain, or submit written records required by la. (2) Falsifying information related to testing~ protocols, ingredients, observations, data equipment, etc. (3) Falsifying information for a permit, registration or any required records.

Consequences of Noncompliance: The FDA states the following consequences of noncompliance: The commissioner will send a written proposal of disqualification to the testing facility. A regulatory hearing on the disqualification will be scheduled. If the commissioner finds that after the hearing, the facility has complied, then a written statement with an explanation of the termination of disqualification will be sent to the facility. Thus, if it can be shown that such disqualifications did not affect the integrity and outcome of the study itself, or did not occur at all, then the study may be reinstated at the will of the commissioner

Upon Disqualification: If the commissioner finds that the facility showed noncompliance, any of the grounds after the hearing, then a final order of noncompliance will be sent to the facility with explanations. If a testing facility has been disqualified, any studies were done before of after the disqualification will need to be determined as essential to a decision (acceptable or not). If the study is determined unacceptable, then the facility itself may need to show that the study was not affected by the noncompliance that led to the disqualification. Once finally disqualified, the facility may not receive or be considered for a research or marketing permit and the study is rejected. The commissioner may notify the public and all interested persons, including other federal agencies the facility may have contacted. The FDA may ask the other agencies to consider whether to support the facility or not under the

1010 the state of being ineligible because of an offense or infringement.

disqualification. Civil or criminal proceedings may occur at the discretion of the commissioner

- Fines of up to $50,000 if one knowingly commits crime and/or 1-year imprisonment~ for registration applicants and producers
- Fines up to $5,000 all others~ civil penalty after failing to improve after a minor violation warning was issued~ only those involved in testing will be given civil penalties
- Those involved in the distribution or sales will be assessed more heavy penalties, such as criminal penalties

REVIEW QUESTIONS

SHORT ANSWER TYPE QUESTIONS

Q1. What is Pilfer proof?

Ans. It means the container/ closure are sealed or strengthened so as to protect the contents from theft.

Q2. Write different tests for closures

Ans. Penetrability, Fragmentation test, Self sealability test, Extractive test, Compatibility test and Light absorption

Q3. What are the different types of plastics?

Ans. They are two types.

i. Thermosetting type – When heated they may become flexible but they do not become liquid e.g. Urea formaldehyde (UF),Phenol formaldehyde.

ii. Thermoplastics type- On heating they are softened to viscous fluid which harden again on cooling. e.g. Polyethylene(HDPE – LDPE), Polyvinylchloride(PVC).

Q4. What is Tamper Resistant Packaging?

Ans. Tamper resistant package is one having an indicator to entry in which, if missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. FDA approves the following configurations as tamper resistant packaging: Film wrappers, Blister package, Strip package, Bubble pack, Shrink seals.

Q5. Enlist the critical dimensions of a vial.

Ans. Flange depth, flange diameter, bore diameter, vial height, body diameter, wall thickness, base thickness, concentricity and verticality

Q6. Write the important chemical tests for glass container?

Ans. Hydrolytic resistance test, water attack test, powdered glass test, light transmission test, arsenic test.

Q7. Enlist different QC test for collapsible tubes.

Ans. Leakage test, lacquer curing test, power of adhesion, flexibility Test.

Q8. Define GLP

Ans Definition- Good Laboratory Practice is defined in the OECD11 principles as "a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported

Q9. What are principles of GLP

Ans. Principles of Good Laboratory Practice

- It is to promote the development of quality test data and provide a tool to ensure a sound approach to the management of laboratory studies, including conduct, reporting and archiving.
- The principles may be considered as a set of standards for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data.
- The principles require institutions to assign roles and responsibilities to staff in order to ensure good operational management of each study and to focus on those aspects of study execution (planning, monitoring, recording, reporting, archiving) that are of special importance for the reconstruction of the whole study. Since all these aspects are of equal importance for compliance with GLP Principles.
- As far as pharmaceutical development is concerned, the GLP Principles, in their regulatory sense, apply only to studies which are non-clinical, i.e. mostly studies on animals or in vitro, including the analytical aspects of such studies; are designed to obtain data on the properties and/or the safety of items with respect to human health and/or the environment; are intended to be submitted to a national registration authority with the purpose of registering or licensing the tested substance or any product derived from it.

Q10. Describe any two responsibilities of study director

Ans. The Study Director should: a) approve the study plan and any amendments to the study plan by dated signature; b) ensure that the Quality Assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the Quality Assurance personnel as required during the conduct of the study

Q11. List the types of studies covered under GLP

Ans. Following classes of studies are covered

- Single dose toxicity

11 The Organisation for Economic Co-operation and Development(OECD) is an intergovernmental economic organisation with 36 member countries, founded in 1961 to stimulate economic progress and world trade

CHAPTER 12

COMPLAINTS

The complaint is defined as a statement that something is wrong or not good enough. Generally, in the pharmaceutical industry, market complaints are regarding the quality of the drug product. Complaints can be about packaging material, such as 'the bottle is leaking', 'the cap is difficult to open'the label color is fading', 'one tablet in the blister is missing' or concerning the product's aspect and effect, such as 'there is no effect', 'the tablet or solution color is different', 'the tablet is broken' and so on. A complaint shows customer dissatisfaction about a product and, consequently, about a company.

Customer complaints are a fact of life in business, and dealing with them is an important part of maintaining customer satisfaction and company reputation. It finds that customer dissatisfaction through two mechanisms: Voice and Exit. If a customer makes "Voice" they do complaints. "Exit" occurs when the customer stops using our products or services. To provide better customer service is a way of retaining the customer. Good customer service is important for ensuring that customers are satisfied.

12.1 SPECIFIC TERMS

Recall: A firm's removal or correction of a marketed product that FDA considers being in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure."Recall" does not include a "market withdrawal" or "stock recovery.

Correction: The repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a product without its physical removal to some other location.

Market withdrawal: A firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by FDA or which involves no violation, e.g., normal stock rotation practices, routine equipment adjustments and repairs etc.

Stock recovery: A firm's removal or correction of a product that has not been marketed or that has not left the direct control of the firm, i.e., the product is located on premises owned by, or under the control of, the firm, and no portion of the lot has been released for sale or use.

12.2 COMPLAINT

Complaint is defined as a statement that something is wrong or not good enough. Generally in the pharmaceutical industry, complaints are regarding the quality of drug product. Complaints may be about: Services, delivery, quality of product, communication, response time, documentation, billing, follow up etc. Complaints can be about packaging material,

such as 'the bottle is leaking', 'the cap is difficult to open', 'the label colour is fading', 'one tablet in the blister is missing' or concerning the product's aspect and effect, such as 'there is no effect', 'the tablet or solution colour is different', 'the tablet is broken' etc. Customer complaints are a fact of life in business, and dealing with them is an important part of maintaining customer satisfaction and company reputation. It finds that customer dissatisfaction through two mechanisms: Voice and Exit. If customer makes "Voice" they do complaints. "Exit" occurs when the customer stops using our products or services. To provide better customer service is a way of retaining the customer. Good customer service is important for ensuring that customers are satisfied.

12.2.1 CLASSIFICATION

A-Type Complaints

Critical complaints in which product is required to be withdrawn from the market. Such as

- Adverse Drug Reaction
- Major health hazard causing permanent deficiency or death
- Purity & Safety
- Potency
- Product Stability

B-Type Complaints

Major complaints such as

- Problem with primary packaging of the product.
- Chemical / Physical attributes of the product.
- Extraneous contamination, mix-ups, etc.

C-Type Complaints

Minor complaints such as

- Problem related to labelling / coding of batch details.
- Shortages of Secondary packaging material problem, etc.

12.2.2 RESPONSIBILITY OF COMPLAINTS

1. Production Head
2. Quality Assurance Head
3. Unit Head

12.2.3 GOOD COMPLAINT HANDLING PROCEDURE

Good complaint handling procedure are implemented in pharmaceutical industries in compliance with the GMP Guidelines of EU, USA, Brazil (ANVISA).

It is divided into four steps:

1. Receiving complaints
2. Technical investigation
3. Corrective And Preventive Actions (CAPA)/feedback to customers
4. Monthly reports/trend analysis.

Step 1: Receiving Complaints

It is important to have open channels with customers in order to receive their suggestions, doubts and complaints. Generally, these channels are toll-free numbers, e-mails, chat-rooms. Whatever the channel, it is necessary to have a person in charge of receiving the complaints and inputting them into an appropriate investigation form that shall be addressed to the Quality Assurance (QA) unit for investigation. The most flexible channels are toll-free numbers and chat-rooms, since the customer is on-line and the company's attendee can interview them getting a lot of details. If the complaint was sent by e-mail or to a P.O. box, the recipient must contact the customer by phone and start the interview. The investigation form must include basic information about the complainant, such as: name, address, phone number and e-mail. Information about the product problem is taken, such as: product name, lot number, manufacturing and expiry date, detailed description of complaint, amount of product with problem and any additional information to note. It is important that each opened complaint has a code, e.g. a sequential and unique number, and the receipt date must be recorded. During the customer interview, it is beneficial to briefly outline the complaint handling procedure to the customer, to let him/her know what will be done about the recently received complaint and what kind of feedback will be given to the customer when the investigation is completed. Therefore, the company representative should request that the possibly defective product be sent to the company for further analysis. This product will is called as 'complaint sample'. It should be documented on the investigation form if the complaint sample will be sent.

Step 2: Technical Investigation

Upon receipt of the investigation form, the QA unit is able to start the investigation, which can be divided in two phases: documentation-based and laboratory analysis. The documentation-based investigation consists of checking if this complaint occurred previously in the same lot or if any non-conformance was found in the lot during its

production that could explain the complaint. The primary documentation to be reviewed in this step consists of the complaint files and the batch records. Complaint files can be consulted to check how many other complaints of the same nature had occurred to a specific lot and how they were handled. Batch records must be verified in order to see if there was any non-conformance during the production that can explain or confirm the quality deviation, and how it was investigated and concluded.

The laboratory analysis phase consists of requesting the Quality Control (QC) laboratory to analyse both complaint samples and retained samples – the reserve samples representative of the lot manufactured. This means that, in parallel to the customer sample, which already passed through distribution and third-party holding, the QC laboratory is performing analysis on retained samples, which were kept under appropriate conditions of temperature, humidity and light so that the identity, strength, quality and purity of the drug product was not affected. If the customer did not send the complaint sample for analysis, the laboratory investigation will be carried out only with retained samples. Similar to the receiving step, it is fundamental that the company elects a person in the QA unit to be in charge of technical investigation of each complaint, e.g. a Complaint Officer. This person must have a comprehensive knowledge of the manufacturing process and QC analysis, since they will be responsible for choosing the analytical approach that best fits investigating if the complaint is confirmed or not, and conclude the investigation. This employee is the contact person that links the QA unit to all others, such as Production, Quality Control, Marketing, Finance, Legal and Regulatory Affairs units in order to determine what really happened and what the implications are for both customer and company. Therefore, these responsibilities must be included in the job description of the Complaint Officer. After receiving the analytical results and after performing the documentation-based investigation, the QA unit is able to finish the complaint investigation. There are three possible conclusions, as follows.

Confirmed Complaint

When both complaint and retained samples showed out-of-specification (OOS) results or when only the complaint sample showed OOS results, but it is clearly a single unexplained failing product. An example of a single unexplained failure may be when one tablet is missing in the intact blister strip in the complaint sample, but no deviation was found in the retained samples or during the in-process controls and final QC analysis recorded in the batch record. But, as a quality problem was identified in the complaint sample, the complaint is classified as confirmed.

Non-Confirmed Complaint

When both complaint and retained samples showed results in compliance with specifications or when only the complaint sample showed OOS results that cannot be

considered a single unexplained failing product. OOS results in a complaint sample can be attributed to misuse or mishandling, when the drug product was not kept under appropriate conditions of temperature, humidity and light so that the identity, strength, quality and purity of the drug product could be affected. An example of a non-confirmed complaint may be when the tablets of the complaint sample show a change in their appearance that is characteristic of a light, humidity or high temperature exposure. This complaint is classified as non-confirmed because the quality problem appeared in the complaint sample due to a product mishandling and cannot be addressed to a manufacturing deviation, since the retained sample, kept under the appropriate conditions of temperature, humidity and light, did not show the same problem.

Counterfeit/Tamper Suspicion

When the retained sample is within the specification but the complaint sample is clearly OOS with no reason for that, such as a counterfeit or tampered drug product. An example of counterfeit is when packaging material is different from the original; an example of tampering is when the colour of the drug product is completely different from the original or when any foreign substance was added to the product. The Legal Affairs unit and the Competent Authorities must immediately be informed for further arrangements. The Complaint Officer must also check if the complaint represents a serious and unexpected adverse drug experience, which is required to be reported to the health authorities, according to the specific safety reporting regulations of the respective countries. The Complaint Officer must also check if the complaint represents a serious and unexpected adverse drug experience, which is required to be reported to the health authorities, according to the specific safety reporting regulations of the respective countries. The Complaint Officer and the QA Manager must sign off the investigation form once the investigation is completed. The time for concluding a complaint investigation and the retention time of complaint files depend on the regulations of each country; however, 30 days is a reasonable time to conclude an investigation. Complaint files should be retained for at least 1 year after the expiry date of the lot.

Step 3: Corrective Actions (CAPA) and Feedback to Customers

For all confirmed complaints, corrective actions must be implemented. These actions can range from a simple and quick training to some employees to a formal Corrective Action and Preventive Action (CAPA) handling. The criteria for choosing appropriate action depends on the nature of the complaint, if the deviation is a single unexplained failing product or not and the complaint incidence. If a CAPA is opened, a multidisciplinary team consisting of representatives of QA, QC, Regulatory Affairs and Production Management must be established. If a quality problem is found in a specific lot, it is important to investigate if the

same problem is also present in other lots. Therefore, the company must evaluate if there is a reasonable probability that the use of or exposure to the product with the confirmed quality problem may cause permanent injury, is life-threatening or may lead to death or to a temporary but medically reversible health problem. In these cases, a recall must be triggered. As feedback to the customer, the company must write a response letter to the complainant to explain the investigation approach taken, the results obtained and any implications, in case the quality problem was confirmed. The customer should be sent a free replacement product together with the response letter, since the customer returned the product (the 'complaint sample') to the company for analysis and a quality problem was found.

Step 4: Monthly reports and trend analysis:

Monthly reports should be elaborated in order to evaluate the amount and the nature of the complaints received and to perform a trend analysis of these complaints. The monthly reports must answer the following questions: How many complaints did the company receive in the period? How many were confirmed? How many were non-confirmed or were counterfeit/tamper suspicion? It is also important to know the 'top 10 products' which received the majority of complaints, the nature of these complaints, batches involved, the rootcauses of confirmed complaints, how many free offer products were given to customers (to reimburse for the 'complaint samples' returned for analysis) and how much the complaint handling cost the company. Another interesting attribute to be monitored is the cycle-time of complaint investigation in order to shorten the feedback time to customers. A controlled copy of the monthly report mustbe delivered to all staff engaged with complaints, as follows: QA, QC, Production Management, Marketing, Finance, Human Resources and Regulatory and Legal Affairs. If the complaint is about any imported product, the original manufacturer must be notified. Some companies also deliver the report to senior management staff. The report must be readily available for Regulatory Agency Inspectors upon request, mainly during GMP inspections. Therefore, these reports can be a major contributor to the Annual Product Review elaboration, since all data concerning complaints is presented monthby- month in these reports.

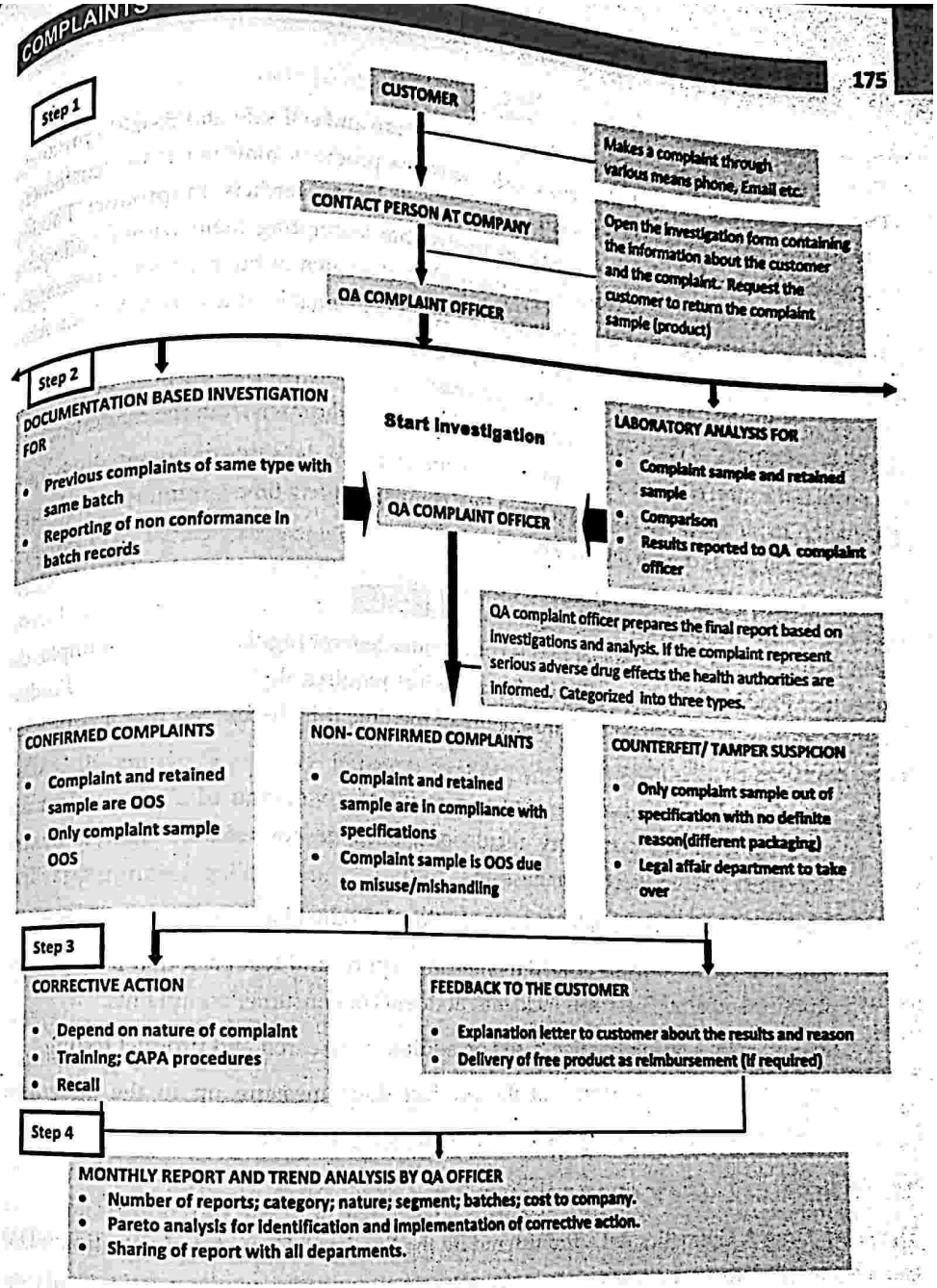

Figure 12.1 : The four steps of a complaint handling system

12.3 RECALL

Despite a company's best efforts to design, manufacture and sell safe and reliable products, the possibility still exists that dangerously defective products may reach the customers. These products may cause accidents, leading to adverse verdicts in product liability litigations. Product recalls are certainly expensive, but attempting them without adequate planning can be much more costly. Once the quality of a batch of the product is primafacie doubtful, it is intended that the product is no more consumable and is recalled for more investigation and decision. Complaints and product recall are inter related in most of the cases of complaints, it may be necessary to recall the products. The purpose of the drug recall is to ensure that the drug is effectively and rapidly withdrawn from the market.

A recall is the most effective way to protect the public from a defective or potentially harmful product. A recall is a voluntary action taken by a company at any time to remove a defective drug product from the market.

12.3.1 PRIMARY REASONS FOR A PRODUCT RECALL

As indicated earlier, some product recalls come under federal regulations. For example, the Consumer Product Safety Act (CPSA), Section 15(b) requires that the Consumer Product Safety Commission be notified within 24 hours of the time it is discovered that a A product recall may be:

- Mandated by a regulatory agency as a result of a violation of a government act, standard or other mandatory regulations, such as toy recalls ordered by the Consumer Product Safety Commission.
- Required to avoid potentially serious additional product liability claims or losses.
- Indicated by the analysis of field monitoring reports and feedback that may point to product tampering, nearmiss incidents, accidents or consumer complaints.
- Suggested by new information based on additional research and product testing.
- Needed when characteristics of the product don't measure up to the advertised claims for safety or effectiveness.

12.3.2 RECALL CLASSIFICATION SCHEME

The Food, Drug & Cosmetics Act administered by the Food and Drug Administration (FDA) classifies recalls into three classes:

Class I Recall: A dangerous or defective product that could cause serious health problems or death. A situation in which there is a reasonable probability that use of, or exposure to, a violate product will cause serious adverse health consequences or death. Class I recalls are

pretty rare, but they should be obeyed as soon as you become aware of them. In the case of Class I Recall, the FDA will develop an individual plan that is specific to the manufacturer and the product involved, to make sure that compliance with the recall is complete and that the recall of the items involved is trackable and appropriate public announcements. The objective here is to be sure that all of the affected items are removed from the market, and from people's homes.

Class II Recall: A product that might cause a temporary health problem, or pose slight threat of a serious nature. A situation in which use of, or exposure to, a violate product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A press release may be required, depending on the reasons for the recall.

Class III Recall: A products that is unlikely to cause any adverse health reaction, but that violates FDA labeling or manufacturing laws. A situation in which use of, or exposure to, a violate product is not likely to cause adverse health consequences. An example of a Class III Recall is the 2010 recall of children's medicines that were potentially contaminated with small pieces of plastic during the manufacturing process. No press release requirements.

Depending on the seriousness of the situation, the company may have a choice whether to repair or modify the product (no cost or reduced cost retrofit by customer or the company), refund the purchase price, or initiate a total or partial recall (voluntary or mandatory). In case of a mandatory recall, the company can circulate the notice of recall through a regulatory agency. This should be done only after a thorough review of the situation and with appropriate legal counsel.

12.3.3 THE GOALS OF A PRODUCT RECALL

A product recall is intended to protect the health of the public. As a meat processor, you are trying to meet two goals during a product recall. The first goal is regain control of all hazardous products. If this goal is met, the recall is successful. In some cases, all products can be successfully recalled without the public ever knowing that a recall occurred. Many times, though, even the best planning and record keeping, will not enable you to retrieve all product. In such situations, your second goal should be to inform the public about the hazardous product so that they do not eat it. This secondary goal is most important for retail operations. For wholesale processors, informing the public becomes more important as time goes by and product gets farther into distribution.

12.3.4 PRODUCT RECALL PROCEDURE

The following steps may be taken while executing the drug recall. These steps may be included in the written procedure for the drug recall.

Step 1: Determine the degree of recall. There are three degree of recall

Degree I:Product with high health risk requiring freezing of stock within 24 hours.

Degree II: Product with minor health risk or substandard requiring freezing of the stock within 72 hours.

Degree III: Product with other reason for recall

Step 2: Disseminate recall instructions using telephone, telegram, postage, mass media, radio TV, depending upon the seriousness of the defect.

Step 3: Freeze the internal stock of the product.

Step 4: Establish the record and report of recalled product.

Step 5: Organize the return of the recalled product.

Following information/data is collected to perform the recall of drug product:

- Reason for recall
- Details of what is covered by recall and what is not covered, for example individual batch or dosage form-the nature of risk, if some patents are at risk, advice has to how they should be managed
- The cause of defects, if known
- Organization of return of the defective product
- Address, telephone number of persons to be contacted at national, provincial levels
- Addresses, telephone, telex number of distributors, wholesalers and hospitals etc.

12.4 HANDLING OF RETURN GOOD

Procedure

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. Record all the details in Returned Goods Record. Inform the Quality Assurance department for evaluation of the returned goods. The Quality Assurance chemist shall evaluate the returned goods for the following:

- Check the COA and other documents with the returned consignment.
- Condition of the Packaging, carton and container.

- Labeling details.

If the returned materials 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, then destroy the material as per the SOP for control sample destruction. If none of the above condition is apparent, then sample the material as per the specific SOP. 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 meets the product specification. In case the sample fails to meet the product specification, destroy the material/product as per the SOP for destruction, and initiate failure investigation. Identify the batches manufactured during the same period &/or manufactured by using the same raw material. Extend the investigation to these batches also.

12.5 WASTE DISPOSAL

Waste includes all items that people no longer have any use for, which they either intend to get rid of or have already discarded. Additionally, wastes are such items which people are require to discard, for example by lay because of their hazardous properties. Biomedical waste is broadly defined as any solid or liquid waste that is generated in the diagnosis, treatment of immunization of human beings or animals in research pertaining thereto, or in the production or testing of biological material.

Regulatory bodies that oversee pharmaceutical waste management

- Environmental Protection Agency (EPA)
- Department of Transportation (DOT)
- Drug Enforcement Administration (DEA)
- Occupational Safety and Health Administration (OSHA)
- State Environmental Protection Agencies,
- State Pharmacy Boards, and
- Local Publicly Owned Treatment Works (POTW)

Pharmaceutical waste is potentially generated thorough a wide variety of activities is a health care facility, includingsyringes, and not limited to intravenous (IV) preparation, general Pharmaceutical waste may include, but is notlimited to:

- Expired drugs;
- Patients' discarded personal medications;

- Waste materials containing excess drugs (syringes, IV bags, tubing, vials, etc.);
- Waste materials containing chemotherapy drug residues;
- Open containers of drugs that cannot be used;
- Containers that held acute hazardous waste (p-listed) drugs;
- Drugs that are discarded; and
- Contaminated garments, absorbents and spill cleanup material.

12.5.1 PHARMACEUTICAL WASTE CLASSIFICATION

Pharmaceutical waste is further classified in 3 categories:-

1. Hazardous waste ,
2. Non-hazardous waste,
3. Chemo waste.

Hazardous waste

Waste that is dangerous or potentially harmful to human health or the environment is called as hazardous waste. It can be liquids, solids, contained gases, or sludges. Hazardous wastes are divided into two categories:

(1) Listed wastes: Listed wastes are wastes from common manufacturing and industrial processes, specific industries and can be generated from discarded commercial products.. These can be four types (F, K, P and U).Pharmaceuticals are found on two of these lists, the P and U lists which both contain commercial chemical products.

(2) Characteristic wastes: Characteristic wastes are wastes that exhibit any one or more of the following characteristic properties: ignitability, corrosivity, reactivity or toxicity. Characteristic wastes are regulated because they exhibit certain hazardous properties

Wastes that are not listed and do not exhibit a characteristic are considered solid waste. Solid wastes should be discarded according to state and/or local regulations, including regulated medical waste requirements.

(1) Listed hazardous waste

P-Listed Pharmaceutical waste: P-listed wastes are commercial chemical products that are categorized as acutely hazardous under RCRA12 as shown in table no.1. One of the primary criteria for including a drug on the P-list as acutely hazardous is an oral lethal dose of 50 mg/kg (LD50) or less. LD50 is the amount of a material, given all at once, which causes the death of 50% of a group of test animals. They are toxic and can cause death or irreversible

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illness at low dose. When a drug waste containing a P-listed constituent of concern is discarded or intended to be discarded, it must be managed as hazardous waste if two conditions are satisfied:

(1) The discarded drug waste contains a sole active ingredient (54 FR 31335) that appears on the P list, and it has not been used for its intended purpose (54FR 31336).

(2) Empty Containers of P-Listed Wastes (40 CFR Part 261.7(b)

A container that has held a P-listed waste is not considered "RCRA empty" unless it has been: Triple rinsed, and the rinsate is managed as hazardous waste.

Since triple rinsing is not practical in healthcare settings, all vials, IVs, and other containers that have held a P-listed drug must be managed as hazardous waste, regardless of whether or not all of the contents have been removed. Some states have chosen to interpret "used" less stringently in the case of solid dosage forms (tablets, capsules) and are not regulating "empty" warfarin stock bottles or unit-dose packaging.

U-Listed Pharmaceutical Wastes: U-listed chemicals include a broader range of pharmaceuticals and again must be the sole active ingredient to come under regulation. Technically, these items would not be regulated as hazardous waste when discarded since neither U-listed ingredient is the sole active ingredient. There are 21 drugs on the U-list some of them are Arsenic trioxide, Nicotine, Nitroglycerin, Physostigmine, Warfarin >0.3%, Physostigmine salicylate.

These chemicals are listed primarily for their toxicity. Similar to a P-listed waste, when a drug waste containing one of these chemicals is discarded, it must be managed as hazardous waste if two conditions are satisfied:

(1) The discarded drug waste contains a sole active ingredient that appears on the U list, and It has not been used for its intended purpose.

(2) Empty Containers of U-Listed Wastes (40 CFR Part 261.7(b)(1)):- A container that has held a U-listed waste is considered "RCRA empty" if two conditions are met:

- All the contents have been removed that can be removed using normal means, such as drawing liquid out with a syringe
- No more than 3% by weight remains. If both of these criteria are not met, the container must be managed as hazardous waste. Any residues removed from the empty container must be managed as hazardous waste.

Nitroglycerin in finished dosage forms has been exempted federally based on a Federal Register Notice dated May 16, 2001 (Volume 66, Number 95). Chloral hydrate and paraldehyde are controlled substances regulated by the Drug Enforcement Administration in schedule IV as an indication of moderate abuse potential. Since controlled substances

must be destroyed through a witnessed destruction process, their status as a RCRA hazardous waste makes disposal difficult.

(2) Characteristics Waste: The EPA defines four characteristics hazardous waste:

- Ignitability (D001)
- Toxicity (D number specific to the chemical)
- Corrosivity (D002)
- Reactivity (D003)

Example: Taxol Injection, Erythromycin Gel 2%, Texacort Solution 1%, Primatene aerosol, Silver nitrate applicators, used for cauterizing.

Non-Hazardous Waste

Materials in this category are considered to present no significant hazardous properties. It is worth noting, however, that this is not an indication that there are no hazardous components present, only that any such components are below the threshold for causing harm to human health. Importantly, this non-hazardous state is subject to change and the addition or removal of specific items from the waste stream may significantly alter the management options available. Pharmaceutically inert: Certain medicinal products have no pharmaceutical properties but are still controlled and administered by medical staff (examples include sodium chloride or dextrose solutions). Through use, however, these products may become contaminated, or mixed with other compounds and therefore require assessment for hazardous properties prior to disposal.

Chemo Waste

Chemo wastes are further classified as trace chemotherapy and bulk chemotherapy waste.

Trace Chemotherapy Waste

The federal RCRA regulations do not address trace chemotherapy waste. There is no recognized distinction between bulk and trace chemotherapy contamination for P- and U-listed hazardous wastes since there isn't a lower concentration limit under which these wastes can exit the regulatory system. Most state regulated medical waste regulations are either silent or not specific on the definition of trace chemotherapy waste. The original reference to segregating trace chemotherapy waste is found in an article written in 1984 by pharmacy personnel at the National Institutes of Health who pioneered applying the RCRA regulations to antineoplastic wastes.

Items that are appropriate for management as trace chemotherapy waste include:

- "RCRA empty" vials, syringes, IV bags, and tubing;

- Gowns, gloves, wipes and other paraphernalia associated with routine handling, preparation, and administration of chemotherapy; and,
- Wipes and other materials used during routine cleaning and decontamination of a Biological
- Safety Cabinet or glove box (unless alcohols, phenols or other hazardous materials are used).

Bulk Chemotherapy Waste

One chemotherapy agent is a P-listed constituent of concern and eight chemotherapy agents are U-listed. Trace chemotherapy containers have long been used to discard listed chemotherapy drug waste that should be managed as hazardous waste. This is not only illegal but also inappropriate since trace chemotherapy waste is incinerated at an RMW incinerator, hazardous waste incinerator. RMW incinerators have less restrictive emissions limits and permit requirements. Discarding "bulk" P- or U- listed chemotherapy agents as trace chemotherapy waste has been the cause of substantial enforcement actions and fines and should be one of the first changes you implement in your pharmaceutical waste management program.

12.5.2 PHARMACEUTICAL WASTE TREATMENT AND DISPOSAL

Pharmaceutical Waste Treatment and Disposal Technologies Specified in India's Pharmaceutical Waste Rules.

1. Incineration

Incineration is a disposal method in which solid organic wastes are subjected to combustion so as to convert them into residue and gaseous products. This method is useful for disposal of residue of both solid waste management and solid residue from waste water management. This process reduces the volumes of solid waste to 20 to 30 percent of the original volume.

Incineration and other high temperature waste treatment systems are sometimes described as "thermal treatment". Incinerators convert waste materials into heat, gas, steam and ash. Incineration is carried out both on a small scale by individuals and on a large scale by industry. It is used to dispose of solid, liquid and gaseous waste. It is recognized as a practical method of disposing of certain hazardous waste materials (such as biological medical waste). Incineration is a controversial method of waste disposal, due to issues such as emission of gaseous pollutants. Incineration is not suitable for such health care wastes as pressurized gas containers, large amounts of reactive chemical wastes, wastes treated with halogenated chemicals, halogenated plastics such as polyvinyl chloride, wastes with

mercury or cadmium (such as broken thermometers, used lead or mercury batteries), or radiographic wastes. Incinerators that meet the CPCB draft incineration regulations must have a sophisticated (for example, double- chamber) design and include a scrubber as the air pollution control equipment. Ash from these incinerators must be disposed of in a secure landfill. Such incinerators are associated with high investment and operating costs and require highly skilled operating personnel.

2. Autoclaving

Autoclaving uses saturated steam in direct contact with the BMW in a pressure vessel at time lengths and temperatures sufficient to kill the pathogens. The Biomedical Waste Rules specify the minimum temperature, pressure, and residence time for autoclaves for safe disinfection. Autoclaving is not suitable for human anatomical, animal, chemical, or pharmaceutical wastes. Before autoclaving, BMWs require shredding to an acceptable size, an operation that would involve frequent breakdown. Autoclaving produces a waste that can be land filled with municipal waste. A wastewater stream is generated that needs to be disposed of with appropriate controls. Autoclave operation requires qualified technicians, and medium investment and operating cost.

3. Microwaving

Application of an electromagnetic field over the BMW provokes the liquid in the waste to oscillate and heat up, destroying the infectious components by conduction. This technology is effective if the ultraviolet radiation reaches the waste material. Before microwaving, BMWs require shredding to an acceptable size and humidification. Microwaving is not suitable for human anatomical, animal, chemical, or pharmaceutical wastes, or for large metal parts. Microwaving produces a waste that can be land filled with municipal waste. The advantages of this treatment technology are its small electrical energy needs and no steam requirement. The disadvantages include the need for qualified technicians and frequent breakdown of shredders. This technology requires medium investment and operating costs.

4. Chemical disinfection

Chemical disinfection is most suitable for treating liquid wastes such as blood, urine, stools, or health care facility sewage. Addition of strong oxidants—like chlorine compounds, ammonium salts, aldehydes, or phenol compounds—kills or inactivates pathogens in the BMW. However, microbiological cultures, mutilated sharps, or shredded solids can also be treated by chemical disinfection. Disinfection efficiency depends on such factors as the type and amount of chemical used, and the extent and duration of contact between the disinfectant and the BMW. As chemical disinfectants have hazardous (in particular, toxic)

properties, users should wear protective clothes. Chemical disinfectants should not be discharged to surface waters, and no large quantities should be allowed into sewers.

5. Deep burial

The Biomedical Waste Rules require that human anatomical and animal wastes in cities with population less than 500,000 and in rural areas be disposed of by deep burial. Accordingly, the deep burial site should be pre- pared by digging a pit or trench of about 2 meters deep in an area that is not prone to flooding or erosion, and where the soil is relatively impermeable, there are no inhabitants or shallow wells in the vicinity, and the risk to surface water contamination is remote. The pit should be half-filled with the BMW, and then covered with lime within 50 cm of the surface, before filling the rest of the pit with soil. On each occasion when BMW is added to the pit, a layer of 10 cm of soil should be added to cover the waste.

6. Secure land filling

Secure land filling involves disposal of solid wastes at a landfill designed and operated to receive hazardous wastes. The Biomedical Waste Rules require disposal of discarded medicines, cytotoxic drugs, solid chemical wastes, and incineration ash in secured landfills. Disposing of waste in a landfill involves burying the waste, and this remains a common practice in most countries. Landfills were often established in abandoned or unused quarries, mining voids or borrow pits. A properly designed and well-managed landfill can be a hygienic and relatively inexpensive method of disposing of waste materials. Older, poorly designed or poorly managed landfills can create a number of adverse environmental impacts such as wind-blown litter, attraction of vermin, and generation of liquid leachate. Another common byproduct of land fillsm is gas (mostly composed of methane and carbon dioxide), which is produced as organic waste breaks down anaerobically. This gas can create odour problems, kill surface vegetation, and is a greenhouse gas. Design characteristics of a modern landfill include methods to contain leachate such as clay or plastic lining material. Deposited waste is normally compacted to increase its density and stability, and covered to prevent attracting vermin (such as mice or rats). Many landfills also have landfill gas extraction systems installed to extract the landfill gas. Gas is pumped out of the landfill using perforated pipes and flared off or burnt in a gas engine to generate electricity.

7. Waste immobilization: encapsulation

Encapsulation involves immobilizing the pharmaceuticals in a solid block within a plastic or steel drum. Drums should be cleaned prior to use and should not have contained explosive or hazardous materials previously. They are filled to 75% capacity with solid and semi-solid pharmaceuticals, and the remaining space is filled by pouring in a medium such as cement or cement/lime mixture, plastic foam or bituminous sand. For ease and speed of filling, the drum lids should be cut open and bent back. Care should be taken to avoid cuts to hands

when placing pharmaceuticals in the drums. Once the drums are filled to 75% capacity, the mixture of lime, cement and water in the proportions 15:15:5 (by weight) is added and the drum filled to capacity. A larger quantity of water may be required sometimes to attain a satisfactory liquid consistency. Steel drum lids should then be bent back and sealed, ideally by seam or spot welding. The sealed drums should be placed at the base of a landfill and covered with fresh municipal solid waste. For ease of movement, the drums may be placed on pallets which can then be put on a pallet transporter.

8. Waste immobilization: Inertization

Inertization is a variant of encapsulation and involves removing the packaging materials, paper, cardboard and plastic, from the pharmaceuticals. Pills need to be removed from their blister packs. The pharmaceuticals are then ground and a mix of water, cement and lime added to form a homogenous paste. Worker protection in the form of protective clothing and masks is required as there may be a dust hazard. The paste is then transported in the liquid state by concrete mixer truck to a landfill and decanted into the normal urban waste. The paste then sets as a solid mass dispersed within the municipal solid waste. The process is relatively inexpensive and can be carried out with unsophisticated equipment. The main requirements are a grinder or road roller to crush the pharmaceuticals, a concrete mixer, and supplies of cement, lime and water.

9. Sewer

Some liquid pharmaceuticals, e.g. syrups and intravenous (IV) fluids, can be diluted with water and flushed into the sewers in small quantities over a period of time without serious public health or environmental affect. Fast flowing watercourses may likewise be used to flush small quantities of well-diluted liquid pharmaceuticals or antiseptics. The assistance of a hydrogeologist or sanitary engineer may be required in situations where sewers are in disrepair or have been war damaged.

12.5.3 HAZARDOUS WASTE MANAGEMENT STRATEGY

1. Waste minimization

An important method of waste management is the prevention of waste material being created, also known as waste reduction. Methods of avoidance include reuse of second-hand products, repairing broken items instead of buying new, designing products to be refillable or reusable (such as cotton instead of plastic shopping bags), encouraging consumers to avoid using disposable products (such as disposable cutlery), removing any food/liquid remains from cans, packaging, and designing products that use less material to achieve the same purpose (for example, light-weighting of beverage cans).

2. Reuse

Re-use means the use of a product on more than one occasion, either for the same purpose or for a different purpose, without the need for reprocessing. Re-use avoids discarding a material to a waste stream when its initial use has concluded. It is preferable that a product be re-used in the same state e.g., returnable plastic pallets, using an empty glass jar for storing items and using second hand clothes. Reuse is normally preferable to recycling as there isn't the same requirement for the material to have gone through a detailed treatment process thus helping to save on energy and material usage.

3. Recycling

Recycling involves the treatment or reprocessing of a discarded waste material to make it suitable for subsequent re-use either for its original form or for other purposes. It includes recycling of organic wastes but excludes energy recovery. Recycling benefits the environment by reducing the use of virgin materials. Many different materials can be recycled. Waste materials can either be recycled for use in products similar to their original use (e.g., paper recycling) or can be recycled into a product which is different than the original use (e.g., recycling plastic bottles into fleece jackets or using construction and demolition waste as road aggregate. In the EU up to 13% of municipal waste is recycled.

4.Energy recovery

The energy content of waste products can be harnessed directly by using them as a direct combustion fuel, or indirectly by processing them into another type of fuel. Thermal treatment ranges from using waste as a fuel source for cooking or heating and the use of the gas fuel (see above), to fuel for boilers to generate steam and electricity in a turbine. Pyrolysis and gasification are two related forms of thermal treatment where waste materials are heated to high temperatures with limited oxygen availability. The process usually occurs in a sealed vessel under high pressure. Pyrolysis of solid waste converts the material into solid, liquid and gas products.

The liquid and gas can be burnt to produce energy or refined into other chemical products (chemical refinery). The solid residue (char) can be further refined into products such as activated carbon. Gasification and advanced Plasma arc gasification are used to convert organic materials directly into a synthetic gas (syngas) composed of carbon monoxide and hydrogen. The gas is then burnt to produce electricity and steam. An alternative to pyrolisis is high temperature and pressure supercritical water decomposition (hydrothermal monophasic oxidation).

Steps that should be followed to manage pharmaceutical wastes:

1. Establish a pharmacy management plan

2. Identify your hazardous and non-hazardous wastes
3. Implement best management practices
4. Determine your waste generator status
5. Comply with guidelines for transport and disposal

12.5.4 MINIMIZING PHARMACEUTICAL WASTE

As design and implement your pharmaceutical waste management program, there are inherent limitations on the substitution of a less hazardous drug since the hazardous nature of the chemical often provides the therapeutic effect. However, waste reduction can minimize compliance hassles, costs and risks. The following section provides a number of minimization opportunities to consider and explore.

1. Considering Lifecycle Impacts in the Purchasing Process
2. Maximizing the Use of Opened Chemotherapy Vials
3. Implementing a Samples Policy
4. Labeling Drugs for Home Use
5. Priming and Flushing IV Lines with Saline Solution
6. Examining the Size of Containers Relative to Use
7. Replacing Prepackaged Unit Dose Liquids with Patient-Specific Oral Syringes
8. Controlled Substances
9. Delivering Chemotherapy Drugs
10. Monitoring Dating on Emergency Syringes
11. Reviewing Inventory Controls to Minimize Outdates
12. Considering the Management Options
13. Getting Ready for Implementation
    - Locating Your Satellite Accumulation Areas
    - Evaluating Your Storage Accumulation Area
    - Conducting a Pilot Program
14. Policies and Procedures: At a minimum pharmaceutical waste management policies and procedures should be:
    - developed to detail the organization's approach to identifying drugs that must be managed as hazardous waste;
    - determining which non-regulated drugs will be managed as hazardous waste;

- labeling drugs to facilitate segregation of hazardous waste;
- segregating waste streams;
- training staff (e.g., which staff, what information and how often);
- setting up and managing satellite accumulation and storage accumulation areas;
- preparing and maintaining hazardous waste manifests;
- determining their hazardous waste generation status;
- what criteria are used for hazardous waste selection;
- scheduling regular program reviews;
- keeping management informed; and,
- using pharmaceutical waste management as a stepping-stone to a facility-wide;
- environmental management system.

CHAPTER 13

DOCUMENT MAINTENANCE IN PHARMACEUTICAL INDUSTRY

Documentation is an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aim is to define the specifications for all materials and the method of manufacture and control, to ensure that all personnel concerned with manufacture have the information necessary to decide whether or not to release a batch of a drug for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. The specifications should describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation. Documentation provides the route for auditors to assess the overall quality of operations within a company and the final product.

13.1 GENERAL REQUIREMENT

- Good documentation constitutes an essential part of the quality assurance system. Clearly written procedures prevent errors resulting from spoken communication, and clear documentation permits tracing of activities performed.
- Documents must be designed, prepared, reviewed, and distributed with care.
- Documents must be approved, signed, and dated by the appropriate competent and authorized persons.
- Documents must have unambiguous contents. The title, nature, and purpose should be clearly stated. They must be laid out in an orderly fashion and be easy to check. Reproduced documents must be clear and legible.
- Documents must be regularly reviewed and kept up-to-date. When a document has been revised, systems must be operated to prevent inadvertent use of superseded documents (e.g., only current documentation should be available for use).
- Documents must not be handwritten; however, where documents require the entry of data, these entries may be made in clear legible handwriting using a suitable indelible medium (i.e., not a pencil). Sufficient space must be provided for such entries.
- Any correction made to a document or record must be signed or initialed and dated; the correction must permit the reading of the original information. Where appropriate, the reason for the correction must be recorded.

- Record must be kept at the time each action is taken and in such a way that all activities concerning the manufacture and control of pharmaceutical products, clinical studies, clinical trials, and the storage of critical records must be in secure place, with access limited to authorized persons. The storage location must ensure adequate protection from loss, destruction, or falsification, and from damage due to fire, water, etc.
- Records which are critical to regulatory compliance or to support essential business activities must be duplicated on paper, microfilm, or electronically, and stored in a separate, secure location in a separate building from the originals.
- Date may be recorded by electromagnetic or photographic means, but detailed procedures relating to whatever system is adopted must be available. Accuracy of the record should be checked as per the defined procedure. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer, access must be restricted by passwords or other means, and entry of critical data must be independently checked.
- It is particularly important that during the period of retention, the data can be rendered legible within an appropriate period of time.
- If data is modified, it must be traceable.

Manufacturing formulae and processing and packaging instructions should specify all the starting materials used and describe all processing and packaging operations. Procedures should give directions for performing certain operations, e.g., cleaning, clothing, environmental control, sampling, testing, and equipment operation. Records should provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

Written records should be maintained so that data can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures should be established and followed for such evaluations and must include provisions for:

- A review of a representative number of batches, whether approved or rejected and, where applicable, the records associated with the batch.
- A review of complaints, recalls, and returned or salvaged drug products, and of the investigations conducted.

All documents related to the manufacture of intermediates, active pharmaceutical ingredients (API), and finished products should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be paper-based or in

electronic form. Documents should be approved, signed, and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

Each specification for raw materials, intermediates, final products, and packing materials should be approved and maintained by the quality control department. Periodic revisions of the specifications must be carried out whenever changes are necessary.

The issuance, revision, superseding, and withdrawal of all documents should be controlled, with maintenance of revision histories. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents. Superseded documents should be retained for a specific period of time.Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.Documents should have unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The process of reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

Documents should not be handwritten; however, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries. Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.Data may be recorded by electronic data processing systems or photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions. Access should be restricted by passwords or other means and the result of entry of critical data should be independently

checked. Batch records that are electronically stored should be protected by back-up transfer onto magnetic tape, microfilm, paper, or other means.

Specifications should be established and documented for raw materials, intermediates (where necessary), and API/formulations, as well as for labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or API/formulations that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls. Master production instructions/master production and control records (MPCR)/master formula card (MFC). To ensure uniformity from batch to batch, master production instructions for each intermediate or API/finished product should be prepared, dated, and signed by one person and independently checked, dated, and signed by a second person in the quality unit(s).

Competent persons experienced in production and quality control should be responsible for the content and distribution within the firm of instructions and master formulae. These should be duly signed and dated. Outdated master formulae should be withdrawn but retained for reference. Copies of the master formula should be prepared in a manner that will eliminate any possibility of transcription error. In certain circumstances, for example, in the first production runs following pilot development, the master formula might need to be amended. Any amendments must be formally authorized and signed by competent person(s). The amended document should be replaced at the earliest opportunity by a newly prepared master formula. Processing should be carried out in accordance with the master formula.

13.2 TYPES OF DOCUMENT

There are various types of procedures that a GMP facility follows. Given below is a list of the common types of documents.

1. Quality manual: A global company document that describes, in paragraph form, the regulations and/or parts of the regulations that the company is required to follow.
2. Policies: Documents that describe in general terms, and not with step-by-step instructions, how specific GMP aspects (such as security, documentation, health, and responsibilities) will be implemented.
3. Standard operating procedures (SOPs): Step-by-step instructions for performing operational tasks or activities.
4. Batch records: These documents are typically used and completed by the manufacturing department. Batch records provide step-by-step instructions for

production-related tasks and activities, besides including areas on the batch record itself for documenting such tasks.

5. Test methods: These documents are typically used and completed by the quality control (QC) department. Test methods provide step-by-step instructions for testing supplies, materials, products, and other production-related tasks and activities, e.g., environmental monitoring of the GMP facility. Test methods typically contain forms that have to be filled in at the end of the procedure; this is for documenting the testing and the results of the testing.
6. Specifications: Documents that list the requirements that a supply, material, or product must meet before being released for use or sale. The QC department will compare their test results to specifications to determine if they pass the test.
7. Logbooks: Bound collection of forms used to document activities. Typically, logbooks are used for documenting the operation, maintenance, and calibration of a piece of equipment. Logbooks are also used to record critical activities, e.g., monitoring of clean rooms, solution preparation, recording of deviation, change controls and its corrective action assignment.

13.3 BATCH PRODUCTION RECORDS/BATCH PRODUCTION AND CONTROL RECORDS (BPCR)/BATCH MANUFACTURING RECORD (BMR)

Defination: Batch manufacturing record is a written document of the batch, prepared during pharmaceutical manufacturing process. It contains actual data and step by step process for manufacturing each batch. Batch manufacturing record is like a proof that batches were properly made and checked by quality control personnel

Batch production records should be prepared for each intermediate and API/formulation and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

Before any processing begins, a check should be performed and recorded to ensure that the equipment and workstation are clear of previous products, documents, or materials not required for the planned process and that the equipment is clean and suitable for use.

These records should be numbered with a unique batch or identification number and dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

The batch number should be immediately recorded in a logbook or by electronic data processing system. The record should include date of allocation, product identity, and size of batch.

Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times
- Identity of major equipment used (e.g., reactors, driers, mills, etc.)
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed
- Signatures of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label
- Representative label (commercial supply)
- Any deviation noted, its evaluation, and investigation conducted (if appropriate) or reference to that investigation (if stored separately)
- Results of release testing
- All analytical records relating to the batch, or a reference that will permit their retrieval
- A decision for the release or rejection of the batch, with the date and signature of the person responsible for the decision
- The production record review

Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure

or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

The following information should be recorded at the time each action is taken (the date must be noted and the person responsible should be clearly identified by signature or electronic password):

- The name of the product, the batch number and the quantity of product to be packed, as well as the quantity actually obtained and its reconciliation
- The date(s) and time(s) of the packaging operations
- The name of the responsible person carrying out the packaging operation
- The initials of the operators of the different significant steps
- The checks made for identity and conformity with the packaging instructions, including the results of in-process controls
- Details of the packaging operations carried out, including references to equipment and the packaging lines used and, when necessary, instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area
- Whenever possible, the regular check for correctness of printing (e.g. batch number, expiry date and other additional overprinting) and specimen samples collected
- Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person
- The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained; this is necessary to permit an adequate reconciliation.

A sample of BMR – Refer Appendix I

13.4 MASTER FORMULA RECORD

13.4.1 Definition: A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls."

13.4.2 Master production instructions should include:

- The name of the intermediate/API/formulation being manufactured and an identifying document reference code, if applicable

- A complete list of raw materials and intermediates (designated by names or codes sufficiently specific to identify any special quality characteristics)
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included wherever justified
- The production location and major production equipment to be used
- Detailed production instructions, including the:
  - Sequences to be followed
  - Ranges of process parameters to be used
  - The methods, or reference to the methods, to be used for preparing the critical equipment (e.g., cleaning, assembling)
  - Sampling instructions and in-process controls, with their acceptance criteria, where appropriate
  - Time limits for completion of individual processing steps and/or the total process, where appropriate
  - Expected yield ranges at appropriate phases of processing or time.
- Where appropriate, special notations and precautions to be followed, or cross-references to these
- Instructions for storage of the intermediate or API/semi-finished formulations to assure its suitability for use; instructions should cover the labeling (specimen labels and packaging materials and special storage conditions with time limits, where appropriate).

Master Formula Record is also called MFR, Master Production Record. MFR is used as reference standard for preparing batch manufacturing record (BMR) by manufacturing units. It is prepared by the research and development team of the company. It contains all information about the manufacturing process for the product. Master Formula Record (MFR) is a master document for any pharmaceutical product. MFR plays an important in consistency for each batch manufacturing. There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by the competent technical staff i.e. head of production and quality control. A Master Formula Record is either prepared based upon experience of competent qualified staff like manufacturing chemist or analytical chemist or prepared based upon batch manufacturing record of a batch size.

MFR includes –

- Product Details : Name, logo and address of the manufacturing company.
- Dosage form name. Brand name, Generic name.
- Product code and Label claim of all ingredients
- Product description : Batch size, Pack size and packing style
- Shelf life and Storage conditions
- MFR number and date: Supersede MFR number and date,
- Effective batch number
- Authorization by the production and quality assurance head
- Equipment: A list of all required equipment and machines required in the manufacturing process with their capacity.
- Special instructions: The precautions and special instructions to be followed during the product manufacturing and packing
- Calculations: Include the calculation steps of all active materials to get the 100% of the active material. The calculation is done using water or LOD to get 100% potency.
- Manufacturing Process: All steps in all stages of the manufacturing process are written. All process steps like shifting, milling, lubricating, granulation, compression and coating are written in detail including the process time and yield. It also include atmospheric conditions as temperature, humidity, and storage conditions for every step.
- Packing Process: List of all packing materials with their quantity is written. Line clearance, reconciliation of printed and unprinted packing materials should be included in details.
- Yield: Include the theoretical, actual yield and acceptance limit of the batch.

Primary Responsibility is of F&D and Production Department and secondary responsibility is of Quality Assurance Department. Accountability lies with Head-Quality Assurance for implementation of SOP.

13.4.3 Steps in preparation of MFR: Production Department in association with F&D prepares MFR. It is divided into two sections;

1)Manufacturing 2) Packaging

The first page of both the sections shall have following details: Name, address and logo of the company, Dosage form, Brand name Generic name Product code Label claim : this should include all ingredients and text included in product permission. Product Description, Shelf Life, Pack Size, Batch Size and Storage conditions.

The secondary page of manufacturing section shall include-Process steps to be monitored. Subsequent pages shall include the processes to be monitored. The list of equipment, machines, utensils to be used, shall be described. The subsequent page shall include any special precautions to be taken for the product during manufacturing and packing. The same page should also include Batch Manufacturing Formula

At the end of every important stage, include a statement of the yield with the acceptable limits. In-process quality checks during and at the end of important steps and stages with their limits are included. The process shall include the process equipment to be used. The methods or the reference of the methods/procedures to employed for preparing, cleaning, assembling,operating the various equipments are given. Detailed stepwise processing instructions(example: checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures, humidity etc.) is included. The requirements for storage conditions of the products is also present.

The secondary page of packaging section of MFR should include complete list of all the packaging materials required for a standard batch size,including quantities,sizes and types. Include line clearance checking during batch cording and batch packaging operations. Includes reconciliation of printed and unprinted packaging materials with acceptable limits. Includes destruction of excess or rejected printed packaging materials Includes description of packaging operation including any significant subsidiary operations and equipments to be used.

Sample of MFR – Refer Appendix II

13.5 SOP

A Standard Operating Procedure (SOP) is a set of written instructions that document a routine or repetitive activity which is followed by employees in an organization. The development and use of SOPs are an integral part of a successful quality system. It provides information to perform a job properly, and consistently in order to achieve pre-determined specification and quality end-result. SOPs should allow for the continual improvement of standards of service, and provide evidence of commitment towards protecting patients.

13.5.1 BENEFITS OF SOP

1. Standard Operating Procedure (SOP) is a set of written instructions that document a routine or repetitive activity which is followed by employees in an organization.
2. To ensure that processes continue uninterrupted and are completed on a prescribed schedule. Ensure against process shut-downs caused by equipment failure or other facility damage.

3. To ensure that no failures occur in manufacturing and other processes that would harm anyone in the surrounding community. Following health and environmental steps in SOPs ensures against spills and emissions that threaten plant neighbors and create community outrage.
4. To ensure that approved procedures are followed in compliance with company and governmen regulations. Well-written SOPs help ensure that government regulations are satisfied. They also demonstrate a company's good-faith intention to operate properly.
5. To serve as a training document for teaching users about the process for which the SOP was written. Thorough SOPs are used as the basis for providing standardized training for employees who are new to a particular job and for those who need re-training.
6. To serve as a checklist for co-workers who observe job performance to reinforce proper performance. The process of actively caring about fellow workers involves one worker coaching another in all aspects of proper job performance. When the proper procedures are outlined in a good SOP, any coworker can coach another to help improve work skills.
7. To serve as a checklist for auditors. Auditing job performance is a process similar to observation mentioned in the previous item only it usually involves record keeping. SOPs should serve as a strong basis when detailed audit checklists are developed.
8. To serve as an historical record of the how, why and when of steps in an existing process so there is a factual basis for revising those steps when a process or equipment are changed. As people move from job to job within and between companies, unwritten knowledge and skills disappear from the workplace. Properly maintained written SOPs can chronicle the best knowledge that can serve new workers when older ones move on.
9. To serve as an explanation of steps in a process so they can be reviewed in accident investigations.Alt hough accidents are unfortunate, view them as opportunities to learn how to improve conditions. A good SOP gives you a basis from which to being investigating accidents

13.5.2 SOP REQUIREMENTS

The data generated through these procedures should be maintained to show compliance with the above mentioned requirements.

- Prepare apex documents like Quality Policy, Quality Manual, Site Master File, Validation Master Plan, etc. to describe the quality commitments of the management

- Define the roles and responsibilities of all personnel working in the organization
- Prepare policy for periodic review of documents. Ensure that the current industrial practices and pharmacopoeial requirements are fulfilled by the current versions of documents
- SOP for document (SOPs, MPCR, BPCR, validation/qualification protocols, formats) preparation, review, approval, training, distribution, control, and its retention
- Procedure for maintaining revision history
- Management, control, and retention of superseded or obsolete documents
- Document archival and retrieval procedure
- Handling, archival, retrieval, and retention of electronic records/documents
- Procedure for control of electronic signatures
- Equipment cleaning and sanitation procedure
- Issuance and control of equipment logs
- Document describing measures taken for avoidance of cross-contamination and its training records
- Cleaning validation master plan
- Procedure for batch-to-batch and product-to-product cleaning and its verification to ensure removal of residue of previous batch/product
- Records for incoming raw materials and packaging materials
- SOP for preparation of process validation protocol and reports
- SOP for preparation of master production control records
- SOP for preparation of batch manufacturing and control records
- SOP for allocation of batch number
- Calibration master plan and calibration reports
- Batch release procedure
- SOP for preparation and control of QC data sheet
- SOP for allocation of analytical control number
- Procedure for review of analytical data
- SOP for investigation of OOS results
- SOP for change control, revision of any process or documents, or upgradation of facility or equipment should be routed through impact assessment and change control procedure

- SOP for deviation handling system
- SOP for corrective and preventive action (CAPA)
- SOP for stability testing
- SOP for product distribution and its control

13.5. 3 FORMAT OF TECHNICAL SOP

In general, technical SOPs will consist of five elements:

- Title page:
- Table of Contents
- Procedures
- Quality Assurance/Quality Control
- References

1. Title Page.

2. Table of Contents

3. Procedures - The following are topics that may be appropriate for inclusion in technical SOPs. Not all will apply to every procedure or work process being detailed.

a. Scope and Applicability (describing the purpose of the process or procedure and any organization or regulatory requirements, as well as any limits to the use of the procedure),

b. Summary of Method (briefly summarizing the procedure),

c. Definitions (identifying any acronyms, abbreviations, or specialized terms used), Health & Safety Warnings (indicating operations that could result in personal injury or loss of life and explaining what will happen if the procedure is not followed or is followed incorrectly; listed here and at the critical steps in the procedure)

d. Cautions (indicating activities that could result in equipment damage, degradation of sample, or possible invalidation of results; listed here and at the critical steps in the procedure)

e. Interferences (describing any component of the process that may interfere with the accuracy of the final product),

f. Personnel Qualifications/Responsibilities (denoting the minimal experience the user should have to complete the task satisfactorily, and citing any applicable requirements, like certification or "inherently governmental function"),

g. Equipment and Supplies (listing and specifying, where necessary, equipment, materials, reagents, chemical standards, and biological specimens

h. Procedure (identifying all pertinent steps, in order, and the materials needed to accomplish the procedure such as:

- Instrument or Method Calibration and Standardization
- Sample Collection
- Sample Handling and Preservation
- Sample Preparation and Analysis (such as extraction, digestion, analysis, identification, and counting procedures)
- Troubleshooting
- Data Acquisition, Calculations & Data Reduction Requirements (such as listing any mathematical steps to be followed)
- Computer Hardware & Software (used to store field sampling records, manipulate analytical results, and/or report data)

i. Data and Records Management (e.g., identifying any calculations to be performed, forms to be used, reports to be written, and data and record storage information).

4. Quality Control and Quality Assurance Section - QC activities are designed to allow self-verification of the quality and consistency of the work. Describe the preparation of appropriate QC procedures (self-checks, such as calibrations, recounting, reidentification) and QC material (such as blanks - rinsate, trip, field, or method; replicates; splits; spikes; and performance evaluation samples) that are required to demonstrate successful performance of the method. Specific criteria for each should be included. Describe the frequency of required calibration and QC checks and discuss the rationale for decisions. Describe the limits/criteria for QC data/results and actions required when QC data exceedQC limits or appear in the warning zone. Describe the procedures for reporting QC data and results.

5. Reference Section - Documents or procedures that interface with the SOP should be fully referenced (including version), such as related SOPs, published literature, or methods manuals. Citations cannot substitute for the description of the method being followed in the organization. Attach any that are not readily available.

3. To ensure that no failures occur in manufacturing and other processes that would harm anyone in the surrounding community. Following health and environmental steps in SOPs ensures against spills and emissions that threaten plant neighbors and create community outrage.
4. To ensure that approved procedures are followed in compliance with company and governmen regulations. Well-written SOPs help ensure that government regulations are satisfied. They also demonstrate a company's good-faith intention to operate properly.
5. To serve as a training document for teaching users about the process for which the SOP was written. Thorough SOPs are used as the basis for providing standardized training for employees who are new to a particular job and for those who need re-training.
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- SOP for allocation of analytical control number
- Procedure for review of analytical data
- SOP for investigation of OOS results
- SOP for change control, revision of any process or documents, or upgradation of facility or equipment should be routed through impact assessment and change control procedure

13.6 QUALITY AUDIT

Defination: A systematic and independent examination to determine whether quality activities and related results comply with the planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

Quality audits are typically performed at defined intervals. Any failure in their proper implementation may be published publicly and may lead to a revocation of quality certification.

13.6.1 TYPES OF AUDIT

- A first party audit is an audit performed by an organisation on itself i.e. an internal audit.
- A second party audit is an audit performed by one organisation on its own behalf on another usually on a supplier by a customer.
- A third party audit is an audit by an independent organisation other than the customer on a supplier

13.6.2 PHASES OF AUDIT

- Phase 1-Preparation: This phase precedes the actual review meeting. It is the responsibility of the chairman and presenter to organize the quality review and notify all those invited
- Phase 2- The review meeting: The central phase of the quality review process is the review meeting itself. During the review meeting the emphasis should be on error detection, in line with the criteria, and only limited discussion of corrective action should occur.
- Phase 3- The Follow-Up Following the quality review meeting there should be a follow-up period during which the errors identified at the review that were committed to the follow-up action list are rectified and signed

13.6.3 OBJECTIVES OF QUALITY AUDIT

Pharmaceutical manufacturers commonly audits as an effective mechanism to verify compliance with GMP regulation . The general objectives of quality audit are as follows: To determine conformity or non conformity of the quality system elements with specified requirements. To determine the effectiveness of the implemented system in meeting specified quality objectives. To afford an opportunity to improve the quality system. To provide Managers with information.

13.6.4 PRINCIPLES OF AUDITING

Ethical Conduct: The foundation of Professionalism, Trust, Integrity, Confidentiality and discretion are essential to auditing.

Fair Presentation: The obligation to report truthfully and accurately.

Due professional care: The application of diligence and judgment in auditing.

Independence: The basis for the impartiality of the audit and objectivity of the audit conclusions. Evidence based approach: The rational method for reaching reliable and reproducible audit.

13.6. 5 TYPES OF QUALITY AUDIT

- Adequacy audit/ document review
- Compliance audit/ on-site audit
- External audit
- Internal audit
- Product or process audit

Adequacy audit/ Document review

This is also known as system or management audit and is normally documented system represented by the quality manual and the associated procedures adequately meets the need of the applicable standard.

Compliance audit/ On-site audit

This is the audit which seeks to establish the extent to which the documented system is implemented and observed by the workforce, i.e. are the people complying with the system

External Audit

This is an audit that a company performs on its own suppliers or subcontractors. Purpose of external audit is to gain confidence in the partnership arrangement. This ensures that requirements are understood. There is a reduction of in-house Q.C testing of starting materials and reduces the risk of failure.

Internal Audit

This is the most important types of audits, which requires the company to look into its own systems, procedures and activities in order to ascertain whether they are adequate and being compiled with. It provides the management with the information on whether or not their policies are being met, if the system is as efficient and as effective as it should be and whether any changes are needed. It can provide a line of communication throughout the company and be a great motivator.

Product/ Process Audit

Product review refers to an in- depth examination of a particular product/service to evaluate whether it conforms to product specifications, performance standards and customer requirements. Process audit refers to an analysis of elements of a process and appraisal of completeness, correctness of conditions and probable effectiveness.

The Audit Life Cycle

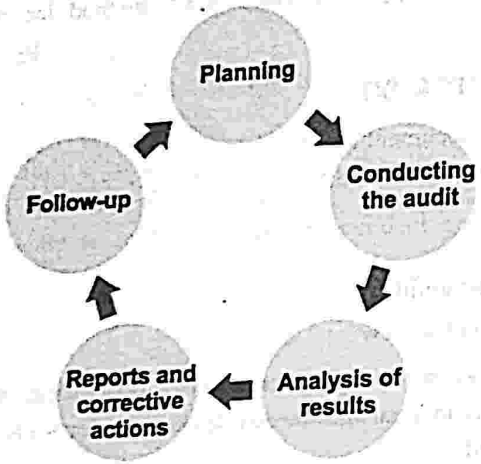

Figure13.1 : Audit Life Cycle

13.6.6 AUDIT METHODS & TECHNIQUES

Audit Methods & Techniques are categorized based on the purpose of audit.

Horizontal Auditing

It involves examination of each functional area of an organization to verify adequacy and implementation of Quality. Used for internal system auditing and second & third party assessment when it is necessary to establish if a basic QMS has been installed and is being implemented and maintained. Each functional area is checked for conformance with quality system requirements, applicable to that area.

Vertical Auditing

It involves examining functional areas of an organization that are actively contributing to a specific work package or contractual requirement.

Random auditing

It examines the various aspects of an organization's operation as determined by the auditor and due to the need to closely examine a particular actively or generally probe the system in arandom manner.

13.6.7 ROLE OF GMP AUDITS IN Q.A AND Q.C PROGRAMMES

- Auditor's review on SOPs employees' practices and behavior
- Compare master specifications against compendia & regulatory requirements.
- Verify the test data and validation testing
- Validation test reports are compared against raw data.
- Verify corrective actions taken in reaction to audit finding.

GMP Regulation Format

The basic elements are derived from the following subparts of regulations:

- Organization and personnel
- Building and facilities
- Equipments Production and Processing controls
- Production and packaging control
- Holding and distribution
- Lab controls
- Records and reports
- Returned and salvaged drug

Written Criteria & SOP has to be established defining which audit data or elements are to be considered in the assessment of program performance. Formal written SOPs should fully describe the details for carrying out the various audit functions like: The responsibility for audit data review Personnel responsible for recommendation Decisions concerning corrective actions Effective use of written criteria to ensure that conditions and practices remain under suitable state of control. SOPs should be established.

Planned periodic frequency

Each firm must establish the optimum time interval between audits based on several important factors like: -intended purpose -objectives, scope and depth -prior history of audit finding Two types of Visits can be done depending on the type of audit: Announced Visit Un-announced Visit

Personnel: The following personnel factors deserve systemic attention.

- Defining audit or Qualification: Auditors are selected based on their knowledge Their work experience in manufacture and Q.C as well as years of first hand dealing

with GMP matters. Essential Auditor skill includes awareness of firm's SOPs and knowledge about its various departments.

- Documentation training skills & Experience: There are usually 2 formats (1) Scientific principles, training under chemistry, engineering, statistics and pharmaceutics. (2) GMP training may include the cumulative knowledge from reasonable years of experience. This knowledge comes from; daily activities and formal training sessions
- Audit teams: The personnel in the audit team are selected based on their experience and knowledge. The team is required to cover many different systems and large amount of data. Composition of team will vary depending upon the nature and scope of the audit. Leader is usually a senior auditor who has extensive knowledge of the firm's operations & has strong leadership qualities. Tem size depends upon: Firm size Total number of products manufactured & control systems

13.6.8 REPORTING AUDIT FINDING

Audit reports should contain complete details of the program detected. Corrective action is taken to eliminate problems and to measure the overall adequacy of the audit program. There are two important reporting phases(1)Preliminary reports during the audit (2)Final report to the management

13.6.9 BENEFITS DERIVED FROM AUDITS

The major benefits that are derived from Audits are as follows:

- Assuring GMP compliance
- Detecting potential problems
- Effecting programmed improvement
- Increasing management awareness

13.6. 10 AUDIT CHECK

- Documentation work.
- QA/QC Issues.
- SOP Manuals.
- Building and Facilities.
- Failure Investigation.
- Process Validation Program
- Master Records.
- Production and In-Process controls.
- Packaging and labelling of API's and Intermediates.

- Equipment Processing.
- Storage and Distribution.
- Material Management.
- House keeping facilities

13.7 QUALITY REVIEW

Quality review is an evaluation conducted at regular periodic or rolling quality reviews of all registered medicinal pharmaceutical products, including export to assess the quality standard of each drug product with the view to verify the consistency of existing process and to check the appropriateness of current specifications and to highlight any tends in order to determine the need to change any drug product specifications or the manufacturing processes or control procedures. It is an effective quality improvement tool to enhance the consistency of manufacturing process and overall quality of the product. A Good Manufacturing Practice ensures that the products are consistently produced and controlled according to quality standards. Annual Product Quality Reviews(APQR) not only are required by GMP but also required for robust quality improvement for manufacturing the pharmaceutical product. It is a written report that is required for every drug product, based on data collected at least annually. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. It is universally accepted by the industry and contents must specify a list of manufactured batches, release data and reviews of deviations, complaints, recall and returned goods.

13.7.1 HISTORY OF PRODUCT QUALITY REVIEW

The US Food and Drug Administration proposed a necessity to prepare written summary for each product in its February 13, 1976 by rewriting the good manufacturing practices (GMPs) for drug products. The purpose of this proposed GMP requirement was to provide reliable procedures for a drug manufacturer to review the quality standards for each drug product. After numerous comments from industry objecting to the preparation of written summaries, US FDA revised the proposal to allow each company to establish its own procedures for the evaluation of product quality standards, by reviewing the records required by the GMPSs on annual basis. This requirement was published as final current good manufacturing practices (CGMP) regulations for drug products (21 CFR 211.180(e)). Since its publication, 21 CFR 211.180(e) has been commonly referred by FDA and the pharmaceutical industry as the "Product Annual Review" (PAR) or the "Annual product review" (APR). In august 2001, FDA also adopted and published the guidance for industry ICHQ7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. This guidance was developed

within the expert Working Group of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. This guidance was then incorporated as Part II of the European Community Guide to GMP (EU GMP Guide) in October 2005.

13.7.2 SIGNIFICANCE OF ANNUAL PRODUCT QUALITY REVIEW (APQR)

1. Verify the consistency of the existing manufacturing process and minimize the risks to pharmaceutical products which will be helpful for the pharmaceutical companies to develop their products consistently of best quality on yearly basis.
2. It determines the quality and process defects of the products.
3. It also determines possible improvements of the analytical methods and manufacturing process.
4. Trend of yield, analytical results, manufacturingparameters of the product are also highlighted.
5. It is helpful to identify the process and product defects.
6. It reviews the quality of the raw material and packaging material which is used for the product.
7. Mainly it indicates the quality of material.
8. Verifies the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements.
9. Out of Specification parameter helps to determine the product defects and the prospective actions are defensing the product from possible risks.
10. If any of the batches is failed, then it is also included in the Annual Product Quality Review to determine reasons for the batch rejection.
11. The review of the stability study results of any long term and on-going stability of the bulk product and the marketed product should be done.

13.8 PRODUCT QUALITY REVIEW ACCORDING TO VARIOUS REGULATORY AGENCIES

European Commission

Regular quality reviews come under EU Guidelines to Good Manufacturing Practice Part I; Chapter 1 Quality Management (issued on 31 January 2013)

Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results
- A review of all batches that failed to meet established specification(s)
- A review of all critical deviations or non-conformances and related Investigations
- A review of any changes carried out to the processes or analytical methods; A review of results of the stability monitoring program
- A review of all quality-related returns, complaints and recalls
- A review of adequacy of corrective actions.

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

Periodic Review of Validated Systems Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

United states

21 CFR Part 211 Sec 211.115 states about reprocessing one that fails to confirm with all established standards, and characteristics. Reprocessing shall not be performed without the review and approval the quality control unit. Sec 211.180 states about general requirements for any production, control, or distribution record shall be retained for at least 1 year after the expiration date of the batch and in case of OTC drug products lacking the expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch. The quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedure. Written procedures shall be established and followed for such evaluation and include provisions for: 1) A review of representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch. 2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted for than 211.192 for each drug product. Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204 or 211.208 of these regulations, any recalls, reports of inspectional observations issued by FDA. Sec 211.192 states about Production Record review, Sec 211.198 states about the all the complaint files related to the product, and then 211.204 are about the returned Drug Products etc. Just because of this, it is not always clear exactly what is expected by the regulatory authority. So it is presently a

standard FDA practice to make additional and quite reasonable demands that make it possible to improve the evaluation possibilities for products. This development is then consistent of with the requirement s of the Guidance for industry Quality Systems Approach to Pharmaceutical CGMP Regulations Published in Sep 2006. The US FDA regulations describe very limited the contents for the review and evaluation of the product but as per EUROPE the contents for the preparation of the APQR are well described.

13.9 QUALITY DOCUMENTATION

Documentation plays a key role in the Quality Management System. Documentation are to define the manufacturers system of information & control to minimize the risk of misinterpretation & errors inherent in oral or casually written communication, to provide unambiguous procedures to be followed to provide confirmation of performance, to allow calculations to be checked & to allow tracing of batch history. Documents are a mirror to show actual image of any pharmaceutical company. Documents and products are produced in pharmaceuticals but regulatory bodies are interested to see documents first. Different documents can describe the different activity in pharma and its actual image. Document is any written statement or proof. Documentation is an essential part of Quality Assurance and Quality Control system and it is related to all aspects of Good Manufacturing Practices (GMP). It is mainly defines the specification for all materials, method of manufacturing and control. It also ensures that personnel concerned with manufacturing should know information to decide whether to release the batch or not for sale it also provides an audit trail which also allows the investigation of history of any suspected defective batch. These documents should be approved, signed, dated by appropriate and authorized person. These documents shall specify their title, purpose and nature. They should be regularly reviewed and kept up to date and if any alterations are made in their entry shall be signed with date. Good documentation encompasses practically all the aspect of pharmaceutical production

13.9.1 QUALITY DOCUMENTATION HIERARCHY

The 4-tiered hierarchy has been established as a best practice for your Quality Documentation System

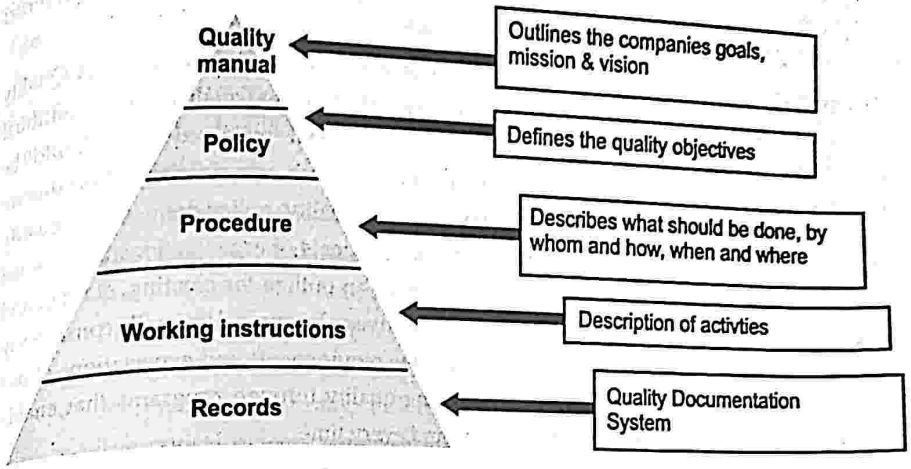

Figure 13.2 : Hierarchy of Quality Documentation System

Quality manual

The top tier in the hierarchy is the Quality Manual. This is the guiding document for which all subsequent decisions should be aligned with.The Quality Manual is a high level document that's authored and approved by upper management and it outlines the companies goals, mission & vision. It should outline what the company stands for & why they exist. It fully describes the scope of QMS i.e. what should be included in the Quality system. It completely explains each and every requirement of the ISO 9001 Standard. It contains complete detail and explanation of exclusions i.e. what should be eliminated in the Quality System. It contains references for the quality procedures used to describe all the QMS processes. A flow chart representing the series and interaction of the key business processes. The organization's quality policies which shows that the organization is strictly committed to quality. The quality policy and the objectives can be part of the manual as well. The quality manual should include most of following elements: title and table of contents; scope of the QMS; exclusions from ISO 9001, versioning information and approval; quality policy and objectives; QMS description, the business process model of the organization; definition of responsibilities for all personnel; references to relevant documents and relevant appendices. It can be used for the folloing purposes:

- To communicate management's expectations for quality to the organization

- To reveal the organization conformity with ISO 9001 requirements
- To serve as a measure for compliance to management's expectations for: Internal audits; ISO Registrar audits; Customer audits

Quality policy : A policy represents a declarative statement by an organization. A Quality policy should state the commitment of the organization to quality and continual improvement. Usually, this policy is used for promotional purposes and should be displayed in the organization's premises and posted on websites, so a clear and short quality policy is convenient and is the general practice. The Quality policy defines the quality objectives to which the organization strives. The quality goals of organizations are defined by quantifying the quality objectives. It should provide an outline for creating, stating, and measuring your performance of the quality objectives. Example: We will consistently provide products and services that meet or exceed the requirements and expectations of our customers. We will actively pursue ever improving quality through programs that enable each employee to do their job right the first time and every time.

Quality procedures. Quality procedures can have different formats and structures. They can be narrative, i.e., described through text; they can be more structured by using tables; they can be more illustrative, i.e., flow charts; or they can be any combination of the above.

Quality procedures should include the following elements:

- Title – for identification of the procedure;
- Purpose – describing the rationale behind the procedure;
- Scope – to explain what aspects will be covered in the procedure, and which aspects will not be covered;
- Responsibilities and authorities of all people/functions included in any part the procedure;
- Records that result from the activities described in the procedure should be defined and listed;
- Document control – identification of changes, date of review, approval and version of the document should be included in accordance with the established practice for document control;
- Description of activities – this is the main section of the procedure; it relates all the other elements of the procedure and describes what should be done, by whom and how, when and where. In some cases, "why" should be clarified as well. Additionally, the inputs and the outputs of the activities should be explained, including the needed resources.
- Appendices may be included, if needed.

Work instructions. Work instructions can be part of a procedure, or they can be referenced in a procedure. Generally, work instructions have a similar structure to the procedures and cover the same elements; however, the work instructions include details of activities that need to be realized, focusing on the sequencing of the steps, tools, and methods to be used and required accuracy. Training of personnel and use of competent personnel decreases the need for highly detailed work instructions. Work Instructions may cover many of the following details:

- The manner in which the work will be done
- The equipment and tools that will be used
- The environment or location associated with the work
- Material handling requirements
- Safety alerts for the employees
- A cross-reference to any other required processes or work instructions
- The critical process parameters to be monitored & the instructions on how to monitor
- The critical product characteristics to be monitored & the instructions on how to monitor
- Equipment maintenance procedures
- Methods for verifying that the product meets specifications
- Other non-product related criteria for the final product

Records: This final tier in the Quality Documentation System. All the data, information, records, forms, etc are archived. Quality Records are the objective evidence to prove that the Quality System is being executed per procedure. Quality Records also describe how the quality of the end product was verified to have met the specifications & thus meets the customer's needs & expectations. Records include the following sources:

- Non-Conformance Investigations
- CAPA's
- Audit Results
- Supplier Documentation
- Calibration Results
- Maintenance Records

13.9.2 THE 'DOCUMENTS" MODEL

The "DOCUMENTS" model, which lists out the areas required for GMP document implementation :

D- Design, development, deviations, dossiers and Drug Master Files for regulated markets, distribution records.

O- Operational procedures/techniques/methods, Out Of Specifications (OOS), Out Of Trend (OOT).

C- Cleaning, calibration, controls, complaints, containers and closures, contamination and change control.

U- User requirement specifications, utilities like water systems, HVAC, AHU etc.

M- Man, materials, machines, methods, maintenance, manufacturing operations and controls, monitoring, master formula, manuals (quality, safety and environment), medical records.

E- Engineering control and practices, Environment control, Equipment qualification documents N- Non-routine activities, New products and substances

T-Technology transfer, training, testing, Trend analysis, Technical dossiers

S- SOPs, safety practices, sanitation, storage, self-inspection, standardization, supplier qualification, specifications and standard test procedures and site master file.

13.10 DOCUMENTS AND RECORDS

Documentation and records are used throughout the manufacturing process, as well as supporting processes (e.g. Quality Control or Quality Assurance), must meet the basic requirements of Good Documentation Process. These include (but are not limited to):

1. Batch Record Forms
2. Bills of Materials (BOMs)
3. Specifications
4. Policies
5. Protocols
6. Standard Operating Procedures (SOPs)
7. Work Instructions (WIs)
8. Checklists
9. Forms/Log sheets
10. Certificate of Analyses or Certificate of Compliance
11. Technical transfer reports
12. Technical agreements

13. Technical reports
14. Test Methods
15. Training Assessments
16. Records
17. Worksheets, note books, and log books
18. Validation documentation
19. Manufacturing and packaging instructions
20. Confidentiality agreements
21. Change control
22. Quality system related documents
23. Quality manual
24. Validation protocols and reports
25. Deviation reports
26. Audit plans
27. Electronic and hard-copy Quality records (e.g. non-conformance, corrective and preventative actions, internal inspection, change control, training records etc.)
28. Validation Master Plans and validation documents including URS, DQ, FAT, IQ, OQ, PQ, and Validation reports.
29. Test material related documents including product specification, test material receipt and reports.
30. Personnel related documents including training records.
31. Facility related documents including floor plans, HVAC plans, and environmental specifications.
32. Deviation forms including unplanned deviations and system failure investigation

Laboratory control records

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number and, where appropriate, the manufacturer and/or supplier;

alternatively, other distinctive code, date of sample taken and, where appropriate, the quantity of the sample and date the sample was received for testing

- A statement of, or reference to, each test method used
- A statement of the weight or measure of sample used for each test as described by the method; data on, or cross-reference to, the preparation and testing of reference standards, reagents, and standard solutions
- A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, all properly identified to show the specific material and the batch tested
- A record of all calculations performed in connection with the test including, for example, units of measure, conversion factors, and equivalency factors
- A statement of the test results and how they compare with established acceptance criteria
- The signature of the person who performed each test and the date(s) on which the tests were performed
- The date and signature of a second person, showing that the original records were reviewed for accuracy, completeness, and compliance with established standards.

Complete records should also be maintained for:

- Any modifications to an established analytical method
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices
- All stability testing performed on APIs/formulations
- Out-of-specification (OOS) investigations

Complete records should be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions; record should also be maintained of periodic calibration of laboratory instruments, apparatus, gauges, and recording devices.

Batch production record review

Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units, following procedures approved by the quality unit(s).

All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

Distribution record should be maintained and must include the batch number; quantity produced; name, address, and contact details of customer; quantity supplied; and date of supply.

13.11 DISTRIBUTION RECORD

- Maintenance of records of finished product is essential to facilitate complete recall of batch if necessary. Distribution13 records are written data related to distribution of drug products from the manufacturer to the distributors. The complete data regarding all batches of drug products should be maintained.

Distribution procedure: It shall include the following:-

- A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.
- A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary
- The manufacturer must maintain records of all distribution transactions involving in process or finished goods
- A variety of distribution recording system must be utilized

13 The division and movement of pharmaceutical products from the premises of the manufacturer of such products, or another central point, to the end user thereof, or to an intermediate point by means of various transport methods, via various storage and/or health establishments.

- Computerized tracking systems are most common but paper systems such as recording the lot or control number on the retained copies of the shipping invoices or recording the dates on which each lot commenced distribution also use

Particulars in Distribution records:-

- Name
- Dosage Form and Strength of the Consignment 14(or delivery)
- The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.
- Name And Address Of Consignee
- Date And Quantity Shipped
- Name, Address And Number Of The Customer That The Product Is Shipped To
- Delivery Order Delivered Date And Number
- Quantity
- Product Batch Number
- Expiry Date
- date of dispatch
- quantity of the products, i.e. number of containers and quantity per container
- Special Storage Requirement Or Precautionary Measures To Handle The Product.
- a unique number to allow identification of the delivery order.

14 Consignment (or delivery) The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

REVIEW QUESTIONS

SHORT ANSWER TYPE QUESTIONS

Q1. What do you understand by pharmaceutical market complaint?

Ans. 'Complaint' is defined as a statement that something is wrong or not good enough. Generally in the pharmaceutical industry, market complaints are regarding the quality of drug product. For example, 'the bottle is leaking', 'the cap is difficult to open' etc.

Q2. Define recall

Ans. A firm's removal or correction of a marketed product that FDA considers being in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure. "Recall" does not include a "market withdrawal" or "stock recovery.

Q3. Define market withdrawl

Ans. A firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by FDA or which involves no violation, e.g., normal stock rotation practices, routine equipment adjustments and repairs etc.

Q4. What are primary reasons for product recall?

Ans. A product recall may be due to:

- Mandated by a regulatory agency as a result of a violation of a government act, standard or other mandatory regulations, such as toy recalls ordered by the Consumer Product Safety Commission.
- Required to avoid potentially serious additional product liability claims or losses.
- Indicated by the analysis of field monitoring reports and feedback that may point to product tampering, nearmiss incidents, accidents or consumer complaints.
- Suggested by new information based on additional research and product testing.
- Needed when characteristics of the product don't measure up to the advertised claims for safety or effectiveness.

Q5. What are the different types of pharmaceutical waste?

Ans. Pharmaceutical wastes are classified into 3 types: hazardous waste, non hazardous waste, and chemo waste.

Q6. Name the common types of documents that are maintained in a GMP facility

Ans. Quality manual, policies, SOP, batch records, test methods, specifications, log books etc.

CHAPTER 14

CALIBRATION AND VALIDATION

14.1 IMPORTANCE OF VALIDATION

The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and well-being of the public. Facilities and processes involved in pharmaceutical production impact significantly on the quality of the products. At the same time, the objective of the pharmaceutical industry is to get high quality at low cost. Objective = High Quality & Low Cost. Therefore, efficient use of resources is the key to success. Thus, validation becomes an integral part of quality assurance. It is the requirement of current Good Manufacturing Practices (cGMPs) for finished pharmaceuticals (21CFR 211) and medical devices (21 CFR 820).

According to the Food and Drug Administration (FDA)

"Validation is 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 characteristics.

Validation is thus the action of proving that any procedure, process, equipment, material, activity will actually lead to expected results and produce a quality product. It includes activities starting from analytical methods used for quality control of a drug substance to drug product validation. There are four components of validation: man, machine, material, and method.

Validation has many benefits as described below

- Fulfillment of regulatory requirement
- Increased output
- Reduction in rejections and reworks
- Safety
- Avoidance of capital expenditures
- Fewer complaints about process related failures
- Reduced testing in the process and finished goods
- More rapid and accurate investigations into process deviations
- Easier and reliable startup of new equipment
- Easier scale-up from development work
- Easier maintenance of the equipment

- Improved employee awareness of proce
- More rapid automation

14.2 SCOPE OF VALIDATION

The scope of validation involves providing the specific elements to verify that all the components of the system operate as predetermined and specified to achieve the desired results. For example, operational qualification of dryer report assures that the dryer works according to the acceptance criteria involving the highest and lowest working limits. Following requirements come under the scope of validation.

- Validation should be done in a structured way according to documentation including procedures and protocols .
- Validation requires an appropriate and sufficient infrastructure including: organization, documentation, personnel and finances.
- Personnel with appropriate qualifications and experience
- Extensive preparation and planning before validation is performed
- A specific programme for validation activities
- 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.
- Manufacturers or top officials to identify the type of validation work needed
- Involvement of management and quality assurance personnel
- Significant changes in facilities, equipment, processes should be validated
- Risk assessment approach should be used to determine the specific scope and extent of validation needed case-by-case basis

14.3 VALIDATION MASTER PLAN CONSISTS OF FOLLOWING ELEMENTS

- Introduction- Firms validation policy and general description
- Organizational Structure- Description of personal responsibility for all validation activities
- Plant, process and product description- Description of the plant layout, process, and product for completing the document in all aspects
- Specific process requirements- mention of the important characteristics of the plant in total that eventually lead to the quality of the product
- List of products, process, systems to be validated- A matrix system comprising of the total list of validations required.
- Key acceptance criteria- explanation and listing of acceptance criteria for all above mentioned validations

- Documentation format- the format used for dossier preparation should be save and refereed
- SOP-A list of relevant SOP's
- Planning and scheduling- description of overall planning including human resource, equipment, time plan
- Change control- description of the method to control changes in critical components including materials, facilities, equipments, or process.

Some other elements:

1. Facility Validation
2. Analytical method validation
3. Equipment Qualification
4. Qualification of input material
5. Product Quality specification and test methods
6. Method validation
7. Process validation
8. Equipment cleaning method validation
9. Trained manpower and competency of personnel
10. Stability studies data evaluation
11. Revalidation criteria
12. Validation report at each step

14.4 VALIDATION PROTOCOL

After preparing Validation Master Plan, the next step is to prepare validation protocol. There are the following contents in a validation protocol.

1. General information
2. Objective
3. Background/Prevalidation Activities Summary of development and tech transfer (from R&D or another site) activities to justify in-process testing and controls; any previous validations.
4. List of equipment and their qualification status
5. Facilities qualification
6. Process flow chart e.g. as given in figure
7. Manufacturing procedure narrative
8. List of critical processing parameters and critical excipients e.g. Critical Process Variables, In Coating it can be Pan RPM, inlet & exhaust temperature, spray rate, gun distance and air pressure.
9. Sampling, tests and specifications e.g. as give in figure
10. Acceptance criteria

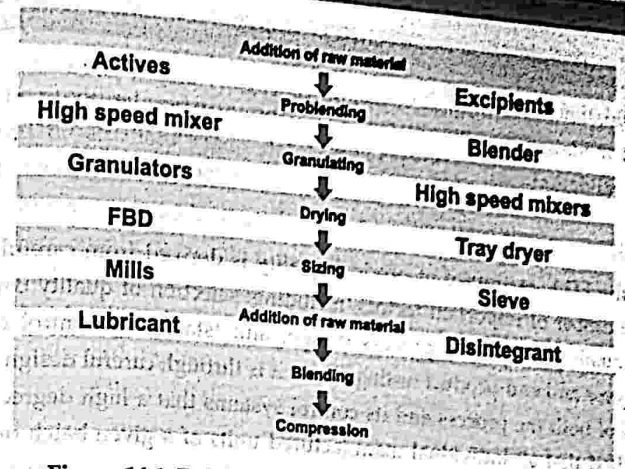

Figure 14.1: Process: Overview of Tablet Manufacturing

Table 14.1 : Typical Variables And Responses During Process Validation Of Tablet Manufacturing Process

Typical Variables and Responses		
Process Step	**Control variables**	**Measured responses**
Probleding	Blending time rpm Load size Order of addition	Blend uniformity
Granulating	Load size Amount of granulating agent Solvent addition rate rpm Granulation time	Density Yield
Drying	Initial temperature Load size Drying temperature program Air flow program Drying time Cooling time	Density Moisture content Yield
Sizing	Screen type Screen size Feed rate	Granule size distribution Loose density Packed density
Blending	Load size rpm Blending time	Blend uniformity Flow characteristics Particle size distribution
Tableting	Compression rate Granule feed rate Precompression force Compression force	Weight variation Friability Hardness Thickness Disintegration time Dissolution Dosage form uniformity

14.5 TYPES OF VALIDATION IN PHARMACEUTICAL INDUSTRY

- Process validation
- Equipment validation
- Analytical validation

14.5.1 PROCESS VALIDATION

According to the FDA, assurance of product quality is derived from careful and systemic attention to a number of important factors, including: selection of quality components and materials, adequate product and process design, and (statistical) control of the process through in-process and end-product testing. Thus, it is through careful design (qualification) and validation of both the process and its control systems that a high degree of confidence can be established that all individual manufactured units of a given batch or succession of batches that meet specifications will be acceptable. The latest guidance document for process validation published by USFDA is "Process Validation:General Principles and Practices, (published on Jan.2011)".

This USFDA guidance describes process validation activities in three stages.

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Defination: The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products" .

There are four types of process validation. The choice of procedure and method to be used to estabilish validation document is left with the manufacturer.

1. Prospective[15] validation (Pre-market validation): to prove or demonstrate that the process will work in accordance with validation protocol prepared for pilot products. Means it can now be scaled up. Following are the key points
   - Done during development stage.
   - Predicts future behavior
   - Process validation be completed prior to the release of the finished product for sale
   - Normally undertaken whenever a new formula, process or facility

15 expected or expecting to be the specified thing in the future.

- Observations made should be sufficient to allow the normal extent of variation

Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, would constitute a validation of the process. Batches made for process validation should be the same size as the intended industrial scale batches. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and with the marketing authorisation.

Output of prospective validation:

- Finished product specifications for release
- List of analytical methods
- Proposed in-process controls with acceptance criteria
- Additional testing to be carried out, with acceptance criteria
- Sampling plan
- Methods for recording and evaluating results
- Functions and responsibilities
- Proposed timetable.

2. Concurrent[16] validation:In some exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts. For example-
   - when a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site
   - where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients
   - when the number of batches produced are limited (e.g. orphan drugs).
   - when the number of lots evaluated under the retrospective validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control

   This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control. At this time IPQC tests are determined like: average unit potency, content uniformity,

16 Occurring or operating at the same time; validation going on simultaneously with the production.

dissolution time, weight variation, moisture content, particle size, weight variation, tablet hardness, pH value etc. The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel. Documentation requirements for concurrent validation are the same as specified for prospective validation.

3. **Retrospective[17] validation:** Only acceptable for well-established processes whose manufacturing processes are considered stable and when on the basis of economic consideration alone and resource limitations, prospective validation programs cannot be justified. Prior to undertaking retrospective validation, historical numerical or end product test data of production batches are subjected to statistical analysis, the equipment, facilities, subsystems used in manufacturing must be approved(qualified) in agreement with cGMP. Generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified. Retrospective validation is conducted in following manner:

- Gather the numerical data from completed batches.
- Organize these data in chronological sequence.
- Eliminate test results from non critical processing steps.
- Draw conclusion on state of control on the manufacturing process.
- Write and release a report on the findings (written evidence).

This approach is rarely been used today because it's very unlikely that any existing product hasn't been subjected to the Prospective validation process. It is used only for the audit of a validated process.

4. **Revalidation[18] :** Revalidation of Equipment and Process in Pharmaceuticals. Revalidation in the pharmaceutical industry is very important as it helps to maintain the validated status of the equipment, plant, manufacturing process as well as the computer systems The objective of revalidation is to make sure that systems are working to a good standard.

Conditions that require revalidation studies are:

- Changes in critical component (Change Control) i.e Changes to the product, the plant, the manufacturing process, the cleaning process, raw material(bulk density) or other changes that could affect product quality. Change control is defined as "a formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state."
- Change in facility or plant i.e The transfer of a product from one plant to another
- Increase or decrease in batch size
- Sequential batches that fail to conform product and process specifications
- The necessity of periodic checking of the validation results

17 related to the past; considereing the data of the already produced batch
18 ensuring that any changes made to the process or its environment have not resulted in adverse effects on product

Revalidation may be divided into two broad categories:

- Revalidation after any change having a bearing on product quality.
- Periodic revalidation carried out at scheduled intervals.

Revalidation after changes: Revalidation must be performed on introduction of any changes affecting a manufacturing and/or standard procedure having a bearing on the established product performance characteristics. Such changes may include those in starting material, packaging material, manufacturing processes, equipment, in-process controls, manufacturing areas, or support systems (water, steam, etc.). Every such change requested should be reviewed by a qualified validation group, which will decide whether it is significant enough to justify revalidation and, if so, its extent.

Revalidation after changes may be based on the performance of the same tests and activities as those used during the original validation, including tests on subprocesses and on the equipment concerned. Some typical changes which require revalidation include the following:

- Changes in the starting material(s). Changes in the physical properties, such as density, viscosity, particle size distribution, and crystal type and modification, of the active ingredients or excipients may affect the mechanical properties of the material; as a consequence, they may adversely affect the process or the product.
- Changes in the packaging material, e.g. replacing plastics by glass, may require changes in the packaging procedure and therefore affect product stability.
- Changes in the process, e.g. changes in mixing time, drying temperature and cooling regime, may affect subsequent process steps and product quality.
- Changes in equipment, including measuring instruments, may affect both the process and the product; repair and maintenance work, such as the replacement of major equipment components, may affect the process.

- Changes in the production area and support system, e.g. the rearrangement of manufacturing areas and/or support systems, may result in changes in the process. The repair and maintenance of support systems, such as ventilation, may change the environmental conditions and, as a consequence, revalidation/requalification may be necessary, mainly in the manufacture of sterile products.
- Unexpected changes and deviations may be observed during self-inspection or audit, or during the continuous trend analysis of process data.

Periodic revalidation:. It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wear may also cause gradual changes. Consequently, revalidation at scheduled times is advisable even if no changes have been deliberately made.

The decision to introduce periodic revalidation should be based essentially on a review of historical data, i.e. data generated during in-process and finished product testing after the latest validation, aimed at verifying that the process is under control. During the review of such historical data, any trend in the data collected should be evaluated.

In some processes, such as sterilization, additional process testing is required to complement the historical data. The degree of testing required will be apparent from the original validation.

Additionally, the following points should be checked at the time of a scheduled revalidation:

- Have any changes in master formula and methods, batch size, etc., occurred? If so, has their impact on the product been assessed?
- Have calibrations been made in accordance with the established programme and time schedule?
- Has preventive maintenance been performed in accordance with the programme and time schedule?
- Have the standard operating procedures (SOPs) been properly updated?
- Have the SOPs been implemented?
- Have the cleaning and hygiene programmes been carried out?
- Have any changes been made in the analytical control methods?

Table 14.2 : Differences between prospective, concurrent and retrospective validation

PROSPECTIVE	CONCURRENT	RETROSPECTIVE
Three(3)consecutive successful validation. Batches (commercial batch size are required	Three(3)consecutive successful validation Batches (commercial batch size are required)	Selection of batches depends upon the requirements
New products	Existing products	Finished product
Highly controlled and monitored	Sell the product during the qualification runs	Review all the documents and confirm that the process was always in the state of control.
To demonstrate that the parameters set for the process is producing the desired product and its quality attributes	Generate documented evidence to show that the process is in the state of control	

The action plan if a test failure observed during process validation

Any test during process validation shall investigate to determine the case of failure. Where the case of failure is not obvious, it may useful to us an investigation procedure to ensure that all the possible areas of potential failure are covered. Once the case of the process validation failure has been identified, the failure shall classify into the following categories.

Type I: where the failure can be attributed to an occurrence which is not intrinsic to the process for example, an equipment failure raw material that it can be agreed to complete the validation exercise substituting another batch for the one that failed. This investigation and the subsequent action shall be included in the validation report.

Type II: where the failure may be attribute failure or where the investigation is inconclusive than the validation exercise has failed. In this case the validation terms decide and justify the course of action to be taken, recording its justification and recommendations.

This decision shall consider:

- Re-testing - if investigation of the analytical results supports the decision.
- Introduction a change in operation parameters, process steps.
- Changing the process equipment or the procedure for using the equipment.

- Suspension of the process validation exercise until further technical evaluation and/or development has been carried out.
- Changing the sampling regime.
- Review of historical data.
- Change of the process validation acceptance criteria.
- Change to an analytical procedure.

14.5.2 EQUIPMENT VALIDATION (QUALIFICATION)

It is predominantly a documentation exercise in which details of the physical components of the system are recorded as definition of the equipment.

Qualification is broken down into three phases:

1. **Design Qualification** (DQ): It provides documented evidence that all key aspects of the design and procurement adhere to the approved design intention and that all the manufacturers' recommendations have been suitably considered. It defines the functional and operational specifications of the instrument. It helps in selection of the supplier. For example, setting wrong functional specifications can substantially increase the workload for OQ testing, adding missing functions at a later stage will be much more expensive than including them in the initial specifications and selecting a vendor with insufficient support capability. Demonstrates design compliance to GMP

2. **Installation Qualification** (IQ): It provides documented evidence that all key aspects of the installation adhere to the approved design intention and that all the manufacturers' recommendations have been suitably considered. It should be performed on new or modified facilities, systems and equipment. It provides following benefits:
   a. Assure proper installation
   b. Verification of materials of construction
   c. Assure all operating manuals are available
   d. Determine calibration requirements

   This is the first step in validation. Tests insure that the system/equipment and its components are installed correctly and is operating according to manufacturer's specifications. For e.g. It is important to demonstrate that during solid dosage equipment qualification that calibrations of components on allmovable equipment is unaffected by movement to change location and the rigors of cleaning using organic solvents and/or water. This includes the strain gauges that control weight on automated tablet presses. Additional consideration for worst-case testing must be made for the extremely dusty conditions in which this equipment operates.

3. **Operational Qualification** (OQ): It provides documented certification that the system and subsystem operate as intended throughout all anticipated operating range according to SOP. It demonstrates that system works acceptable. It challenge the system to operating conditions. Tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as "worst case" conditions. For e.g. Power failure and recovery tests are performed to document the effects of these events on the control of the system. Alarm and interlocks are tested to verify the proper operation of the system. Software security access levels are verified to ensure system cannot be modified without specific authorization. OQ involves development of SOP and training of personnel. All tests' data and measurements must be documented. The completion of a successful Operational qualification should allow the (i) Finalization of calibration, operating and cleaning procedures, operator (ii)Training and preventative maintenance requirements. (iii) It should permit a formal "release" of the facilities, systems and equipment. It is possible to run a placebo batch during this phase to minimize the financial loss in case of an equipment failure.

4. **Performance Qualification** (PQ): This is the final phase of equipment validation. It provides documented verification that the system performs acceptably and does for what it is made for. PQ is performed on the manufacturing process as a whole. Individual components of the system are not tested individually. The test are done using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities,systems or equipment. Tests to include a condition or set of conditions encompassing upper and lower operating limits.

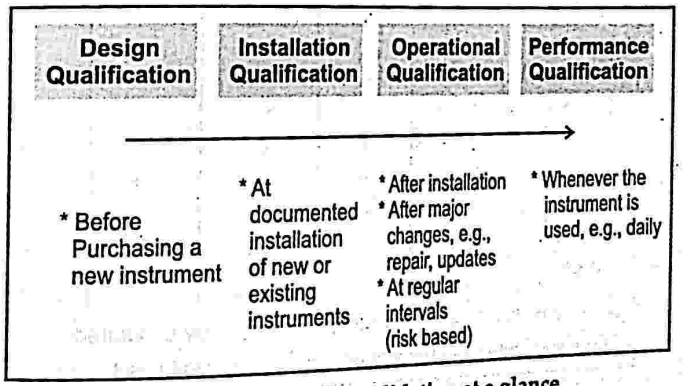

Figure 14.2 : Equipment validation at a glance

14.5.3 ANALYTICAL VALIDATION

Analytical method validation is the process used to prove that the analytical procedure employed for a specific test is fit for its intentional use. Outcome from method validation can be used to judge the quality, reliability and consistency of analytical results. It is an integral part of any good analytical practice. There must be assurance that "the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm are established and documented." (CFR Title 21-Part 211).

According to ICH Guidelines, the following four types of methods require validation

- Identification tests- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard
- Quantitative tests for impurities content -Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample.
- Limit tests for the control of impurities- Limit test is defined as quantitative or semi quantitativetest designed to identify and control small quantities of impurity which is likely to be present in the substance
- Assay- Quantitative tests of the active in samples of drug substance or drug product or the selected components in the drug product.

Characteristic	Identification	Impurities Testing		Assay
		Quantitative	Limit	
Accuracy	–	+	–	+
Precision				
a. Repeatability	–	+	–	+
b. Intermediate precision	–	+	–	+
Specificity	+	+	+	+
LOD	–	–	+	–
LOQ	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– signifies that this characteristic is not normally evaluated
+ signifies that this characteristic is normally evaluated

Figure 14.3 : Application of analytical validation on particular tests

An analytical method should be validated when it is necessary to verify that its performance parameters are adequate for use for a particular analytical problem. For example:

- Method just developed
- Revised method or established method adapted to a new problem;
- When a review of quality control indicates an established method is changing with time
- When an established method is used in a different laboratory, with different analysts or with different equipment
- Demonstration of the equivalence between two methods, e.g. a new method and a standard.

Types of analytical method validation

1. Specificity (Selectivity)
2. Linearity
3. Range
4. Accuracy
5. Precision
6. Detection Limit
7. Quantitation Limit
8. Robustness
9. System Suitability Testing

Table 14.3 : Validation parameters given by different regulatory bodies

GMP	FDA	USP	ICH
Sensitivity			
Specificity	Specificity (& Determination Limit)	Specificity	Specificity
Accuracy	Accuracy	Accuracy	Accuracy
Reproducibility			
	Recovery		
	Ruggedness	Ruggedness	

	Precision	Precision	Precision Repeatability Intermediate Precision Reproducibility
	Linearity (& Range)	Linearity and Range	Linearity Range
		Limit of Detection	Limit of Detection
		Robustness	
		Limit of Quantitation	Limit of Quantitation

1. **Specificity (Selectivity):** It is the ability of the method to assess unequivocally the analyte in presence of components which may be expected to be present. ((typically impurities, degradants, matrix)). This should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis and oxidation.

This definition has the following implications:

- **Identification:** to ensure the identity of an analyte.

  Suitable identification tests should be able to discriminate between compounds of closely related structures which are likely to be present. The discrimination of a procedure may be confirmed by obtaining positive results from samples containing the analyte, coupled with negative results from samples which do not contain the analyte. The identification test may be applied to materials structurally similar to or closely related to the analyte to confirm that a positive response is not obtained.

- **Purity Tests:** to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte. the discrimination may be established by spiking drug substance or drug product with appropriate levels of impurities and demonstrating the separation of these impurities individually and/or from other components in the sample matrix.
- **Assay (content or potency):** To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample. When impurities are available, this should involve demonstration of the discrimination of the analyte in the presence of impurities and/or excipients. This can be done by spiking pure substances with appropriate levels of impurities and/or excipients and demonstrating that the assay result is unaffected by the presence of these materials. If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure e.g. pharmacopoeial method or other validated analytical procedure.

2. **Linearity:** Ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample. Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. For the establishment of linearity, a minimum of five concentrations is recommended. Linearity results should be established by appropriate statistical methods. Transformations are also acceptable and may include log, square root, or reciprocal (other transformations are acceptable). If linearity is not attainable, a nonlinear model may be used. The goal is to have a model (whether linear or nonlinear) that describes closely the concentration-response relationship.

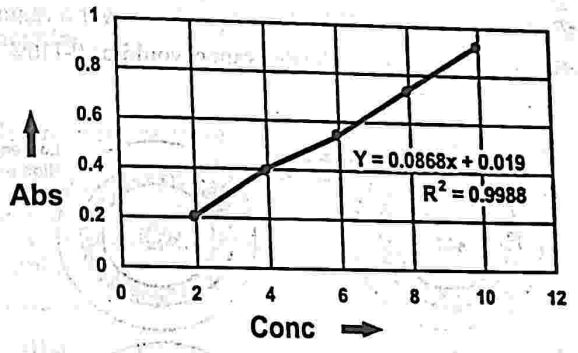

Figure 14.4 : Linearity in standard graph

The following parameters should be determined:

- correlation coefficient- indicates the relationship chosen is correct
- y-intercept indicates response for no analyte (interference)
- slope of the regression line-indicates sensitivity of the method
- Residual sum of squares- indicates uncertainty of intercept(in blank response)

Acceptance criteria: Correlation Coefficient should be not less than 0.999 for assay, dissolution and 0.99 for impurities test method and 0.99 for impurities test method.

The range of the procedure is validated by verifying that the analytical procedure provides acceptable precision, accuracy, and linearity when applied to samples containing analyte at the extremes of the range as well as within the range

3. **Range:** Range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. The specified range is normally derived from linearity studies and depends on the intended application of the procedure

The following minimum specified ranges should be considered:

- for the assay of an active substance or a finished product: normally from 80 to 120 percent of the test concentration;
- for content uniformity, covering a minimum of 70 to 130 percent of the test concentration,
- for dissolution testing: +/-20 % over the specified range

e.g., if the specifications for a controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0-110% of the label claim

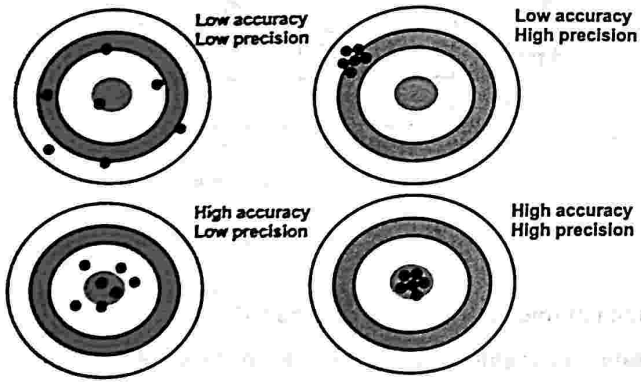

Figure 14.5 : Concept of accuracy and precision

4. **Accuracy:** Accuracy means closeness of test results obtained by that method to the true value. The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted which is accepted either as a conventional true value or an accepted reference value and the value found. Sometimes it is termed trueness.

Procedure

- Assay/Dissolution:- Known amount of drug substance is spiked[19] with synthetic mixtures of drug product components (excipients) – minimum of three levels (80%, 100% & 120% of test concentration) each level is triplicate.
- Impurities: - drug substance/drug product spiked with known amounts of impurities- minimum of three levels and triplicates

Acceptance criteria

- Assay:- Recovery should be between 98% to 102%
- Dissolution:- 95% to 105%
- Impurities:- if, Specification is ≤ 0.2% : 85% to 115%
  if, Specification is > 0.2% : 90% to 110%

Accuracy for Drug Substance and Drug Product

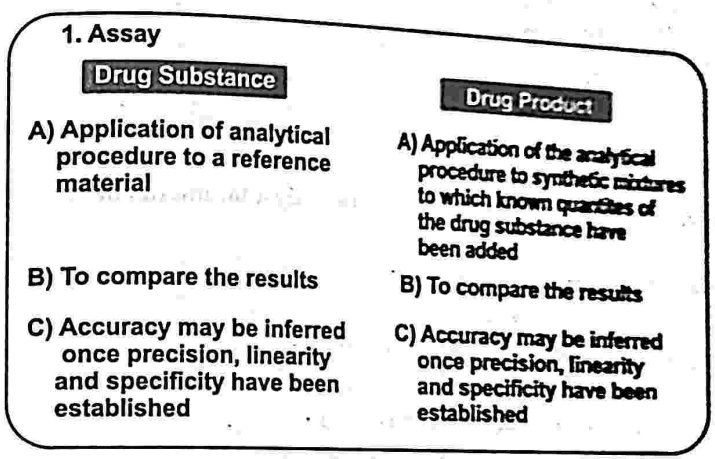

Figure 14.6 : Difference between Accuracy for Drug Substance and Drug Product

5. **Precision:** Degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of a homogenous sample. A sufficient number of aliquots of a homogeneous sample are assayed to be able to calculate statistically valid estimates of standard deviation or relative standard deviation. Minimum 9 determinations over a minimum of 3 concentration levels (e.g., 3 concentrations/3 replicates each of the total analytical procedure). Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

[19] Spiking of sample means addition of known concentration of standard drug to the pre quantified sample.

- **Repeatability:** Repeatability expresses the precision under the same operating conditions over a short interval of time. (with-in a laboratory over a short period of time using the same analyst with the same equipment). Repeatability is also termed intra-assay precision.
- **Intermediate precision:** Intermediate precision expresses within-laboratories variations (within-laboratory variation, as on different days, or with different analysts, or equipments)

Injection	Peak area analyst 1	Peak area analyst 2	Peak area analyst 3
1	173865	175656	177965
2	174926	175878	178556
3	172933	176004	177342
4	175011	176344	178011
5	179557	175332	179466
6	176425	174959	179688
Mean	175453	175695	178504
SD (σ)	2329	495	918
RSD	1.32%	0.28%	0.51%

Figure 14.7 : Results obtained by different analyst for intermediate precision

- **Reproducibility:** precision between laboratories. Can be considered during the standardization of a procedure before it is submitted to the pharmacopoeia. As per CDER guidelines, it is not normally expected if intermediate precision is accomplished

6. **Detection Limit/** limit of detection(LOD): detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated, under the stated experimental conditions. Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental.
   - Based on visual examination
   - Based on signal to noise ratio(baseline noise) 2:1or 3:1
   - Based on the Standard Deviation of the Response and the Slope

7. **Quantitation limit/ Limit of quantification(LOQ):**

LOQ of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental.

- Based on visual examination
- Based on signal to noise ratio(10:1)
- Based on the Standard Deviation of the Response and the Slope

Procedure

SD of response & Slope (S): Prepare linearity curve with a series of related substance(s) solutions at different concentrations (3 concentrations below 50 % °of specification level and 3 more concentrations above 50 % specification level)

RSD criteria: Prepare a series of related substance(s) solutions of concentrations below to specification level (generally about 10%, 20%, 30%, 40% and inject six replicate into HPLC. Precision should be established (if predicted from other than RSD criteria) at LOQ and LOD level as per ICH, USP & EP guidelines.

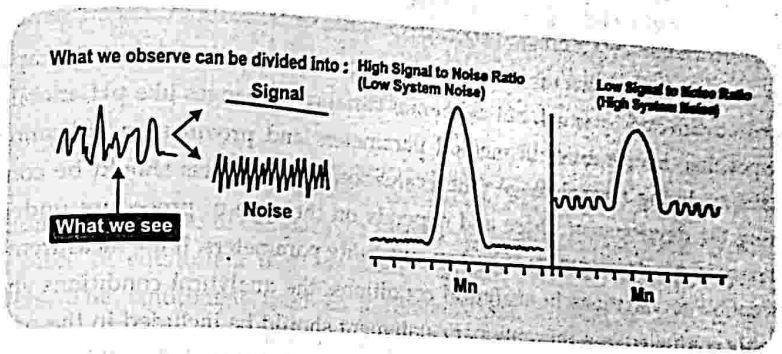

Figure 14.8 : Understanding of signal and noise

Approach	LOD	LOQ
Visual inspection	Minimum level detectable	Minimum level quantifiable
Signal-to-Noise ratio	2:1 or 3:1	10:1
SD of response (σ) & Slope (S)	[3.3 xσ] / S	[10.0 xσ] / S
RSD Criteria	Concentration at which RSD 10 to 33.0%	Concentration at which RSD ≤10

Figure 14.9 : Summary of LOD and LOQ

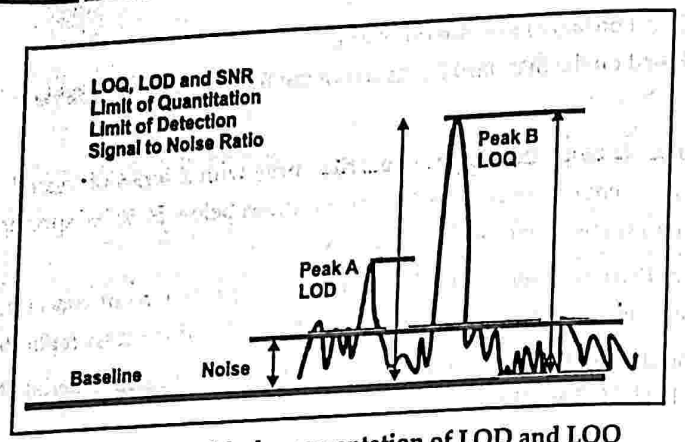

Figure 14. 10: Graphical representation of LOD and LOQ

8. **Robustness:** Robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations (changes like pH, mobile phase composition, temperature) in method parameters and provides an indication of its reliability during normal usage. The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. Consequence is development of system suitability parameters. If the measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure, such as: Use solution within 24 hours; Maintain temperature below 25 degrees.In the case of liquid chromatography, examples of typical variations are: influence of variations of pH in a mobile phase influence of variations in mobile phase composition different columns (different lots and/or suppliers) temperature flow rate In the case of gas-chromatography, examples of typical variations are: different columns (different lots and/or suppliers) temperature flow rate

9. **System Suitability Testing:** System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. It ensures that system is working properly at the time of analysis. Determination made are repeatability, tailing factor (T), capacity factor (k'), resolution (R), and theoretical Plates (N)

Table 14.4 Parameters and recommendation for system suitability testing

Parameters	Recommendations
K'	In general K'≥2.0
R	R > 2 between the peak of interest and the closes potential interferent (degradant, internal STD, impurity, excipient, etc...)
T	T≥2
N	In general N > 2000
Repeatability	RSD≤2.0% (n≥5)

14.6 CALIBRATION

Calibration is the process of comparing a reading on one piece of equipment or system, with another piece of equipment that has been calibrated and referenced to a known set of parameters. The equipment used as a reference should itself be directly traceable to equipment that is calibrated to a national standard. Calibration defines the accuracy and quality of measurements recorded using a piece of equipment. Over time there is a tendency for results and accuracy to 'drift' particularly when using particular technologies or measuring particular parameters such as temperature and humidity. To be confident in the results being measured there is an ongoing need to maintain the calibration of equipment throughout its lifetime for reliable, accurate and repeatable measurements. The goal of calibration is to minimise any measurement uncertainty by ensuring the accuracy of test equipment. Calibration quantifies and controls errors or uncertainties within measurement processes to an acceptable level.

Table 14.5 : Difference between Calibration and validation

CALIBRATION	VALIDATION
Purpose of calibration is to demonstrate that, a particular Instrument or device produces results with in specified limits by comparisons with those produced by a reference or traceable standard over an appropriate range of measurements	Purpose of validation is to produce documented verification that provides high degree of assurance that a specific process, equipment, method or system consistently produces a result meeting pre-determined acceptance criteria.
Performance of an instrument or device is compared against a reference standard.	No such reference standards are using in validation program.
Calibration ensures that instrument or measuring devices producing accurate results	Validation provides documented evidence that a process, equipment, method or system produces consistent results (in other words, it ensures that uniforms batches are produced).
Shall be performed periodically, to identify the 'drift' of the measuring device or equipment and make them accurate	No such requirements. Shall be performed when changes or modifications happen to the existing system or once revalidation period is reached
Shall be performed as per calibration SOP	Shall be performed as per validation protocol.
It adjusts the precision and accuracy of measurement equipment	It confirms the precision and accuracy of measurement equipment
It helps to eliminate or reduce bias in an instrument's readings over a range for all continuous values	It confirms that no bias exists in instruments reading

14.7 CALIBRATION OF PH METER

The calibration of a pH meter is important to ensure that the readings returned from that meter are accurate. Digital & analog pH meters offer calibration buttons or dials that are used to adjust the sensitivity of the meter.

Steps for calibration:

1. **Turn on pH meter:** Allow adequate time for the meter to warm up. This generally takes around 30 minutes, operating manual for exact times should be checked.
2. **Clean the electrode.** Take the electrode out of its storage solution and rinse it with distilled water under an empty waste beaker. Once rinsed, blot dry Be sure to rinse your electrode in a waste beaker that is different from the beaker you will be calibrating in. Avoid rubbing the electrode as it has a sensitive membrane around it.
3. **Prepare buffers.** Generally more than one buffer is needed for calibrating a pH meter. The first is a "neutral" buffer with a pH of 7, and the second should be near the expected sample pH, either a pH of 4 or 9.21. Buffers with a higher pH (9.21) are best for measuring bases, whereas buffers with a low pH (4) are best for measuring acidic samples. Once the buffers the buffers are selelcted allow them to reach the same temperature as the pH meter because pH readings are temperature dependent. Buffers should be kept in a beaker for no longer than two hours

   Discard the buffer when you are finished. Do not return it to its original container.
4. **Place electrode in the buffer with a pH value of 7 and begin reading.** Press the "measure" or calibrate button to begin reading the pH once electrode is placed in the buffer. Allow the pH reading to stabilize before letting it sit for approximately 1-2 minutes.
5. **Set the pH.** Once a stable reading apears, set the pH meter to the value of the buffer's pH by pressing the measure button a second time. Setting the pH meter once the reading has stabilized allows for more accurate and tuned readings.
6. **Rinse the electrode with distilled water.** Rinse and pat dry with a lint-free tissue in between buffers.
7. **Place the electrode in the appropriate buffer for sample reading.** Press the measure button to begin reading the pH once the electrode is placed in the buffer.
8. **Set the pH a second time.** Once the reading has stabilized, set the pH meter to the value of the buffer's pH by pressing the measure button.
9. **Rinse the electrode.** Distilled water can be used to rinse. A lint-free tissue should be used to dry the electrode.

14.8 QUALIFICATION OF UV-VISIBLE SPECTROPHOTOMETER

The suitability of a specific instrument for a given procedure is ensured by a stepwise life cycle evaluation for the desired application from selection to instrument retirement: design qualification (DQ); installation qualification (IQ); an initial performance-to-specification

qualification, also known as operational qualification (OQ); and an ongoing performance qualification (PQ). For more details, see Analytical Instrument Qualification á1058ñ. The purpose of this chapter is to provide test methodologies and acceptance criteria to ensure that the instrument is suitable for its intended use (OQ), and that it will continue to function properly over extended time periods as part of PQ. As with any spectrometric device, a UV-Vis spectrophotometer must be qualified for both wavelength (x-axis) and photometric (y-axis, or signal axis) accuracy and precision, and the fundamental parameters of stray light and resolution must be established. OQ is carried out across the operational ranges required within the laboratory for both the absorbance and wavelength scales.

Installation Qualification The IQ requirements provide evidence that the hardware and software are properly installed in the desired location.

Operational Qualification Acceptance criteria for critical instrument parameters that establish "fitness for purpose" are verified during IQ and OQ. Specifications for particular instruments and applications can vary depending on the analytical procedure used and the desired accuracy of the final result. Instrument vendors often have samples and test parameters available as part of the IQ/OQ package. Wherever possible in the procedures detailed as follows, certified reference materials (CRMs) are to be used in preference to laboratory-prepared solutions. These CRMs should be obtained from a recognized accredited source and include independently verified traceable value assignments with associated calculated uncertainty. CRMs must be kept clean and free from dust. Recertification should be performed periodically to maintain the validity of the certification.

Control of Wavelengths Ensure that the accuracy of the wavelength axis (x-axis) over the intended operational range is correct within acceptable limits. For non-diode array instruments, wavelength accuracy and precision are determined over the operational range using at least six replicate measurements. For wavelength accuracy, the difference of the mean measured value to the certified value of the CRM must be within ±1 nm in the UV region (200–400 nm), and in the visible region (400–700 nm) must be within ±2 nm. For wavelength precision, the standard deviation of the mean must not exceed 0.5 nm. For diode array instruments, only one wavelength accuracy measurement is required, and no precision determination needs to be performed. The difference between the certified and measured value of the CRM must not exceed ±1 nm in the UV region (200–400 nm), and in the visible region (400–700 nm) must not exceed ±2 nm.

Control of Absorbance To establish the transmittance accuracy, precision, and linearity of a given system, it is necessary to verify the absorbance accuracy of a system over its intended operational range by using acidic potassium dichromate solutions in 0.001 M perchloric acid as appropriate for the wavelength and absorbance ranges required.

Limit of Stray Light (Stray Radiant Energy) Although the measurement of absorbance or transmittance is a ratio measurement of intensities and therefore theoretically is independent of monochromatic source intensity, practical measurements are affected by the presence of unwanted radiation called "stray radiant energy" or "stray light"

Resolution If accurate absorbance measurements must be made on benzenoid compounds or other compounds with sharp absorption bands (natural half-bandwidths of less than 15 nm), the spectral bandwidth of the spectrophotometer used should not be greater than 1/8th the natural half-bandwidth of the compound's absorption.

Performance Qualification The purpose of PQ is to determine that the instrument is capable of meeting the user's requirements for all the parameters that may affect the quality of the measurement and to ensure that it will function properly over extended periods of time.

Procedure With few exceptions, compendial spectrophotometric tests and assays call for comparison against a USP Reference Standard. This helps ensure measurement under identical conditions for the test specimen and the reference substance. These conditions could include wavelength setting, spectral bandwidth selection, cell placement and correction, and transmittance levels. Cells that exhibit identical transmittance at a given wavelength may differ considerably in transmittance at other wavelengths. Appropriate cell corrections should be established and used where required. Comparisons of a test specimen with a reference standard are best made at a peak of spectral absorption for the compound concerned. Assays that prescribe spectrophotometry give the commonly accepted wavelength for peak spectral absorption of the substance in question. Different spectrophotometers may show minor variation in the apparent wavelength of this peak. Good practice demands that comparisons be made at the wavelength at which peak absorption occurs. Should this differ by more than ±1 nm (in the range 200–400 nm) or ±2 nm (in the range 400–800 nm) from the wavelength specified in the individual monograph, recalibration of the instrument may be indicated. The expressions "similar preparation" and "similar solution" as used in tests and assays involving spectrophotometry indicate that the reference comparator, generally a USP Reference Standard, should be prepared and observed in an identical manner for all practical purposes to that used for the test specimen. Usually when analysts make up the solution of the specified reference standard, they prepare a solution of about (i.e., within 10%) the desired concentration, and they calculate the absorptivity on the basis of the exact amount weighed out. If a previously dried specimen of the reference standard has not been used, the absorptivity is calculated on the anhydrous basis. The expressions "concomitantly determine" and "concomitantly measure", as used in tests and assays involving spectrophotometry indicate that the absorbances of

both the solution containing the test specimen and the solution containing the reference specimen, relative to the specified test blank, must be measured in immediate succession

Sample Solution Preparation For determinations using UV or visible spectrophotometry, the specimen generally is dissolved in a solvent. Unless otherwise directed in the monograph, analysts make determinations at room temperature using a path length of 1 cm. Many solvents are suitable for these ranges, including water, alcohols, lower hydrocarbons, ethers, and dilute solutions of strong acids and alkalis. Precautions should be taken to use solvents that are free from contaminants that absorb in the spectral region under examination. For the solvent, analysts typically should use water-free methanol or alcohol or alcohol denatured by the addition of methanol but without benzene or other interfering impurities. Solvents of special spectrophotometric quality, guaranteed to be free from contaminants, are available commercially from several sources. Some other analytical reagent-grade organic solvents may contain traces of impurities that absorb strongly in the UV region. New lots of these solvents should be checked for their transparency, and analysts should take care to use the same lot of solvent for preparation of the test solution, the standard solution, and the blank. The best practice is to use solvents that have NLT 40% transmittance (39.9%T = 0.399A) at the wavelength of interest. Assays in the visible region usually call for concomitantly comparing the absorbance produced by the assay preparation with that produced by a standard preparation containing approximately an equal quantity of a USP Reference Standard. In some situations, analysts can omit the use of a reference standard (e.g., when spectrophotometric assays are made with routine frequency) when a suitable standard curve is available and is prepared with the appropriate USP Reference Standard, and when the substance assayed conforms to the Beer–Lambert law within the range of about 75%–125% of the final concentration used in the assay. Under these circumstances, the absorbance found in the assay may be interpolated on the standard curve, and the assay result can be calculated. Such standard curves should be confirmed frequently and always when a new spectrophotometer or new lots of reagents are put into use.

CHAPTER 15

GOOD WAREHOUSING & DISTRIBUTION PRACTICES

15.1 GOOD WAREHOUSING

Good warehousing practices (GWP) means storing supplies so that products are always available, accessible, and in good condition. Bad warehousing lead to damages resulting in losses. Pharmaceutical warehousing, therefore, is much more than the simple storage of products. It is an operation that preserves the integrity of drugs. According to cGMP Drugs must be stored to prevent contamination, and be positioned to allow for inspection and cleaning of the area. Each lot of drug products must be identified with a distinctive (and traceable) code, and the lot's status must be identified (approved, quarantined, rejected). Written procedures must describe the distribution process for each drug. This includes procedures for recalls. Written procedures must describe the appropriate storage conditions for each drug. Different drugs can have vastly different requirements in terms of temperature, humidity, and lighting. The warehousing official ensures that the storage of each drug is in line with its specific requirements defined by the manufacturer. This can involve temperature-controlled warehousing and/or climate-controlled warehousing space[20], both of which require state-of-the-art control and monitoring equipment to keep the space within specific environmental parameters.

Figure 15.1 : Reprentation of Good and Bad warehousing

20 Temperature-controlled space requires sophisticated control and monitoring equipment to ensure that the temperature of the facility stays within very specific parameters.Climate-controlled space regulates and monitors both the temperature *and* humidity of the space

15.1.1 IMPORTANCE OF GOOD WAREHOUSING PRACTICES

- To optimize the resources available for a large scale storage in a specified manner.
- As a integral part of the supply chain.
- Making the best use of the real time data for effective supply chain and optimization of the stock put away and Bin utilization.
- To save time and effort in identifying and locating goods.
- To maintain a safe, clean and segregated environment.
- To control the movement and storage of material within the stores.
- To help in easy stock take and stock verification & reconciliation and help in stock corrections if necessary.
- Regulatory requirement for pharmaceuticals
- To develop a zone concept for product wise segregation.
- To streamline the process of receival, storage & distribution.

15.1.2 GOOD WAREHOUSING PRACTICES

Warehousing & storage is an act of storage and assorting the finished goods so as to create maximum time utilization at the minimum cost. The key activities concerned with warehousing are.

- Receiving
- Identifying
- Holding
- Assembling and processing of the orders to meet the demand.

15.1.3 FUNCTIONS OF WAREHOUSING

1. Receiving & Recording of goods: While receiving the goods it is the responsibility of the warehouse dept to check and verify the goods that are coming into the warehouse by weighing the shipper coming in and counting the same. The correctness and quantity of the goods coming in should be verified at the time of receipt and recorded in a document. It should be mutually agreed and signed between the person transferring the goods and the person receiving the goods.
2. Storage: Major function of storage is to ensure that the product is protected and stored in a manner to ensure that the goods are easy to identify and as per the category. It is advisable to have zoning concept where the products can be stored as per the zone.

3. Order picking: After the receipt of the order the line manager shall ensure that he has picked the same order as indicated in the picking list and the same batch number should appear in all the documents i.e. the invoice, the picking list and the delivery note.
4. Distribution: The line managers hand over the goods to the packers who verify the goods against the delivery note and do the necessary marking on the shippers as per the customer. • It is the responsibility of the loading supervisor to check the vehicle and confirm that it is matching as per the requirements and is clean and tidy for loading pharmaceutical good

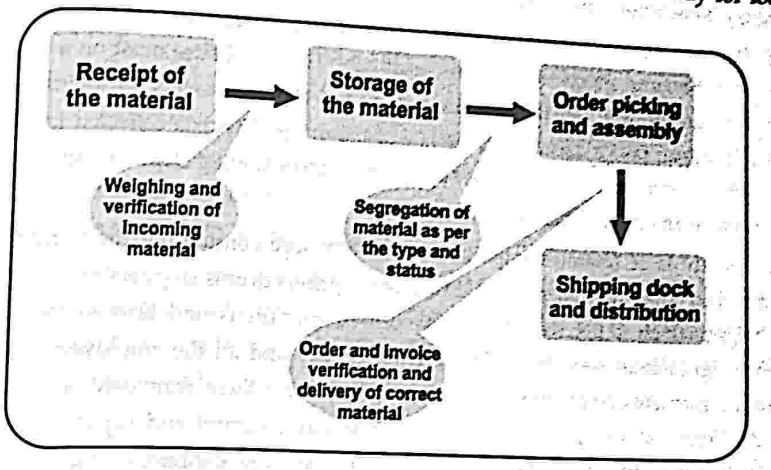

Figure 15.2 : Steps of material flow

- The incoming material in the warehouse to be immediately sent to quarantine.
- The quarantine goods to be sampled by the Quality Dept and sent for analysis.

  (In case of manufacturing unit the samples may be taken online before the batch is transferred to Quarantine).
- After getting release from the Quality Dept the goods need to be transferred to the Approved area.
- In case if the goods are rejected they are supposed to be transferred to the Rejected area the keys of the rejected area shall remain with the Quality Dept.
- There should also be provision for customer returned goods and market returned Goods which should go through the Quality Dept for further segregation into either approved or rejected.
- Provision for goods to be stored under controlled temperature is a must.
- This area should be mapped for temperature distribution.

- Another important area is for the controlled substances which can be misused and are required to be stored under BOND by the law.

15.1.4 ELEMENTS OF GOOD WAREHOUSING PRACTICES

Costs involved in warehouse: As a practice it is good to follow first expiry first out (FEFO) for the finished goods, which helps to maintain the inventory with the maximum shelf life. FIFO is also equally valid as FEFO. The imported goods need to be scrutinized and checked for expiry dates at the time of receipt.

Stock Verification. Orderly, timely and frequent stock verification is the key to correct stocks and the same affects the business positively. The warehouse must on a routine basis share the data on the non moving, dead stock and the near expiry products so that the management can take a decision on the fate of the drugs. The data collected from the stock review should also be shared with the supply chain and planning Dept on regular basis so as to facilitate in an effective planning process.

Safety: Safety is of foremost important in a warehouse considering the various types of activities and equipment like the forklift, Trolley, pallets drums shippers etc. Some are kept at a height which if not stored properly can be precarious and lead to fatal accidents. OHSAS[21] guidelines need to be followed religiously and all the employees should wear protective garments commonly called PPE[22], to protect them from any accidental harm. Helmets, Safety shoes, garments, masks are necessary. Abrupt and rapid movements are uncalled for and cause more damage than benefits. So the warehouse employees need to be disciplined and cautious in their approach. Any and every accident should be reported immediately. The fire end emergency exit plans shall be well laid out and fire drills to be performed to validate the exit plan. The entire warehouse has to be subjected for pest control activities and the rodent baits should be checked at regular intervals.The baits[23] and chemicals should be kept away from the pharmaceutical preparations and at any given point should not come in contact with the workmen of the products kept in the area.

Premises, Health & Hygiene: The area should be kept clean and away from objectionable odors, smoke dust and other contaminants. The warehouse should be well ventilated. It should protect the goods from adverse weather conditions. Opening leading to entry of rodents, pests, birds and vermin should be closed. Floors should be non slip evenly graded

21 Occupational Health and Safety Assessment Series, (officially BS **OHSAS** 18001) is a British Standard for occupational health and safety management systems.
22 Personal Protective Equipment (PPE) - Specialized clothing or equipment worn by employees for protection against health and safety hazards. Personal protective equipment is designed to protect many parts of the body, i.e., eyes, head, face, hands, feet, and ears.
23 Bait is any substance used to attract prey, e.g. in a mousetrap

to prevent stagnation and can be drained to trapped outlets protected by a grill. The floor should be constructed using material that is impervious, non-toxic, non-adsorbent and crack resistant. Walls should be made of smooth,durable,impervious,non adsorbent and crack resistant material that can be cleaned easily. All ceiling are to be constructed and finished so as to prevent condensation, leakage and formation of molds and should be easily and regularly cleaned. Door should be easily cleanable surfaces. Adequate lighting and lux[24] levels. Toilets must not open directly into any place where the products are stored. The recommended storage conditions for the cold storage is 2-8°C. which should be mapped and the temperature sensor to be placed at the hot spot identified manual temperature recording. Cold storage should not be overloaded should have racks inside for proper storage. It should be in sanitary condition at all times. The cleaning equipment should be placed in a well designated area with proper labelling. Eating,drinking,smoking,chewing of gum or tobacco, littering and undesirable behavior at the designated areas in the premises is prohibited. Any person who has open wounds and lesions, boils sores or infectious disease must be sent on leave till they achieve complete recovery. Attested by a medical supervisor.

Good documentation: Last but not the least is the documentation for the activities done. • It's a common saying in GMP that "if it is not documented it never happened". • SOP, records & Bin card need to be checked, updated and religiously followed. • Maintain the invoices, delivery notes and other documents

15.2 WHO GOOD DISTRIBUTION PRACTICES FOR PHARMACEUTICAL PRODUCTS

Distribution is an important activity in the integrated supply-chain management of pharmaceutical products. Various people and entities are generally responsible for the handling, storage and distribution of such products. In some cases, however, a person or entity is only involved in and responsible for certain elements of the distribution process. The objective of these guidelines is to assist in ensuring the quality and identity of pharmaceutical products during all aspects of the distribution process. These aspects include, but are not limited to, procurement, purchasing, storage, distribution, transportation, repackaging, relabelling, documentation and record-keeping practices. The storage, sale and distribution of pharmaceutical products are often carried out by various companies, institutions and individuals. This document sets out appropriate steps to assist in fulfilling the responsibilities involved in the different aspects of the distribution process

24 The lux is the SI derived unit of illuminance and luminous emittance, measuring luminous flux per unit area. It is equal to one lumen per square metre. In photometry, this is used as a measure of the intensity, as perceived by the human eye, of light that hits or passes through a surface.

within the supply chain and to avoid the introduction of counterfeits into the marketplace via the distribution chain. The relevant sections should be considered by various participants as applicable to the particular role that they play in the distribution of pharmaceutical products. The nature of the risks involved is likely to be similar to that for risks encountered in the manufacturing environment, e.g. mix-ups, adulteration, contamination and cross-contamination. When the distribution chain is interrupted by manufacturing steps such as repackaging and relabelling, the principles of good manufacturing practices (GMP) should be applied to these processes. Counterfeit pharmaceutical products[25] are a real threat to public health and safety. Consequently, it is essential to protect the pharmaceutical supply chain against the penetration of such products. Weak points in the distribution processes of pharmaceutical products provide an avenue for counterfeit as well as illegally imported, stolen and substandard medicines to enter the supply chain. This is a concern in both developed and developing countries. The methods by which such products enter the supply chain have become increasingly complex and have resulted in the development of thriving secondary and grey markets throughout the world. The involvement of unauthorized entities in the distribution and sale of pharmaceutical products is a particular concern. Only a joint approach including all parties involved in the supply chain can be successful in the fi ght against counterfeit pharmaceutical products and, therefore, all parties active in the market should take an active part in collaborative activities. Different models for the distribution of pharmaceutical products are used in different countries and sometimes within the same country, for example, TRS957.indd 236 21.04.10 11:04 237 in the public and the private sector. These guidelines are intended to be applicable to all persons and outlets involved in any aspect of the distribution of pharmaceutical products from the premises of the manufacturer of the product to the person dispensing or providing pharmaceutical products directly to a patient or his or her agent. This includes all parties involved in trade and distribution of medicines, pharmaceutical manufacturers, including the manufacturers of finished products and pharmaceutical wholesalers as well as other parties such as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents and their employees. To maintain the original quality of pharmaceutical products, every party active in the distribution chain has to comply with the applicable legislation and regulations. Every activity in the distribution of pharmaceutical products should be carried out according to the principles of GMP, good storage practice (GSP) and good distribution practice (GDP) as applicable. These guidelines do not deal with all aspects

25 A pharmaceutical product which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and counterfeit pharmaceutical products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an incorrect quantity of active ingredient or with fake packaging.

of the standards for the storage of pharmaceuticals which are covered in the WHO guide to good storage practices for pharmaceuticals . The dispensing to patients is addressed in the WHO good pharmacy practice (GPP) guide. These guidelines should also be read in conjunction with other WHO guidelines. Although medical devices are not included in the definition of pharmaceutical products for the purposes of this document, the main principles established in this document may also be used where applicable for medical devices.

Definition

That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur during the distribution process as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products.

15.2.1 GENERAL PRINCIPLES

The principles of GDP are applicable both to pharmaceutical products moving forward in the distribution chain from the manufacturer to the entity responsible for dispensing or providing pharmaceutical products to the patient and to products which are moving backwards in the chain, for example, as a result of the return or recall thereof. There should be collaboration between all parties including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of pharmaceutical products to patients to ensure the quality and safety of pharmaceutical products and prevent the exposure of patients to counterfeit pharmaceutical products.

15.2.2 ORGANIZATION AND MANAGEMENT

There should be an adequate organizational structure for each entity defined with the aid of an organizational chart. The responsibility, authority and interrelationships of all personnel should be clearly indicated. At every level of the supply chain, employees should be fully informed and trained in their duties and responsibilities. A designated person should be appointed within the organization, who has defi ned authority and responsibility for ensuring that a quality system is implemented and maintained. The responsibilities placed on any one individual should not be so extensive as to present any risk to product quality

15.2.3 PERSONNEL

All personnel involved in distribution activities should be trained and qualifi ed in the requirements of GDP, as applicable. Training should be based on written standard operating

procedures (SOPs). There should be an adequate number of competent personnel involved in all stages of the distribution of pharmaceutical products in order to ensure that the quality of the product is maintained. Personnel involved in the distribution of pharmaceutical products should wear garments suitable for the activities that they perform. Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to pharmaceutical products must be designed and administered to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities. Codes of practice and punitive procedures should be in place to prevent and address situations

15.2.4 QUALITY SYSTEM

Within an organization, quality assurance serves as a management tool. There should be a documented quality policy describing the overall intentions and requirements of the distributor regarding quality, as formally expressed and authorized by management. Where electronic commerce (e-commerce) is used, i.e. electronic means are used for any of the distribution steps, defi ned procedures and adequate systems should be in place to ensure traceability and confi dence in the quality of the pharmaceutical products concerned. Electronic transactions (including those conducted via the Internet), relating to the stribution of pharmaceutical products, should be performed only by authorized persons or ntities. Inspection, auditing and certification of compliance with a quality system (such as the applicable International Standardization Organization (ISO) series, or national or international guidelines) by external bodies is recommended. Such certification should not, however, be seen as a substitute for compliance with these GDP guidelines and the applicable principles of GMP relating to pharmaceutical products. Distributors should from time to time conduct risk assessments to assess potential risks to the quality and integrity of pharmaceutical products.

15.2.5 PREMISES, WAREHOUSING AND STORAGE

Precautions must be taken to prevent unauthorized persons from entering storage areas. Employees should comply with the company policies to maintain a safe, secure and effi cient working environment. Storage areas should be of suffi cient capacity to allow the orderly storage of the various categories of pharmaceutical products, namely commercial and non-commercial products, products in quarantine, and released, rejected, returned or recalled products as well as those suspected to be counterfeits. Storage areas should be clean and free from accumulated waste and vermin. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas. Radioactive materials,

narcotics and other hazardous, sensitive and/ or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fi re or explosion (e.g. combustible or flammable liquids and solids and pressurized gases) should be stored in a dedicated area(s) that is subject to appropriate additional safety and security measures. A system should be in place to ensure that the pharmaceutical products due to expire fi rst are sold and/or distributed fi rst (first expiry/ first out (FEFO)). Exceptions may be permitted as appropriate, provided that adequate controls are in place to prevent the distribution of expired products Storage conditions for pharmaceutical products should be in compliance with the recommendations of the manufacturer. Equipment used for monitoring of storage conditions should also be calibrated at defined intervals. Stock discrepancies should be investigated in accordance with a specified procedure to check that there have been no inadvertent mixups, incorrect issues and receipts, thefts and/or misappropriations of pharmaceutical products. Documentation relating to the investigation should be kept for a predetermined period.

15.2.6 VEHICLES AND EQUIPMENT

Vehicles and equipment used to distribute, store or handle pharmaceutical products should be suitable for their purpose and appropriately equipped to prevent exposure of the products to conditions that could affect their stability and packaging integrity, and to prevent contamination of any kind. Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security of pharmaceutical products while in the vehicle. Where special storage conditions (e.g. temperature and/or relative humidity), different from, or limiting, the expected environmental conditions, are required during transportation, these should be provided, checked, monitored and recorded. All monitoring records should be kept for a minimum of the shelf-life of the product distributed plus one year, or as required by national legislation.

15.2.7 SHIPMENT CONTAINERS AND CONTAINER LABELLING

Shipping containers should bear labels providing sufficient information on handling and storage conditions and precautions to ensure that the products are properly handled and secure at all times. The shipment container should enable identification of the container's contents and source. Normally, internationally and/or nationally accepted abbreviations, names or codes should be used in the labelling of shipment containers. Special care should be taken when using dry ice in shipment containers. In addition to safety issues it must be ensured that the pharmaceutical product does not come into contact with the dry ice, as it may have an adverse effect on the quality of the product.

15.2.8 DISPATCH AND RECEIPT

Prior to the dispatch of the pharmaceutical products, the supplier should ensure that the person or entity, e.g. the contract acceptor for transportation of the pharmaceutical products, is aware of the pharmaceutical products to be distributed and complies with the appropriate storage and transport conditions. Records for the dispatch of pharmaceutical products should be prepared and should include at least the following information:

— date of dispatch; — complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number and names of contact persons; — complete business name, address (no acronyms), and status of the addressee (e.g. retail pharmacy, hospital or community clinic); — a description of the products including, e.g. name, dosage form and strength (if applicable); — quantity of the products, i.e. number of containers and quantity per container (if applicable); — applicable transport and storage conditions; — a unique number to allow identifi cation of the delivery order; and — assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt to facilitate traceability).

Care should be taken to ensure that the volume of pharmaceutical products ordered does not exceed the capacity of storage facilities at the destination. Incoming shipments should be examined to verify the integrity of the container/closure system, ensure that tamper-evident packaging features are intact, and that labelling appears intact.

15.2.9 TRANSPORTATION AND PRODUCTS IN TRANSIT

Products and shipment containers should be secured to prevent or provide evidence of unauthorized access. Vehicles and operators should be provided with additional security, as appropriate, to prevent theft and other misappropriation of products during transportation. Pharmaceutical products should be stored and transported in accordance with procedures such that:

- The identity of the product is not lost.
- The product does not contaminate and is not contaminated by other products.
- Adequate precautions are taken against spillage, breakage, misappropriation and theft.
- Appropriate environmental conditions are maintained, e.g. using cold chain for thermolabile products.

Spillages should be cleaned up as soon as possible to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.

15.2.10 DOCUMENTATION

Written instructions and records which document all activities relating to the distribution of pharmaceutical products, including all applicable receipts and issues (invoices) should be available. Records should be kept for seven years, unless otherwise specified in national or regional regulations. Distributors should keep records of all pharmaceutical products received. Records should contain at least the following information: — date; — name of the pharmaceutical product; — quantity received, or supplied; and — name and address of the supplier.

The nature, content and retention of documentation relating to the distribution of pharmaceutical products and any investigations conducted and action taken, should comply with national legislative requirements. Where such requirements are not in place, the documents should be retained for at least one year after the expiry date of the product concerned. Procedures should be in place for temperature mapping, security services to prevent theft or tampering with goods at the storage facilities, destruction of unsaleable or unusable stocks and on retention of the records.

15.2.11 REPACKAGING AND RELABELLING

Repackaging and relabelling of pharmaceutical products should be limited, as these practices may represent a risk to the safety and security of the supply chain. Where they do occur, they should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international guidelines, i.e. in accordance with GMP principles. In the event of repackaging by companies other than the original manufacturer, these operations should result in at least equivalent means of identification and authentication of the products. Procedures should be in place for the secure disposal of original packaging.

15.2.12 COMPLAINTS

There should be a written procedure in place for the handling of complaints. A distinction should be made between complaints about a product or its packaging and those relating to distribution. In the case of a complaint about the quality of a product or its packaging, the original manufacturer and/ or marketing authorization holder should be informed as soon as possible. Where necessary, appropriate follow-up action should be taken after investigation and evaluation of the complaint. There should be a system in place to ensure that the complaint, the response received from the original product manufacturer, or the results of the investigation of the complaint, are shared with all the relevant parties.

15.2.13 RECALLS

There should be a system, which includes a written procedure, to effectively and promptly recall pharmaceutical products known or suspected to be defective or counterfeit, with a designated person(s) responsible for recalls. The system should comply with the guidance issued by the national or regional regulatory authority. This procedure should be checked regularly and updated as necessary. The original manufacturer and/or marketing authorization[26] holder should be informed in the event of a recall. Where a recall is instituted by an entity other than the original manufacturer and/or marketing authorization holder, consultation with the original manufacturer and/or marketing authorization holder should, where possible, take place before the recall is instituted. Recalled pharmaceutical products should be segregated during transit and clearly labelled as recalled products. Where segregation in transit is not possible, such goods must be securely packaged, clearly labelled, and be accompanied by appropriate documentation.

15.2.14 RETURNED PRODUCTS

A distributor should receive pharmaceutical product returns or exchanges pursuant to the terms and conditions of the agreement between the distributor and the recipient. Both distributors and recipients should be accountable for administering their returns process and ensuring that the aspects of this operation are secure and do not permit the entry of counterfeit products.

Counterfeit pharmaceutical products. Provision should be made for the appropriate and safe transport of returned products in accordance with the relevant storage and other requirements. Rejected pharmaceutical products and those returned to a distributor should be appropriately identifi ed and handled in accordance with a procedure which involves at least: — the physical segregation of such pharmaceutical products in quarantine in a dedicated area; or — other equivalent (e.g. electronic) segregation

26 A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence"). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products — the register — and is often said to be "registered" or to "have registration". Market authorization may occasionally also be referred to as a "licence" or "product licence".

15.2.15 COUNTERFEIT PHARMACEUTICAL PRODUCTS

Counterfeit pharmaceutical products found in the distribution chain should be kept apart from other pharmaceutical products to avoid any confusion. They should be clearly labelled as not for sale and national regulatory authorities and the holder of the marketing authorization for the original product should be informed immediately. Upon confirmation of the product being counterfeit a formal decision should be taken on its disposal, ensuring that it does not re-enter the market, and the decision recorded.

15.2.16 IMPORTATION

The number of ports of entry in a country for the handling of imports of pharmaceutical products should be limited by appropriate legislation. Such ports could be designated by the state. The chosen port(s) of entry should be those most appropriately located and best equipped to handle imports of pharmaceutical products. At the port of entry, consignments of pharmaceutical products should be stored under suitable conditions for as short a time as possible. All reasonable steps should be taken by importers to ensure that products are not mishandled or exposed to adverse storage conditions at wharves or airports.

15.2.17 CONTRACT ACTIVITIES

Any activity relating to the distribution of a pharmaceutical product which is delegated to another person or entity should be performed by parties appropriately authorized for that function and in accordance with the terms of a written contract. The contract should defi ne the responsibilities of each party including observance of the principles of GDP and relevant warranty clauses. It should also include responsibilities of the contractor for measures to avoid the entry of counterfeit medicines into the distribution chain, such as by suitable training programmes. Contract accepters should be audited periodically.

15.2.18 SELF-INSPECTION

The quality system should include self-inspections. These should be conducted to monitor implementation and compliance with the principles of GDP and, if necessary, to trigger corrective and preventive measures. Self-inspections should be conducted in an independent and detailed way by a designated, competent person. The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and, where applicable, proposals for corrective measures. There should be an effective follow-up programme. Management should evaluate the inspection report and the records of any corrective actions taken.

15.3 MATERIAL MANAGEMENT

Material management is an important management tool which will be very useful in getting the right quality & right quantity of supplies at right time, having good inventory control & adopting sound methods of condemnation & disposal will improve the efficiency of the organization & also make the working atmosphere healthy any type of organization, whether it is Private, Government ,Small organization, Big organization and Household.

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. Material management is a scientific technique, concerned with Planning, Organizing &Control of flow of materials, from their initial purchase to destination.

15.3.1 OBJECTIVES OF MATERIAL MANAGEMENT:

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

15.3.2 FOUR BASIC NEEDS OF MATERIAL MANAGEMENT

1. To have adequate materials on hand when needed
2. To pay the lowest possible prices, consistent with quality and value requirement for purchases materials
3. To minimize the inventory investment
4. To operate efficiently

15.3.3 BASIC PRINCIPLES OF MATERIAL MANAGEMENT

1. Effective management & supervision

It depends on managerial functions of

- Planning
- Organizing
- Staffing
- Directing
- Controlling
- Reporting
- Budgeting

2. Sound purchasing methods
3. Skillful & hard poised negotiations
4. Effective purchase system
5. Should be simple
6. Must not increase other costs
7. Simple inventory control programme

15.3.4 ELEMENTS OF MATERIAL MANAGEMENT

1. Demand estimation
2. Identify the needed items
3. Calculate from the trends in Consumption during last 2 years
4. Review with resource constraints

15.3.5 FUNCTIONAL AREAS OF MATERIAL MANAGEMENT

1. Purchasing
2. Central service supply
3. Central stores
4. The print shops
5. The pharmacy
6. Dietary & Linen services

15.3.6 PROCUREMENT

1. Directorate general of supply & disposal (DGS & D, Govt. Of India]
2. Medical stores depot (M. S.D. Government of India, Ministry of H & FW]
3. Private or public sector undertakings.
4. Receiving donations

Procurement cycle

- Review selection
- Determine needed quantities
- Reconcile needs & funds
- Choose procurement method

- Select suppliers
- Specify contract terms
- Monitor order status
- Receipt & inspection

Objectives of procurement system

- Acquire needed supplies as inexpensively as possible
- Obtain high quality supplies
- Assure prompt & dependable delivery
- Distribute the procurement workload to avoid period of idleness & overwork
- Optimize inventory management through scientific procurement procedures

FLOW OF PROCUREMENT DECISIONS

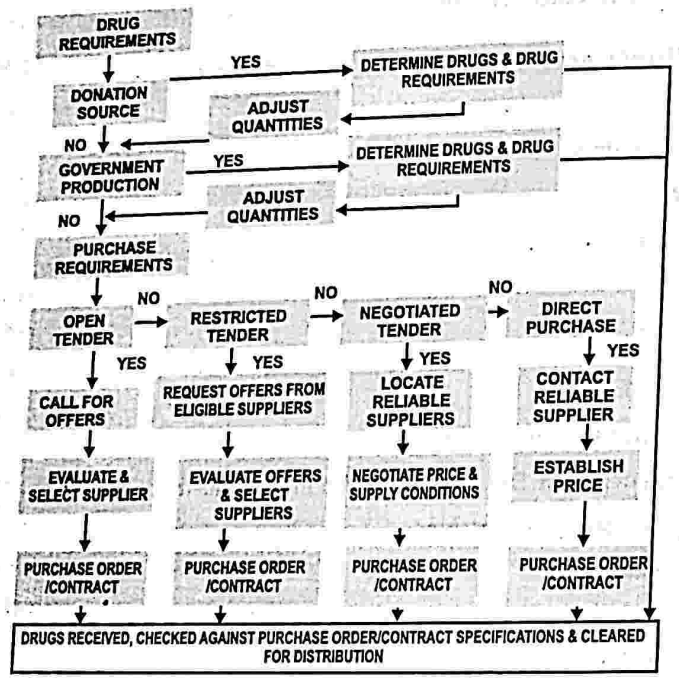

Figure 15.3 : Flow of procurement process

Open tender

- Public bidding, resulting in low prices
- Published in newspapers
- Term - 4 weeks
- Quotations must be sent in the specific forms that are sold, before the time &date mentioned in the tender form
- In technical items, 'two packets or two bins' system is followed. Offers are given in two separate packets.
- Technical bid
- Financial bid

Points to remember while purchasing

- Proper specification
- Invite quotations from reputed firms
- Comparison of offers based on basic price, freight & insurance, taxes and levies
- Quantity & payment discounts
- Payment terms
- Delivery period, guarantee
- Vendor reputation

  (reliability, technical capabilities, Convenience, Availability, after-sales service, sales assistance)
- Short listing for better negotiation terms
- Seek order acknowledgement

Storage

- Store must be of adequate space
- Materials must be stored in an appropriate place
- in a correct way
- Group wise & alphabetical arrangement helps in
- identification & retrieval
- First-in, first-out principle to be followed
- Monitor expiry date
- Follow two bin or double shelf system, to avoid

- Stock outs
- Reserve bin should contain stock that will cover
- lead time and a small safety stock

Issue & use: Can be centralized or decentralized

15.3.7 INVENTORY CONTROL

It means stocking adequate number and kind of stores, so that the materials are available whenever required and wherever required. Scientific inventory control results in optimal balance

Functions of inventory control

- To provide maximum supply service, consistent with maximum efficiency & optimum investment.
- To provide cushion between forecasted & actual demand for a material

Economic order of quantity

EOQ = Average Monthly Consumption X Lead Time [in months] + Buffer Stock – Stock on hand

- Re-order level: stock level at which fresh order is placed.
- Average consumption per day x lead time + buffer stock
- Lead time: Duration time between placing an order & receipt of material
- Ideal – 2 to 6 weeks.

ABC ANALYSIS

(ABC = Always Better Control)

- This is based on cost criteria.
- It helps to exercise selective control when confronted with large number of items it rationalizes the number of orders, number of items & reduce the inventory.
- About 10 % of materials consume 70 % of resources
- About 20 % of materials consume 20 % of resources
- About 70 % of materials consume 10 % of resources

'A' ITEMS Small in number, but consume large amount of resources

Must have:

- Tight control
- Rigid estimate of requirements

- Strict & closer watch
- Low safety stocks
- Managed by top management

'B' ITEM

Intermediate

Must have:

- Moderate control
- Purchase based on rigid requirements
- Reasonably strict watch & control
- Moderate safety stocks
- Managed by middle level management

'C' ITEMS

Larger in number, but consume lesser amount of resources

Must have:

- Ordinary control measures
- Purchase based on usage estimates
- High safety stocks

ABC analysis does not stress on items those are less costly but may be vital

VED Analysis

Based on critical value & shortage cost of an item It is a subjective analysis.

Items are classified into:

Vital: Shortage cannot be tolerated.

Essential: Shortage can be tolerated for a short period.

Desirable: Shortage will not adversely affect, but may be using more resources. These must be strictly Scrutinized

Procurment of equipment

Points to be noted before purchase of an equipment:

- Latest technology
- Availability of maintenance & repair facility, with minimum down time
- Post warranty repair at reasonable cost
- Upgradeability
- Reputed manufacturer

- Availability of consumables
- Low operating costs
- Installation
- Proper installation as per guidelines

Preventive maintenance

- Purchase with warranty & spares.
- Safeguard the electronic equipments with: (as per guidelines)
  - Voltage stabilizer, UPS
  - Automatic switch over generator
- Requirement of electricity, water, space, atmospheric conditions, etc. Must be taken into consideration
- Well equipped maintenance cell must be available
- All equipment must be operated as per instructions with trained staff
- Monitoring annual maintenance contracts. (AMC)
- Maintenance cell
- Communications between maintenance cell & suppliers of the equipment.
- Follow-up of maintenance & repair services
- Repair of equipment
- Outside agencies
- In-house facility

Condemnation[27] & disposal

Criteria for condemnation: The equipment has become:

Non-functional & beyond economical repair

- Non-functional & obsolete
- Functional, but obsolete
- Functional, but hazardous
- Functional, but no longer required

Procedure for condemnation

- Verify records.
- History sheet of equipment
- Log book of maintenance & repairs .

27 ***Condemnation*** is the act of declaring something useless

- Performance record of equipment
- Put up in proper form & to the proper authority

Disposal

- Circulate to other units, where it is needed
- .Return to the vendor, if willing to accept
- Sell to agencies, scrap dealers, etc
- Auction
- Local destruction

REVIEW QUESTIONS

SHORT ANSWER QUESTIONS

Q1. Define validation

Ans. According to the Food and Drug Administration (FDA)
Validation is 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 characteristics.

Q2. Name the elements of Validation Protocol:-

Ans. After preparing Validation Master Plan, the next step is to prepare validation protocol. There are the following contents in a validation protocol.

1. General information
2. Objective
3. Background/Prevalidation Activities Summary of development and tech transfer (from R&D or another site) activities to justify in-process testing and controls; any previous validations.
4. List of equipment and their qualification status
5. Facilities qualification
6. Process flow chart
7. Manufacturing procedure narrative
8. List of critical processing parameters and critical excipients
9. Sampling, tests and specifications
10. Acceptance criteria

Q3. Name the different types of validation in Pharmaceutical Industry

Ans. Process Validation, Analytical Validation and Equipment validation

Q4. How Many Batches To Be Considered For Process Validation?

Ans. The EMA draft guideline states "a minimum of three consecutive batches", with justification to be provided (there are some exceptions to this statement).The US FDA guidance states that the