QUALITY ASSURANCE, GMP & GLP

UNIT - I

Concept of Quality assurance, philosophy of GMP, CGMP and GLP.

LO: To understand Concept of Quality assurance, philosophy of GMP, CGMP and GLP.

Quality management in the drug industry (CONCEPT AND PHILOSOPHY)

In the drug industry at large, quality management is usually defined as the aspectof management function that determines and implements the "quality policy",i.e. the overall intention and direction of an organization regarding quality, asformally expressed and authorized by top management. The basic elements ofquality management are:

— an appropriate infrastructure or "quality system", encompassing the organizationalstructure, procedures, processes and resources;

— systematic actions necessary to ensure adequate confidence that a product(or service) will satisfy given requirements for quality. The totality of theseactions is termed "quality assurance".

Within an organization, quality assurance serves as a management tool. Incontractual situations, quality assurance also serves to generate confidence inthe supplier. The concepts of quality assurance, GMP and quality control areinterrelated aspects of quality management. They are described here in order toemphasize their relationship and their fundamental importance to the productionand control of pharmaceutical products.

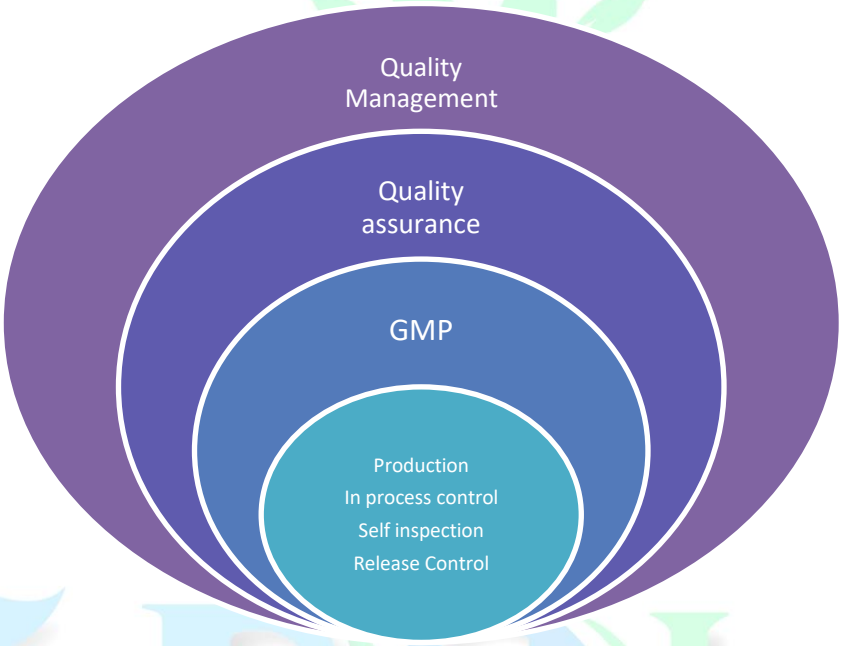


Fig 1: Model of Quality management system showing interrelationship between quality assurance, GMP, quality control and production

Elements of TQM: Total quality is a description of culture, attitude and organisation of a company that strives to provide customers product and services that satisfy their needs. Successful implementing TQM an organisation must concentrate on 8 key elements are:

i. Ethics
ii. Integrity
iii. Trust
iv. Training
v. Team work
vi. Leadership
vii. Recognitions
viii. Communications

These elements have been coined to describe a philosophy that makes quality the driving faces and leadership design, planning and improvement initiatives.

1. Quality assurance (Concept and Philosophy)

1.1 ***Definition***: "Quality assurance" is a wide-ranging concept covering allmatters that individually or collectively influence the quality of a product. It isthe totality of the arrangements made with the object of ensuring that pharmaceuticalproducts are of the quality required for their intended use. Qualityassurance therefore incorporates GMP and other factors, including thoseoutside the scope of this guide such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

(a) pharmaceutical products are designed and developed in a way that takesaccount of the requirements of GMP and other associated codes such asthose of good laboratory practice (GLP)and good clinical practice(GCP);

(b) production and control operations are clearly specified in a written form and GMP requirements are adopted;

(c) managerial responsibilities are clearly specified in job descriptions;

(d) arrangements are made for the manufacture, supply and use of the correctstarting and packaging materials;

(e) all necessary controls on starting materials, intermediate products, andbulk products and other in-process controls, calibrations, and validationsare carried out;

(f) the finished product is correctly processed and checked, according to thedefined procedures;

(g) pharmaceutical products are not sold or supplied before the authorizedpersons have certified that each productionbatch has been produced and controlled in accordance with therequirements of the marketing authorization and any other regulations relevantto the production, control and release of pharmaceutical products;

(h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceuticalproducts are stored by the manufacturer, distributed, and subsequentlyhandled so that quality is maintained throughout their shelf-life;

(i) there is a procedure for self-inspection and/or quality audit that regularlyappraises the effectiveness and applicability of thequality assurancesystem;

(j) deviations are reported, investigated and recorded;

(k) there is a system for approving changes that may have an impact onproduct quality;

(l) regular evaluations of the quality of pharmaceutical products should beconducted with the objective of verifying the consistency of the processand ensuring its continuous improvement.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceuticalproducts to ensure that they are fit for their intended use, comply withthe requirements of the marketing authorization and do not place patients atrisk due to inadequate safety, quality or efficacy. The attainment of this qualityobjective is the responsibility of senior management and requires the participationand commitment of staff in many different departments and at all levelswithin the company, the company's suppliers, and the distributors. To achievethe quality objective reliably there must be a comprehensively designed and correctlyimplemented system of quality assurance incorporating GMP and qualitycontrol. It should be fully documented and its effectiveness monitored. All partsof the quality assurance system should be adequately staffed with competentpersonnel, and should have suitable and sufficient premises, equipment, andfacilities.

2. Good manufacturing practices for pharmaceuticalproducts (GMP)- (Schedule M)

Good manufacturing practice is that part of quality assurance which ensuresthat products are consistently produced and controlled to the quality standardsappropriate to their intended use and as required by the marketing authorization.GMP are aimed primarily at diminishing the risks inherent in anypharmaceutical prouction. A draft of GMP regulations were prepared in 1975 which are finalized and implemented in 1988. Such risks are essentially of two types: cross-contamination(in particular of unexpected contaminants) and mix-ups(confusion) caused by, for example, false labels being put on containers.

UnderGMP:

(a) all manufacturing processes are clearly defined, systematically reviewed inthe light of experience, and shown to be capable of consistently manufacturingpharmaceutical products of the required quality that comply withtheir specifications;

(b) qualification and validation are performed;

(c) all necessary resources are provided, including:

(i) appropriately qualified and trained personnel;

(ii) adequate premises and space;

(iii) suitable equipment and services;

(iv) appropriate materials, containers and labels;

(v) approved procedures and instructions;

(vi) suitable storage and transport;

(vii) adequate personnel, laboratories and equipment for in-processcontrols;

(d) instructions and procedures are written in clear and unambiguouslanguage, specifically applicable to the facilities provided;

(e) operators are trained to carry out procedures correctly;

(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;

(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(h) the proper storage and distribution of the products minimizes any risk to their quality;

(i) a system is available to recall any batch of product from sale or supply;

(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

SELF-INSPECTION AND QUALITY CONTROL:

Principle. The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and torecommend the necessary corrective actions.Self-inspections should be performed routinely, and may be, in addition, performedon special occasions, e.g. in the case of product recalls or repeated rejections,or when an inspection by the health authorities is announced. The teamresponsible for self-inspection should consist of personnel who can evaluate theimplementation of GMP objectively. All recommendations for corrective actionshould be implemented. The procedure for self-inspection should be documented,and there should be an effective follow-up programme.

Items for self-inspection

Written instructions for self-inspection should be established to provide aminimum and uniform standard of requirements. These may include questionnaireson GMP requirements covering at least the following items:

(a) personnel;
(b) premises including personnel facilities;
(c) maintenance of buildings and equipment;
(d) storage of starting materials and finished products;
(e) equipment;
(f) production and in-process controls;
(g) quality control;
(h) documentation;
(i) sanitation and hygiene;
(j) validation and revalidation programmes;
(k) calibration of instruments or measurement systems;
(l) recall procedures;
(m) complaints management;
(n) labels control;
(o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-inspection report

A report should be made at the completion of a self-inspection. The report should include:

(a) self-inspection results;
(b) evaluation and conclusions;
(c) recommended corrective actions.

Follow-up action

There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality control

It may be useful to supplement self-inspections with a quality control. A quality control consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors

Current Good Manufacturing Practices (cGMP):

cGMP is defined as the part of quality assurance, which ensures that products are consistently produced and controlled to the quality standards appropriate for their intended use and legal requirements. cGMP is thus concerned with both production and quality control. It deals with every activity at each stage of manufacturing.

- cGMP are designed to ensure that the entire process, from purchase of approved material through detailed, defined production processes, using approved facilities and trained personnel operating in well designed buildings through QC department to final distribution outlets. This results in the achievement of consistent and uniformly good quality products.
- cGMP is a set of guidelines that are required by the US FDA for pharmaceutical manufacturers to make use of and develop their own part procedures.
- cGMP help ensure that quality includes entire manufacturing procedures and are maintained throughout the product life.
- This starts with raw materials received and through the product creation and testing and does not even end after the product sold and consumed.

- Following cGMP is not compulsory but it is necessary to ensure a greater issue of consumer safety and confidence.
- cGMP are so called because they are always changing, as they should, to match the current science and change in nature of products and manufacturing.
- cGMP – also defined as "practices which are used to assure that a product or any of its component parts, meets the requirements as to safety, has the identity and strength and meets the quality and purity and characters which it is intended to possess".
- It is a comprehensive system, designed, documented, implemented and controlled and furnished with personnel equipment and other resources as to provide assurance that products will be consistently of a quality appropriate to their international standards.
- Thus, the attainment of this quality object requires involvement and commitment of a concerned at all stages.

OBJECTIVES OF cGMP:

To assure quality of a product and finally the safety, well being and protection of patient.

- To perform every operation with the objectives of maintaining the identity and integrity and products of effective production.
- To establish systems of control at all levels of manufacturing, right from the receipt of raw materials by continuous working, using correct equipment to dispatch finished goods from factory.
- cGMP is just a guideline, system and quality theme for compliance.
- It is a way to built quality in a product.
- Improves productivity and minimizes rejection and mistakes.

TEN PRINCIPLES OF GMP

1. Design and construct the facilities and equipments properly
2. Follow written procedures and Instructions
3. Document work
4. Validate work
5. Monitor facilities and equipment
6. Write step by step operating procedures and work on instructions
7. Design,develop and demonstrate job competence
8. Protect against contamination
9. Control components and product related processes
10. Conduct planned and periodic audits

GOOD LABORATORY PRACTICES (GLP):

Good Laboratory practices complements GMP and without GLP it is difficult to achieve accurate results which may in turn lead to reprocessing or reworking of the final product. One important challenge for any analytical laboratory is staying in regulatory compliance while maintaining maximum output. Simultaneous productivity and compliance can only be achieved by laboratories that have competent chemists, high quality managers and a strong QA system.

Analytical laboratories are not prone immune from unexpected problems like power failure, instrument breakdown, accidental spills etc. These however don't cause any regulatory problems as they can be justified by repetition of the process. It is the unexplainable data which results in loss of productivity and regulatory problems.

A QA system includes regularly scheduled equipment calibration, coupled with management tools will be able to determine whether the problems in data are due to analytical system, equipment, method or personnel.

Common mistakes made in the laboratories (only few were mentioned):

- Weighing
- Using pipettes, burettes, liquid samples
- Titrations

Weighing:

- Weighing hot or warm samples
- Weighing material that lose water rapidly in an open balance pan or in open vessel
- Weighing objects that are too large for the balance pan
- Weighing off the centre
- Accidental weighing of the stopper, magnetic stirrer bars
- Using contaminated spatula
- Using a balance that is out of calibration or out of level
- Spilling sample on the balance pan
- An inappropriate weighing range
- Weighing of lumps of powders or weighing substances that possess electrostatic charges without suitable neutralization.

Using appropriate balance:

Minimum weights for the balance:

- Top loading balance: 0.00 $\pm$ 0.01 gm
  - For weighing equal to or greater than 5 gms, top loading balance is used
- Analytical balance: 0.0000 + 0.0001 gm
  - For weights between 100mg and 5 gms analytical balance is appropriate
- Semi-Micro balance: 0.000000 $\pm$ 0.000001 gm
  - For weighing less than 100 mg semi micro balance is used

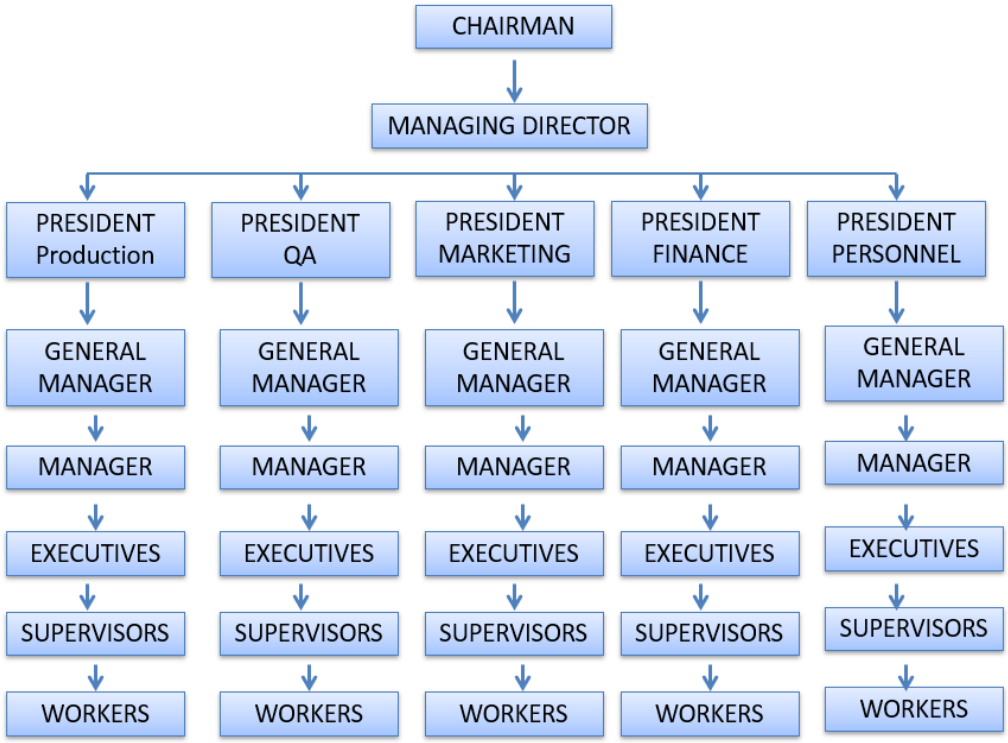
UNIT - II

Organization and personnel, responsibilities, training hygiene - Premises: Location, design, plant layout, construction, maintenance and sanitations, environmental control, sterile areas, control of contamination.

LO : To understand organization and personnel, responsibilities, training hygiene - Premises: Location, design, plant layout, construction,
maintenance and sanitations, environmental control, sterile areas, control of contamination.

ORGANIZATION

- The manufacturer should have an organization chart. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel covered with application of GMP.
- Every organization should have a recorded organization chart. This organization chart should clearly show the organizational structure. Normally, two levels of charts are prepared. The chart shows the levels starting from the Chairman of the organization to the functional heads as shown below:



- Each person engaged in the manufacture processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to enable that person to perform the assigned functions.
- Each person responsible for supervising the manufacture, processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to perform assigned functions in such a manner as to provide assurance that it purports or is represented to possess
- There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing or storage of each medicine.

WHO Guidelines on Personnel:

The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to prevent any risk to quality.

Academic qualifications required in the various areas of specialization:

- **Production**: B.Pharm, M.Pharm, Ph.D
- **QC/ QA**: B.Pharm, M. Pharm, Ph.D, M.Sc in microbiology, Organic chemistry and M.Sc in total quality management. Presently some post graduate diplomas are also available in analytical and technical chemistry, which are also suitable.
- **Engineering**: Diploma in Engineering, B.E, ME in suitable areas like Civil, Electrical, Electronics, Mechanical, Chemical, Environmental engineering etc.
- **Stores**: Post graduates in materials management or postgraduate from Indian Institute of Materials Management etc
- **Personnel**: MBA (Personnel, HR), PG Diploma in Training and Development, Master of Social Works (MSW) in Personnel Management and Industrial relations, MHRD (Master in Human Resource Development)
- **Finance**: M.Com, MBA (Finance), Chartered Accountants etc

Organizational positions- Age and Experience:

Organization Position	Years of Experience Required or seen	Age of the Employee
1.Supervision	Freshers	22 years
2.Executive	3-5 years	25-28 years
3.Manager	8-10 years	30-32 years
4.General Manager	15 years	35 years
5.Vice-President	15-20 years	35-40 years

TYPES OF PERSONNEL

a. Research
b. Quality control
c. Production
d. Marketing

a. Research

Requires team work ability to understand appreciate problems of one another.

b. Quality Control

Should have capacity to work meticulously with precision.

c. Production

Should be capable of successfully co-ordinating the manpower, materials, machinery to produce maximum quality output.

d. Marketing Personnel

Should possess good communication skill, good personality, convincing ability.

RESPONSIBILITIES

A Pharmaceutical unit should have the following personnel and their responsibilities are discussed below.

a. In-charge Production
b. In-charge Quality Control
c. Supervisors / Analyst
d. Other Technical Personnels

a. In-charge Production

- The in-charge of Production should have enough practical experience and adequately trained to make professional judgements correctly.
- He/She is responsible to manage production of drugs, storage, control of starting materials and finished products.

b. In-charge Quality Control

- Every manufacturing establishment shall have a quality control unit supervised by approved expert staff directly responsible for the management which is independent of other departments.
- QC department has control on raw materials, monitors all in-process quality checks, control the quality & stability of finished products.

The responsibilities of QC department are -

a. to prepare detailed written instructions for carrying out analysis
b. to release (or) reject each batch of raw materials
c. to release / reject semi-finished products if any
d. to release (or) reject packaging & labelling materials to the final containers in which drugs are to be packed
e. to release (or) reject each batch of finished products ready for distribution
f. to evaluate adequacy of storage conditions of raw materials & semi-finished products also for raw materials.
g. to establish revise control procedures and specifications when required
h. to examine returned products as to whether such products should be released / reprocessed (or) destroyed.

c. Supervisors

- Manufacturing of drugs carried out under personal vigilance of supervisors
- They should be responsible to a level of management and must have a questioning nature.

d. Analyst

Should be given training in Q.C. Systems. They will execute analysis of starting materials, semi-finished & finished products.

e. Other Technical Personnel

It comprises of skilled workers who are able to read and understand written directions. After recruitment they should be adequately trained on

i. Characteristics of pharmaceuticals their handling & dangers if any
ii. Cleanliness of general hygiene, personal cleanliness & health
iii. Their duties & responsibilities
iv. Principles of GMP

TRAINING

The objective of training is to indicate awareness in the employee in advantage and importance of adhering to GMP. The training development is a continuous process performance appraised should play a key role in this cycle. People in an organization are the main

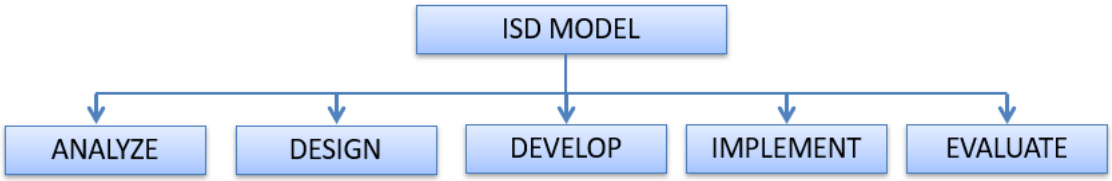
resource, has more value and importance than other resources like facilities, equipment and materials, provided these people are trained appropriately to carry out their assigned task. A trained person generally has the knowledge, skill and attitude relevant to their job and that too in the appropriate level. The activities involved in the development of personnel include:

- **Training**: Training is defined as the acquisition of technology which permits employees to perform their present jobs to standards. It improves human performance on the job, the employee is presently doing or is being hired to do. Also training is imparted when new technology is introduced into the workplace.
- **Development**: Development is training people to acquire new horizons, technologies or viewpoints. It enables leaders to guide their organizations into new expectations by being proactive than reactive. It enables workers to create better products, faster services and more competitive organizations. It is learning for growth of the individual, but not related to a specific or future job. Unlike training and education, which can be completely evaluated, development cannot always be fully evaluated. This does not mean that development programmes are abandoned because helping the people to grow keeps the organization in cutting edge in the competitive environment. Development can be considered the forefront of what many now call as the learning organizations. Development involves changes in a person that are systematic, organized and successive and are thought to serve as an adaptive function.
- **Education**: Education is training people to do a different job. It is often given to people who have been identified as being promotable being considered for a new job either lateral or upward or to increase their potential. Unlike training which can be fully evaluated immediately upon the learners returning to work, education can only be completely evaluated when the learners move on to their future jobs or tasks.

There are many methods of training employees during employment. One of the latest method to train the people in employment is by Instructional System Design (ISD). This involves the basic concept of IPO system ie Input, Process and output.

Input- Input is the people who need to acquire knowledge, skill and attitude
Process- Process is learning that takes place within the system
Output-Output is the trained person.

The ISD training model can briefly be shown as follows:



Analyse: Analyse the system in order to completely understand it, and then describe the goals you wish to achieve in order to correct any shortcomings or faults within the system
Design: Design a method to achieve your goals
Develop: Develop the model into a product (in training, this product is called courseware)
Implement: Implement the courseware
Evaluate: Evaluate the courseware and audit-trail throughout the four phases and in the field to ensure it is heading in the right direction and achieving the desired results.
Personnel are assigned in the operation involved in the processing, manufacturing, packaging control of drug products. Hence, they must possess sufficient enough knowledge by virtue of education, training and experience to competently perform the assigned tasks.

TRAINING & DEVELOPMENT CYCLE:

POSITION REQUIREMENT: The GMP regulations do not define education knowledge, skill or experience in required to work in pharmaceutical company Some basic skills required are

Ability to understand written instructions
Ability to write coherently to enter information for documentation in the records
Ability sufficient mathematical knowledge to perform some statistical calculation process control.

APPLICANT SCREENING:

Pre- employment screening for identify potential security is essential specifically when pharmaceutical manufacturing involves handling of control substances screening includes. Careful scrutiny of potential employees personal and previous history employment references. Review of possible criminal back ground. Basic technical education qualification experience

Types of Training: There are five types of training namely:

1.Induction training: It refers to the process of introducing the new employees to the organization as well as to the existing employees to meet the requirements of the higher post. Such a training is called as promotional training.
It includes

After employment initial or induction training
A back ground on the industry.
The policies procedure of company
Some fundamentals on the importance of the employee role to the health in the well being of the ultimate consumer

3.**Basic Training**:
This will take place over the period of time during which the employee will be closely supervised. During this stage the employees must be fully trained in all relevant techniques associated with the equipments involved. Must be aware of the potential problems that can be created by non- adherence to these procedures.
3.Promotional training: In many organizations, training is given to the existing employees to meet the requirements of the higher post. Such a training is called promotional training.
4. Refresher Training: The training is given to the employees in order to update their knowledge with respect to the latest development in their respective fields.
5. Job training: This training is given to the newly recruited employees. The instructions are given by a supervisor to the new workers so that they can work smoothly in the new environment.
6. Safety training: The training is given to the workers to handle the dangerous machines and materials in order to avoid any fatal accidents.

EVALUATION & APPRAISAL REPEAT TRAINING:
Training programs must include appropriate evaluation steps this involve some type of evaluation at the end of each module followed by job appraisal to confirm that the lesson learned have been put into practice. The regular employee performs appraisal process should also identify further training needs

As refreshes to existing knowledge skills
To meet the changing need of the operation
In preparation for a job requiring additional skills

TRAINER: Administered by professional trainer in house staff members, including the supervisor. The advantage of having in house staff members as trainers is the continuing report interaction which exists between them and the employee. Scope and Length of Programme: Member of participants should not exceed 10 at one time. The program shall spread over a total period of 3 to 6 days which could be divided in to several sessions.
TRAINING MATERIAL:

- Audio visuals such as video, slides, drawing etc
- Work book
- Problem solving examples
- Circulations of journals other publications

PROGRAM CONTENTS:
A training session should cover the following aspects
1. Introduction to essential aspects of GMP
2. Introduction to drugs and cosmetics Act rules there under
3. Material segregation & quarantine
4. Correct weighing
5. Cross contamination
6. Correct labeling and causes of minutes
7. Cleanliness, general hygine, personal cleanliness and health
8. Equipments cleaning and calibration
9. Special process requirement
10. Batch records and documentation process
11. Role of QA
12. Characteristics of pharmaceuticals their handling and dangers if any
13. Duties and responsibilities of personnel
14. Sterile technique packaging operation of machines
15. Safety procedures

TRAINING RECORDS: A record of all employees who have undergone the above training should be kept which includes

- Name of the employees and trainees
- Department and location
- Programmer contents
- Signature and date of employee and trainees

Training records must be maintained and kept current FDA inspectors may ask for confirmation of adequate training. The responsibility for a training employees should reside with the departmental management. The QC dept should monitor audit to ensure that appropriate training has been given, including review of training module content of training records. APPRAISAL: It is important to both employee and trainee. It is an aid to

- Evaluate performance
- Reward and develop an employee
- Plan career

TYPES OF APPRAISAL:

- Confirmation appraisal
- Periodical performance appraisal
- Potential appraisal
- Script based appraisal system

a.Confirmation Appraisal: The appraisal determines whether the assessment of the organization as regards the knowledge, skills and experience of employees has been proven during the testing. Individuals are recruited for a particular job and are then positioned in a totally different work environment job profile, if the current job does not fit, such discrepancy out to be brought into the notice of the appraises of the senior.

b.Periodical Performance Appraisal: Such appraisals are conducted at a fixed frequency where several organization have a practice of appraising the performance against set targets and also assessing the candidates traits, they help the employee role in experience history.

c.Potential appraisal: It is different from performance appraisal by nature it is more subjective than objective. Fore castes the future with limited information these are carried out by people who are senior most level of thereby. Carried out after a person who has four to five years experience in the company. The appraiser generally takes a look at the history of the employee for taking up additional job responsibilities. **d.Script based appraisal system:** Is the role conversation where both managers and the employee has a chance of discussing with maximum bureaucracy.

First stage - two participants will be given a set of objectives to be achieved within a period.

Second stage - After four to six months schedule another meeting to undertake conversation modify some of objectives accordingly.

RECORDS:

1. Personal Records:

Educational and training records are maintained up to date. It maintains

Health: The minimum health requirement of personnel working in the factory must be given in writing. A pre- employment medical examination inclusive of eye- testing must be insisted. Periods health check-ups should be carried to all personnel. Special attention to be paid to persons with any communicable disease. Employees are taken back from due to illness are only allowed to work after complete assessment by a competent medical officer /nurse. Staff should report about any infectious diseases of their (or) of the family enabling their temporary transfer to other work areas. Staff should report any boils, carbuncles, open wounds or exposed surfaces of the body. They must be executed from operations involving direct contact with materials equipment until the condition is corrected. Supervisory staff should look for signs and symptoms of unhealthy conditions of persons working in their areas.

PERSONAL CLEANLINESS:

Staff should be advised and encouraged to have regular baths and to change their underclothes frequently, washing and toilet facilities should be provided. Hands should be cleaned regularly and always after visiting the toilet.

The hair should be kept clean and well controlled at all times. Combing of hair must be strictly forbidden other than clock room. Wearing of costumes, jewelers etc should be discouraged. Women operators wear the minimum of make false eye lashes and beauty aids that are likely to fall. Records maintained in central location with limited access considered as employees confidential files annual set by the personal department the employee indicates in concern individual performance position with the company.

HEALTH RECORDS:

Records of medical examination of factory persons are required for following reasons

1. To provide a medical history of every patient
2. To ensure product quality not jeopardized by contact people to carry infection
3. To ensure that the health of operator not affected by repeated handling of highly potent toxic sensitizing materials.
4. Personal control measures include pre-employment medical examination for all employees chest x- ray Wassermann test, tuberculosis test.
5. Periodic reexamination performed annually update

PERSONNEL HYGINE

A major factor for contamination is human body carrying many organisms and particulate matters, some minimum requirements of health personal cleanliness and hygiene behavior, clothing to protect himself from the product. It applies to all persons including visitors, maintenance staff, senior management staff and other inspecting authorities.

HYGIENE BEHAVIOUR:

- It is a personal responsibility of each person to follow these elementary rules.
- Food and drink must not be consumed in the manufacturing packaging, storage and lab areas.
- Smoking must not be permitted in any processing storage (or) lab areas.
- No smoking signs should be displayed in prominent positions.
- Food, drinks and smoking materials should not be stored in manufacturing areas.
- Personnel medication should not be permitted in such areas.
- Staff should be trained to keep working areas clean.
- Staff must keep their lockers clean and testing.

PROTECTIVE CLOTHING:

- It not protects the individual but also the protection of the product from the individual.

- All persons at entering period should wear protective garments provided for the purpose appropriate for process being carried out.
- Clean working garments and protective apparel such as head, face, hand, shock and arm covering must be worn as directed.
- While handling dangerous (or) volatile material, personnel must be protected with suitable clothing and additional devices such as head covering, anti- dust masks, safety goggles etc.
- Protective clothing should be always clean and should be changed regularly with frequents laundering. Clothing worn properly buttons should be fastened.

PREMISES

Objectives:

1. To review general requirements.
2. To list key requirements for site choice.
3. To consider specific requirements for main areas.
4. To list major facilities required in a site.

Principle: Premises must be located, designed, constructed, and maintained for the operations like
Minimize risks of errors and cross-contamination.
Permit effective cleaning.
Permit effective maintenance.
Minimize build-up of dirt and dust.
Eliminate any adverse effects on quality.
Premises must be located to minimize risks of cross-contamination; e.g. not located next to a malting factory with high airborne levels of yeast.

Location

Ideally the location of the premises should be in a hygienic surrounding. The pollution sources must be minimum
The site for selecting the pharma industry must be away from open drainage, public lavatory and sewage
It must be separated from obnoxious odour fumes or large quantity of soot dust or smoke

Factors which must be mainly taken into consideration while selecting the site for pharma industry are

Transportation facility
Availability of water, electricity
Maintenance facility for repair
Fuel availability, sewage and waste stream removal from plant
Proximity for civil facilities for factory personals
Adequate space for future expansion
Adequate security arrangements

BUILIDINGS

Any building used for pharma industry must be of suitable size
Construction of it must be off with facilities for cleaning maintenance and proper operations

DESIGN PRINCIPLES

Process flow.
Material flow.
People flow.

LAYOUT:

Layout of the pharmaceutical plant layout is a coordinated effort to achieve the final objective to integrate machines, materials and personnel for economic production. Layout can be described as location of different departments and arrangement of machinery in a department. A proper layout has the advantage from the point of workers, labour costs, other production costs, production controls, supervision and capital investment. Layouts are of two types:

A. Process layout or functional layout
B. Product or straight-line layout

Process layout or functional layout:

In this type, all machines of a particular class responsible for a particular type of work or process are arranged together in a separate department. For example, all cutting machines may be placed in one department. The advantages of this type are:

- More effective supervision can be achieved
- Division of labour or specialized work can be provided
- Less disruption of production is possible
- Good scope for expansion

This type of layout may not be possible in the pharmaceutical and chemical industry, because a number of unit operations should be performed in sequence.

Product or straight-line layout: In this type, all machines doing various operations are arranged in a line. The advantages of this type of layout are:

- Facilitates quick and smooth processing of work
- Reduces cost of material handling using conveyor
- Reduces manufacturing time and speeds up the manufacturing cycle
- Facilitates proper use of floor space
- Reduces inventory of work in progress
- Reduces inventory of finished goods

Procedure for layout:

A proper layout includes arrangement of processing areas, storage areas and handling areas for efficient coordination. The layout of processing units in a plant, the equipment within these units must be planned. Then detailed piping, structural and electrical design should be developed. This layout can play an important role in determining construction and manufacturing costs. Thus, these must be planned carefully with attention being given to future problems that may arise.

Some factors which guide the layout are:

a. New site development or additions to a developed site
b. Type and quantity of products to be produced
c. Type of process and product control
d. Space available and space required
e. Operational convenience and accessibility
f. Economic distribution of utilities and services
g. Type of buildings and building code requirements
h. Health and safety considerations
i. Waste disposal problems
j. Auxillary equipment
k. Possible future expansion

Scale drawings indicating complete description with elevation can be used for determining the best location for equipment and facilities. Elementary layouts are developed first. By analysing all the factors that are involved in the plant layout, detailed recommendations can be presented finally. Drawings and elevations including isometric drawings of the piping systems can be prepared.

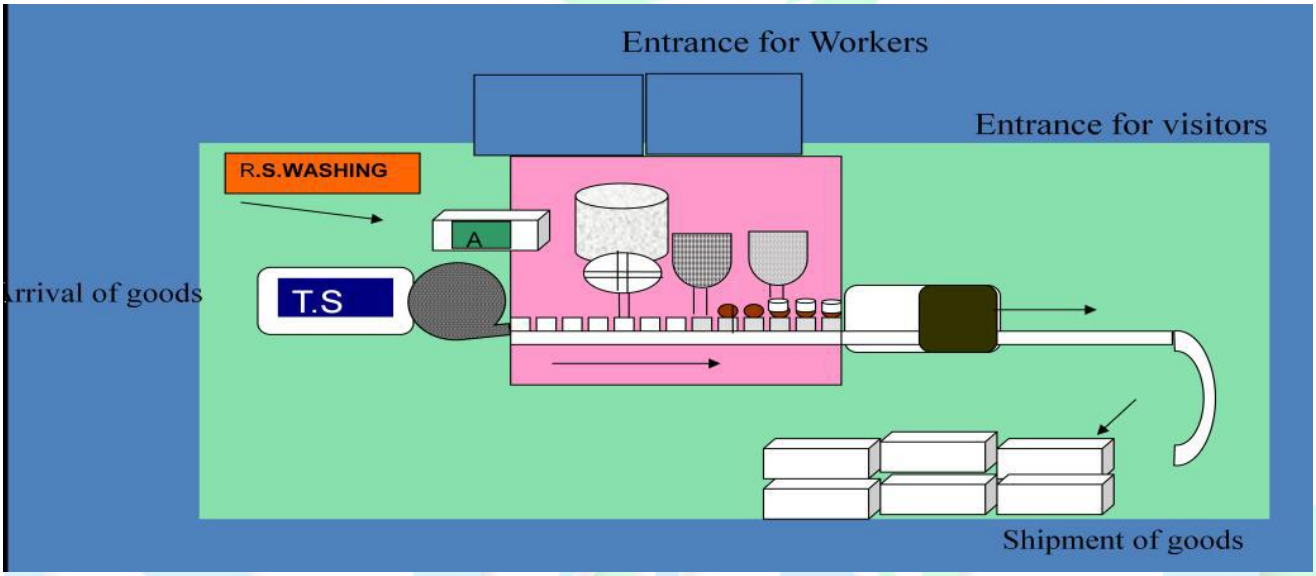


Fig: Example of Material and People flow

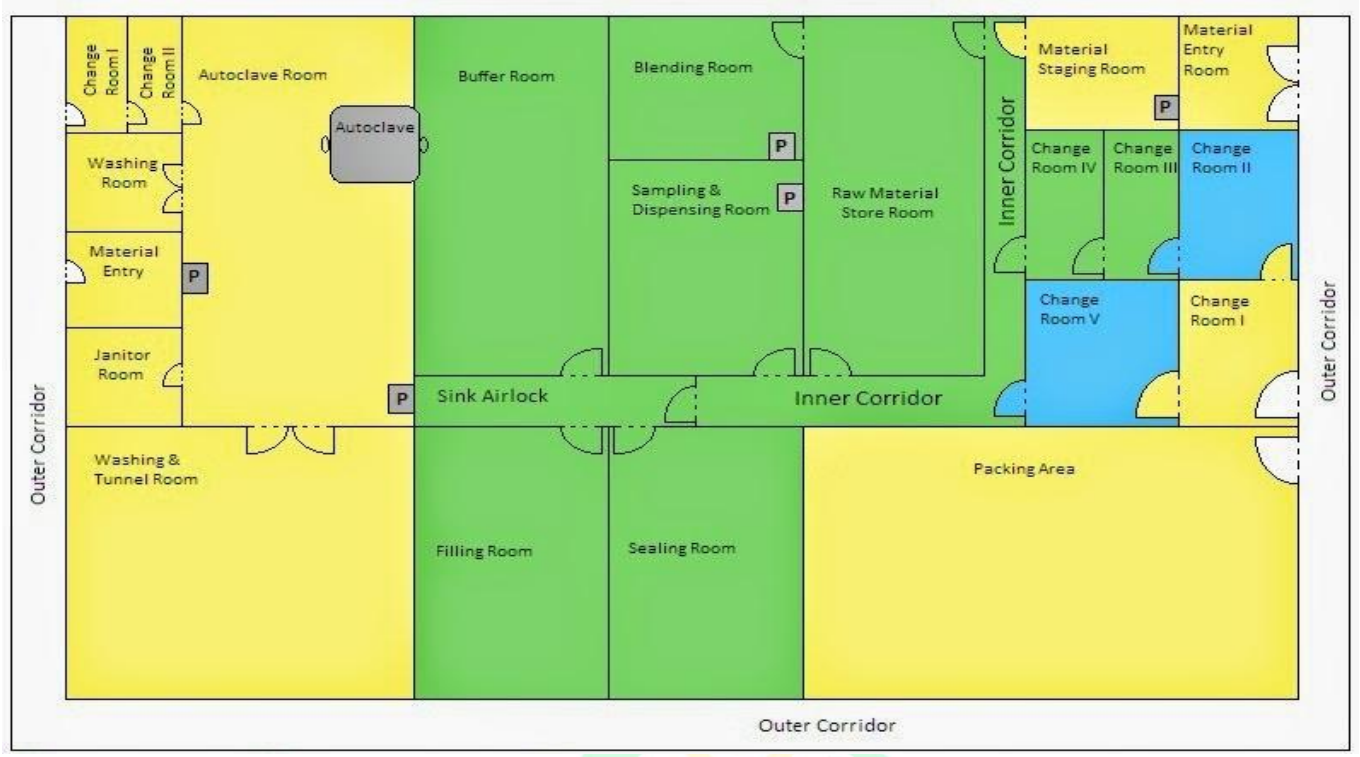


Fig: A Typical plant layout

CONSTRUCTION

Construction of the building should be such that

- it ensures protection of the product from contamination
- It must permit efficient cleaning facilities
- It must be in such a way that it must avoid accumulation of dust and dirt
- It must be prevented from entry of insects, birds, rodents etc

Provisions should be satisfactory to the factory act 1948. It must be mainly related to -

- Cleaning
- Disposal of waste
- Temperature
- Artificial humidification
- Ventilation
- Lighting
- Drinking water supply
- Toilet facilities
- Safety aspects

The main elements of the building to be considered are Functional requirements: a detailed plan should be taken for defining the room size with ceiling height door and window location and mainly the equipment location Ancillary Areas (supportive areas)

- Rest and refreshment rooms.
- Changing, washing and toilet areas.
- Maintenance workshops.
- Animal houses.

CONSTRUCTION MATERIALS:

The materials used for the construction must be of good quality

WALLS:

- The position of the walls should provide an orderly movement of materials and personnel.
- Walls in the industry must be made up of plaster finish on high quality concrete blocks or gypsum board.
- The finishing must be smooth and must be usually done by enamel or epoxy paints.
- In packing areas prefabricated portions may be used.
- Flush and projections of the walls must be avoided

FLOORS:

- Floor covering selection must be for durability as well as alienability and resistance to the chemical with which it is likely to come into contact.

- Most preferable things for flooring are terrazzo, ceramic and vinyl tiles, welding vinyl sheets, epoxy flooring etc

CEILINGS:

- Suspend ceilings may be provided in office area, laboratories, toilets,cafetarias.
- Manufacturing area requires a smooth finish often of seamless plasters or gypsum boards.
- All ceiling fixtures such as light fitting air outlet and returns, sprinkler heads should be design to assure case of cleaning and to minimize the potential for accumulation of dust.

DOORS AND WINDOWS:

- Doors and windows must be hard smooth and impervious, should close tightly.
- Windows of the manufacturing area should be tightly closed and not permitted to open.
- Outside doors must be tightly closed and sealed except for entry or exit.

SERVICES:

- In the building design provisions were made for drains water steam electricity or other services to allow for ease of maintenance
- Open channels of drains must be avoided; if not they should be shallow to facilitate cleaning and disinfection
- Passage of adequate width of 4-5 feet‘s were provided to facilitates movements of personnel‘s, machineries, and materials
- It must have orderly placement of equipments and materials to prevent for mix ups between different components
- Drug products labeling in process materials or drug product must be prevented from contamination
- Sufficient space must be provided to allow adequate separation adjacent equipment and operations

WORKING SPACE AND STORAGE AREA

- There should be adequate working space in factory premises
- Space should be there for orderly placement of equipments machinery and materials
- It must allow smooth movements of materials , personnel so that the risk of mix up of drugs or raw materials is minimized or eliminated and possibility of cross contamination of one drug by another
- There should be adequate space for storage areas for materials under test, approved or rejects
- For certain categories of formulation requirement of space laid down under schedule m of drug and cosmetic act and it should be maintained
- If there is more than one building access roadways services distribution and covered accesses between building should be provided

The importance points while designing a storage area are:

- Storage area should be of sufficient capacity so that various categories of materials stored can be done
- Segregated storage area must be provided for rejected, recalled for returned goods.
- In addition to quarantine area for materials received there should be flame proof area for inflammable substances.
- Physically isolated and separate area for toxic or sensitizing materials
- Separate area for secured materials with locking facilities may be available
- Special storage conditions like air conditioning, temperature humidity must be made for materials which require that Racks , wooden platforms etc may be provided in storage area so that materials are stored off the floor and away from the walls
- Adequate material handling equipment should be provided in storage areas

LIGHTING:

- Adequate lighting in pharmaceutical units is necessary
- The important points in providing adequate lighting are Position of source of light
- Selection of candescent or fluorescent bulbs,intensity of light
- Different type of operations may require different intensity of light supply and it must be provide as required
- Once the light levels are fixed its necessary to measure it periodically and the results should be recorded

AIR CONDITIONING:

- Factory premises of pharmaceutical units should be provided with adequate ventilation
- When the natural ventilation is not sufficient then exhaust fans must be provided
- Some areas may require conditioned air and this may be achieved by window type air conditioners or central air conditioners

Objectives of air conditioning system:

It should prevent the air bone contaminants into working areas.
Enclosed or semi enclosed systems should recirculation particulate free air
In coming volume of the air should be adequate so that particulate contamination are swept into exhaust
Dust or floating particulate matter generated in manufacturing areas should be removed before setting
Temperature and humidity should be so controlled that these do not affect the product and comfort of the workers
No turbulence in incoming air

PLUMBING:

Adequate supply of water is essential for a pharmaceutical unit In pharma industry mainly used types of water are

- Potable water
- Purified water
- Water for injection

- The frequency of examination of the water is necessary and it may depend upon the size of the population served.
- The FDA will not enquire if the industry connects the potable water line to a public supply which meet the standards
- Purified water is used to reduced the microbial count and can be achieved by membrane filtration or UV radiation
- Water for injection is the water which must be free from pyrogens. LAL test or rabbit test is performed to ascertain the sterility of the water for injection

SEWAGE AND REFUSE:

- Any products requiring disposal should initially be separated from it packing appropriate. This is because packing materials may delay the destruction, then they are safely disposed in the procedure preferred
- The disposal of printed packing components like labels inserts and cartons poses no health risk
- In effective disposal in public land fill preferably be incinerated
- It may destroyed under the supervision of an authorized person
- Waste containing dangerous or highly toxic materials may be disposed after suitable treatment.

WASHING AND TOILET FACILITES:

Adequate washing facilities may be provided including hot or cold water, soap or detergent water, air drier or single service towels. It must provided with neat and cleaned toilets There must be eating facilities laboratories or lockers

MAINTENANCE:

- All building used in the manufacture processing, packing or holding of a drug product shall be maintained in a good state of repair
- Deterioration of buildings not only make a poor image of the facility but also it may make an impact on the product quality
- Cracks and holes in walls floors or ceiling provide access for insect's rodents, birds and also hinder the cleaning and sanitation
- Low maintenance may increase the potent of cross contamination or microbial multiplication
- Ingress of water from roof tops may cause a significant damage to materials,equipment and may give rise to electrical failure
- Light fitting may need regular cleaning to remove any accumulation of dust acts as potent source of contamination and reduced light intensity.
- Temporary repair should be made for the correction of the building deficiencies
- Route line maintenance is required for the essential services which includes water supply HVAC (Heating, Ventilation and Air Conditioning), steam, vacuum, compressed air, other gases, electricity, dust extraction, pipe lines , drainages and sprinkler system

SANITATION

- Objectives of sanitation are
- Removal of dust and dirt and other waste materials
- Minimize the risk of cross contamination between different products in the same area
- Reduce the no of micro-organisms in work areas
- Controls pests so that these do not affect the quality of materials to be used in the manufacturing of drugs
- Sanitation of the manufacturing area is more important than other area because risk of contamination is more in these areas Protection from outside environment too is necessary

STERILE AREA: Sterile products are manufactured in the area specially designed and maintained Since most of the sterile products are injected directly into human body. so it must be very careful in designing and maintaining sterile area Sterile area provided for manufacturing of sterile products are given below

- Equipment and component washing area
- Water for injection preparation are compounding area
- Filling and sealing area
- Multiple air lack entrance
- Sterilization area containers visual examination area
- Quarantine area

Filling and sealing area must be separated from other areas in such a way that aseptic conditions are maintained by sealing the partitions Floors of the areas must be hard, smooth, impervious. It should not affect by detergents and disinfectants. Floor coverings are used in these areas. Walls and ceiling materials should be smooth and low particle shedding and easy to clean. Air locks should provide air seals to provides pressurization of aseptic room. The air lock may be designed in such a way that only one door opens at one time

ENVIRONMENTAL CONTROL& CONTROL OF CONTAMINATION:

Contaminates in the pharma industry includes dust, micro-organisms etc. Such contaminants normally float in air but settle down on counter floor and other exposed surfaces Exhaled breath of personals also contain micro-organisms. Air is main source of contamination and so the prevention of dust particle in air can also cause the control of number of micro-organisms Clean air is required to be feed into the sterile product This can be achieved by series of treatments or by air cleaning It must be done as follows:-

- Air first must be passed through primary filter mad of glass or wool. This primary filter must remove the larger particles
- Next pass through a passage narrowing electrostatic precipitator
- Finally, the air is passed through HEPA filter and thus it may filter up to the particle size of 0.3 microns and may remove with better efficiency
- Direction of air flow is horizontal or vertical
- The laminar flow may be carried out and it may sweeps the enterer confined area with uniform velocity with maximum eddies
- Air cleanness classes defined under fed standards no 209B
- Classification is based on the particle count with maximum allowable number of particles per unit volume

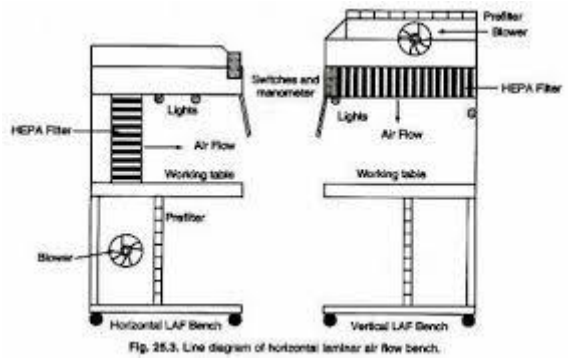


Fig. 25.3. Line diagram of horizontal laminar air flow bench.

MEASURES OF CROSS CONTAMINATION:

1. Segregated areas
2. Airlocks and pressure differentials
3. Treatment of recirculated air
4. Protective clothing
5. Effective cleaning procedures
6. Closed production systems
7. Residue testing
8. Status labelling

PREVENTION OF CROSS CONTAMINATION:

1. When dry materials and products are used in production, special precautionsshould be taken to prevent the generation and dissemination of dust.Provision should be made for proper air control (e.g. supply and extraction ofair of suitable quality).
2. Contamination of a starting material or of a product by another materialor product must be avoided. This risk of accidental cross-contamination arisesfrom the uncontrolled release of dust, gases, particles, vapours, sprays or organismsfrom materials and products in process, from residues on equipment, fromintruding insects, and from operators' clothing, skin, etc. The significance ofthis risk varies with the type of contaminant and of the product being contaminated.
3. Among the most hazardous contaminants are highly sensitizingmaterials, biological preparations such as living organisms, certain hormones,cytotoxic substances, and other highly active materials. Products in which contaminationis likely to be most significant are those administered by injection orapplied to open wounds and those given in large doses and/or over a long time.
4. Cross-contamination should be avoided by taking appropriate technicalor organizational measures, for example:
   (a) carrying out production in dedicated and self-contained areas (which maybe required for products such as penicillins, live vaccines, live bacterialpreparations and certain other biologicals);
   (b) conducting campaign production (separation in time) followed by appropriatecleaning in accordance with a validated cleaning procedure;
   (c) providing appropriately designed airlocks, pressure differentials, and airsupply and extraction systems;
   (d) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
   (e) wearing protective clothing where products or materials are handled;
   (f) using cleaning and decontamination procedures of known effectiveness;
   (g) using a "closed system" in production;
   (h) testing for residues;
   (i) using cleanliness status labels on equipment.
5. Measures to prevent cross-contamination and their effectiveness shouldbe checked periodically according to standard operating procedures.
6. Production areas where susceptible products are processed shouldundergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

TEMPERATURE AND RELATIVE HUMIDITY:

This is main factor which is to be controlled. In working areas, the temperature preferred is 25 ^{0}C. Regulation of humidity may depend upon the materials to be processed. If the material to be processed is not highly sensitive to moisture the humidity must be maintained below 50 If it is not possible to construct and maintain entire room as laminar air flow rooms then laminar air flow benches can be used.

UNIT - III

Equipments: Selection, purchase specifications, maintenance, clean in place, sterilize in place - Raw materials: Purchase specifications, maintenance of stores, selection of vendors, controls and raw materials.

LO: To understand selection, purchase specifications, maintenance, clean in place, sterilize in place - Raw materials: Purchase specifications, maintenance of stores, selection of vendors, controls and raw materials.

EQUIPMENTS

Introduction: Equipment is very important factor which can affect the quality of the formulation to a great extent therefore, the design, construction, installation, location, cleaning and the maintenance of equipment should be considered very carefully. Equipment used in the manufacture processing or holding of drug product should be of appropriate design adequate size and suitably located to facilitate operations for its internal use and its cleaning and maintenance.

Purchase selection:

- Manufacture, model number,serial number.
- Purchased from, date, cost.
- Size and output lay.
- Location in plant.
- Maintenance responsibility and schedule.
- Modifications made after purchase.
- Test performed before and after purchase.

These are the steps to be considered mainly while purchasing an equipment.

Objectives:

- To review the requirements for equipment selection, design, use and maintenance.
- To discuss problems related to issues around selected items of equipment

Principle: Equipment layout and design must aim:

- to minimize risks of error.
- to permit effective cleaning.
- to permit effective maintenance.

And to avoid:

- cross-contamination.
- dust and dirt build-up.
- any adverse effect on the quality of products.

Equipment must be installed to:

- minimize risks of error.
- minimize risks of contamination

Purchasing specifications:

Purchase of materials is one of the important functions of material management. It is one of the key functions in the success of manufacturer concern. Purchase specifications are detailed plan or set of directions. A proper purchase of materials and merchandise and the control of stock are of great importance in any manufacturing activity. The objective of purchasing is not only to procure the raw material at the lowest price but also to reduce the cost of the final product.

All the parameters which are concerned with the quality of raw material should be stated in the purchase specifications. The following are the purchasing specifications which are to be taken into consideration while purchasing the raw materials:

1. **Right Source:** The source from where the material is procured, must be dependable and capable of supplying the items of uniform quality. The buyer has to decide about the proper source to procure the material
2. **Right quality**: Before purchasing the material, a sample should be procured, and its quality is determined. After verifying the right quality, the order may be placed with the supplier for its purchase.
3. **Right quantity**: It is an important factor in buying while deciding the right quantity, factors such as price structure, discounts and availability of items are to be taken into consideration
4. **Right price**: The materials should be purchased at right price. The right price does not mean the lowest price. For determination of the right price, the cost structure of the product is to be taken into consideration.
5. **Right time**: For determining the right time of purchase, the lead time information is taken into consideration. Lead time means the total time consumed between the recognition of the need of an item, till its receipt for use
6. **Right place of delivery**: The supplier should supply the raw materials at the premises of the business
7. **Right mode of transportation**: The goods may be supplied by road, rail or air. The mode of transportation is to be decided between the supplier and the purchaser.

PURCHASING:

DEFINITION: It is the procurement of materials, supplies, machinery, tools, implements, equipment and services, which are necessary forthe production of certain goods includes the planning and policy and activities, research and development and selection of source of supply etc. It is a basic function of material management. It is important for:

- Maintaining continuity
- Contributing to competitiveness by enhancing the quality of final product.
- Reduce the overall cost of the end product.
- Ensure high productivity

THREE CLASSES OF PURCHASING

- Those of large capital expense which are usually purchase for one time.
    - **Example** - Purchasing of machines tools(Printer)
- Purchased of small quantity infrequently purchased low cost
    - **Example** - The instruments that are useful for running o machinery (Printer Cartridge)
- High volume Used items

TYPES OF PURCHASING:

There are 3 types of purchasing, namely

•**Speculative purchasing:** Buying material by manipulating the price at the time of high price

•**Contract purchasing:** Supply certain quantity for particular period. Usually contract made when price are low.

•**Scheduled purchasing:** For a pre-scheduled period of time.

FUNCTIONS & RESPONSIBILITIES OF PURCHASE DEPARTMENT

OBJECTIVES

- To maintain uninterrupted flow of materials to support the development schedules.
- To procure materials economically at a cost consistent with the quality and service required. However, generally all purchases may be attempted at the lowest cost.
- To provide the necessary expertise, advice, information with regard to the best quality of material available in the market, supplier‘s capability and performance etc.
- To develop and maintain good buyer-seller relationship.
- To promote source development.
- To maintain reputation and credibility in the market by fair dealings and prompt payments.

FUNCTIONS:

The main functions of the Purchase Department are defined as follows:

- Procurement of stores through indigenous and foreign sources as required in accordance with the rules in force.
- Checking of requisitions/purchase indents.
- Selection of suppliers for issue of enquiries.
- Issuing enquiries/tenders and obtaining quotations.
- Analyzing quotations and bids etc., and preparation of comparative statement (quotation charts).
- Consultation with the Indenter for selection and approval of quotations and with Accounts Officer for pre-audit.
- Negotiating contracts.
- Checking legal conditions of contracts. Consulting Administrative Officers or supervisors wherever necessary.
- Issue of Purchase Orders.
- Follow-up of purchase orders for delivery in due time
- Verification and passing of supplier’sbill to see that payments are made promptly.
- Correspondence and dealing with suppliers, carriers etc., regarding shortages, rejections etc., reported by the Stores Department.
- Maintenance of purchase records.
- Maintenance of vendor performance records/data.
- Arrangement for Insurance Surveys, as and when necessary.
- Serving as an information center on the material’s knowledge i.e. their prices, source of supply, specification and other allied matters

ALLOCATION OF WORK IN PURCHASE DEPARTMENT

(a) Internally the Purchase work to be divided into three main groups:

Group A: Foreign purchase

Group B: Indigenous purchase

Group C: Vendor rating, source development and other miscellaneous matters. Further sub-division and allocation of work on commodity basis or work basis may be resorted to for convenience of work.

(b) STAFF

Provision of staff for the Purchase Department is an administrative matter for the company to decide depending upon the volume of work-load. However, a basic minimum staff headed by the Stores & Purchase Officer must be provided as soon as the Purchase and Stores Activities of the company commence.

LOCATION OF PURCHASE DEPARTMENT

Proximity of the Purchase Department to the Stores Department is considered of great important as the relationship between the two is inherently so close and so basic that both should be near each other for better co-ordination and control. If located near each other where accommodation facilities are available it would provide an integrated system as a whole for better performance with the facility to interact.

CENTRALISED PURCHASING:

As every company has a Purchase Department, all purchases of stores shall be centralized in the interest of economy, uniformity and as a matter of policy since custodian and consumer should not be the same. Accordingly, the purchase of raw materials, maintenance

consumables, office stationery, forms, furniture etc., shall be made by the Purchase Department and not by the administration sections. Transfer/adjustment of staff shall be made where necessary. Local/cash purchase of stores shall continue to be made in exceptional cases by the Heads of Divisions/projects under their power but as far as possible Purchase Officer should be associated even while making such purchases.

PURCHASING PROCEDURE:

The purchasing procedure means the sequence of steps in which the purchase transaction is carried through. The purchasing procedure starts when it si felt that further supply of a material is required. The purchasing procedure generally involves the following stages:

1. **Purchase requisition**: Whenever the existing stock of a material approaches a minimum limit or the re-order level, the person in charge of the store ledger, fills the requisition form and sends it to the purchase department. The purchase requisition indicates the type, quantity and quality of the item to be purchased.
2. **Selection of suppliers**: A list of items to be purchased is sent to various suppliers or a tender is invited through leading newspapers. On receiving the quotations from different suppliers, the comparative statement of the quotations received is prepared. The supplier who have quoted the lowest rate is generally selected. However, apart from the price, other relevant considerations like the ability to supply the required volume, maintenance of quality of goods, ability to deliver the goods as per schedule and terms of payment are also taken into consideration
3. **Placing the order**: QC and purchase department together finalizes the list of suppliers. After the selection of the supplier, the order is placed on the standard purchase order form commonly known as Supply order. The supply order gives the detailed specification for the items, quantity required, the price and other terms and conditions of the supply. It is signed by the authorized persons. The supply order gives the detailed specifications of the items, quantity required, the price and other terms and conditions of the supply. It is signed by the authorized persons. The supply order is a legal document. Generally, 5-6 copies of a supply order are prepared. Two copies are sent to the suppliers, who is expected to sign one copy as an acknowledgement and return it to the supply department. One copy is sent to the store incharge. One copy goes to the accounts department and one copy goes to the accounts department and one copy remains with the purchase manager.
4. **Receiving and Checking of material**: The material which is supplied by the supplier is received and inspected for its quantity and quality. The goods are compared with challan form or invoice or the bill sent by the supplier. If the goods received do not conform to the specifications on the purchase order, the goods are rejected and defects or deficiency, if any, recorded on the invoice or the challan form
5. **Checking of invoice or bill**: If the goods are received in satisfactory condition, the invoice or bill is checked before it is approved for payment. The rates of various items charged in the bill and the other terms and conditions are thoroughly checked and compared with the supply order
6. **Recording and documentation of bills**: The bills are then sent to the accounts section, where the bills are entered into the accounts books. The receipt of damaged material, excessive material, short supply and supply of inferior quality of material, if any, is reported to the concerned authority for further necessary action.
7. **Releasing the payment to the supplier**: According to the terms and conditions of the supply order, the payment is released by the accounts section to the supplier. However, in small organizations, the payment is released by the purchase department itself

SELECTION OF VENDORS:

The materials are obtained from the vendors who are in the approved list of purchasing department. This is done to ensure timely supplies and of required quantity. In order to prepare the approved list of vendors, questionnaire is send to the various suppliers. After receiving these questionnaires, the approved list of suppliers is prepared. The following points should be generally taken into consideration while preparing the approved list of vendors:

- Business Reputation of the vendor in the market which includes the performance capability
- Financial condition of the vendor
- Internal quality assurance program
- Manufacturing capabilities of the vendor
- Performance capability of the vendor to supply at a short notice
- After sale service facilities provided by the vendor
- Terms and conditions of the payment

Selection of Vendors by using Tenders:

In order to avoid favouritism during the purchasing of goods from the market, the tenders are invited from the approved vendors.

"A tender or a quotation is a written offer to do a work or to provide a material at a given price within a prescribed period and under specified conditions"

Types of Tenders:

Tenders are of following types:

1. **Open tender**: These tenders are called by advertisement when the source of supply are many and total value of items to be purchased is large. The tenders are given in leading newspapers. After receiving the tenders from various suppliers, a comparative statement of rates as well as terms and conditions quoted by different firms is prepared. Generally, the order is placed with the vendor who has quoted the lowest rate. The method of purchasing goods through open tender is costly and time consuming.
2. **Limited tenders**: This system is used only in those cases where the value of tender is moderate. The tenders are invited only from those vendors which are on the approved list of supplier. The main advantages of this method are as under:-
    a. The suppliers are well conversant with the items to be supplied
    b. The suppliers generally submit realistic quotations because they are regular suppliers of the materials
    c. There are less chances of any error in supplying the items of required specification

d. There are chances of progressing reduction in price

3. **Single tenders**: When the items to be purchased are proprietary in nature or the order is to be repeated within a short period, the tender is sent only to a single vendor who is dealing with the materials of specific specification.
4. **Oral tenders**: In case, the supplies are of minor character and are urgently required, a person or a committee is deputed to purchase the specified items from the market. After collecting the information regarding the price charged and quality of product to be supplied from three to four suppliers, the items are purchased from the vendor who has quoted the minimum price of the specified items
5. **Global tenders**: The tenders are invited from all parts of the world. These are for large contracts for supplies from foreign countries or when the foreign collaboration is required in the proposed project.
   The tenders are invited from the various vendors or firms which deal in the supply of materials that are required to be purchased. The notice containing the following information is issued to call the tender:
   a. Name and detailed specification of material to be purchased. In it, the drawing of material or particular make should be mentioned
   b. Quantity to be purchased
   c. Period of delivery
   d. Earnest money to be deposited
   e. Terms and conditions of purchase
   f. Date, time and place for receiving and opening of the tenders

The tenders are sent by suppliers in sealed envelope before the due date. The word tender or quotation and its date of opening must be written on the top of the envelope. After opening the tender on due date and time in the presence of representatives of the suppliers, the purchase officer writes on each tender, the serial number of tender, total number of tenders received and number of page in a particular tender. Any correction or over writing is also attested during that period in order to avoid any dispute at a later stage.
A comparative statement is prepared from the tenders or quotation which are received. Generally, the order is placed with the vendor who has quoted the lowest rate. The factors like sample specification, make, guarantee period, period of supply, other expenses like freight, sales tax, packing and forwarding charges are also to be considered.

Clean-in-place (CIP):
Clean-in-place (CIP)is a method of cleaning the interior surfaces of pipes, vessels, process equipment, filters and associated fittings, without disassembly.Up to the 1950s, closed systems were disassembled and cleaned manually. The advent of CIP was a boon to industries that needed frequent internal cleaning of their processes. Industries that rely heavily on CIP are those requiring high levels of hygiene, and include: dairy, beverage, brewing, processed foods, pharmaceutical, and cosmetics.

The benefit to industries that use CIP is that the cleaning is faster, less labor-intensive and more repeatable, and poses less of a chemical exposure risk. CIP started as a manual practice involving a balance tank, centrifugal pump, and connection to the system being cleaned. Since the 1950s, CIP has evolved to include fully automated systems with programmable logic controllers, multiple balance tanks, sensors, valves, heat exchangers, data acquisition and specially designed spray nozzle systems. Simple, manually operated CIP systems can still be found in use today.

Depending on soil load and process geometry, the CIP design principle is one of the following:

- Deliver highly turbulent, high flow-rate solution to effect good cleaning (applies to pipe circuits and some filled equipment).
- Deliver solution as a low-energy spray to fully wet the surface (applies to lightly soiled vessels where a static sprayball may be used).
- Deliver a high energy impinging spray (applies to highly soiled or large diameter vessels where a dynamic spray device may be used).

Elevated temperature and chemical detergents are often employed to enhance cleaning effectiveness.
Factors affecting the effectiveness of the cleaning agents

1. **Temperature of the cleaning solution:** Elevating the temperature of a cleaning solution increases its dirt removal efficiency. Molecules with high kinetic energy dislodge dirt faster than slow moving molecules of a cold solution.
2. **Concentration of the cleaning agent:** A concentrated cleaning solution will clean a dirty surface much better than a dilute one due to the increased surface binding capacity.
3. **Contact time of the cleaning solution**: The longer the detergent contact period, the higher the cleaning efficiency. After some time, the detergent eventually dissolves the hard stains/soil from the dirty surface.
4. **Pressure exerted by the cleaning solution (or turbulence):** The turbulence creates an abrasive force that dislodges stubborn soil from the dirty surface.

Apart from Pharmaceutical manufacturing, CIP is commonly used for cleaning bioreactors, fermenters, mix vessels, and other equipment used in biotech manufacturing food and beverage manufacturing. CIP is performed to remove or obliterate previous cell culture batch components. It is used to remove in-process residues, control bioburden, and reduce endotoxin levels within processing equipment and systems. Residue removal is accomplished during CIP with a combination of heat, chemical action, and turbulent flow.

The U.S. Food and Drug Administration published a CIP regulation in 1978 applicable to pharmaceutical manufacturing. The regulation states, “Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements.”

Repeatable, reliable, and effective cleaning is of the utmost importance in a manufacturing facility. Cleaning procedures are validated to demonstrate that they are effective, reproducible, and under control. In order to adequately clean processing equipment, the equipment

must be designed with smooth stainless steel surfaces and interconnecting piping that has cleanable joints. The chemical properties of the cleaning agents must properly interact with the chemical and physical properties of the residues being removed.

A typical CIP cycle consists of many steps which often include (in order):

- Pre-rinse with WFI (water for injection) or PW (purified water) which is performed to wet the interior surface of the tank and remove residue. It also provides a non-chemical pressure test of the CIP flow path.
- Caustic solution single pass flush through the vessel to drain. Caustic is the main cleaning solution.
- Caustic solution re-circulation through the vessel.
- Intermediate WFI or PW rinse
- Acid solution wash – used to remove mineral precipitates and protein residues.
- Final rinse with WFI or PW – rinses to flush out residual cleaning agents.
- Final air blow – used to remove moisture remaining after CIP cycle.

Critical parameters must be met and remain within the specification for the duration of the cycle. If the specification is not reached or maintained, cleaning will not be ensured and will have to be repeated. Critical parameters include temperature, flow rate/supply pressure, chemical concentration, chemical contact time, and final rinse conductivity (which shows that all cleaning chemicals have been removed).

Sterile in Place (SIP):

Same as that of Clean in Place as mentioned above, replace the word Cleaning with Sterilization in the explanation. Sterilization is the process of complete removal of both vegetative and dormant (spores) forms of microorganisms by using suitable physical, chemical and mechanical methods.

RAW MATERIALS

RAW MATERIAL

Raw materials refers to the unfinished goods used by the manufacturer for providing finished goods. The quality of pharmaceutical preparation depends solely on the quality of raw material.So, testing of raw material is very important to:

- Confirm the material.
- Check that the raw material has the characteristics to provide the desired quality in the dosage form.
- To provide assurance in the final product.

TYPES OF RAWMATERIALS

Two types of raw materials are present

- Active (or) therapeutic raw materials. Ex: antibiotics, bulk drugs, drug intermediates
- Inactive (or) inert raw materials. Ex.Starch, cellulose etc

INDIAN GMP'S FOR RAW MATERIALS

The licensee shall keep an inventory of all raw materials to be used at any stage of manufacture of drugs and maintain records as per schedule U of Drugs and Cosmetics Act. All such material shall be

- Identified and the container examined for damage
- Stored at optimum temperature &relative humidity
- Conspicuously labelled indicating name of material, name of manufacturer and shall be specifically labelled under test, approved, or rejected.
- Systematically sampled by quality control personnel
- Tested for compliance with required standard
- Released from quarantine by quality control personnel through written instruction.
- So organized that stock rotation is on the basis of first in & first out principle in storage area.

SPECIFICATION FOR RAW MATERIAL

- Should have a written specification for each raw material & must be authorized by QC manager
- The specification should include at least requirements for identification, limits for specified impurities.
- Each written specification should carry a date of issue and should include
- Name of the material with common synonym if any
- A code reference number, if the organization has a system of using code number for easy identity.
- Special requirements, if any, of the container pack
- Handling hazards
- Sampling instruction
- Special storage requirements
- Frequency of re-testing the stored material
- A description of the physical form of material
- Reference to the appropriate analytical method of specific nature
- Signature of authorizing persons.

RAW MATERIAL CONTROL

- Good raw material specification should be in precise terminology
- Should provide details of test methods
- Type of instruments & manner of sampling &proper identification should be explained.

- The FDA GMP states that the components be received, sampled, tested &stored in a reasonable way.
- The manufacturer physically inspects & assign lot number to all raw material received.
- Each raw material sampled according to standard procedures & sent to quality control for testing
- According to written procedure, if acceptable the raw materials are moved to release storage area, indicating the item number, name of the material lot number, date of release
- QA inspector, QA personnel should keep samples twice the quantity required for testing.
- Raw material not meeting specification should be isolated.

MAINTENANCE OF STORES

Maintenance of Stores includes **receipt, storage, sampling and testing of raw materials**.

RECEIPTS OF RAW MATERIALS

Receipts of each ordered raw material should be recorded.
Each delivery of raw material should be:

- Examined visually on receipt
    - Visual examination includes check for
        - intact containers, lids, seals.
        - Evidence of water damage
        - Evidence of rodents or insects
- Identified for proper labelling
- Container damage
- Contamination
- Damaged materials should be separated from other materials

The receiving log has the following data

- Data for receipt
- Control number assignment by receiving company
- Product identification number and the name used by receiving company
- Quantity in each control number
- Supplier or vendor
- Stock or control number assigned by supplier
- Purchase order number
- Bill of lading number of shipping.
- Supervisor must assign a separate control number for each log with a different vendors indicating
- Name or initial of person sampling the component
- Final disposition following inspection
- Dates for these operations
- The properly identified, received material must be labelled conspicuously to show its quarantine status.

STORAGE OF RAW MATERIAL

- Properly identified raw material is labelled for quarantine status & stored in quarantine area prior to QC dept approval.
- Responsible person from QC dept would draw samples from each lot after receipt.
- Quarantine label is then replaced by approval label.
- Stored under controlled temperature.
- Rack material platform is provided. So that the materials are stored off the floor to permit easy cleaning & inspection.
- Stocks are inspected for cross contamination and proper labelling.

TESTING OF MATERIAL

- Number of batch or lot of consignments of raw material pass into production area until it passes the standard.
- Specification authorization by QC department
- Detailed written methods of sampling analysis
- Procedures should be reviewed regularly with current version
- Sampling performance in accordance with authorized procedure
- Sample should be tested for compliance and identification to rule out incorrect labelling
- Statutory method of testing (eg: Pharmacopoeia) alternative test method may be used.

RELEASE OF RAW MATERIAL

- Raw material that meets the specification may be approved and released
- Release is ensured by the QC manager that storage conditions are satisfactory
- Container must have authorized PASSED labels
- The period of time up to which the raw material may be expected to comply is determined
- The retesting is ensured by having the words ―valid up to‖ and ―rest on‖ passed labels
- Passed labels should have the following details
    - Name of the material
    - Code number
    - Reference no or laboratory reference no

- Date of issue or approval
- Retest date
- Passed or approved in bold capitals

- The raw materials that do not meet specification must have authorized REJECTED labels
- Issue of raw material must be according to procedures as in documents
- Materials should be retested on or before retest dates
- No materials should have a retest date of more than 12 months
- For issue of hazardous materials require certain safety
- Signature should be recorded for all personnel handling the materials.

Label color

- Red -- reject
- Green -- passed
- Pink -- under test

SAMPLING OF RAW MATERIAL

Samples are taken for two main purposes

•For Quality control - to check for compliance with specification

•For Reference - so that they can be examined afterwards in case of anysuspicion.

DEFINITIONS

Batch (or Lot): a defined quantity of material that is intended to be uniform in character & quality and has been produced during a defined cycle of manufacture.

Batch number (or lot number): a combination of number& letter in which specifically identifies a batch (or) lot permits its history to be traced

Sampling: the process of abstraction of a portion of material from a larger quantity of it.

SAMPLING EQUIPMENT

- Sampling material should not contaminate the sample taken.
- Glass, stainless steel, plastic are suitable.
- Sampling equipment must be cleaned and sterilized whenever required before use.
- Suitable carrier like trolleys or basket must be used for transporting and protecting samples.

CONTAINERS

- Wide mouth, amber or colorless bottles closed by screw caps with inert wads are suitable for solids.
- For hygroscopic material fitting with polythene sieves are used
- For liquids narrow mouthed amber or colorless bottles with tight fitting stoppers are used.

SAMPLING TOOLS

- Spears are used for crystalline & granular solids
- Plastic or stainless-steel scoops are used for liquid, stainless steel ladles, sampling cylinders, tubes can also be used.

SAMPLING PERSONNEL:

- Must be carried out only by the trained personnel.
- The staff must be familiar with the precaution while handling hazardous material.
- Staff must wear protective cloth.
- Sampling staff must be responsible to the QC manager.

SAMPLING PLAN:

- Extent of sampling depend upon the nature of material, no. of batches, history of the supplies &reliability of manufacturer.
- Container must be chosen in random and also container which shows damage must be sampled.
- Every batch of material in a consignment must be sampled.
- The quantity of sample withdrawn must be sufficient for test as well as control
- Label samples with information present in the container of component.
- Reseal and replace sample containers and mark it as ―sampled.

MAINTENANCE

DEFINITION The combination of all technical and administrative actions, including supervision actions, intended to retain an item in, or restore it to, a state in which it can perform a required function. & Maintenance is a set of organised activities that are carried out in order to keep an item in its best operational condition with minimum cost acquired.

Maintenance Activities: Activities of maintenance function could be either repair or replacement activities, which are necessary for an item to reach its acceptable productivity condition and these activities, should be carried out with a minimum possible cost.

Maintenance Objectives Maintenance objectives should be consistent with and subordinate to production goals. The relation between maintenance objectives and production goals is reflected in the action of keeping production machines and facilities in the best possible condition.

Maintenance objectives should be consistent with and subordinate to production goals. The relation between maintenance objectives and production goals is reflected in the action of keeping production machines and facilities in the best possible condition.

- Improving equipment efficiency and reducing scrap rate.
- Minimising energy usage.

- Optimising the useful life of equipment.
- Providing reliable cost and budgetary control.
- Identifying and implementing cost reductions.

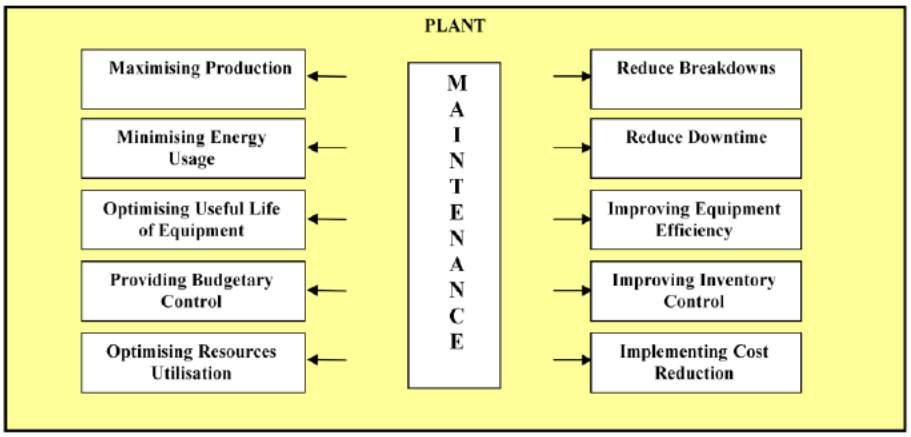


Figure 2.3 Maintenance Objectives

Types of Maintenance

Run to Failure Maintenance (RTF)
Preventive Maintenance (PM)
Corrective Maintenance (CM)
Improvement Maintenance (IM)
Predictive Maintenance (PDM)

Run to Failure Maintenance (RTF)

The required repair, replacement, or restore action performed on a machine or a facility after the occurrence of a failure in order to bring this machine or facility to at least its minimum acceptable condition.

Preventive Maintenance (PM)

It is a set of activities that are performed on plant equipment, machinery, and systems before the occurrence of a failure in order to protect them and to prevent or eliminate any degradation in their operating conditions.

British Standard 3811:1993 Glossary of terms defined preventive maintenance as: "The maintenance carried out at predetermined intervals or according to prescribed criteria and intended to reduce the probability of failure or the degradation of the functioning and the effects limited." The advantage of applying preventive maintenance activities is to satisfy most of maintenance objectives

The factors that affect the efficiency of this type of maintenance:
The need for an adequate number of staff in the maintenance department in order to perform this type of maintenance.
The right choice of production equipment and machinery that is suitable for the working environment and that can tolerate the workload of this environment.
The required staff qualifications and skills, which can be gained through training.
The support and commitment from executive management to the PM programme.
The proper planning and scheduling of PM programme.
The ability to properly apply the PM programme.

Corrective Maintenance (CM) In this type, actions such as repair, replacement, or restore will be carried out after the occurrence of a failure in order to eliminate the source of this failure or reduce the frequency of its occurrence.

In the British Standard 3811:1993 Glossary of terms, corrective maintenance is defined as: the maintenance carried out after recognition and intended to put an item into a state in which it can perform a required function. The way to perform corrective maintenance activities is by conducting four important steps:

1. Fault detection.
2. Fault isolation.
3. Fault elimination.
4. Verification of fault elimination.

In the fault elimination step several actions could be taken such as adjusting, aligning, calibrating, reworking, removing, replacing or renovation.

Improvement Maintenance (IM) It aims at reducing or eliminating entirely the need for maintenance. This type of maintenance is subdivided into three types as follows:

1. Design-out maintenance which is a set of activities that are used to eliminate the cause of maintenance, simplify maintenance tasks, or raise machine performance from the maintenance point of view.
2. Engineering services which includes construction and construction modification, removal and installation, and rearrangement of facilities.
3. Shutdown improvement maintenance, which is a set of improvement maintenance activities that are performed while the production line is in a complete stoppage situation.

Predictive Maintenance (PDM)

Predictive maintenance is a set of activities that detect changes in the physical condition of equipment (signs of failure) in order to carry out the appropriate maintenance work for maximising the service life of equipment without increasing the risk of failure. It is classified into two kinds according to the methods of detecting the signs of failure:

Condition-based predictive maintenance

Statistical-based predictive maintenance

Some researchers classified predictive maintenance as a type of preventive maintenance. The main difference between preventive maintenance and predictive maintenance is that predictive maintenance uses monitoring the condition of machines or equipment to determine the actual mean time to failure whereas preventive maintenance depends on industrial average life statistics.

UNIT - IV

Manufacture and controls on dosage forms, manufacturing documents masterformula, batch formula records, standard operating procedures, quality auditsof manufacturing processes and facilities - In process quality control onvarious dosage forms: sterile, biological products and non-sterile, standardoperating procedures for various operations like cleaning, filling, drying,compression, coating. Packaging and labeling controls.

LO: To understand manufacture and controls on dosage forms,manufacturing documents master formula, batch formula records,standard operating procedures, quality audits of manufacturingprocesses and facilities - In process quality control on various dosage

MANUFACTURE AND CONTROLS ON DOSAGE FORMS

Manufacturing Documents:

- Documentation is an all providing feature of good manufacturing practices. (GMP)
- It defines a system of information and control so that, misinterpretation or error in oral communication is minimized.
- Documentation is responsible for the specific clear, unambiguous instructions to follow and results in consistent quality.
- Written documentation of all activities associated with the manufacture of pharmaceuticals including bulk pharmaceutical chemicals,is a legal requirement in most parts of world.

Documentation in all aspects of Pharmaceutical manufacture:

Manufacturing Area	Record Maintenance
Building and premises	Installation, validation, cleaning and maintenance.
Equipment	Installation, validation, cleaning and maintenance.
Materials	Specifications, testing, warehousing, use, rejection and disposal.
Processing controls	Individual steps in the process of manufacturing.
Finished goods	Specifications, testing, storage, distribution, rejection and disposal.
Complaints	Investigations, actions, including recall if necessary.

General Requirements:

- For effective use of documents, there should be designed and prepared with utmost care. It is normal to use the format of standard operating procedure for all documents. Each document shall
  - Have a clear title
  - Have a identification number
  - Be approved by authorized person
  - Have the date of issue
- Were the document carries instructions (eg, batch processing), the instructions should be precise and not ambiguous.
- Headings should clearly indicate what is to be entered and who is responsible. All entries should be in ink and should be clear and legible.
- Person making the entries should confirm the entry by initialising / sign in the same. An error in entry should be so corrected that the original (wrong) entry is not last.
- Such correction should also be initialised and dated. Where necessary, reasons for correction should also be recorded, initialised and dated.
- Documentation system should provide for a periodic review, revision, if necessary, of any document or part thereof. Such revised versions should also be approved by the authorized persons.
- Outdated / superseded document should be immediately removed from active use, and copy retained only for reference.
- If documentation is through electronic data processing system(computerized system) there should be adequate, reliable systems in place to check and ensure correctness of data and to record changes(addition / deletion)
- Documentation should be retained in such a manner that permits quick, easy and reliable retrieval of data, allows review up to a predetermined time in the past and should meet regulatory requirements.

Equipment cleaning and Use record:

- A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product and lot number of each batch processed.
- If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follows numerical sequence.
- The persons performing and double checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. The entries in the log shall be in chronological order.
- The selection requires written designation of which equipment is — “major”. The intent of the regulation is not to include the small items such as ladles, scoops, stirrers and spatulas.
- The exclusion of — “non major” items from the record keeping requirement does not, however, exclude them from the requirements that they be properly cleaned.
- Log maintenance is a repetitive operation; the record may be initialized rather than signed. As new computerized technology becomes available for log maintenance to move to paperless control of manufacturing process.
- These computerized controls have several advantages over manual systems,
  - More consistent control.
  - Only approved (trained) personnel can perform a process.
  - Précised recording of the times of operation is possible.

Packaging and Labelling records: These records are shall include the following:

- The identity and quality of each shipment lot of components, drug product containers, closures, and labelling; the name of the supplier; the supplier's lot number(s); the receiving code as specified and the date of receipt.
- An individual inventory record of each component, drug product container and closure and for each component, a reconciliation of the use of each lot of such component is required.
- The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container and closure.
- Documentation of the examination and review of labels and labelling for conformity with established specifications.
- The disposition of rejected components, drug product containers, closure and labelling.
- Most regulations require identification and recording of the name of the producer of the components, product containers, closures and labelling.
- As with every aspect of the regulations, documentation is required

MASTER FORMULA: (MASTER PRODUCTION AND CONTROL RECORDS)

It is defined as 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, in process controls.

A formally authorized master formula should exist for each product and batch size to be manufactured. The purpose of this document is to assure uniformity from batch to batch.

The preparation of master production and control records should be described in written procedures. It should be dated and signed by one person and independently checked, signed by second person. The master formula should include following:

- The name of the product, with a product reference code relating to its specifications
- A description of the dosage forms, strength of the product and batch size.
- A list of all starting materials to be used, with the amount of each, described using the designated name and a reference that is unique to that material.
- A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields.
- A statement of the processing location and the principal equipment to be used.
- The methods or reference to the methods, to be used for preparing and operating the critical equipment e.g. cleaning, assembling, calibrating, sterilizing, use.
- Detailed step wise processing instructions (e.g. checks on materials, pre-treatment's, sequence for adding materials, mixing times, temperatures)
- The instructions for any in process controls with their limits
- Where necessary, the requirements for storage of the products, including the containers, the labelling and any special storage conditions.
- Any special precautions to be observed. The master manufacturing records should also clearly identify:
    - Equipment to be utilized designated by name and where appropriate, by number.
    - Stepwise manufacturing process with details of conditions such as time, temperature, speed and sequence of adding ingredients.
    - Critical in process checks and controls, including limits thereof
    - Special precautions and hazardous conditions that may exist and the necessary safety equipment to be used.
    - Theoretical yields and actual yields(action levels)
    - Space for signature and date of operator/supervisor performing or checking each significant step

Master Packaging instructions:

Formally authorized packaging instructions should exist for each product, pack size and type. These include:

- The name of the product
- A description of its pharmaceutical form, strength and method of application
- The pack size expressed in terms of the number, weight or volume of the product in the final container
- A complete list of all the packaging materials required for a standard batch size
- Special precautions to be observed, including a careful examination of the packaging area and equipment area
- A description of the packaging operation, including any significant subsidiary operations and equipment to be used
- Details of in process controls with instructions for sampling and acceptance limits

BATCH FORMULA RECORDS(BATCH PRODUCTION AND CONTROL RECORDS)

Batch manufacturing record is a product- and – batch specific document designated to give a complete and reliable picture of the manufacturing history of each batch of every product. The method of preparation of such records should be designed to avoid errors. Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents not required for the planned process, and that the equipment is clean and suitable for the use. This check should be recorded. The batch records provide information for operations and also serve as a means for documenting which ingredients were added, which control measures were exercised, in process and final assay of the drug product and the huge amount of information produced during manufacturing cycle. The batch manufacturing record should have following details

- Dates

- Identify of individual major equipment and lines used
- Specific identification of each batch of component or in process material used
- Weights and measures of components used in the course of processing
- Inspection of packing and labelling area before and after and after use
- A statement of actual yield and a statement of the percentage of theoretical yield at appropriate faces of processing
- Complete labelling control records; including specimens or copies of all labelling used
- Description of drug product container and closures, any sampling performed
- Identification of the persons performing and directly supervising or checking each significant step in the operation
- Details of any investigation made
- Results of examination made

Batch Packaging Records:

It should be based on the relevant parts of the approved packaging instructions and the method of preparing such records should be designed to avoid errors.

- The name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product.
- The date (s) and time (s) of the packaging operations
- The name of the responsible persons 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 instruction including results of in process quality controls

STANDARD OPERATING PROCEDURES

- SOP is an authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (Ex: Equipment operation, maintenance and Cleaning, cleaning of premises and Environmental control, Sampling and inspection). Certain SOP‘s may be used to supplement product-specific master and batch production documentation.
- SOP‘s are important part of Good Manufacturing Practice (GMP), they defines now things are to be done. It also acts as basis for training (for new/Re-located persons).
- SOP‘s ensure that all personnel will use exactly the same procedures for the operations and thus it is an Instrument to minimize the introduction of random error, due to individually varied procedures.
- SOP‘s need to be written by Persons who are experienced in the procedures to be described, and thus introduction of systematic error can also be minimized.
- Written SOP‘s should be available which describes how to review the documents and who should be approved.
- When an updating of SOP happens, it is important to ensure that out dated copies are replaced current SOP is reached at designed departments in time.
- A procedure to alert people that an SOP has been revised also is suggested.
- The procedures for production and process control are to reviewed and approved by quality control unit while reviewing it should be ensured that
    - All the procedures are in accordance with various GMP regulations.
    - In compliance with various regulatory requirements.
- There shall appropriate supporting data such as process validation, analytical method validation etc.
- The reasons for any proposed changes should be clearly defined and supported.
- The procedures should be reviewed and signed by appropriate functions such as Production or other technical Services.
- Haring provided return and approved procedures the next stage is to ensure that they are followed. This involves two steps.
    - Training
    - Verification
- The verification can be done by conducting quality audits.

CONTENTS OF SOP:

- Basically an SOP should contain, besides the more administrative parts like Title, Version number, Author and all approval dates and signatures.
- There is a two logical parts in SOP those are, first one should provide reason for, or the purpose of SOP. The second one should describe the activity to the regulator
- SOP should be sufficiently detailed that trained laboratory personnel would not only under stand it but could perform the tasks described there in a uniform way.
- Another aspect is description of activities that is very often over looked in the drafting of SOP‘s.
- For such SOP‘s not only describe the actual procedure for calibrating the instrument, but they also exactly advised two additional points:
    - a) The admissible magnitude of deviations from expected calibration value.
    - b) Necessary steps to be taken, if calibration results in an unacceptable value.

SOP FORMAT:

STANDARD OPERATING PROCEDURE NAME OF THE COMPANY		
TITLE (Standard Operating Procedure (SOP) for particular operation)		**Ref. No.:** QA/ GEN/01 **Version:** **Supersedes**
Department Name:		**Page No:**
Effective Date:		**Review Date:**
Prepared by: **USER Dept.** **Designation** **Signature & Dt**	**Approved by:** **Dept. Head** **Designation** **Signature & Dt**	**Authorized/ Issued by:** **QA Dept.** **Designation** **Signature & Dt**
Purpose: **Scope:** **Responsibility:** **Procedure:** **References:**		
Distribution: **Original** **Department Name** **Copy 1** **Department Name** **Copy 1** **Department Name**		

QUALITY AUDIT

Quality audit is defined as "A systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

System audit: A quality system audit is defined as a "systematic and independent examination used to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives." Think of the quality system audit in terms of "an inch deep but a mile wide," **Process audit:** The process audit is "an inch wide but a mile deep." It revolves around *verification* of the manner in which: 1) people; 2) material; 3) machines, etc., mesh together to produce a product. A process audit compares and contrasts the *manner* in which the end product is produced to the written procedures, work instructions, workman-ship standards, etc., used to guide the manufacturing process responsible for building the product in the first place. *Process audits are appraisal and analytical in nature.* The process audit is also concerned with the validity and overall reliability of the process itself.

Product audit: The word "audit" in *product audit* is somewhat of a misnomer. Actually, a product "audit" is a detailed *inspection* of a finished product performed *prior* to delivering the product to the customer. It is a test of both attribute and variable data i.e., cosmetic appearance, dimension properties, electrical continuity etc.

Compliance audit: During a compliance audit, the auditor examines the auditee's written procedures, work instructions, contractual obligations, etc., and attempts to match them to the actions taken by the auditee to produce the product. In essence, it's a "say what you do—do what you say" type of audit.

Final Quality Audit (FQA):

FQA Process, in manufacturing world, is the last process flow before shipping a product. This process is established to ensure the following:

- the unit has gone through all the manufacturing or test process
- the unit has passed through all the test process
- the unit is in good quality

QUALITY AUDITS OF MANUFACTURING PROCESS AND FACILITIES:

MANUFACTURING PROCESS:

Manufacturing process audit is one of the many quality tools to assess the effectiveness of manufacturing process and quality performance. They are commonly used in the effort to diagnose, maintain and improve quality management system. It is made compulsory for the organization to maintain their quality management system based on ISO9001 standard to conduct an internal audit. Manufacturing process audits should ensure that procedures are properly followed, problems are quickly corrected, there is consistency in the process, and there is continuous improvement and corrective action as needed.

DEFINITION AND PURPOSE OF MANUFACTURING AUDIT

It is also important to understand the definition of audit before any audit is initiated to avoid confusion on how the audit should be conducted (or audit method) and the process of auditor selection.

DEFINITION: Manufacturing process is defined as a process of making and fabricating by converting the raw material (input) to finished goods (output) OR manufacturing process audit can be defined as a process to evaluate the process and making and fabricating effectiveness and efficiency

PURPOSE:

Purpose of the audit can be divided into compliance audit and management audit (Arter, 1994). Compliance audit look for conformance to the audit criteria, while management audit look for conformance to the audit criteria and the effectiveness of the process and opportunities for improvement in achieving organization goals.

The purpose of manufacturing process audit is to improve quality performance, it is recommended to be conducted either by independently (ISO, 2002), internally (ISO, 2002) or self-assessment (Karapetrovic and Willborn, 2002) since the goal is to improve quality performance. We cannot limit on how to conduct the audit for manufacturing performance improvement since independent, internal or self-audit have the advantages.

The areas covered in manufacturing audit included manufacturing strategy, new product introduction, process optimization, flexible manufacturing, production system, performance measurement system, and technology audit. All of these areas interact with manufacturing process.

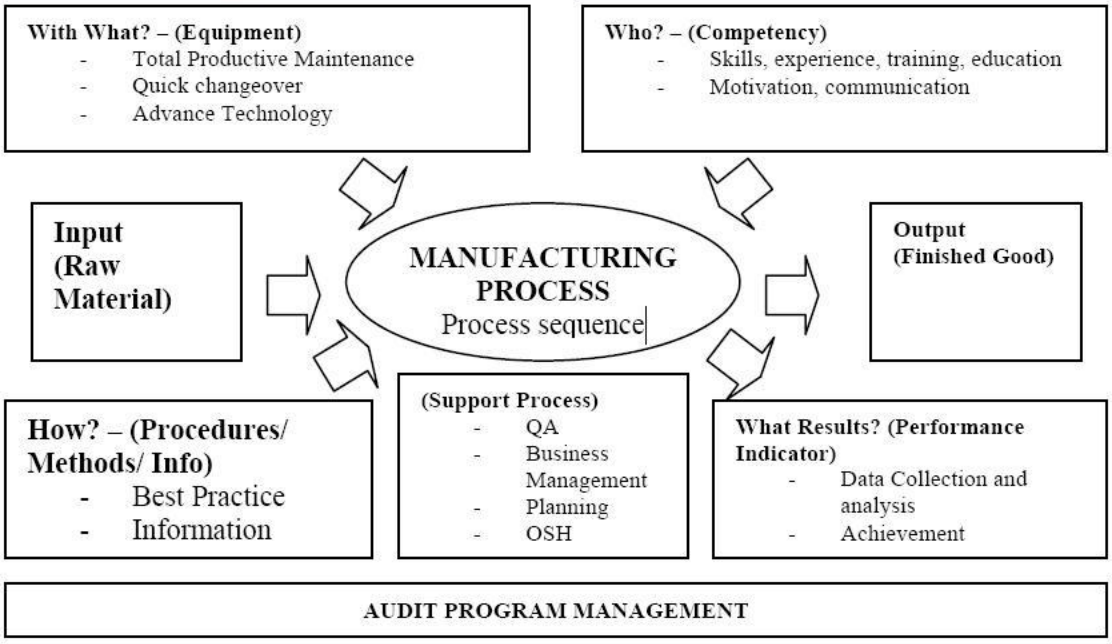
MANUFACTURING AUDIT FRAMEWORK:

Typical manufacturing audit problems or failures are due to lack of audit preparation, audit criteria elements or checklist driven, auditor skills and knowledge, commitment from the management, and bureaucratic reporting (Askey, Dale, Karapetrovic, Barthelemy).

Systematic approach to the auditing is the first element for successful manufacturing process audit. The audit activities framework based on ISO19011 (2002) and VDA6.3 audit process is useful to provide guideline for the systematic approached to auditing.

The systematic audit program includes initiating the audit, preparing for on-site audit, conducting on site audit, report preparation and follow-up activities. The follow-up activities in this context are the improvements activities result from the audit finding.

The second element for manufacturing process audit, the audit shall cover more than the manufacturing process, which shall include all supporting process in order the manufacturing to be effective.



The suggested conceptual framework divided the manufacturing process into seven elements, which are the effective supply (input), infrastructure (with what), personnel (who), operational control (how), support process (management system) and performance measure indicator for the output and related process. All this process elements can be benchmark and opportunities of improvement or weaknesses (audit findings) can be identified.

Instructions for audit of manufacturing process:

1) Select a process to be audited. Prioritize the processes that can be audited in terms of importance and risk to the overall operation. Begin auditing the highest-risk areas first

2) Select a team to conduct the audit. The audit team should be familiar with the process being audited. They should also be familiar with audit techniques such as sampling and analyzing results. They must have the necessary expertise to identify problems and determine the corrective actions needed.

3) Decide how often the process should be observed (the frequency of the audit). If there are significant problems or noncompliance, the process should be observed more often until the situation is under control.

4) Announce the audit in advance so there are no surprises. The objective is to improve the process, which will require the cooperation of everyone involved.

5) Set up an audit schedule for the entire shift and follow the established audit schedule. The number of observations will be your sample of the work for that shift. The audit schedule should be determined in advance and should be as random as possible. Once established, the audit schedule should be followed to provide results based on a random sample.

6) Document any problems discovered and inform all those affected. The idea is not to assign blame but to find a solution. The problems discovered become the basis for corrective actions and follow-up. Everyone affected by the problem should be informed so they are aware and can provide input to the resolution. Also, the process being audited will likely affect other processes in the over-all operation.
7) Determine and perform corrective actions. Let employees make suggestions for corrective actions and select any that are appropriate, but management should make the final decision as to which corrective actions to implement.
8) Monitor corrective-action results. Perform follow-up monitoring to determine if the corrective actions have actually eliminated the problem or if further action is required. Also verify that no new problems have developed or entered into the process.

FACILITIES:

As an internal auditor, we should make sure to pay attention to such considerations as the actual facility itself. Take a look at the grounds and make sure that everything is being maintained properly. Ensuring safety is a keyresponsibility of an internal audit and this falls under the realm of facility control. Environmental controls, such as lighting and clean air, need to be inspected to assure proper functionality. Facility maintenance and housekeeping also includes any pest control programs. These need special consideration for industries that produce food or medicine.

Check list for quality audit on facilities:

The internal auditor should check the following facilities in manufacturing area for effective process and product, those are:
1. Is there adequate space in the building for the orderly placement of equipment, materials and product?
2. Is the plant layout conductive to smooth product flow? (e.g.,uni-directional flow, avoiding back and forth movements).
3. Are operations performed within separate or defined areas of adequate size?
4. Are there dedicated and self-contained facilities (building and equipment)for the manufacturer, processing and packaging of penicillins?
5. Are there adequate sanitary facilities and designated eating, drinking and smoking areas separate from manufacturing areas?
6. Do the eating and smoking areas have drinking water?
7. Do change rooms and lavatories:
    I. Have running water?
    II. Have soap or detergent?
    III. Have hard dryers or single-use towels?
    IV. Have ―wash hands‖ signs?
    V. Appear clean and sanitary?
8. Are change rooms designed and used so as to minimize contamination of protective garments?
9. Are the tops of the employee lockers clean? (Check by touching with finger)
10. Is there a written sanitation procedures (sop) containing assignments of responsibility, schedules, methods, equipment and materials to be used to properly clean the building and facilities?
11. Are records available for sanitation and housekeeping?
12. Is there a formal maintenance schedule for manufacturing equipment and list kept visible near each piece of equipment?
13. Are waste containers with lids located in appropriate areas?
14. Is there an adequate disposal collection system?
15. Are drains to sewers designed with an air or mechanical break to prevent back siphon age?

By using these check lists, the internal auditor should maintain a document which is checked, dated and signed by him, super checked by second person.

IN PROCESS QUALITY CONTROL OF STERILE DOSAGE FORMS

Sterile dosage Forms: These are the products which aremanufactured using sterilization or aseptic processingconditions.
There are two types of sterile dosage forms
1. Parenteral preparation
2. Opthalmic formulations

The in-process quality control test includes the leakageand clarity testing. The quality control of finished productrequired the pyrogen and sterility testing.12

Leakage Test

Leakage test is employed to test the package integrity.Package integrity reflects its ability to keep the product inand to keep potential contamination out". It is becauseleakage occurs when a discontinuity exists in the wall of apackage that can allow the passage of gas under pressureor concentration differential existing across the wall.Leakage test can be done by dye bath test.

Dye Bath Test

The test container is immersed in a dye bath. Vacuum andpressure is applied for some time. The container isremoved from the dye bath and washed. The container isthen inspected for the presence of dye either visually orby means of UV spectroscopy. The dye used may be ofblue, green, yellowish-green color. The dye test can beoptimized by use of a surfactant and or a low viscosityfluid in the dyesolution to increase the capillarymigration through the pores. The dye test is widelyaccepted in industry and is approved in drug use. The testis inexpensive and is requires no special equipmentrequired for visual dye detection. However, the test isqualitative, destructive and slow. The test is used forampoules and vials.

Clarity Test

Clarity testing is carried out to check the particulatematter in the sample. In this test transparent particles orwhite particles observed against the black backgroundand the black or dark particles observed against the whitebackground.

Pyrogen Test

Limulus Amebocyte Lysate (LAL) Test

The LAL Assay is an in vitro assay used to detect thepresence and concentration of bacterial endotoxins indrugs and biological products. Endotoxins, which are atype of pyrogen, are lipopolysaccharides present in thecell walls of gram-negative bacteria. Pyrogens as a

classare fever-inducing substances that can be harmful oreven fatal if administered to humans above certainconcentrations. This test is based upon the gellingproperty of an enzyme, the limulus amebocyte lysateextracted from the horse shoe crab, limulus polyphormus.The enzyme gels in the presence of bacterial endotoxinand the degree of gelling is related to the amount ofendotoxin present. A no. of instrument is available formeasuring the degree of gelling of enzyme. The test canbe used for quantifying the amount bacterial endotoxin present and provide a better information regarding thequality of a product than rabbit pyrogen test which ismore of a qualitative test.

Sterility Test

The tests for sterility are intended for detecting thepresence of viable microorganism in pharmaceuticalpreparation that is designed to be sterile. The test isbased on the principle that if micro-organism are placedin a medium that provide optimum condition of nutrition,moisture, PH, aeration, temperature, they can grow andtheir presence will be indicated by the presence ofturbidity in clear medium. Test for sterility may be carriedout by one of the following two methods.

Membrane Filtration Method

Use membrane filters having a nominal pore size notgreater than 0.4µm whose effectiveness to retainmicroorganisms has beenestablished. Cellulose nitratefilters, for example, are used for aqueous, oily, andweakly alcoholic solutions; and cellulose acetate filters,for example, are used for strongly alcoholic solutions.Specially adapted filters may be needed for certainproducts (e.g., for antibiotics). The technique describedbelow assumes that membranes about 50 mm indiameter will be used. If filters of a different diameter areused, the volumes of the dilutions and the washingsshould be adjusted accordingly. The filtration apparatusand membrane are sterilized by appropriate means. Theapparatus is designed so that the solution to be examinedcan be introduced and filtered under aseptic conditions: itpermits the aseptic removal of the membrane for transferto the medium, or it is suitable for carrying out theincubation after adding the medium to the apparatusitself. After filtration the preparation membrane is cutinto two halves. One halve is transferred in to 100ml ofculture medium meant for the growth of the bacteria andincubated at 30 to 35°C for not less than 7 days. Theanother halve is transferred to 100 ml of culture mediummeant for fungi and incubated at 20 - 25 oC for not lessthan 7 days.

Direct Inoculation Method

Although international pharmacopoeias recommendusing standard membrane filtration for sterility testing,there are certain products that are not filterable ordeformable. These products are normally tested usingdirect inoculation. In this method, the test sample isadded directly into the required media, ensuring that theamount of sample is below 10%.

In this method an aliquotquantity of the material being tested is drawn asepticallyfrom the container and transferred to a vessel containing

a measured quantity of a suitable culture medium. Theculture is incubated at appropriate temperature for notless than 14 days. The culture medium is observed atperiodic intervals during the incubation period and at theend to detect presence of any microbial growth.

Content Uniformity & Weight

Determine the content of the active ingredient of each of10 containers taken at random. The preparation underexamination complies with the test if the individualvalues thus obtained are all between 85 and 115 percentof the average value. The preparation under theexamination fails to comply with the test if more thanone individual value is outside the limits 85 to 115percent of the average value or if any one individual valueis outside the limits 75 to 125 percent of the averagevalue. If one individual value is outside the limits 85 to 115 percent but within the limits 75 to 125 percent of theaverage value, repeat the determination using another 20containers taken at random. The preparation underexamination complies with the test if in the total sampleof 30 containers not more than one individual value isoutside the limits 85 to 115 percent and none is outsidethe limits 75 to 125 percent of the average value.

Limits for Uniformity of Weight

Pharmaceutical Formulation	Average Mass	Percentage Deviation (%)
Powders for parenteral use	More than 400 mg	10
Powders for eye drops	Less than 300 mg	10
Powders for eye lotions	300 mg or more	7.5

Extractable Volume

a) Single Dose Containers

Method I: Where the nominal volume does not exceed5ml.

Use 6 containers, 5 for the tests and 1 for rinsing thesyringe used. Using a syringe with appropriate capacity,rinse the syringe and withdraw as much as possible thecontents of one of the containers reserved for the testand transfer, without emptying the needle, to a drygraduated cylinder of such capacity that the totalcombined volume to be measured occupies not less than40% of the nominal volume of the cylinder.

Repeat the procedure until the contents of the 5containers have been transferred and measure thevolume.The average content of the 5 containers is not less thanthe nominal volume and not more than 115% of thenominal volume. Alternatively the volume of contents inmilliliter can be calculated as mass in grams divided bythe density.

Method II: Where the nominal volume is more than 5ml.Transfer the contents of not less than 3 containersseparately to dry graduated cylinders such that thevolume to be measured occupies not less than 40% of thenominal volume of the cylinder and measure the volume transferred. The contents of each container are not lessthan the nominal volume and not more than 110% of thenominal volume.

8. Particulate matter in injections

The preparations intended for parenteral use should befree from particulate matter and should be clear wheninspected visually.Two methods are described by USP according to the filledvolume of the product to be tested. For large volumeparenteral (LVP's), a filtration followed by microscopicalexamination procedure is used. For small volumeparenterals (SVP's) a light obscuration based sensorcontaining electronic liquid-borne particle counter systemis used. The USP standards are met if the LVP's under testcontain NMT 50 particles per ml of 10µ m, and NMT 5particles per ml of 25µm in an effective lineardimensional fashion. The USP standards are met if theSVP's under test contain NMT 10,000 particles percontainer of 10 µm, and NMT 1000 particles percontainer of 25µm in an effective spherical diameter.

The general IPQC of Biological products include:

- **Sterility Test:**Same as above mentioned under sterile products
- **Pyrogen Test:**Same as above mentioned under sterile products

Specific IPQC of biological products are:

FOR VACCINES:

Vaccines are microbial preparations of killed or modified microorganisms that can stimulate an immune response in the body to prevent future infection with similar microorganisms.

Quality control tests:

1. Staining test:

Approximately 10 mL of the test sample is centrifuged in a pointed centrifuge tube at approximately 2,000 xg for 30 minutes. The sediment or the bottom portion is spread on a slide glass, dried and heat-fixed over a flame. The smear is then stained by the Gram's Method and, unless otherwise specified, examined microscopically at an approximately 1,000-fold magnification.

Criterion for judgment:

No bacterial shall be observed other than those defined in the individual monographs.

2. Inactivation test:

- Each purified bulk material shall be tested in mice for effective inactivation of the virus before the addition of preservative and other substances.
- The test should be performed with undiluted purified bulk material injected intra-cerebrally into at least 20 mice, each weighing between 15 and 20 g. these mice shall be observed for 14 days. Any symptoms caused by the virus shall be confirmed by
- Immuno-florescence assay. At the end of the observation period, no cytopathetic effects should be observed.

3. **Freedom from abnormal toxicity**:

4. Sterility test and Pyrogen test

B) Immune sera

It contain antibodies to specific bacteria or viruses and it is of 2 types

1. *Antitoxin:* It contains an antibody capable of destroying microorganisms including viruses and bacteria.

2. *Antivenom:* It contains an antibody that is active against the venom of a snake, spider, or other venomous animal or insect.

Quality control tests:

1. Immunoglobulin test

- The cellulose acetate membrane electrophoretic test is used to analyze the protein constituents in a test sample by differences in mobility of the protein solutions in electric fields.
- Dilute the test sample with diethylbarbiturate buffer solution (pH 8.6) to render the protein solution approximately 5%.
- Electrophorise the solution and stain it through the membrane with Ponceau 3R.
- Protein constituents and relative concentrations are analyzed by densitometry.

Acceptance criteria:

NLT 95% of the total proteins shall be immunoglobulin.

2. Test for residual proteolytic enzymes

When measured by a suitable method for the detection of proteolytic enzyme activity, the test material shall be practically free from residual proteolytic enzyme activity.

3. Test for antitoxin/ antivenom content.

- In order to determine the antitoxin/antivenom content of the preparation under examination its potency is determined with respect to the standard antitoxin preparation of the test preparation by carrying out the assay.
- The antitoxin/ antivenom content of each test sample shall be determined by statistical analysis of assay results. The final product shall contain antitoxin/ antivenom at no less than the value stated on the label.

C) Toxoids

A toxin that has been treated, as with chemicals or heat, so as to eliminate the toxic qualities while retaining the antigenic properties.

Quality control tests:

1. Purity Test

Each bulk material shall be tested for

- Protein nitrogen content
- Toxoid content.

Protein nitrogen content test

- The protein nitrogen content test is a method used to determine protein content by measuring nitrogen in heated trichloroacetic acid-precipitable protein in the test sample by the micro-Kjeldahl method. The criterion for judgment shall be given in the individual monographs.
- Dilute the sample if necessary with water and transfer to centrifuge tube.
- Add 1/10th volume of 50% w/v trichloroacetic acid solution to render trichloroacetic acid concentration 4.5% w/v or higher.
- Heat the mixture at 100 oC for 15 minutes and then cool it to room temperature.
- Centrifuge the mixture at greater than 1400 xg for 10 minutes.
- Add appropriate amount of 5% w/v of trichloroacetic acid solution to the precipitate, shake and centrifuge it again.
- Measure the nitrogen content in the precipitate using an appropriate method such as the micro-Kjeldahl method.

Calculation of protein content

The protein content is calculated from the nitrogen content by the formula:

1 mg protein nitrogen (N) = 6.25 mg protein

Toxoid content test

The test shall be conducted by the flocculation test. The bulk material shall contain no less than 1,500 Lf toxoid of per mg protein nitrogen.

2. Detoxification test

The test shall be conducted on two kinds of the sample: the one shall be prepared by diluting the test sample with 0.017 mol/L phosphate-buffered sodium chloride solution (pH 7.0) to the concentration of x Lf/ml, and the other to a concentration higher than that of the final bulk not exceeding y Lf/ml. The latter sample shall be preserved at 37 °C for 20 days prior to the test. Following test shall be conducted on the samples with and without preservation at 37 °C for 20 days. Concentration of the diluted samples depends upon on the type of the toxoid and is given in the monograph of that particular toxoid.

Procedure

Each sample shall be given by subcutaneous injection at a dose of 5 mL into at least 4 guinea pigs weighing 300−400 g. The injected animals shall be observed for at least 21 days. No animal shall die due to intoxication, or show specific symptoms of intoxication or other abnormal signs during the observation period.

3. Sterility test – common for all the biological products

D) Blood products

- Human plasma protein fraction
- Freeze dried human fibrinogen
- Platelet concentrate
- Whole human blood
- Concentrated red blood cells
- Human albumin
- Dried human serum
- Human normal immunoglobulin

Quality control tests:

1. Identification tests

- Precipitation tests with specific antisera are used to show that only human serum proteins are present.
- The characteristic mobilities of blood proteins in an electrophoretic field are a sensitive means of identifying fibrinogen, immunoglobulin, and the plasma protein fraction.
- Proteins can also be identified by their sedimentation rate in an ultra-centrifuge; this method is suitable for identifying and quantifying the different types of gamma globulins

2. Sterility and Pyrogen test

- All blood products must comply with the official tests for sterility, and those preparations (i.e., immunoglobulin and the plasma protein fractions) that are exposed to special risk of contamination with pyrogens due to lengthy processing must also pass the pyrogen test.

3. Solubility

- Complete solubility in an appropriate volume of the usual solvent, sometimes a specified time is required for all solid preparations except fibrin foam. This indicates that the protein constituents have not deteriorated.

4. Assay

- For whole blood and concentrated red cells the assay is a determination of the hemoglobin value. For the remaining products, except fibrin foam and thrombin, the protein content is determined chemically.
- The hemoglobin value is a measurement of concentration and is the amount of hemoglobin present in a fixed volume of the patient's blood. It is normally expressed as grams per deciliter (g/dL) or grams per liter (g/L).

a) Human plasma

- **i. Inspection:** Fresh-frozen Human Plasma, upon visual inspection, shall be free from marked hemolysis, change in color or other abnormal findings
- **ii. Coagulation test:** Take 0.1 mL of the test material in a test tube & kept in a water-bath at 37 °C, 0.1 mL of thromboplastin solution and 0.1 mL of 0.025 M calcium chloride solution shall be added, and the time until the formation of a fibrin clot shall be recorded, and it shall be within 20 seconds.

b) Frozen thawed human blood cells

- **i. Weight:** When weighed by a suitable method, NLT 63g of red cells shall be recovered from 200 mL of source material.
- **ii. Test for hemoglobin content:** When the test for Hemoglobin Content is applied, 1mL of the final product shall contain NLT 0.24 g of hemoglobin.

c) Platelet concentrate

- **i. Inspection:** Platelet, upon visual inspection, shall be free from marked hemolysis, change in color or other abnormal findings.
- **ii. Platelet count test:** The final product shall have a platelet count of NLT 0.2×10^{11} of Platelet count.

iii. Red blood cell count and white blood cell count tests: The final product shall contain normal counts of red blood cells and white blood cells.

E) Allergenic products

Allergen extracts are biological products that are administered to humans to diagnose, prevent and treat allergic diseases.

Quality control tests:

- Measurements of the total allergenic activity of individual batches of an allergen extract should be undertaken preferably by IgE inhibition or by direct IgE-binding or other immunoassay.
- The estimated potency derived from the assay of total allergenic activity should be NLT 50% and NMT 200% of the stated potency.

In-vivo diagnostics for allergenic products:

- The most widely used of these are the tuberculin employed of infection to detect sensitization by mycobacterial proteins and hence the possible presence.
- Apart from standardization of potency, which also serves as an identity test, the material must be checked for sterility and for the absence of viable mycobacteria.
- The product is also checked for absence of reactogenicity in unsensitized guinea pigs and if required by the regulatory authority, for abnormal toxicity.

IN PROCESS QUALITY CONTROL OF NON-STERILE PRODUCTS:

Non-Sterile Products are:

1. Granules (starting materials)
2. Tablets (finished products)
3. Capsules
4. Liquid dosage form

Granules

a) Appearance: The general appearance of a granule, itsidentity and general elegance is essential for componentsin manufacturing, for control of lot-to-lot uniformity andtablet-to-tablet uniformity. The control of generalappearance involves the measurement of size, shape, color, presence or absorbance

b) Size and Shape:

(1) Sieving: Particle having the size range between 50 and150 m are estimated by this method. In this method thesize is expressed as d sieve which describes the diameterof a sphere that passes through the sieve aperture as theasymmetric article .The method directly gives the weightdetermination.

Method:

Standard sieves of different mesh numbers are availablecommercially as per the specification of IP and USP. Thesieves are arranged in nest with the coarsest at the top Asample 50 gm of the powder is placed on the sieve thissieve set is fixed to the mechanical shaker apparatus andshaken for the certain period of time (20) min.The powder retained on each sieve is weighed it isexpressed in terms of arithmetic or geometric mean ofthe two sieves.

(2) Sedimentation: Sedimentation method may be usedover a size range of 1 to200 m in this method size isexpressed as stokes diameter which describes thediameter of an equivalent sphere having the same rate ofsedimentation as that of the symmetric particlesSedimentation of particles may be evaluated by differentmethods like E.g.: Andersen pipette method.

Andersen Pipette Method

Principle

The rate setting of particles in a suspension of emulsionmay be obtained by stokes. However this equation can beextended to irregularly shaped particles of various sizeswhen the power is suspended in a vehicle initially theparticles of large diameter settled due to heavy weighafter sometime particles of intermediate diameter finallythe particles of smaller size settled. Hence the studyinvolves the sampling during sedimentation at differenttime intervals.

Procedure

- Prepare 1-2 %suspension of powder in a suitable medium.
- A deflocculating agent can be added for uniform dispersion of the suspension.
- Transfer the suspension into the Anderson vessel.
- Place the stopper and a shake the vessel to distribute the suspension uniformly.
- Remove the stopper end the two way pipette and securely suspend the vessel in a constant temperature in a water bath.
- At different time intervals 10 ml samples are withdrawn using two way stop cork and collected in watch glass. Samples were evaporated and weighed.
- The weight of the amount of particles obtained in each time intervals is referred to as weight under size. The weighs are converted into cumulative weight under size.
- Particles diameter was calculated from stokes law with in (h) in equation being the height liquid above the lower end of the pipette at the time with drawing sample.

3) Optical microscope: Most direct method here theparticles size and size distribution is determined bypreparing a suspension and absorbing under, microscope.

c) Surface area: Surface area of the drug can have asignificant effect upon the dissolution rate it isdetermined by Gas adsorption, Air permeability.

d) Bulk Density and Tapped Density:

Bulk Density: The bulk density of a powder is the ratio ofthe mass of an untapped powder sample and its volumeincluding the contribution of inter particulate voidvolume.

$$\text{Bulk Density} = \frac{\text{Mass of powder (W)}}{\text{Bulk volume (Vb)}}$$

It is determined by 3 methods

- Measurement in a Graduated Cylinder,
- Measurement in a Graduated Cylinder
- Measurement in a Vessel

Tap Density: The tapped density is an increased bulkdensity attained after mechanically tapping a container containing the powder sample.

$$\text{Tap Density} = \frac{\text{Mass of powder (W)}}{\text{Tapped volume (Vt)}}$$

e) Angle of Repose (θ): The flow characteristics aredetermined by angle of repose, it is defined as maximumangle possible between the surface of a pile of thepowder and horizontal planes,

$$\theta = \text{Tan-1}(h/r)$$

h = height of pile

r = Radius of the base of pile

The lower the angle of repose the better the flowproperty Rough and irregular surface of the particlesgives higher angle of repose. Limits for angle of repose is

Angle of Repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

f) Moisture Content: When there is high moisturecontent, then there will be greater risk of cohesion andadhesion. Moisture content is commonly determined by:

Loss on Drying

Mix and accurately weigh the substance to be

- If the test specimen is in the form or large crystals reduce the particles size to about 2mm by quicklyccrushing
- Weight and empty dried glass stopper shallowweighing bottle
- Put the test specimen in the bottle replace the coverand accurately weigh the bole and the contents
- By gentle sideways shaking distributed the testspecimen as evenly as practicable deep of about5mm generally more than 10 mm in case of bulkymaterials (w1)
- Place the loaded bottle in the drying chamberremoving the stopper end leaving it also in thechamber
- Dry the tests specimen at the temperature and forthe time specified in monogram
- Upon opening the chamber close the bottle promptlyand allow it to come to room temperature indesiccators' before weighing (w2)
- The substance melts at a lower temperature then thespecified for the determination of loss on dryingmaintain the bottle with it content for 1-2 hrs at atemperature at 5-10 degrees below the meltingtemperature than dry at the specified temperature
- When the specimen under test is capsules use aportion of mixed contents of fewer than 4 capsules Ifit is tablets use powder from not fewer than 4 tabletsgrind to a fine powder Where drying in a desiccatorsis specified exercise particular care to ensure that thedesiccant is kept fully effective by frequentreplacement
- Other method employed for moisture contentmeasurement is Karl fisher method

g) Compressibility Index

It demonstrates the relation between the flow andcompressibility of powder

$$\% \text{ Compressibility} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \text{ x } 100$$

h) Hausner Ratio

Hausner predict the flow property of powder by usinginter particle friction

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Compressibility index, Hausner's ration and type of flow of the formulatedgranules is

Compressibility Index	Hausner's Ratio	Powder flow
5-15	1.00 - 1.11	Excellent
12-16	1.12 - 1.18	Good
18-21	1.19 - 1.25	Fair
23-28	1.26 - 1.34	Poor
28-35	1.35 - 1.45	Slightly Poor
35-38	1.46-1.59	Poor
> 40	> 1.60	Very Poor

Tablets

a) Physical Appearance

The general appearance of a tablet, its identity andgeneral elegance is essential for consumer acceptance,for control of lot-to-lot uniformity and tablet-to-tabletuniformity. The control of general appearance involvesthe measurement of size, shape, colour, presence orabsence of odour, taste etc.

b) Weight Variation Test

Weigh individually 20 units selected at random andcalculate the average weight. Not more than two of theindividual weights deviate from the average weight bymore than the percentage shown in the table and nonedeviates by more than twice that percentage.

c) Uniformity of Content

The test for uniformity of content of single-dosepreparations is based on the assay of the individualcontents of active substance(s) of a number of singledoseunits to determine whether the individual contentsare within limits set with reference to the averagecontent of the sample.

Method

Determine the content of active ingredient(s) in each of10 dosage units taken at random using the method givenin the monograph or by any other suitable analyticalmethod.Acceptance limits for tablets, suspensions for injectionand ophthalmic inserts:

The preparation complies with the test if each individualcontent is 85-115 % of avg content. The preparation failsto comply with the test if more than one individualcontent is outside these limits or if one individual contentis outside the limits of 75-125 % of the average

content. Ifone individual content is outside the limits of 85 to 115%of the average content but within the limits of 75 to125%, repeat the determination using another 20 dosageunits. The preparation complies with the test if not morethan one of the individual contents of the total sample of30 dosage units is outside 85 to 115 per cent of theaverage content and none is outside the limits of 75 to 125% of the average content.

d) Disintegration Test: Disintegration test is a measure oftime required under a given set of conditions for a groupof tablets to disintegrate into particles.

Apparatus

The apparatus consists of a basket-rack assembly, a 1-litrebeaker, a thermostatic arrangement for heating the fluidand a mechanical device for raising and lowering thebasket in the immersion fluid at a constant frequencyrate. The basket rack assembly holds 6 plastic tubes, openat top and the bottom of tubes is covered with 10- meshstainless steel wire screen. The basket rack is immersed ina bath of suitable liquid, held at 37±2 ^{0}C. For compressed,uncoated tablets, testing fluid is usually water butsometimes monographs refer to use simulated gastricfluid. Tablets are placed in each of 6 cylinders along withplastic disc over the tablet if mentioned in monograph.

Through the use of a mechanical device, the rack movesup and down in the fluid at a specified rate, the volume of liquid is such that the wire mesh at its highest point is atleast 25 mm below the surface of the liquid, and at itslower point is at least 25 mm above the bottom.

End point of the test is indicated when the tablets arecompletely disintegrated and any residue remaining is a soft mass with no palpably firm core. The preparationcomplies with the test if the time to reach this end pointis below a given limit.

Limit

If 1 or 2 tablets fail to disintegrated, test is repeated using12 tablets. of the 18 tablets tested, 16 must havedisintegrated within given period of time.

e) Hardness Test

Hardness of the tablet also termed as its crushingstrength. The hardness of the tablet may be defined asthe compression force required breaking the tablet whensuch force is applied diametrically. The tablet is requiredto posse's sufficient hardness to resist breakage during the transport, storage or use. The hardness of a tablet isrelated to its disintegration and has more vital role to playin controlling the rate of drug release from the tablet.

(i) By Manual Testing: Manual testing method wasemployed previously. In this, method, the thumb acts as afulcrum, while the tablet is held between the second andthird hand fingers. When the pressure is applied thetablet which breaks with a sharp snap deemed to posses' sufficient hardness.

(ii) Monsanto Hardness tester method: The instrumentmeasures the force required to break the tablet when theforce generated by a coil spring is applied diametrically tothe tablet.

(iii) Pfizer Hardness Tester: Force required to breaktablets recorded on dial and may be expressed in keypounds

Other devices:

- Strong-Cobb Hardness Tester
- Erweka Hardness Tester.
- Schleuniger or Heberlein Hardness Tester.

Acceptance criteria: A force of 4 kg/inch2 is considered tobe the minimum requirement for a satisfactory tablet.

f) Friability Test

The friability of a tablet may be defined as its resistanceto shock and abrasion encountered during the process ofmanufacture, packing, transport and ultimately its usage.Friability in addition to hardness gives measure of tabletsstrength. It is determined through the use of a friabilator.

Method

A no. of tablets are weighed and placed in tumblingapparatus where they are exposed to rolling andrepeated shocks resulting from free fall within theapparatus. After given no. of rotations, the tablets areweighed. Resistance to loss in weight indicates ability of tablet to withstand this type of wear. For tablets with anaverage weight of 0.65g or less take a sample of wholetablets corresponding to about 6.5g and for tablets withan average weight of more than 0.65 g take a sample of10 whole tablets. De dusts the tablets carefully and weighs accurately the required number of tablets. Placethe tablets in the drum and rotate it 100times.Removethe tablets, remove any loose dust from them and weighthem accurately.

Criteria

A maximum loss of weight (from a single test or from themean of the three tests) not greater than 1.0% isacceptable for most tablets. If obviously cracked, chippedor broken tablets are present in the sample aftertumbling, the sample fails the test. This test is applicable to compressed tablets and is intended to determine thephysical strength of tablets.

Capsules

Capsules are solid dosage forms in which medicinalagents are enclosed in small shell of Gelatin. Capsuleshells may be hard or soft, depending on theircomposition.

Physical Appearance

The general of a capsule, its identity and general eleganceis essential for consumer acceptance, for control of lot-to-lotuniformity and capsule uniformity. The control ofgeneral appearance involves the measurement of size,shape, color, presence or absence of odour, taste etc.

Weight Variation Test

Weigh an intact capsule. Open it without losing any partof the shell and remove the contents as completely aspossible.

For soft gelatin capsules, wash the shell with a suitablesolvent and keep aside until the odor of the solvent is notperceptible. Weigh the shell. The difference between theweighing gives the weight of the contents. Repeat theprocedure with another 19 capsules.

Uniformity of Content

The preparation complies with the test if not more thanone individual content is outside the limits of 85-115% ofthe average content and none is outside the limits of 75-125% of the average content. The preparation fails tocomply with the test if more than three individual
contents are outside the limits of 85-115% of the averagecontent or if one or more individual contents are outsidethe limits of 75-125 % of the avg. content.

If two or three individual contents are outside the limitsof 85-115% of the average content but within the limits of
75-125%, repeat the determination using another 20dosage units.

The preparation complies with the test if not more than3individual contents of the total sample of 30 dosageunits are outside the limits of 85-115% of the averagecontent and none is outside the limits of 75-125 %of theaverage content.

Closing Length

The Acceptance criteria 0.2mm

Moisture Permeation Test

To assure the suitability of containers for packagingcapsules, USP has started some rules and regulations.According those rules and regulations, the moisturepermeating feature of capsules packaged in single unitcontainers is to be determined.

Procedure

For performing this test, one capsule is packaged alongwith the dehydrated pellets, which have the property ofchanging colour in the presence moisture.The packaged capsule is then placed for a certain periodof time in an atmosphere of known humidity.

Any change in the colour of dehydrated pellets revealsthe absorption of moisture.The weight of this capsule is then compared with theweights of the capsules under test.The differences in the weights give the amount ofmoisture absorbed.

Liquid Dosage Forms

It is prepared by dissolving active ingredients or bysuspending the drug (if drug is insoluble) or byincorporating the drug into one of the two phases of oiland water systems. Liquid dosage form comprises ofsolution, suspension and emulsion and a variety of
preparation can be considered under each category.These dosage form are categorized by their homogene,promote action and easy of Administration.

Liquid dosage forms are suitable for both internal andexternal use.

This is a general term used to describe a solution,suspension or emulsion in which the active ingredient isdissolved or dispersed in a suitable liquid vehicle.

Liquid dosage forms are 2 types:

(i) Monophasic: a) Syrups, b) Elixirs, c) Tinctures etc.

(ii) Biphasic: a) Suspensions, b) Emulsions.

STANDARD OPERATING PROCEDURES FOR CLEANING:

Cleaning In pharmaceutical production operation has to be carried out in clean area to avoid any contamination. Cleaning of area, cleaning of manufacturing equipment , microbiological monitoring of manufacturing area and equipment are very important. Manufacturing area requires regular cleaning and disinfection and these are to perform in order to Create and maintain a safe working environment. Remove dust and dirt which can be a hazardous to quality of product Minimize the risk of cross contamination occurring between different product made in the same area. Reduce level of contamination of micro organisms Water alone is not sufficient for cleaning and disinfection . specific aid such as cleaning agents and disinfecting agents are necessary for this purpose.

Cleaning agents: these are materials which help to remove extraneous material from surfaces and objects Antiseptics: these are reasonable non toxic substances and be applied to the tissues for killing micro organisms or to prevent their growth.

GENERAL PRECUTIONS: Cleaning agents and disinfecting agents should be handled with care as they are potent and often hazardous, gloves , eye shield , aprons ,safety foot ware etc must be used while handling them. Cleaning agents and disinfecting agents should not be mixed as certain mixture are known to be chemically reactive and dangerous.

Shelf life of the diluted disinfectant should be specified in the standard operating procedure. Disinfectants containing alcohol or other inflammable solvents should be stored and handled in a safe manner Care should be taken to ensure that the disinfectant does not cause corrosion or discoloration of metal surface or flooring.

General cleaning procedure: Disconnect the machine from the main electric supply Dismantled the machine parts which comes in direct contact with the product Wash all parts with 0.5%v/v teepol solution and rinse with portable water and clean the equipment Wash all rubber gaskets with 0.5% v/v teepol solution or other cleaning agent The part of the machine are to be dusted and then wiped with a clean cloth damped with 0.5% teepol solution in water ,this procedure may be repeated until the machine parts are absolutely clean. Wipe all the cleaned dismantled parts of the equipment with clean lint free cloth. Assemble the other parts of the machine and set it up as it was before dismantling for cleaning. Certify the effectiveness of the cleaning system by sampling and analysis for the residue left behind. Take a trial run to check if the machine is working properly. Put the status cleaned label. Cover the machine with a machine cover stitched from limit free synthetic fiber so as to prevent it from getting recontamination with dust. Complete all the related documents record and equipment log sheet.

CLEANING SHEDEDULE: This is again entirely dependent upon the validated cleaning procedure. Some of the general guidelines are given below Complete and thorough cleaning is absolutely necessary at the time of product change over to make sure that even the traces of the previous product so not remain and thereby avoiding all chances of any cross contamination. A cleaning procedure is desired at the end of the working shift only for equipment in which a wet processing stage has been carried out. All equipment need a week end cleaning which is generally done in the last working shift which include all equipment used for processing manufacturing process.

PROCEDURE: Any spoilages of the materials must be cleaned up as soon as it takes place for this the vacuum cleaner should be used. Cleaning of the floor and the walls is done at the end of the day or shift only after all the equipments machine containers have cleaned and suitably covered. Initially clean with vacuum cleaner all the floors and walls edges as necessary to dislodge any accumulation of dust. The entire floor is then cleaned with water and disinfecting agents of the specified concentration and subsequently the floor is dried.

Whenever the product change over take place the production supervisor will carefully inspect all the area and ensure that there is no residue. Cleaning agent to be changed for every fortnight.

STANDARD OPERATING PROCEDURES FOR FILLING:

Various standard operating procedures are followed for the filling of ampoules, capsules , vials and liquid formulations etc. It is the responsibility of the production manager and technical manager to follow the procedure. The QA manager is responsible for the SOP compliance.

1. AMPOULE/VIAL FILLING

Purpose To describe the validation guide lines for ampoule and vial filling machine to be free from contamination during the filling cycle. Procedure Procedures to ensure that it meets installation operational and performance qualification requirements.

A. INSTALLATION QUALIFICATION

- Installation can be conducted per instruction provided in the manual
- Ensure all relevant documentation is received
  - o User manual
  - o Maintenance manual
  - o Electrical drawings
  - o Medical drawings

B. OPERATIONAL QUALIFICATIONS

- Verify alarm control
- Perform calibration requirements identified in the manual or established by the validation team
- Operate the equipment at low , medium and high speed per operation manuals to verify the operation control
- Verify that all switches and push buttons are working properly
- Establish procedures for operation , maintenance and calibration
- Establish training programmes for relevant staffs

CLASSIFICATION AT FILLING POINT

Procedure The particle load should be examined at the location near filling point with particle counter Requirements

- ≤ 100 particles ≥ 0.5 µm left or ≤ 3000 particles ≥ 0.5 µm
- 0 particles ≥ 5µm left

D. PARTICLE CONTAMINATION OF AMPOULES AND VIALS DURING FILLING PROCEDURE

Ampoules and vials should be filled with water for injection and afterward be inspected on the contamination with particles. The injection can be performed with a particle counter. Requirements The USP requirements for particulate water in injection , small volume injection must be fulfiled.The contaminations with particles during the filing step should be equivalent at all available machines.

E. FILLING VOLUME ACCURACY

The filling volume accuracy should be with in ± % of adjusted and desired filling volume in accordance with machine specification etc.

2. TUBE FILLING

Purpose To determine the procedure for validation of tube filling and dosing machine to ensure that it meets installation and operational qualifications requirements. Procedure

A. INSTALLATION QUALIFICATION

- Verify approved purchase
- Verify approved purchase orders
- Verify invoice
- Check manufacturer and supplier
- Verify model number and serial number
- Check for any physical damage

Confirm location and installation requirement per recommendation of manufacturer

- Verify that utilities required are available
- The following should be checked to ensure the fulfil installation qualifications
  - Control panel
  - Cream pump control unit
  - Cream torrer control unit
  - Outlet valve temperature control of cream hopper
  - Heating jacket temperature control of cream hopper
  - Feeding of empty tube
  - Code reading for checking of the position of the tube prior to filing station
  - Code reader for tube

B. OPEATIONAL QUALIFICATION

- Verify alarm control
- Perform calibration requirements identified in the manual or established by validation team
- Operate the equipment at low , medium and high speed per operation manuals to verify the operation control
- Verify that all switches and push buttons are working properly
- Establish procedures for operation , maintenance and calibration
- Establish training programmes for relevant staffs
- The following critical points should be evaluated

- Product feeding to the filter
- Product filling
- Electric and electrical check device
- Application of tube code

C. PERFORMANCE QUALIFICATION

- Tube closure properly closed
- Check of filled quantity
- Quality of tube filling
- Correct functioning of code readers
- Visual appearance of tub
- Correct code embossed or printed on the tube

3. LIQUID FILLING

Purpose To describe the procedure for validation of liquid filling Procedure

A. INSTALLATION QUALIFIATION

The following machine characteristics should be checked to ensure successful installation qualification

- Control panel
- Feeding of empty bottle
- Detector for presence of bottle
- Detector for presence of liquid
- Terminal sterile filter unit
- Filling unit
- Detector for correct liquid level in the bottle
- Feeding of bottle to the dosing machine
- Detector for presence of filled bottles
- Feeding of dropper and pouring ring
- Detector for dropper or pouring ring prior to dosing
- Feeding of closures

B. OPERATIONAL QUALIFICATIONS

- Verify alarm control
- Perform calibration requirement identified in the manual or established by validation team
- Operate the equipment at low , medium and high speed per operation manuals to verify the operation control
- Verify that all switches and push buttons are working properly
- Establish procedures for operation , maintenance and calibration
- Establish training programmes for relevant staffs

C. PERFORMANCE QUALIFICATIONS

- Identify check of used material
- Tamper evidence of closure fulfilled
- Bottle closure properly closed
- Visual inspection of closed bottle
- Check of bottle content
- Dropper or pouring not damaged
- Time interval ; before daily production start ; every 2 hour during packaging

CHECKS DURING FILLING

Purpose The purpose is to provide a procedure for the fill check (by w/v) for liquid product (ampoules/vials) and for powder by weight and prefilled syringes.

Precautions

- Make sure that no air space is left on the top of syringe
- while transferring , liquid should not touch the walls of cylinder
- cylinders and syringe should be completely dry before use

STANDARD OPERATING PROCEDURES FOR DRYING:

Drying is defined as removal of liquid from a material by the application of heat and is accomplished by the transfer of a liquid from surface into an unsaturated vapor phase. Drying is most commonly used in pharmaceutical manufacturing as a unit process in the preparation of granules which can be dispensed in bulk or converted into tablet or capsules. It found application in the processing of materials.

CLASSIFICATIONS OF DRYERS

1. Static bed dryer

System in which there is no relative movement among the solid particles being dried, although there may be bulk motion of the entire drying mass. Eg: tray drier

2. Moving bed dryer

Systems in which the drying particles are partially separated so that they flow over each other. Eg: pan dryer, turbo tray dryer

3. Fluidized bed dryer

Systems in which the solid particles are partially suspended in an upward moving as stream.

4. Pneumatic dryer

System in which the drying particles are entrained and conveyed in high velocity gas stream. Eg: spray drying

VALIDATION OF FLUID BED DRYER PURPOSE

To describe the procedure for validation of the fluid bed dryer to ensure that it meets installation, operation and performance qualifications requirements.

RESPONSIBILITY It is the responsibility of production manager, technical service manager to follow the procedure. The QA manager is responsible for SOP compliance.

1. INSTALLATION QUALIFICATIONS

- Verify approved purchase order
- Verify invoice
- Check manufacturer and supplier
- Verify model no and serial no
- Check for any physical damage
- Confirm location and installation requirement for recommendation of manufacturer
- Ensure that all relevant document sis received
    - User manual
    - Maintenance manual
    - List of change parts
    - electrical drawings

Instruments for measuring temperature, humidity, time, air volume and pressure as well as record device for these variables should be calibrated. Air temperature distribution Place several thermocouples at different locations in an empty FBD E.g

Inlet air channel below product container mesh bottom

- Product container
- Below filter bag
- Above filter bag
- Exhaust air channel

Delay time for achieving constant air condition Determine by the use of thermocouple and hygrometer, the necessary delay time required at an adjusted inlet air temperature in relation to drying process for reaching constant air conditions. Microbiological quality of inlet air , Determine , by use of bio test RCS, centrifugal air sampler, the microbiological quality of the inlet air. Requirements:

- 200 cfu/m3 inlet air
- Influence of air on inlet air condition
- Inlet air installation
- Delay time for achieving constant air condition

2. Operational qualification

- Verify alarm control
- Perform calibration requirements identified in the manual or established by the validation team
- Operate the equipment at low, medium, high speed per operations manual to verify the operating control
- Verify that all switches and push buttons are functioning properly
- Establish procedures for operation, maintenance and calibration
- Establish training programmes for relevant staffs

3. Performance qualifications

Run each product type Requirements Each product shall meet the product characteristic per SOP OPERATION OF FLUID BED DRIER Caution

- Check and verify that, area and equipment are clean and suitable for starting the operation
- Ensure that main switch is in OFF position before dismantling FBD for loading

Assembling

- Unclamp the fixing bolts of retarding chamber and allow it to rest on the trolley. Take out trolley along with the retarding chamber.
- Check and certify the suitability of the clean finger bag.
- Fix the finger bag in a steel hanger. Fix the loops of the finger to the hooks of the shaker.
- Place the bag in between the retarding chamber and fluidising chamber.
- Clamp the retarding chamber on the body with fitting bolts.

OPERATION

Loading

- Load the bowl material to be dried
- Rake the product uniformly in bowl to avoid lumps
- Move the product bowl below the retarding chamber keeping the window in viewing position
- Position the bowel
- Lift the bottom of the FBD by moving this jack handle to the opposite side and seal the trolley to the retarding chamber
- Check and ensure that there is no leakage
- Set the timer and switch on heating, fluidization, maintaining the desired inlet air temperature
- Stop drying at intervals of specification in BMR and de-dust the finger bag by shaking it
- Take the trolley and rake the granules to avoid formation of lumps

- Watch the fluidized flow through the Perspex window
- Continue heating till required outlet air temperature is achieved. Air dry, if mentioned in BMR
- Put off the heaters and bring the time to zero

Unloading

- After drying is complete, put off the main switch
- Shake the finger bag vigorously
- Unlock and withdraw the bowl

STANDARD OPERATING PROCEDURES FOR COMPRESSION

DEFINITION

It is a process in which the force is applied to a granulated blend or granulated powder material to form a solid unit dosage form which is called as tablet. Tablet compression machine are designed with following parts

- Hopper (for holding and feeding granules to b compressed)
- Punches(compressing granules with in dyes)
- Dies(define size and shape)
- Feeding machine (moving granulation from hopper into dyes)

Types of compression machine Single punch machine Multi station rotary press For formulation of tablets following ingredients are required

- Diluents
- Binders & Adhesives
- Disintegrants
- Lubricants
- Glidants
- Colors

The SOP is applicable to

- Production officer
- Quality assurance officer
- Engineers & Operators

Procedure

1. Switch _on‘ mains of machine

Removed CLEANED label, affix USE FOR to the machine

2. Before starting any activation or operation , first see the cleanliness of all parts, (machine ,floor , electrical balance)
3. 2.After checking take cleaned container for storage of compressed tablets
4. 3.Then issue granulated blend from granulation department to compression department
5. The temperature should be maintained at 22 ± 3•c
6. Take one scoop of blend of drug and put in power hopper
7. Adjust parameters according to issued by quality assurance department
8. Ser Rpm, rate, flow of powder, speed of machine, hardness, thickness and weight etc.
9. After setting all parameters ,do one complete rotation of Current assembly

Check limit for the following tests

- Hardness
- Thickness
- Weight of tablet
- Disintegration
- Dissolution
- Diameter

10. After start production, check all these tests at one hour interval
11. During continuous running of batch have to check temperature and humidity of that area every two hours
12. At the end of batch, checked tablets with a label‖ SAMPLE FOR ANALYSIS‖ and send to the quality control department
13. After completion of batch compressed tablets are stored in fresh transparent poly bags ,kept in container, stored in bulk finished storage finished area.
14. After completion of batch remove USE FOR and affix TO BE CLEANED label
15. Rejected tablets are transferred to deactivation

STANDARD OPERATION PROCEDURE FOR CLEANIG AND ASSEMBLING OF COMPRESSION MECHINE

1. Remove USE FOR label and affix TO BE CLEANED label
2. Switch off the mains of machine
3. Dismantle the following parts

- Hopper
- Acrylic guard
- Cover plate
- feed frame
- Turrent guard

- die screw
- dust collecting assembly

4. Clean the mentioned parts with relevant holes thoroughly with purified water and finally with compressed air
5. Remove the upper and lower punches by removing plug and keep these punches on a trolley
6. Remove all the dyes
7. Clean all interior parts of machine like base plate on which turrent is fitted, cam tracks, die sets, upper and lower punch holes etc
8. Wipe clean the exterior areas of machine with help of fine free duster soaked in a special denatured spirit
9. Clean dies with purified water
10. Then cleaned punches and dyes are put in a clean separate trays
11. Wipe it with dry duster or clothes

FITTING OF DYES
Place die face downward on die hole
Apply slight pressure on top face of die to locate centrally

FITTING OF LOWER PUNCHES
Wipe it dry Smear with liquid paraffin and introduce it through lower punch die hole
Allow lower punches introduced should move freely up and down

FITTINGOF UPPER PUNCHES
Clean and dry should smeared and introduced into corresponding holes
Put back all turrent guards
Fit clean and dried feed frame
Assemble cleaned dust collecting hood
Affix CLEANED label over the machine

STANDARD OPERATING PROCEDURES FOR COATING

Mainly five steps are involved in the coating purpose and they are,

- SEAL COATING
- SUBCOATING
- SYRUP COATING
- FINISHING
- POLISHING

SEAL COAT

- Starts the tablet rolling pan at a speed of 10rpm and make the continuous air supply to the pan at 30 degree Celsius.
- Apply 3 applications of zein solution 800 ml application.
- Allow 15 to 20 minutes between applications to ensure that the tablets are dry.
- If the tablets become tacky between applications, apply just enough talc to prevent sticking to the walls of the pan and to stick to each other.

SUBCOATING

- Turn heat and inlet air off. Use exhaust only.
- Start pan speed at 10 rpm. Apply 3 to 9 coats to the tablets. Use 1.5 liters of warm gelatin or acacia solution for the first coat.
- Reduce the subsequent amounts accordingly to obtain the correct thickness.
- Allow at least 20 minutes between each coats to permit adequate drying.

SYRUP COAT

- Remove excess dust in the pan thoroughly. Then turn on the exhaust outlet air.
- Then set the inlet air temperature to provide in exhaust temperature of 45 to 48 degree Celsius.
- Set pan speed at 12 rpm.
- Apply 5 to 15 coats of the crossing syrup immediately after each proceeding. the application must be drying and slightly dusty. Apply several heavy colored syrup coats in a similar manner, until specific tablet volume is obtained.
- Turn off heat and reduce inlet and exhaust air.
- Apply several coats of the regular colored syrup solution to achieve a final smoothness, size and color development.

FINISHING

- The pan used must be made sure to be properly cleaned.
- Operate pan with heat turned off, no supply and greatly reduced exhaust air. Set the pan speed at 12 rpm.
- Apply 3 to 4 coats of regular colored syrup rapidly without permitting the tablet bed to frost or to become dusty.
- Apply the last coat without and colorant. Shut off the exhaust fan during this time.
- Mixing must have to be achieved uniformly and after that shut off the pan switch.
- Leave the tablets in the pan to dry slightly overnight.

POLISHING

- For this canvas lined pans are used and it must be cleaned properly.
- Supply the air to the pan and exhaust air heat should be turned.
- Put the tablets into the pan and rotate the pan with 12 rpm.

- After proper polishing had achieved shut off the pan power supply.

PACKAGING AND LABELING CONTROLS:

Line clearance: The procedures have been established to prevent mix-ups of products, container, component and labels and mistakes while preparing a product.

A) Equipment Design The design of equipment and process areas should be considered with respect to impact

Upon area/line clearance efficiency Ex includes:

- Premises should have adequate space for the orderly placement of equipment and materials to prevent cross contamination and line clearance failures.
- Clear guards should be used where possible to aid visibility.
- Guards which should be removed should be clearly identified.
- Equipment should be designed such that it is easy to disassemble and reassemble.

B) Assessing risks:

i) After setting up a new line or area assessment of clearance risk should be made by the Following guide lines:

- The assessor/ checking person should take in to consideration where opportunity for contamination occurs particularly where product may be exposed such as emptying centrifuges, off loading product, sampling and any other process.
- The level of risk of contamination/ Mix-ups increases in line with the following potential operational Scenarios:
    - Batch to batch changeover of the same product within a campaign(Lowest risk)
    - Campaign changeovers of the same product.
    - Campaign changeovers of product X to Product Y (Highest risk)

When completing the risk assessment pay particular attention to:

- Tools available to assist area/line clearance e.g.: Torches, Mirrors(To make all areas of the equipment visible)
- Guards are they fixed/removable/clear?
- Reject stations, are these fixed/removable/clear?
- Operator activities.

ii) The procedure that are framed should be sufficient to prevent cross contamination and area/line Clearance failure.

iii) Once the area/line clearance has been in use the risk assessment should be repeated to ensure all risks have been covered. So that areas where cleaning and clearing is problematical is identified and Can be rectified. If not possible these areas should be highlighted in SOP‘s and Check list.

C) Area/Line Clearance Procedures: A line clearance procedure is having three stages i.e. clearing, cleaning, and checking. Clearing:- Remove the previous product related items from the area/line i.e. pre printed ampoules , plugs , left over solution/material , product , labels, printed cartons , batch coding , packed products , documents

Cleaning:-

- Cleaning to be carried out only after clearing of previous products.
- Clean the as per current SOP.
- Clean the equipment as per current SOP and send the rinse water / swap to Q.C for analysis where required i.e. product change over.

Checking:-

- Checking to be carried out only after clearing and cleaning of previous products.
- Area/ line incharge ensure the clearing and cleaning. Then Q.A has to cross check the area / line. The same should be recorded in the BMR.
- Area / line clearance failure should be recorded in deviation format and Investigation to be carried out.

LINE CLEARANCE PROCEDURE IS APPLICABLE FOR THE FOLLOWING STAGES:

1) Dispensing
2) Decartoning
3) Washing and sterilization
4) Manufacturing and filtration
5) Filling
6) Leak test
7) Batch coding
8) Packing

a) During the line clearance process a sign should be posted stating ―Line clearance in progress‖ at the end of the line

b) A Line clearance is done prior to an operation start up or after a controlled stoppage.

c) If the checklist is half done and another operator takes- over they must redo the whole Procedure before signing.

d) Batch documentation can only be signed off after the line clearance has been completed and signed D) Control of rejected Material:

- Rejected item should be kept in separate container with lid.
- Rejected status label (red color) should be described with details.
- Online rejected items should be kept in closed container with status label.

Live line clearance (LLC):

LLC may be used as a Training and competency checking tool for staff. It is a successful training tool for new operators or to periodically assess the effectiveness of area/line clearance practices particularly following a lineclearance failure. Procedure involves

placing of dummy articles and new operators are asked to find the dummies. If they are failed to found it indicates the need for further operator training modification for procedures. While placing the dummies the following should be considered:

- Dummies should be stored in identified lockable boxes and kept in a secure area off line.
- Dummies should not be capable of being confused for the Genuine article
- Dummies used should not be capable of being packed or further processed.
- Placers for dummies should be authorized to perform the LLC technique after receiving appropriate training.
- The number and positions of dummies should be recorded

LLC should not be used in sterile areas or other parts of the process where introduction of the models could compromise integrity or quality Packaging and labeling Controls

- Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale, and use. Packaging also refers to the process of design, evaluation, and production of packages.
- Labeling (en-US) is any written, electronic, or graphic communications on the packaging or on a separate but associated label.

Requirements for Packaging and labeling and control

I. Materials examination and usage criteria:

- Any labeling or packaging materials that do not meet specifications shall be rejected to prevent their use in operations for which they are unsuitable.
- Use of gang-printed labeling for different drug products is prohibited unless the labeling from gang-printed sheets is differentiated by size etc…
- If cut labeling is used, operations shall include one of the following:

a. Dedication of labeling and packaging lines to each different strength of each different drug product.
b. Use of electromechanical equipment to make a 100% correct labeling during or after completion of finishing operations.
c. Printing devices used to imprint labeling upon the drug product shall be monitored

II. Labeling issuance:

a. Strict control shall be exercised over labelling issued for use in drug product labelling Operations.
b. All excess labeling bearing control numbers shall be destroyed.
c. Procedures in sufficient detail shall be employed for the issuance of labeling.

III. Packaging and labeling operations:

a. Identification need not be applied to each individual container.
b. Identification of the drug product with a control number that permits history of Manufacture.
c. Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operation.

IV. Tamper-evident packaging requirements for OTC human drug products:

a. A tamper-evident package may involve an immediate container and closure system to Provide a visual indication of package integrity.
b. In addition to the tamper-evident packaging feature hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.

V. Expiration dating:

a. Expiration dates shall appear on labeling in accordance with the requirements.
b. Homeopathic drug products shall be exempt from the requirements.

Reconciliation of labels: It is a method and means for reconciliation between faulty labels identified during a labeling operation and removed from the operation. It is plays an imp role during label issuance. It is an important to reconcile all the packaging material; especially the over printed packing materials like labels, cartons and wrappers because it leads to misuse and product mix-ups if not accounted. Procedure

a) On the completion of packing of particular batch determine the,

- Quality of labels used
- Quality of labels rejected.
- Labels used for quality control for testing, for control samples.
- Quality used for relabeling and balance labels.

This totally reconcile quantity is compared with the intended quantity. Note the variance and destroy all the balance and rejected labels under proper supervision. B) Boxes, cartons, wrappers At the end of packing operation, determine the number of boxes, cartons, wrappers used. To this add the quality taken by the quality control for checking, for control samples, rejection online due to defects and the balance quantity of the packaging. Calculate and note the variance, the rejected and balance packing material should be destroyed Under proper super vision.

UNIT – V

Quality Control Laboratory: Responsibilities, good laboratory practices, routine controls,instruments, protocols, non-clinical testing, controls on animal house, data generation andstorage, quality control documents, retention samples, records, audits of quality control facilities- Finished products release: quality review, quality audits, and batch release document.

L.O: To understand responsibilities, good laboratory practices, routine controls, instruments,protocols, non-clinical testing, controls on animal house, data generation and storage, qualitycontrol documents, retention samples, records, audits of quality control facilities – Finishedproducts release: quality review, quality audits, and batch release document.

QUALITY CONTROL LABORATORY

RESPONSIBILITIES

Quality control laboratory has very responsibility from the purchase of raw material to the finished product going to the customer in the pharmaceutical company. It involves in each and every part of the production.

SPECIFICATION OF RAW MATERIAL

- The quality of a pharmaceutical formulation is largely governed by the quality of the raw material that go into it.
- Testing of raw material is very important.
- These testing are to be done by quality control.
- The responsibility of the QCL is to make the testing procedure for raw material, testing and to label them.
- This document of raw material should be maintained by QCL.

EXAMINATION OF PACKING MATERIAL

- The packing materials are any materials that are issued to pack a drug for the purpose of storage, distribution and sale.
- The packaging materials like bottles, vials, ampoules, tin, tube, foils are tested by the lab to have a check over the quality control laboratory.

SAMPLING AND TESTING OF INTERMIDIATE, BULK AND FINISHED DRUG PRODUCTS.

- Manufacturing process needs a close monitoring as it may cause variation in the characteristic of the final drug.
- The QCL has the responsibility to sample and test the intermediate product and document the result.
- Compliance with the QCL specification is very important factor in ensuring consistency of quality of a finished drug.
- Quality control lab should give approval to release the product and expiry dates of these products should be noted.

STABILITY TESTING OF FINISHED PRODUCT

- Stability testing done in order to find how long the drug products are expected to remain within the specification under recommended storage form.
- QCL should ascertain the hazards that are that are associated with the drug product such as sub potency, physical instability or the effect of degraded products to the consumer

HANDLING OF PRODUCT COMPLAINCE

- All the product complaint must be watched carefully by the quality control manager.
- The complaint from with complete details of product can be recorded and maintained for atleast one year after the expiry date.

RECORDS OF ANALYSIS

- Lab records provide complete data obtained from the tests that are done on raw materials, packaging materials and finish products.
- These records should maintained properly by QCL.
- These records are necessary to know whether or not a drug product is in compliance with established standards.

MAINTAINENCE OF RECORDS

- Batch records with are documented during production must be checked for complaints and accuracy.
- All records are clear, neat and legible stored for future reference.
- Glass wares breakage should be recorded for the purpose of inventory updating and control improper handling of the glass wares.

LAB HOUSE KEEPING AND SANITATION

- There should be a manual to define good housekeeping practices with covers facilities available safety devices and its places and safe storage chemicals and glass wares and their operating procedure.
- There should be clearly written sanitation programme with includes, weekly, monthly, cleaning schedules for the lab.

LABORATORY RECORDS

A good lab should maintain standard operating procedure

- Standard analytical procedure
- Raw materials
- finished product
- In-house specification
- Product and process information
- Analytical records
- Data calculation books
- Stability testing records

✓ These documents should be completed, updated and properly filled.

✓ All files must be covered under an index and should help to trace any record or paper readily

DESIGN, MAINTANANCE AND CALIBRATION OF EQUIPMENT

- ✓ Equipment used in manufacture of drugs should be appropriate design and should have adequate capacity to function according to the protocol and should be suitably located for operation in quality control test.
- ✓ Equipment used for the generation, measurement or assessment of data should be adequately tested, calibrated and standardized by quality control lab.
- ✓ In quality control lab each and every instrument should have a standard operating procedure and proper validation procedure and these procedures should be made by quality control lab itself.

INSTRUMENTS

- ✓ The instrument used in the generation, measurement or assessment of data and equipment used for facility environment control should be of appropriate design and of adequate function according to protocol.
- ✓ Instrument should be suitably located for operation cleaning and maintenance.
- ✓ The instrument should have a good standard operating procedures and validation procedures to ensure that the instrument in of appropriate design and adequate capacity and will consistently function as intended.

GOOD LABORATORY PRACTICES (GLP)

GLP DEFINITION:

- ✓ GLP is based on four pillars which have to supper the implementation and daily observation of its principle.
  - o THE MANAGEMENT
  - o THE QUALITY ASSURANCE
  - o THE STUDY DIRECTORS
  - o THE NATIONAL AUTHORITY

RESPONSIBLITIES IN GLP

- ✓ 1. The responsibilities of the various partners in the glp system have been defined in the principles in order to distribute and assign the various task in clear cut way.
- ✓ 2. Description and delineations of the respective responsibilities from a very important part of the system of GLP.
- ✓ 3. There are some mutually exclusive tasks where responsibilities have to be un-equivocally fixed in order to create a real quality system.

MANAGEMENT

- ✓ To provide an optimal environment for the GLP is of the test facility and GLP compliant studies condition with in the test facility.
- ✓ To ensure that a sufficient no of qualified personnel, appropriate facilities equipment and material are avails for the timely and proper conduct of the study.
- ✓ Ensure that appropriate qualification training and experience in designated by the management.
- ✓ To ensure that there is QA program with design personnel.
- ✓ To assure that the QA responsibility is being performed in accordance with these principles of GLP.

STUDY DIRECTOR AND PRINCIPLE INVESTIGATOR

- ✓ He has the responsibilities for the overall conduct of the study and for its final report.
- ✓ Study director has the scientific responsibilities for study plan design and approval.
- ✓ S.D should ascertain that management have committee adequate test material and test system and adequate resource are available to perform the study
- ✓ S.D responsibility is to alert the test facility the management about any deficiencies and so insist on their remediation
- ✓ The principle investigator is not allowed to issue and sign amendments to the study plan.

STUDY PERSONNEL

- ✓ The personnel involved in a GLP study should knowledgeable in those parts of the principles of GLP.
- ✓ Their responsibility to comply with the instruction given into which they have to have access.
- ✓ 3. Their responsibilities to document any deviation from these instruction and to communicate such deviation directly to the responsible study director.
- ✓ 4. The study personnel responsible for recording promptly and accurately and in compliance with the principles of GLP.
- ✓ 5. Study personnel should exercise health precaution to minimize risk to themselves and ensure the intensity of the study

SPONSOR

- ✓ 1. All sponsors should be knowledgeable in the requirement of the GLP principles.
- ✓ 2. Their responsibilities to submit full dessier to regulatory authority.
- ✓ 3. To ensure that there would at least be no mix up of test items.
- ✓ 4. The sponsor has to make the decision based on the out come of the studies with the respective test item.

ROUTINE CONTROLS

Quality of any pharmaceutical product in particular in greatly influenced by routine control at quality control laboratory. Improper routine controls may affect the final drug product. For having proper routine controls we should establish, standards, sampling plans test procedures and record maintenance. Normally practiced routine control includes

- The lab and instrument should be cleaned daily.
- The day works should be labelled neatly.
- The persons who are attended should be noted. All the instruments are to be validated and checked and the results rate to be recorded.
- The samples with arrived at lab should be noted in incoming register and they should be taken to test.

- The humidity and temperature of the lab should be recorded daily.
- Log book should be filled correctly and properly for the instruments used in the test.
- The results of the tests are recorded and filled according to report number.
- The control samples are registered and maintained properly these registers are maintained till their expiry date.
- Any fault in instruments or equipments should be immediately notified to the quality control manager
- Any complaints arise from the samples should be properly take care off there samples should be tested with reference to the controls.

ANALYTICAL INSTRUMENTS

All laboratories have analytical instruments

Manuals

- All have elaborate operation procedure &provided with manuals

Calibration

- All machines are calibrated on digital system
- Calibration done respect with standard reference point

REAGENTS FOR TEST

- Laboratory reagents must handled carefully
- Reagents must be with safety warnings
- Reagents should be stored with proper safety precaution

PROTOCOL

PROTOCOL FOR NON-CLINICAL LABORATORY STUDY

Each study shall have an approved written protocol that clearly indicates the objective and all methods for the conduct of study. Protocol should contain the following items:-

- Title and statement of the purpose of the study
- Identification of the test and control articles by names, chemical number or code number
- The name of the sponsor and the name and address of the testing facility at which the study is being conducted
- The number, body weight range, sex, source of supply, strain, sub strain and age of the test system
- The procedure for identification of the system
- A description of the experimental design including the method for the control
- A description or identification of the diet used in the study
- Each dosage level expressed in milligrams per kilograms of body weight or other appropriate unit and frequency of administration
- Type and frequency of test, analysis and measurements to be made
- Records to be maintained
- The date of approval of the protocol by the sponsor and the dated signature of the study director
- Statistical method to be used

All changes in or revision of an approved protocol and the reason therefore shall be documented, signed by the study director, dated and maintained with the protocol

PROTOCOL

CLINICAL TRIALS

Clinical trials should be organized, research studies conducted in the humans to determine the values of a therapeutic agent. Carefully defined group of patients or subjects are selected according to proper experimental design

DESIGN OF THE CLINICAL PROTOCOL

Abstract and Table of contents:-

An abstract is optional but can be very useful especially when a protocol is large or complex.

The introduction :-

The introduction of the protocol varies depending on the phase of drug development and the relative amount of preclinical and clinical experience with the drug

Objectives :-

The objective of a clinical trial is to assess the value of a drug in the treatment or diagnosis of a disease as determined by the drug‘s benefits relative to its risks or undesirable effects

Study designs:-

The components of a good study design are

Type of design :-

A suitable study design should be chosen, considering such factors as the trial setting institution, number of the therapies and severity and prevalence of the disease

Basic Test Group:-

The selection of patients is a major aspect of the design, if the test sample is not representative of the population the results will be unreliable.

Number of subjects or patients :-

There are important statistical and ethical implications to consider in determining sample size

Practical aspects such as limitation of time and availability of patients should be considered.

Method of randomization :-

Randomisation allows the choice of treatment for each patient to be made in an independent manner.

- Duration of study :-

- Over all duration)
- By test agent
- Length of wash out period
- Post treatment period

Drugs and Dosages :-

1) Name of experimental Drugs
   a) Test drugs b) Active control
2) Dosage Forms
   a) Strength of unit dose b) Route of administration
3) Dosage Instruction
   a) Unit dose b) Total daily dose c) Number of capsules or tablets d) Frequency and manner of administration
   e) Time of administration

NON CLINICAL PROTOCOLS

Personnel

- Each individual engaged in the supervision of non clinical laboratory will have education, training and experience.
- Each testing facility shall maintain a current summary of training and experience.
- There shall be sufficient number of personnel for the proper conduct of study.
- Personnel should have necessary personal hygiene and health precaution.

TESTING FACILITY MANAGEMENT

- Study director
- Replace the study director promptly if it becomes necessary.
- There must be a quality assurance unit.
- Assure that personnel, resources facilities equipment, materials and methodologies are available as scheduled
- Assure that personnel clearly understood the function that they have to perform.

QUALITY ASSURANCE UNIT

- A testing facility will have a quality assurance unit which shall be responsible for monitoring each study.
- Quality assurance unit shall maintain copy of a master schedule sheet of all non clinical laboratory studies.
- Maintain copies of all protocols pertaining to all non clinical laboratory studies.
- If any problem found during course immediately inform the study director.
- Reports should be submitted periodically to the management.
- Determine that there is no deviation from the approved protocol or standard operating procedure.
- The record shall maintain the following:
  - Inspection dates
  - Study inspected
  - Phase inspected
  - Name of performing inspection

CONTROL ON ANIMAL HOUSE

LOCATION OF THE ANIMAL HOUSE

- Animal house should be preferably in separate building from routine work place in calm atmosphere un disturbed by others
- The animal should be clean and ventilation.
- It should have veranda encircling the area so that there will be maximum protection from rain.
- Animal house should have maximum number of rooms.
- Plantation in the surroundings of the animal house could help to keep atmosphere cool.
- It should have extra space for office, surgery, washing and sterilizing , kitchen.
- In the simplest form of animal house should have four departments
  - NORMAL ANIMAL
  - EXPERIMENTAL
  - ANIMAL CLEAN STORE FOR FOOD AND FEEDING
  - WASHING, CLEANING AND INCENARATING
- The design of animal house should be such that it possesses built in efficacy meet the requirement.
- Good ventilation should be provided by air conditioning or air circulation by fans and exhaust fans to away the odor.
- Air conditioning mill should present to maintain good humidity and to help successive breeding

MAINTAINANCE OF ANIMALS

- Animals should lie in comfort and psychologically acceptable habitat.
- No over crowding should be permitted because it is against animals general well being.
- Anodized aluminium cages are most suitable as it is light weight and resistant to corrosion.
- The size of the cages should be such that animals can move about freely and there is no over crowding.
- The bedding should be clean in-order to prevent infection as well as the entry of insects.

DIET

- Diet must be sufficient in quantity to cover energy requirements.
- Be appetizing it must stimulate the refluxes that liberate digestive juices, enzymes and is must promote peristalsis.
- Confirm as nearly as positive to racial dietary habit.

- Diet can be obtained in the form of cubes or can be placed in hoppers so that food is available at all times /
- In case of caged hoppers are not available, pellets may be placed in dishes inside the cage.

CLEANLINESS

- Animals will not grower under dirty condition. unless they are kept clean there is a considerable risk of epidemic disease .
- Breeding animals should not be changed frequently because they may loss the weight.

BEDDINGS

- A layer of absorbent material should be spread to a depth of half inches to one inches on the bottom of the cage.
- Fine soft wood, sugar cane pipe can be used as absorbent.
- Pregnant animals must be supplied with nesting materials

CAGES

- Each species of animals requires its own type of cage and the design must ensure is enough room for free moment and space for resting.
- Cages should be spacious enough to allow the animal to do some exercise this is especially important one case of monkeys.
- Breeding cages should be labelled so that breeding animal can be easily identified especially if the breeding program is being carried out.

VENTILATION

- Ideally the animal house should be air conditioned if not, adequate ventilation from window should be ensured.
- Great care must be taken not to expose the cages to draughts.
- Animal kept in badly ventilated room are more liable to respiratory disease.

TEMPARATURE AND HUMIDITY

- Depending on the animals own temp, the animal house temperature must be maintain.
- In-order to keep the stock healthy and able to breed sudden fluctuation in temp must be avoided.
- The humidity of the animal house must be moderate depending on the animals habitat

PREVENTION OF DISEASE

- The animals should be kept in a special quantitative room and kept for observation 10-14 days .
- During this period, any animal sick or dead, the stock should be held in hygiene

STERLIZATION:

Act or process of freezing from all using pathogenic organism

METHOD:

- HEAT
- CHEMICAL
- IRRADIATION

DATA GENERATION AND STORAGE

- Implementation of comprehensive internal quality control programmes and participation in external quality assessment scheme to monitor analytical performance of lab test have been widely accepted as an essential and integral part of food laboratory practice.
- This program involves a great deal of repetitive statistical calculation and graphic presentation of data on quality control material.
- The computer system has unabled our laboratory to check for the existence of some of the errors.
- The role of computers in minimizing transcription errors
- Reducing turn-around time of testing reporting as well as improving the quality lab reports is also mentioned.

COMPUTER PROGRAM FOR QUALITY CONTROL IN THE BLOOD GAS LABORATORY

- In blood gas laboratory quality assurance programs which are routinely included with materials sold for quality control raw data processing center for reduction to statistics meaningful to the laboratory quality control effort.
- This data reduction service usually requires a turnaround time of 2 weeks or more.
- One describe a computer program for the more timely, in-house computation of a laboratory mean standard deviation and coefficient of variation.
- This program useful in calculating values for a new lot number of control during the period receipt of the control and receipt of the first set of statistics from the data processing centre.
- Compared these values to the assayed values in the manufacture insert provides timely for inter laboratory proficiency testing programs.
- A computer model to assess their capability to correctly characterize intra laboratory performance.
- We developed a computer model of inter laboratory survey program to study the ability of proficiency testing programmes to detect intra laboratory population of 400 laboratories and test lab each with uniquely defined intra-lab.

AN ASSESMENT OF THE USE OF FIXED LIMITS TO CHARACTERIZE INTRA LABORATORY PERFORMANCE BY PROFICIENCY TESTING

- PT- programs are expanding the use of fixed limits to evaluate the inter laboratory performance. These limits are an attempt to relate total allowable intra laboratory analytical error and performance in a PT program.
- Fixed limits, a means of countering the effects of overly stringent performance requirement derived from the inter laboratory group mean and standard deviation achieved by today‘s very precise analytical system.
- Our previously described computer model of a PT program is used delineate the quantitative relationship between the magnitude of inter laboratory coefficient of variation and bias that is compatible with fixed intra laboratory limits of ,10,15 and relative error.

FINISHED PRODUCTS RELEASE

INTRODUCTION

Finished product means a product which has been manufactured and packaged with the intention of sale or distribution. Before a finished product released for sale or distribution, it should be examined that it meets all the desired requirements.

Finished product should be tested for all the tests prescribed under Indian standards, for that product. A product should be released for sale or distribution only when it found conforming to the pre – determined specification.

OBJECTIVES

Testing of finished products can never be the sole basis of certifying a batch of finished product mainly because of the limitations of sampling methodology. No lit or batch of any drug should be available for sale unless it complies with the specifications for drug. Compliance can ensured only by testing.

TESTING

a) Samples of each batch of each product and where necessary, of intermediate products, must be drawn according to a documented procedure authorized by Q.C. manager.

b) The analytical methods to be followed should be well documented.

c) Methods of testing of the final product according to I.P or B.P. or alternative methods may be used.

d) Result of the testing should be recorded.

RELEASE

a) Any batch of finished product that meets the appropriate written specifications may be approved for release by a person authorized by the Quality Control Manager.

b) It is advisable to release a batch, only after Quality control manager has taken into account relevant factors such as review of manufacturing records of the batch and the environmental checks carried out in the manufacturing areas.

c) Un explained descriptions in yield or failures to comply with specifications should be thoroughly investigated and documented.

QUALITY AUDIT

Definition:

Periodic, independent, and documented examination and verification of activities, records, processes, and other elements of a quality system to determine their conformity with the requirements of a quality standard such as ISO 9000. Any failure in their proper implementation may be published publicly and may lead to a revocation of quality certification. Also called conformity assessment or quality system audit.

Quality audit is the process of systematic examination of a quality system carried out by an internal or external quality auditor or an audit team. It is an important part of organization's quality management system and is a key element in the ISO quality system standard, ISO 9001.

Quality audits are typically performed at predefined time intervals and ensure that the institution has clearly-defined internal system monitoring procedures linked to effective action. Audits are an essential management tool to be used for verifying objective evidence of processes, to assess how successfully processes have been implemented.

For the benefit of the organization, quality auditing should not only report non-conformances and corrective actions, but also highlight areas of good practice. In this way other departments may share information and amend their working practices as a result, also contributing to continual improvement.

Audits are performed to ascertain the validity and reliability of information; also to provide an assessment of a system's internal control. The goal of an audit is to express an opinion on the person / organization / system (etc.) in question, under evaluation based on work done on a test basis.

As a result, there are now audit professionals who specialize in security audits, information systems audits, and environmental audits. The Definition Auditing is the independent examination of financial information of any entity, whether profit oriented or not, and irrespective of its size or legal form, when such an examination is conducted with a view to expressing an opinion thereon.‖ Due to the increasing number of regulations and need for operational transparency, organizations are adopting risk-based audits that can cover multiple regulations and standards from a single audit event.

- Exercise caution before relying upon un sourced claims.
- If you can provide a reliable source for the claim, please be bold and replace the "Citation needed" template with enough information to locate the source.

Types of auditors

Auditors of financial statements can be classified into two categories:

- External auditor / Statutory auditor is an independent Public accounting firm engaged by the client subject to the audit, to express an opinion on whether the company's financial statements are free of material misstatements, whether due to fraud or error. External auditors may also be engaged to perform other agreed-upon procedures, related or unrelated to financial statements. Most importantly, external auditors, though engaged and paid by the company being audited, are regarded as independent auditors.
- Internal auditors are employed by the organization they audit. They perform various audit procedures, primarily related to procedures over the effectiveness of the company's internal controls over financial reporting. Due to the requirement of Section 404 of the Sarbanes Oxley Act of 2002 for management to also assess the effectiveness of their internal controls over financial reporting (as also required of the external auditor), internal auditors are utilized to make this assessment.
- Though internal auditors are not considered independent of the company they perform audit procedures for, internal auditors of publicly-traded companies are required to report directly to the board of directors, or a sub-committee of the board of directors, and not to management, so to reduce the risk that internal auditors will be pressured to produce favourable assessments.

- Consultant auditors are external personnel contracted by the firm to perform an audit following the firm's auditing standards. This differs from the external auditor, who follows their own auditing standards. The level of independence is therefore somewhere between the internal auditor and the external auditor. The consultant auditor may work independently, or as part of the audit team that includes internal auditors. Consultant auditors are used when the firm lacks sufficient expertise to audit certain areas, or simply for staff augmentation when staff are not available.
- Quality auditors may be consultants or employed by the organization.

Preparing for Quality Audit

Thorough procedures need to be defined, controlled, communicated and used.

Thorough	Procedures should cover all aspects of work where conformity and standards are required to achieved desired quality levels. For example, one might decide to control formal program testing, but leave the preliminary testing of a prototype to the programmer's discretion.
Procedures	Any recurring aspect of work could merit regulation. The style and depth of the description will vary according to needs and preferences, provided it is sufficiently clear to be followed.
Defined	A major tenet is that the defined procedures are good and will lead to the desired levels of quality. Considerable thought, consultation and trialing should be applied in order to define appropriate procedures. Procedures will often also require defined forms or software tools.
Controlled	As with any good quality management, the procedures should be properly controlled in terms of accessibility, version control, update authorities etc.
Communicated	All participants need to know about the defined procedures - that they exist, where to find them, what they cover. Quality reviewers are likely tocheck that team members understand about the procedures.
Used	The defined procedures should be followed. Checks will be made to ensure this is the case. A corrective action procedure will be applied to deal with shortcomings. Typically the corrective action would either be to learn the lesson for next time, or to re-work the item if it is sufficiently important.

There is no reason why these Quality Audit techniques should conflict with the project's Quality Management processes. Where project work is recurring, the aim should be for the Quality Methods and other procedures to be defined once for both purposes.

Problems may occur where the current project has significant differences from earlier ones. Quality standards may have been set in stone as part of a quality certification. In extreme situations this can lead to wholly inappropriate procedures being forced upon the team, The Project Manager may need to re-negotiate quality standards with the organization's Quality Manager.

Characteristics of quality audits:

System audit: A quality system audit is defined as a "systematic and independent examination used to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives." Think of the quality system audit in terms of "an inch deep but a mile wide."

Process audit: The process audit is "an inch wide but a mile deep." It revolves around verification of the manner in which: 1) people; 2) material; 3) machines, etc., mesh together to produce a product. A process audit compares and contrasts the manner in which the end product is produced to the written procedures, work instructions, workman-ship standards, etc., used to guide the manufacturing process responsible for building the product in the first place.

Process audits are appraisal and analytical in nature. The process audit is also concerned with the validity and overall reliability of the process itself.

Product audit: The word "audit" in product audit is somewhat of a misnomer. Actually, a product "audit" is a detailed inspection of a finished product performed prior to delivering the product to the customer. It is a test of both attribute and variable data i.e., cosmetic appearance, dimension properties, electrical continuity etc.

Compliance audit: During a compliance audit, the auditor examines the auditee‘s written procedures, work instructions, contractual obligations, etc., and attempts to match them to the actions taken by the auditee to produce the product. In essence, it‘s a "say what you do—do what you say" type of audit.

Final Quality Audit (FQA):

FQA Process, in manufacturing world, is the last process flow before shipping a product. This process is established to ensure the following:

- the unit has gone through all the manufacturing or test process
- the unit has passed through all the test process
- the unit is in good quality

QUALITY AUDITS OF MANUFACTURING PROCESS AND FACILITIES:

MANUFACTURING PROCESS:

Manufacturing process audit is one of the many quality tools to assess the effectiveness of manufacturing process and quality performance. They are commonly used in the effort to diagnose, maintain and improve quality management system. It is made compulsory for the organization to maintain their quality management system based on ISO9001 standard to conduct an internal audit.

Manufacturing process audits should ensure that procedures are properly followed, problems are quickly corrected, there is consistency in the process, and there is continuous improvement and corrective action as needed.

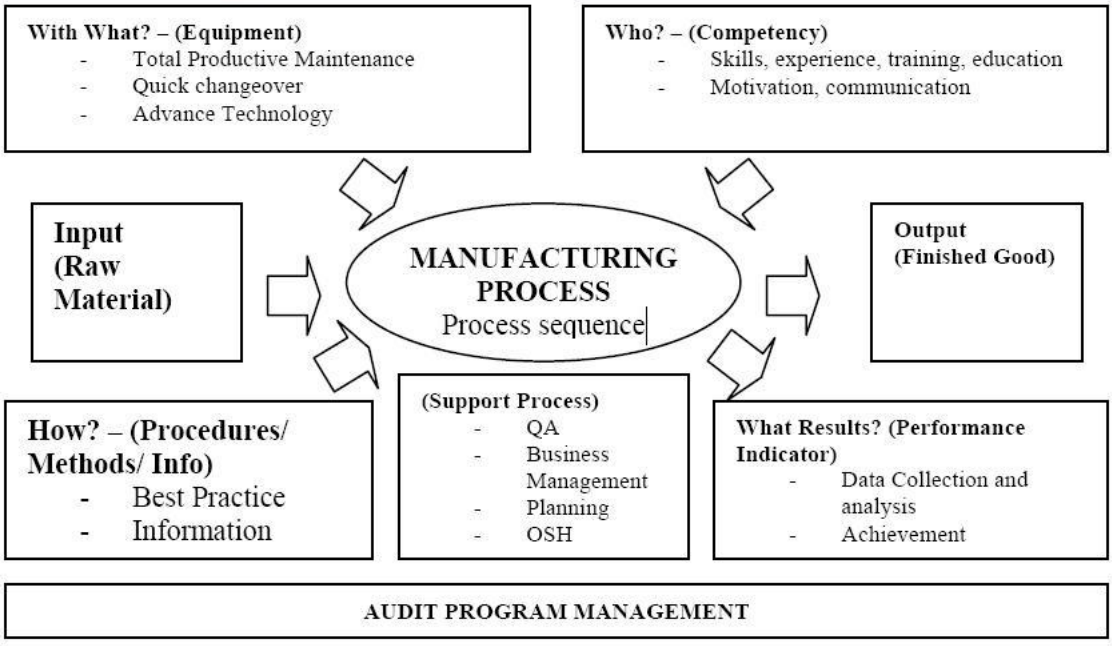
DEFINITION AND PURPOSE OF MANUFACTURING AUDIT

It is also important to understand the definition of audit before any audit is initiated to avoid confusion on how the audit should be conducted (or audit method) and the process of auditor selection.

DEFINITION: Manufacturing process is defined as a process of making and fabricating by converting the raw material (input) to finished goods (output) OR manufacturing process audit can be defined as a process to evaluate the process and making and fabricating effectiveness and efficiency

PURPOSE: Purpose of the audit can be divided into compliance audit and management audit (Arter, 1994). Compliance audit look for conformance to the audit criteria, while management audit look for conformance to the audit criteria and the effectiveness of the process and opportunities for improvement in achieving organization goals. The purpose of manufacturing process audit is to improve quality performance, it is recommended to be conducted either by independently (ISO, 2002), internally (ISO, 2002) or self-assessment (Karapetrovic and Willborn, 2002) since the goal is to improve quality performance. We cannot limit on how to conduct the audit for manufacturing performance improvement since independent, internal or self-audit have the advantages. The areas covered in manufacturing audit included manufacturing strategy, new product introduction, process optimization, flexible manufacturing, production system, performance measurement system, and technology audit. All of these areas interact with manufacturing process.
MANUFACTURING AUDIT FRAMEWORK: Typical manufacturing audit problems or failures are due to lack of audit preparation, audit criteria elements or checklist driven, auditor skills and knowledge, commitment from the management, and bureaucratic reporting (Askey, Dale, Karapetrovic, Barthelemy). Systematic approach to the auditing is the first element for successful manufacturing process audit. The audit activities framework based on ISO19011 (2002) and VDA6.3 audit process is useful to provide guideline for the systematic approached to auditing. The systematic audit program includes initiating the audit, preparing for on-site audit, conducting on site audit, report preparation and follow-up activities. The follow-up activities in this context are the improvements activities result from the audit finding.

The second element for manufacturing process audit, the audit shall cover more than the manufacturing process, which shall include all supporting process in order the manufacturing to be effective.



The suggested conceptual framework divided the manufacturing process into seven elements, which are the effective supply (input), infrastructure (with what), personnel (who), operational control (how), support process (management system) and performance measure indicator for the output and related process. All this process elements can be benchmark and opportunities of improvement or weaknesses (audit findings) can be identified.

Instructions for audit of manufacturing process:

1) Select a process to be audited. Prioritize the processes that can be audited in terms of importance and risk to the overall operation. Begin auditing the highest-risk areas first

2) Select a team to conduct the audit. The audit team should be familiar with the process being audited. They should also be familiar with audit techniques such as sampling and analyzing results. They must have the necessary expertise to identify problems and determine the corrective actions needed.

3) Decide how often the process should be observed (the frequency of the audit). If there are significant problems or noncompliance, the process should be observed more often until the situation is under control.

4) Announce the audit in advance so there are no surprises. The objective is to improve the process, which will require the cooperation of everyone involved.

5) Set up an audit schedule for the entire shift and follow the established audit schedule. The number of observations will be your sample of the work for that shift. The audit schedule should be determined in advance and should be as random as possible. Once established, the audit schedule should be followed to provide results based on a random sample.

6) Document any problems discovered and inform all those affected. The idea is not to assign blame but to find a solution. The problems discovered become the basis for corrective actions and follow-up. Everyone affected by the problem should be informed so they are aware and can provide input to the resolution. Also, the process being audited will likely affect other processes in the over-all operation.

7) Determine and perform corrective actions. Let employees make suggestions for corrective actions and select any that are appropriate, but management should make the final decision as to which corrective actions to implement.

8) Monitor corrective-action results. Perform follow-up monitoring to determine if the corrective actions have actually eliminated the problem or if further action is required. Also verify that no new problems have developed or entered into the process.

FACILITIES:

As an internal auditor, we should make sure to pay attention to such considerations as the actual facility itself. Take a look at the grounds and make sure that everything is being maintained properly. Ensuring safety is a keyresponsibility of an internal audit and this

falls under the realm of facility control. Environmental controls, such as lighting and clean air, need to be inspected to assure proper functionality. Facility maintenance and housekeeping also includes any pest control programs. These need special consideration for industries that produce food or medicine. Check list for quality audit on facilities: The internal auditor should check the following facilities in manufacturing area for effective process and product, those are:

1. Is there adequate space in the building for the orderly placement of equipment, materials and product?
2. Is the plant layout conductive to smooth product flow? (e.g.,uni-directional flow, avoiding back and forth movements).
3. Are operations performed within separate or defined areas of adequate size?
4. Are there dedicated and self-contained facilities (building and equipment)for the manufacturer, processing and packaging of penicillins? 5. Are there adequate sanitary facilities and designated eating, drinking and smoking areas separate from manufacturing areas?
6. Do the eating and smoking areas have drinking water?
7. Do change rooms and lavatories:

I. Have running water?
II. Have soap or detergent?
III. Have hard dryers or single-use towels?
IV. Have ―wash hands‖ signs?
V. Appear clean and sanitary?

8. Are change rooms designed and used so as to minimize contamination of protective garments?
9. Are the tops of the employee lockers clean? (Check by touching with finger)
10. Is there a written sanitation procedures (sop) containing assignments of responsibility, schedules, methods, equipment and materials to be used to properly clean the building and facilities?
11. Are records available for sanitation and housekeeping?
12. Is there a formal maintenance schedule for manufacturing equipment and list kept visible near each piece of equipment?
13. Are waste containers with lids located in appropriate areas?
14. Is there an adequate disposal collection system?
15. Are drains to sewers designed with an air or mechanical break to prevent back siphon age?

By using these check lists, the internal auditor should maintain a document which is checked, dated and signed by him, super checked by second person.

BATCH RELEASE DOCUMENT

Finished Product Verification, Storage, and Handling

I. Do written procedures indicate how and who verifies that correct containers and packages are used for finished product during the finishing operation?
II. In addition, do written procedures require that representative sample of units be visually examined upon completion of packaging to verify correct labelling?
III. Are expiration dates stamped or imprinted on labels?
IV. Are expiration dates related to any storage conditions stated on the label?
V. Are all finished products held in quarantine until QC has completed its testing and releases product on a batch to batch basis for sale?
VI. Is finished product stored under appropriate conditions of temperature, humidity, light, etc.

Finished Product Inspection, Sampling, Testing, and Release for Distribution

- Has the formulation for each product been tested for stability based on a written protocol? (Containers must duplicate those used in final product packaging.)
- Are written sampling and testing procedures and acceptance criteria available for each product to ensure conformance to finished product specifications?
- Is a quantity of samples equal to at least twice the quantity needed for finished product release testing maintained as a reserve sample?
- Are sterility and pyrogen testing performed as required?
- Are specific tests for foreign particles or abrasives included for any ophthalmic ointments?
- Does controlled release or sustained release products include tests to determine conformance to release time specification?

Distribution Controls

- Does a written procedure manage stocks to ensure that oldest approved product is sold first?
- Are deviations to the policy above documented?
- Does a written procedure identify the steps required if a product recall is necessary?
- Is the recall policy current and adequate?

RELEASE

- Any batch of finished product that meets the appropriate written specifications may be approved for release by a person authorized by the Quality Control Manager.
- b) It is advisable to release a batch, only after Quality control manager has taken into account relevant factors such as review of manufacturing records of the batch and the environmental checks carried out in the manufacturing areas.
- c) Un-explained descriptions in yield or failures to comply with specifications should be thoroughly investigated and documented.

UNIT – VI

Distribution and Distribution records: Handling of returned goods, recovered materials andreprocessing. Complaints and recalls, evaluation of complaints, recall procedures, related recordsand documents.

L.O: To understand handling of returned goods, recovered materials and reprocessing.Complaints and recalls, evaluation of complaints, recall procedures, related records anddocuments.

DISTRIBUTION AND DISTRIBUTION RECORDS:

Introduction –

- Any production, control or distribution record that is required to be maintained in compliance with this part.
- It is specifically associated with a batch of drug product which shall be retained for at least 1 year after the expiration date of the batch or for the certain OTC drug products – 3 years after the distribution of the batch.
- Records shall be maintained for all components, drug product, containers and closures.
- All records required under this part shall be readily available for authorized inspection during the retention period.
- Records required under this part may be retained either as original records or as true copies such as photocopies and microfilms etc.
- Written records required under this part shall be maintained so that data can be used for evaluating the quality standards of the drug products.
- Written procedures shall be established and followed for such evaluation and shall include the provisions for:-
    - a). A review of each batch whether approved or rejected.
    - b). A review of complaints, recalls or returned goods.

Procedures shall be established to ensure that the responsible officials of the firm, if they are not personally involved, immediately they should be aware of this.

Various types of records:

- a). Equipment cleaning and use log records.
- b). Component, drug product container, closure and labeling records.
- c). Master production and control records.
- d). Batch production and control records.
- e). Laboratory records.
- f). Distribution records.

A). Equipment cleaning and use log records:

- A written record of major equipment cleaning and maintenance is maintained.
- Use of this record shall be maintained in the individual equipment logs that show the –
    - i. Department
    - ii. Item of equipment
    - iii. Date
    - iv. Time
    - v. Product and batch processed.

If the equipment is dedicated to the manufacture of one product, then individual equipments log is not required.

- The persons performing and checking the cleaning and maintenance shall enter the date and time in the log indicating that the work was performed.
- Entry in the log shall be in Chronological order.
- This section requires written designation of the major equipment. Small items such as scoop, stirrer and spatula are not included, but they should also be cleaned properly.
- The data referring to the cleaning should also be incorporated into the appropriate batch record so that they are readily available for the review prior to release.

B). Component, Drug product container, Closure and labeling records:

These records shall include the following:

- The identity of each component, drug product container, closure, labeling the name of the supplier, the supplier‘s lot number. The receiving code and date of receipt. The name and location of prime manufacture.
- The results of any test or examination performed and the conclusions derived.
- An inventory record of each component, drug product container and closure.
- Documentation of examination and review of labels.
- The deposition of rejected compounds, drug product container, closure and labeling.

C). Master production and control records: To assure uniformity from batch to batch. Each batch shall be prepared, signed (full-hand written signature) by one person and independently checked, dated and signed by a second person.

This must include;

- The name and strength of the product and a description of dosage form.
- The name and weight or measure of each active ingredient of dosage form.
- A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic.
- A statement concerning any calculated excess of each component in order to prevent errors.
- A statement of theoretical yield.

- A description of drug product container, closures and packaging materials.

D). Batch production and control records:

- This should be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch.
- It provides a detailed description of all processing operation and controls when they are performed by whom and where.
- Steps in the manufacturing processing, packaging each batch was documented which includes;
    - Dates
    - Identity of individual major equipment
    - Specific identification of each batch of component
    - Weights and measures of components used in the course of processing.
    - In-process and laboratory control results.
    - Inspection of packaging and labeling area before and after use.
    - Identification of persons performing and directly supervising each step in operation.

E). Distribution records:

It shall contain.

- Name and strength of the product
- Description of dosage form
- Name and address of the consignee
- Date and quantity shipped
- Lot and control number of the drug

- The recording dates which a specific lot of product commenced and ceased distribution may be used.
- It includes a wide range of documentation such as invoices, bills and lading, customer receipts and internal warehouse storage and inventory records.
- Above items are maintained for a minimum of 3 years after distribution process has been completed or 1 year past the expiration date.
- Compliance policy guide suggests the regulatory action should not be taken if a company is using up existing stock of labels in a reasonable time and that the product or material is otherwise in compliance with the new monograph.

HANDLING OF RETURNED GOODS

Objective:-

- Goods may be returned to the company or its authorized nominee.
- Such returned goods may either be destroyed or reconditioned and made it for use.
- If the returned goods are made fit for use then the associated risks must be well understood and for these clear guidelines should be followed.

Authority and Responsibility:- Head of the Q.C or the authorized nominee shall be primarily responsible to formulate the detailed procedure for dealing with the handling of returned goods and implement the said procedures.

Classification of Returned goods:- Returned goods, received by the company at any of its warehouse, may be classified in relation to the primary cause necessitating their return as;

- Date expired goods
- Damaged / broken containers.
- Leaky and broken seals of closure of the container.
- Mutilated / smudged labels rendering the products unidentifiable as to their name / batch number etc.
- Soiled labels rendering the products aesthetically unpresentable, but otherwise clearly identifiable.
- Product recalled voluntarily for any reasons by the company.
- Product recalled as per directives from drug control authorities.

Handling Procedures:- All the returned goods shall be properly,

- Documented
- Inspected
- Accounted
- Labelled (to identify) the primary cause for their return.
- Segregated / quarantined till further and final action.

It must be ensured that, irrespective of the cause for return and subsequent actions taken by the company:

- i. Statutory requirements are adhered to
- ii. All operations / actions are well documented.

A). Date expired goods –

- Destruction shall be authorized by the designated person.
- All destruction shall be carried out under the supervision of a responsible person.
- The content shall be so destroyed that the product is no longer usable in any manner whatsoever.
- All primary, as well as secondary containers with printed texts shall be destroyed in such a manner as to render them unusable.
- All the operations shall be documented and stocks received and destroyed reconciled.
- Safety and healthy of employees involved and the environment must be considered.

B). Damaged / broken primary containers –

- Such goods shall be examined by a person so designated for this job who shall ascertain as to whether the contents within are fit for recovery / reuse.
- If, in the opinion of the designated person, the damage to the primary container is likely to have rendered the contents unusable / unsafe, the same shall be destroyed.

C). Leaky / Broken seals of primary containers –

It is almost certain that the contents have by now been exposed to unknown environment and almost without exception such returned goods shall be considered unsafe for reuse. Such returned goods shall therefore be destroyed.

D).Mutilated labelling:

Product unidentifiable – Since the product is no longer identifiable it shall not be considered fit for rework / reuse and thus shall be destroyed.

E). Soiled labeling: Product identifiable –

- Designated responsible person shall examine such returned goods.
- He shall also decide the method of re-dressing the product, and the balance shelf-life.
- Documentation covering the re-dressing operation shall be maintained.
- Such re-dressed stocks shall be separately identifiable throughout their shelf-life.
- If the returned goods, in the opinion of the designated person, are not considered fit for re-dressing, the same shall be destroyed.

RECOVERED MATERIALS AND REPROCESSING

Objective: In any manufacturing process material or residues of drug products may be recovered. These are recovered by an appropriate and authorized method which has been validated to demonstrate suitability for such reprocessing, so that resultant product meets its specifications without any alteration in product quality.

Scope:

- Ideally a fully validated manufacturing process should not have any materials that need to be recovered.
- However even in the most robust process occasions arise when quantities of materials may have to be recovered.
- It is certainly not a good practice to recover material from filled ampoules, whereas recovery of filled hard gelatin capsules may be appropriate.
- Recovery and use of residues have to be addressed as product and specific for each procedure validated.

General Guidelines for Handling of Recovered materials:-

- Residues and Re-worked or Recovered material which might adversely affect product quality, efficacy or safety must not be used in subsequent batches.
- The deciding factor for determining whether or not a residue of a product can be used in subsequent batches is the stability of the final product containing known amounts of residues.
- Stability information should be collected on formulations incorporating varying amounts of residues as well as residues of varying ages.
- The stability pattern of lots containing residues should not be significantly different from that of normal production lots which do not contain any residues.
- Where the stability is significantly different, the period up to which the product will meet the end-of-life specifications must be ascertained and the life period of such batches should be suitably amended.
- Residues arising at the inspection stage from product units which show defects such as foreign matter, metal particles etc. should not be reused.
- Batches containing residues should not be released by quality control until the batches from which the residues originated have been tested and certified as suitable for use.

Specific Requirements:-

- The method of handling residues including their addition to fresh batches should be well documented and approved by the Q.C manager.
- Batches containing residues may have to be subjected to additional testing before release.
- The batch manufacturing records must clearly indicate that the batch contains residues and include details of the origin of the residues and the qualities used.
- If the reduction of the normal life period is recommended by the quality control, this information must be recorded in the batch packaging order and labelling order or labelling instruction.

General Guidelines for Batch Re-Processing:-

- A minimum value of material below which re-processing will not be considered, other than under exceptional circumstances, should be set.
- The reasons /causes rendering the material(s) out of specification should be thoroughly investigated and appropriate action taken to minimize the recurrence.
- A register giving the quantities for re-processing and reasons there of, shall be maintained and reviewed regularly.
- Re-processing and or Re-labelling a material / product because of its being ―out of specification‖ should be a rare occurrence.
- Methods of re-processing must be specifically authorized and fully documented, once potential risks, if any, have been evaluated and found negligible.
- The need for additional testing of any finished product which has been re-processed (or to which residue have been added) must be considered before the operation is carried out, in the light of the investigations into the cause leading to re-processing,
- Sometimes the original release specifications of the product may not be applicable to the re-processed product.
- The quality of re-processed batches should be constantly reviewed.

COMPLAINTS AND RECALLS

COMPLAINTS

DEFINITION:- Complaint means any allegation in writing made by a complainant that

- As a result of any unfair trade practice adopted by any trader, the complainant suffered loss or damage.
- The goods mentioned in the complaint suffer one or more defects.
- Deficiency in services.
- Trader has charged extra price on the goods than the price mentioned.

CLASSIFICATION OF COMPLAINTS:-

There are two types. They are as follows –

1). Quality Complaints –

- Usually originate at consumer level related to physical, chemical, biological properties.
- Conditions of labelling or packaging of product.
- ADR may be allergic or any unfavoured reaction of fatal or near fatal reaction.

2). Medically related complaints –

- Lack of efficiency
- Lack of clinical response
- The most potent method which the performance of product in the channels of market is monitored and is by means of a properly organized mechanism for receiving, sorting, investigating and evaluating oral & written complaints. This is particularly true during the first month after the introduction of a new drug product.
- The handling of all written / oral complaints must be documented as a procedure.

STEPS IN EVALUATION OF COMPLAINTS

1). Receiving –

- Received from several sections like doctors, medically registered practitioners.
- Complaints are recorded.
- Critically important complaints will be skipped if the MSP (marketing sales person) doesn't have a medical background. So the complaints should be screened and investigated by professional field personnel.
- It is the responsibility of quality control manufacturer too.

2). Sorting of Complaint –

- Once the complaint is recorded it should be screened thoroughly to find out which one needs investigation.
- They are sorted according to batch wise or product wise deficiency complaints.
- The history of the past is also to be reviewed.

3). Handling of complaints –

- The complaint should be forwarded to the Q.C department.
- Report of ADR should be handled by a committee of experts. The in-charge of Q.C department should be the member of the committee.
- The medical advisor of the company is the competent person to handle ADR complaints.

4). Investigation of Complaints –

- After receiving the complaint, quality control should review all the incoming information.
- If the sample has been received along with the complaint, it should be examined and tested.
- The sample should be properly examined to find out the condition of the pack, visible appearance of the contents, evidence of deterioration, the quantity returned and any sign of misuse.
- The reserved sample of batch should be examined for visible sign of decomposition.

5). Evaluation –

- All the complaints oral and written should promptly be brought to the attention of the Q.C manager.
- A complaint form shall be designed and used for all complaints. The form should provide the following information.
    - Name and strength of the product
    - The batch number
    - The name and address of the complaint
    - The nature of the complaint
    - The results of investigation of the complaint
    - The recommended reply to the complainant
    - Action to be taken as a following measure.
- The complaint sample and the complaint form and the relevant details filled should be sent to the Q.C manager for investigation.
- Where the complaint samples are not available and only oral or written complaints have been sent, this information should be passed onto the Q.C manager.
- On receipt of the complaint sample, it should be closely examined for the condition of the pack, visible appearance of the content, evidence of deterioration if any etc. the quantity returned and any signs of misuse should be noted / recorded.
- The reserve samples of the batch shall also be examined at least for visible signs of decomposition (where applicable).

- The complaint sample shall then be subjected to whatever tests are relevant to the nature of the complaint, and where the quantity is adequate; a complete analysis shall be performed. Where the complaint is of toxic or adverse reaction, the relevant biological tests shall be carried out.
- If the complaint appears to be substantiated, the relevant reserve sample shall be tested to ascertain whether the complaint is an isolated one or extends to the whole batch.
- If the quality of the batch appears to have been affected it is advisable to test reserve samples of batches adjacent to the one in question. This will help to reveal the extent of the quality defect.
- Where input materials from the same lot or batch have been used in batches of the product other than the one in question, it is recommended that all these batches be also tested.
- The test results shall be recorded and evaluated by the Q.C manager to enable him to recommend the action to be taken.
- The reply to the complainant may be sent either by the Q.C manager or the Marketing manager on the basis of the findings of the investigation.
- Where the investigations reveal specific problems requiring attention in the factory, this information must be conveyed to the persons concerned.
- Recall should be initiated if there is a reason to believe that the batch in question fails to meet any of its specification.

RECALL PROCEDURES

RECALL:- It is the most expeditious and effective method of removing or correcting defective products that have been distributed commercially, particularly when those products present a danger to health.

OBJECTIVE:- To define a system for:

1). Speedy and efficient removal of unsatisfactory material from the market.

2). Assigning the responsibility for implementation once the decision of recall has been made.

CLASSIFICATION:- Recall classification means the numerical designation i.e. I , II , III assigned by the FDA to a particular product recall to indicate the "relative degree of health hazard" presented by the product being recalled.

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

Class II : It is a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

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

RECALL APPROVING AUTHORITY:-

- Managing director
- President
- Proprietor
- Head of Company

Administration:-

1).There must be a written procedure which must define:

2). Who is responsible for deciding to initiate a recall and the means by which the product, including samples, can be traced and removed from the market.

NEED FOR RECALL :- The need for a product recall must be considered as a matter of urgency and implemented without delay if:

- There is a evidence that the use and continued presence of the batch or batches of product(s) on the market present a risk to the health of the user.
- A local regulatory authority directs a recall.

RECALL STRATEGY:-

The following factors are taken into account by recall strategy:

- Results of health hazard evaluation.
- Base in identifying the product.
- Degree to which the products deficiency is obvious to the consumer.
- Degree to which the product remains unused in market place.

ELEMENT OF A RECALL STRATEGY:

A recall strategy will address the following elements regarding the conduct of the recall.

a). Depth of recall: Depending on the product degree of hazard and extent of distribution, the recall strategy will specify the level in distribution chain to which the recall is to extend as follows.

- Consumer (or) User level
- Retail level
- Wholesale level

b). Public Warning:

- Purpose of public warning is to alert the public that a product being presents a serious hazard to health.
- Reserved for urgent situations.
- General public warning: Through general news media
- Public warning through specialized news media
- e.g. Professional trade press (or) to specific segments or population such as physicians, hospitals, etc. c). Effectiveness checks: To verify that all the consignees at the recall depths specified by the strategy have received notification about the recall and have taken appropriate action.

LEVELS:
Level A: 100% of the total number of consignees to be contacted.
Level B: In this level the % of total number of consignees to be contacted is determined on a case by case basis, but is greater than 10% and not less than 100%.
Level C: 10% of the total number of consignees to be contacted.
Level D: 2% of the total number of consignees to be contacted.
Level E: No effectiveness checks.
RECALL PROCEDURE:

- The designated member of the recall Co-ordination committee shall be primarily responsible to take actions as may be necessary to ensure speedy, effective and efficient recall.
- Further distribution and or sale, of the product(s) batch (es) shall be stopped immediately. Speedy and clear directives to this effect shall be given to all key points in the distribution chain.
- Recall communication shall also seek, and obtain, information on stocks of products which are being recalled and conformation that further distribution and / or sale has been stopped and such stocks are quarantined.
- In case the product defect is likely to be so dangerous as to be life threatening, public announcements shall be made to reach retail outlets, hospitals, medical practitioners and even individual users.
- On receiving the Recall communication from the manufacturer, it shall be the responsibility of all key elements, including the end user to ensure immediate stoppage of distribution/use/sale of the product(s) being recalled.

The Recall Co-ordination Committee shall meet as frequently as necessary to asses and review the status.

- The designated member of the Recall Committee shall liaise with Drug Regulatory Agencies.
- In the event of the recall being affected by virtue of a directive from the Drug Regulatory Agency / Authority and / or a life threatening situation, an approval for appropriate disposal / destruction on stocks recalled shall be sought and obtained from the Drug Regulatory Agency / Authority.
- The Recall Co-ordination Committee shall decide the most effective and safe method for disposing / destroying the recalled stocks, including packaging materials, so as to render them unusable in any manner whatsoever.
- The Recall Committee shall authorize the disposal / destruction of the recalled stocks.
- The disposal / destruction shall be carried out
    - i. At site(s) approved by the Recall Committee.
    - ii.Under supervision of person(s) so designated by the Recall Committee.
- Appropriate documentation giving details of product(s) name (including brand name if any) BATCH No.(including Date of manufacture and Expiry Date on the product), Quantity destroyed, and signed by the persons under supervision the operation was done, shall be maintained.
- Recall Co-ordination Committee shall finally review the complete recall operation, including all documentation, and close the recall as “RECALL COMPLETED”.