Chapter - 17

6.3 QUALITY ASSURANCE

6.3.1 INTRODUCTION

Quality assurance plays a central role in determining the safety and efficacy of medicines. The assurance of product quality is dependent on proper sampling and adequate testing of various components and the finished dosage form. The responsibility for maintaining the quality of the product rests with the manufacturing department. The irresponsibility of manufacturing personnel may result in imperfect composition, such as ingredient missing, subpotent or superpotent addition of ingredients or mixup of ingredients, mistakes in package or filling. Such as product contamination, mislabelling or deficient package and lack of conformance to product registration. The quality assurance personnel must establish check points for inprocess control and final product control. Highly specific and sensitive analytical techniques hold the key to the design, development, standardisation and quality control of medicinal products.

6.3.2 Sources Of Quality Variation

The increasing complexity of modern pharmaceutical manufacture arising from a variety of unique drugs and dosage forms,complex ethical legal and economic responsibilities that are placed in manufacture are the main sources for quality variation.

The personnel should be aware of all these factors involved in the development, manufacture, control and marketing of quality products. The sources of quality variation may be raw material, in-process, packaging material, labeling and finished product variables.

6.3.3 Control Of Quality Variation

(a) **Raw Materials Controls :** The raw materials used in the manufacture should meet the specifications laid.The received raw material are sampled, tested and stored in a reasonable way. The rejected materials should be disposed and the samples of tested components are retained and the records are to be maintained. Each raw material is sampled according to the standard. Sampling procedures should be sent to the quality control laboratory for testing according to the written procedures. If the raw materials are acceptable, it is moved to the release storage area after properly stickering to indicate the item number, name of material, lot number, date of release, re-assay date and signature of quality assurance inspector.

The personnel should keep the preservation samples of raw materials for further testing. To verify the suppliers conformance the specifications, supporting assurance is done by means of on-site periodic inspections. This procedure assures that cross-contamination does not take place because of improperly cleaned equipment or poor housekeeping practices. Raw materials are usually classified into active or therapeutic and inactive or inert compounds.

(i) **Active or Therapeutic Materials :**

Antibiotics : Antibiotics can be tested chemically, microbiologically, biologically or by all three methods. The sample must be taken in a relatively dry atmosphere, free from dust and free of both chemical and microbial airborne contamination. The assay for potency of antibiotic raw materials must be done with careful attention. Since, the potency value in terms of micrograms per milligram obtained for sample is used in calculating the number of grams or kilograms required for manufacture.

Other Active Materials : The raw materials should meet the requirement for purity of about 97%. The specifications normally include solubility, identification, melting range, loss on drying, residue on ignition, special metal testing and specific impurities that are pertinent to the method of synthesis of each raw material. The methods of assay are usually chemical in nature. They cannot be adequately evaluated by instrumental methods. Specific tests for raw materials include critical tests such as particle size, crystal shape and crystal versus amorphous forms.

(ii) **Inactive Or Inert Materials :** Inactive or inert materials form the major portion of the final dosage form. In addition to chemical purity, their physical characteristics such as color, odour and foreign matter are important. The other specifications of inactive or inert materials are particle size, heavy metal content, arsenic, selenium, water, content, microbial limit, foreign matter, residue on ignition and P^H. The flavours or volatile oils used in flavoured dosage forms are to be tested for refractive index, specific gravity, solubility and alcohol content.

(b) **In-Process Items Control :** The In-process quality assurance program is an important function to ensure the uniform purity and quality of finished dosage forms within a batch and between batches. The critical steps in the manufacturing process are

(i) **Quality Assurance Before Start-up :**

Environmental and Microbiologic Control and Sanitation : To assure the high standards of quality and purity of finished dosage forms an effective sanitation program is required at all facilities where the products are manufactured. The plant should be controlled from insects and rodents. Personal cleanliness and proper hair covering and clothing are required. Floors, walls and ceilings should be resistant to external forces and are capable of being easily cleaned. Adequate ventilation, proper temperature and proper humidity are other important factors.

Manufacturing Working Formula Procedures : The formula for working procedure should be prepared for each batch size that is to be produced. The quality assurance personnel must review and check the working formula procedures for each production batch before, during and after production. The procedure should include the calculation of both active and inactive materials for a batch, starting and finishing times of each operation, Equipment to be used and specifications of its set-up and proper labelling of released components and equipment indicating product name, strength, lot number and item number.

Raw Materials : The raw materials released for manufacturing are to be checked by quality assurance personnel for their specifications and are released for manufacture.

Manufacturing Equipment : The quality assurance personnel must ensure that the equipment is designed, located and maintained so that it facilitates thorough cleaning and is suitable for intended use and the contamination during manufacture is minimum. Weighing and measuring equipment such as balances and thermometers should be calibrated and checked. at suitable intervals by appropriate methods.

(ii) Quality Assurance At Start-up :

Raw Material Processing : The released and properly labelled raw materials are allowed in the in-processing area. Quality assurance personnel should verify and document the proper equipment, addition of ingredients, mixing time, drying time, filtering time and mesh size of sieves used in screening. Samples are taken at certain points and are assayed for potency to ensure batch uniformity and purity.

Compounding : Current Good Manufacturing practices are to be followed during compounding to assure the quality. The inprocess controls measures the characteristics including physical appearance, colour, odour, thickness, diameter, friability, hardness, weight variation, disintegration time, volume check, viscosity and P^H to ensure control of problems during manufacturing.

Packaging Materials Control : The packaging materials used should not interact physically or chemically with the finished product to alter its strength, quality and purity beyond specified requirements. The following features are to be considered in developing container specifications.

1. Properties of container tightness.
2. Moisture and vapour tightness regardless of container construction.
3. Toxicity and chemical/physical characteristics of materials needed in container construction.
4. Physical or chemical changes of container upon prolonged contact with product.
5. Compatibility between container and product.

Finished Product Control :

- **Specifications :** The final testing of finished product is done in quality control laboratories. The tests are designed to conform the standards prior to release of the product for packaging and then distribution. The design of test parameters, procedures and specifications is made during product development. The result may be subjected to statistical analysis to determine the precision and accuracy of each procedure.
- **Bulk Product Testing :** The lot of each product should be tested to ensure identity, quality, potency and purity. Tests required by the official compendia on the ingredients and the dosage form applies to all manufacturers of a specific compendial product.

(iii) Quality Assurance During Packaging Operation : If the product complies with the analysis by quality control department it is released to the packaging department. Quality assurance personnel should periodically inspect the packaging lines and should check filled and labelled containers for compliance with specifications. The samples taken for analysis should be twice in number and must be preserved for atleast one year after the expiry date.

Auditing : The manufacturing process should be documented throughout all stages of operation for previous use. The records should include.

1. Individual components, raw materials, and packaging materials. Master formula and procedure.
2. Batch production.
3. Packaging and labelling operation.
4. Laboratory in-process and finished control testing.
5. Proper signing and dating by atleast two individuals independently for each operation in the proper spaces.
6. Reconciliation of materials supplied with amounts of tablets produced, taking into account allowable loss limits.

6.3.4 Validation Methods

Validation is a documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Importance Of Validation :

1. The quality, safety and effectiveness of a process can be designed and built into the product.
2. The quality of the finished product cannot be inspected or tested.

3. Each step of the manufacturing process can be controlled and the probability of maximising the quality and design specifications of the finished product can be met.

Methods Of Validation : There are mainly four types of validation methods. They are :

1. Prospective validation
2. Retrospective validation
3. Concurrent validation and
4. Revalidation

1. **Prospective Validation :** If validation programme is designed and implemented before the equipment of facility comes on stream i.e. before starting the production, then it is called as prospective validation.

2. **Retrospective Validation :** Some times, the systems or processes are in place that have not been previously validated but are functioning well and consistently producing good production. Validation of such facilities or process is called retrospective validation. It is activated by the review of historical manufacturing and testing data.

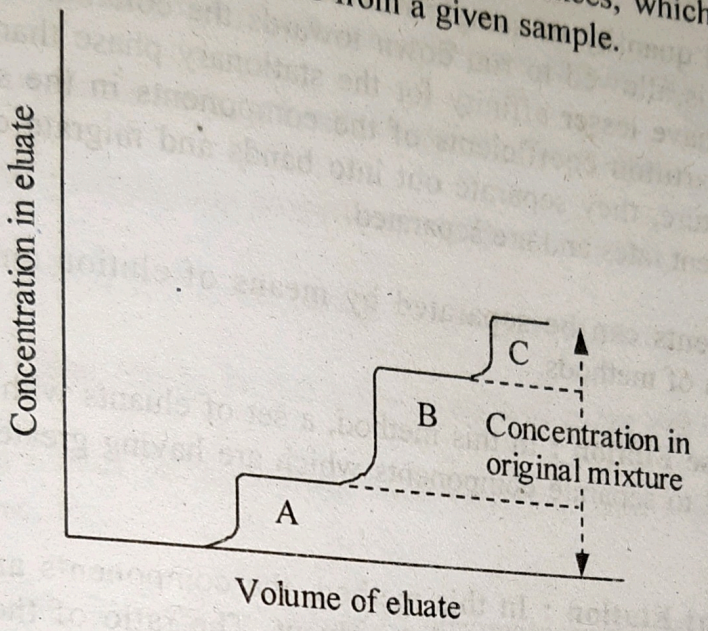
   Prospective and retrospective validation may be combined advantageously in sequence to provide a higher level of assurance that is given by the pre-marketing prospective validation alone.

3. **Concurrent Validation :** Concurrent validation is a newer term that is applied either to ongoing prospective validation or to the ongoing review and evaluation of historical data associated with retrospective validation.

4. **Revalidation :** Revalidation is the act of repeating all or a portion of the validation as a result of any modification to the process or facility that may lead to changes in quality or reproducibility of the product. It also refers to the regular, planned repetition of validation steps for equipment or process, where performance may change with time.

be used for separation of readily eluated component from others with greater affinity and is also termed as preparative method. This method is used to remove relatively smaller quantities of unwanted substances, which are strongly adsorbed than that of desired components from a given sample.

Figure : Frontal Analysis: Curve for a mixture of three substances, A, B & C



2. **Displacement Analysis :** In this method, the sample mixtue is introduced first into the column. Then, the components in the mixture are separated by running a solution which is consisting of a substance which is more strongly adsorbed than any of the components of the sample mixture. The substance which is employed to separate components is called as displacing agent.

The displacing agent is adsorbed by the column strongly and is adsorbed at the top of the column and spreads downwards forcing out the components of the sample mixture from adsorption sites. The least adsorbed component leaves the column first followed by others depending upon the degree of the adsorptivities.

In this process, the components are separated basing on their differences in properties of adsorption. The separation is not sharp and may contain some fractions of mixtures which can be collected and treated further.

Figure : Displacement analysis : curve for a mixture of three substances, A, B & C displaced by a fourth, D