

sucrose, glucose, mannitol, lactose, crystalline and liquid sorbitol, and such artificial sweetening agents as saccharin, sodium saccharin, calcium saccharin, and aspartame.

Testing for unwanted impurities resulting from synthesis side reaction in the manufacturing procedure is essential in the analysis of sweetening agents, for example, furfuraldehyde in lactose, and reducing sugars in mannitol. Sweetening agents are usually tested for water content, heavy metals, residue on ignition, arsenic, and special tests such as specific rotation, melting range, selenium, and readily carbonizable substances.

In-Process Items Control

Conformance to compendial standards as the sole basis for judging the quality of a final dosage form can be grossly misleading. Obviously, a compendial monograph could never cover all possibilities that might adversely affect the quality of a product. The difficulty lies in part in the fact that final dosage forms are frequently produced in batches of hundreds of thousands or even millions of units. The numbers of units assayed at the end of the process is not likely to be representative of more than a small fraction of the actual production.

There is a real and significant difference between a finished product compendial standard and the quality assurance of the manufacturing process. The FDA-CGMP regulations emphasize environmental factors to minimize cross-contamination of products and errors in labeling and packaging, and the integrity of production and quality control records; however, they do little to minimize within-batch and batch-to-batch variation in the output of production. Therefore, it is an important function of the in-process quality assurance program to ensure that finished dosage forms have uniform purity and quality within a batch and between batches. This is accomplished by identifying critical steps in the manufacturing process and controlling them within defined limits.

Quality Assurance Before Start-Up

ENVIRONMENTAL AND MICROBIOLOGIC CONTROL AND SANITATION

To assure that finished dosage forms meet high standards of quality and purity, an effective sanitation program is required at all facilities where such products are manufactured. A successful extermination program must be enforced within and outside the plant to control insects

and rodents. People are the mainstay of any plant housekeeping and sanitation program. Consequently, personal cleanliness and proper haircovering and clothing should be required. Floors, walls, and ceilings should be resistant to external forces, capable of being easily cleaned, and in good repair. Adequate ventilation, proper temperature, and proper humidity are other important factors. Ventilation in manufacturing departments is usually designed so that dust can be contained and removed. In such departmental operations, dust collectors, air filters, and scrubbers to clean the air are checked on a routine schedule. Air quality monitoring at the work station could indicate the adequacy of these elements.

The water supply may be potable, distilled, or deionized, and must be under adequate pressure to keep the water flowing. Deionization units should be monitored, and the resins changed or regenerated frequently, to deliver water of consistently high chemical and microbial quality as per written compendial or inhouse specifications.

Quality assurance should review and monitor the following programs, based on written procedures that specify the details of each:

Sanitation: Example is shown in Table 27-5 for one insecticide.

Cleaning: Building and equipment.

Ventilation: Filter conditions and changes; pressure gauge; humidity monitoring; temperature monitoring; microbial monitoring (Table 27-6); light intensity.

Water: Release at point of use after checking by quality control; proper flushing period and/or volume before water use.

MANUFACTURING WORKING FORMULA PROCEDURES (MWFP)

Documentation of the component materials and processing steps, together with production operation specifications and equipment to be used, make up the MWFP.

A working formula procedure should be prepared for each batch size that is produced. To attempt expansion or reduction of a batch size by manual calculations at the time of production cannot be considered good manufacturing practice.

Quality assurance personnel must review and check the working formula procedures for each production batch before, during, and after production for the following details:

the case of compendial weight variation or pH specifications, the deviation is such that units produced prior to the corrective action are isolated, accounted for, and rejected.

In addition to the foregoing, portions of the initial, final, and in-process samples are used for collecting average run samples for the quality control laboratory to perform final batch analysis and release.

PACKAGING MATERIALS CONTROL

The USP defines the container closure system as that device that holds the drug and is or may be in direct contact with the drug. The immediate container is that which is in direct contact with the drug at all times. The closure is a part of the container.

Packaging materials should not interact physically or chemically with the finished product to alter the strength, quality, or purity beyond specified requirements. The compendium provides specifications and test procedures for light resistance: well-closed, tightly closed, and four different types of glass containers.

Specifications and test methods are designed for containers on the basis of tests performed on the product in the container. The following features are to be considered in developing container specifications:

Properties of container tightness.

- ✓ Moisture and vapor tightness regardless of container construction.
- ✓ Toxicity and chemical/physical characteristics of materials needed in container construction.
- ✓ Physical or chemical changes of container upon prolonged contact with product.

Compatibility between container and product.

Good Manufacturing Practices require that stability data be submitted for the finished dosage form of the drug in the container closure system in which it is to be marketed.

LABELS CONTROL

Production control issues a packaging form that carries the name of the product; item number; lot number; number of labels, inserts, and packaging materials to be used; operations to be performed, and the quantity to be packaged. A copy of this form is sent to the supervisor of label control, who in turn counts out the required number of labels. Since labels may be spoiled during the packaging operation, a definite number in excess of that actually required is usually

issued; however, all labels must be accounted for at the end of the operation, and unused labels must be accounted for before their destruction.

If the lot number and expiration date of the product are not going to be printed directly on the line, the labels are run through a printing machine, which imprints the lot number and expiration date. The labels are recounted and placed in a separate container with proper identification for future transfer to the packaging department. The packaging department then requests, according to the packaging form, the product to be packaged, along with all packaging components, such as labels, inserts, bottles, vials, ampuls, stoppers, caps, seals, cartons, and shipping cases. Quality assurance personnel inspects and verifies all packaging components and equipment to be used for the packaging operation to ensure that it has the proper identification, that the line has been thoroughly cleaned, and that all materials from the previous packaging operation have been completely removed. Proper reconciliation and disposition of the unused and wasted labels should occur at the end of the packaging operation.

FINISHED PRODUCT CONTROL

Specifications. Final testing of finished product is made in the quality control laboratories. These tests are designed to determine compliance with specifications. Thus, the testing of the finished product for compliance with predetermined standards prior to release of the product for packaging and subsequent distribution is a critical factor for quality assurance. This testing, along with in-process testing, assures that each unit contains the amount of drug claimed on the label, that all of the drug in each unit is available for complete absorption, that the drug is stable in the formulation in its specific final container closure system for its expected shelf-life, and that dosage units themselves contain no toxic foreign substances.

Normally, the design of test parameters, procedures, and specifications is made during product development. It is a good manufacturing practice to base such parameters on experiences developed from several pilot and production batches. Furthermore, the results of these studies should be subjected to statistical analysis where appropriate, to appraise the precision and accuracy of each procedure correctly for each characteristic. In the long run, with additional production experience, specifications may possibly be modified to upgrade product specifications.

Bulk Product Testing. Each lot of bulk

Raw material control :

- Good raw material specifications must be written in precise terminology, must be complete, must provide specific details of test methods, type of instrument and manner of sampling and must be properly identified.
- The FDA current good manufacturing practice states that "components" be received, sampled, tested and stored in a reasonable way, that rejected material be disposed of, that samples of tested component be retained and that appropriate record of these steps be maintained.
- In practice, the manufacturer physically inspects and assign lot numbers to all raw material received and quarantine them until they are approved for use. Each raw material is sampled according to standard sampling procedure and is sent to quality control laboratories for testing. If accepted it is moved to the release storage area, after being properly stickered to indicate item number, name of material, lot number, date of release, re assay date and signature of QA inspector. It is retested to assure that it still conforms to specification at time of use.
- QA personnel should keep samples of active raw materials that consist of at least twice the necessary quantity to perform

all tests required. These samples should be retained for at least 7 years. Approved material should be rotated so that oldest stock is used first. Any raw material not meeting the specification must be isolated, stickered as rejected and returned to supplier or disposed off.

→ To verify suppliers conformance to the specification, further on site periodic inspections are done. This procedure assures that cross contamination does not take place because of improperly cleaned equipment or poor housekeeping procedures.

Two groups ① Active or therapeutic ② Inactive

① Active or therapeutic.

Antibiotics : Antibiotics are one of the few drugs for which the official analytical method appears in code of federal regulation. The number of tests varies from one antibiotic to other.

- Testing of antibiotic is usually performed either chemically, microbiologically, biologically or by all three methods. Caution must be exerted in testing to assure that it is not altered during sampling procedure.

The sample must be taken in relatively dry atmosphere, relatively free from dust and free of both chemical and microbiological airborne contamination and exposure must be reduced to minimal time of sampling.

- Since the potency value in terms of $\mu\text{g}/\text{mg}$ obtained for this material is used in calculating number of grams or kg required for working formula procedures, it is recommended that at least two separate weighings of such antibiotic be assayed on each of 3 different days. If all the individual results are not within the normal distribution of the group or show too much variance, additional assays should be performed until a mean potency is obtained with confidence limits of $\pm 2.5\%$. (or better) at $P = 0.05$

(iv) other active materials :

It is not uncommon to find an appreciable variation in degree of purity between samples of same raw material purchased from different commercial source.

In general typical raw material has a purity requirement of at least 97%.

Specifications : Solubility, identification, melting range, loss on drying, residue on ignition, special metal testing, specific impurities

Methods of assay are chemical in nature.

special instrument : spectrophotometry, titrimetry,

GLC may be used.

For certain products specification should include additional critical test such as particle size, crystal shape & crystalline vs amorphous form. Acc. to cGMP all raw material active or inactive be assigned a meaningful reassay date that assures purity & potency of raw material.

(II) Inactive or Inert materials :

Inactive or inert materials usually make up the major portion of final dosage form.

∴ Physical characteristics → color, odour, foreign matter, important

Other specifications : Particle size, heavy metal content, arsenic, selenium, water content, microbial limit pH.

A typical analysis colour contains identity test & test for total volatile matter, heavy metals, water insoluble matter, synthetic impurities.

A FDC colour lake has test for Cl^- , SO_4^{2-} & inorganic matter.

Flavours or volatile oils are usually tested for refractive index, specific gravity, solubility and alcohol content.

Testing of unwanted impurities resulting from synthesis side reaction is essential in the analysis sweetening agent eg furfuraldehyde in lactose.

Also tested for water content, heavy metals, residue on ignition, arsenic and special tests such as specific rotation, melting range, selenium.

- Conformity with Pkg. instructions.
- Quantity as per instruction.
- Identity through label.
- All audit's & inspection's authorities are very much rigid & strict on records of "Printed" PM as unaccounted "Printed PM" have a potential danger of its misuse.
- Access to all storage areas should be limited to Authorized persons only.
- A separate sampling room should be provided for "Primary PM" which should be a fairly clean area.

3 In Process Quality Control:

In process control, generally termed as IPQC in entire operation of manufacturing & packaging are most important to insure that each & every steps & stages of operation are carried out as per written down procedures (Called Standard Operating Procedures – SOP) and outcome & resultant of each intermediate bears the same "Quality" as expected out of the system.

To do so, critical steps should be identified in each process & specifications to be defined, within narrow range possible, for the critical parameters to be tested at identified stages;

- **For manufacturing operations:**

- Assay, Angle of Repose, Moisture of granules.
- Bulk density of granulated materials.
- Particle size distribution of granules.
- Physical parameters for Tablets like;
 - ❖ Weights variation.
 - ❖ Thickness.
 - ❖ Hardness.
 - ❖ Friability.
 - ❖ Surface characteristics.
 - ❖ Disintegration time.
 - ❖ Dissolution time.
- Fill volume/weight in ampoules/vials/bottles.
- pH of the solution /clarity/color.
- Bulk volume of liquid.
- For operational machinery / equipments
 - Rotational speed.
 - Time.
 - Rate of transfer.
 - Temperature.

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either "Accepted" or "Rejected".

UCL = 2.54%

- Performance of online detector.
 - Environmental condition conformation ;
 - Temperature.
 - Relative Humidity.
 - Differential Pressure.
- These are basic & vital checks that IPQC personnel in consultation with production should do & also identify what other checks can be incorporated as the product and process demands.*

- For packaging operations:

- During entire packaging operations, each packaging line should be continuously monitored to insure that the integrity of the finished product has not been compromised anywhere.
- SOP & tabulated check list should be signed at regular interval / frequency by competent or trained personnel.
- Automated control & monitors should be checked regularly & validated / calibrated / verified / challenged time-to-time.
- Online checks should include;
 - ❖ General Appearance, physical defects.
 - ❖ Filled weight / volume / Unit qty.
 - ❖ All components of package inside without fail.
 - ❖ Correctness of all materials including products.
 - ❖ Correctness of overprinted details.
 - ❖ Proper functioning of all online monitor installed.
 - ❖ Monitoring & recording of environment.
 - ❖ Collection of samples at random during the entire packaging. Operation.
 - ❖ Availability of SOP & IPQC Records.



4 Sanitization and its monitoring:

Maintaining cleaned area & atmosphere implementing laid down cleaning procedure at stated frequency / interval with predefined schedule & use of detergent & disinfectant of given concentration is called "Sanitization".

- *Sanitization in Manufacturing premises :*

- Validated cleaning & sanitizing procedures to be used
- Certain areas of operation to be marked for collection of dust, debris, waste or trash materials.
- Suitable plastic, preferably Stainless Steel container to be placed at marked areas.
- A recycled plastic bag to be placed inside for collection of waste.

- On completion of packaging operations, for any batch, any unused batch coded material should be destroyed & recorded. A documented procedure to be followed, in case, any un-coded pkg. material is returned to store for recirculation.

6 Finished Product or Finished Goods (FG) Control: -

Packs ready for customer, are defined as finished product. Finished product of one manufacturer can be raw material for other manufacturer. A manufacturer can send a semi finished product as a finished product to a customer who can take it for further processing for another customer.

Releasing Finished Product / Goods (FG) is the last activity done by the factory in manufacturing & packaging operations. Commercial movement starts once the "Released" status is given to the FG. Hence Release is very important activity to be carried out with most care following each & every laid down procedures & specifications.

- FG once come from production / packaging must be placed in the "Quarantine" till it gets released.
- Drawn online samples at specified frequency during entire packaging operations, as per SOP, must be retained for test by QC laboratory & for future reference purpose.
- Documentation should be reconciled, completed & sent for complete documentation audit by QA.
- When all required parameters are satisfied, including document audit, QC may recommend released putting "Released" status over "Quarantine".
- Finished product must be "Released" by QA person only, who is authorized to do so for commercial out way.]

7 Documentation

Definition: - Document is any statement or proof filled in standard format for future reference / evidence.

Scope: -Good documentation encompasses (includes) practically all the aspects of pharmaceutical production:

1. **Building and Premises:** Installation, validation, cleaning and maintenance.
2. **Personnel** : Qualification, Training, hygiene, etc.
3. **Equipment** : Installation, calibration, validation, Maintenance, cleaning.
4. **Materials** : Specifications, testing, ware-housing, use, rejection / disposal.
5. **Processing** : Individual steps in the process of