SHREE H. N. SHUKLA INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH

B.PHARM

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SUBJECT NAME: QUALITY ASSURANCE

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UNIT 02 (c): EQUIPMENTS AND RAW MATERIALS

Content

Equipments and raw materials: Equipment selection, purchase specifications, maintenance, purchase specifications and maintenance of stores for raw materials.

Equipment

Equipment may be defined as a physical entity which is used to carry out a general or specific activity in the pharmaceutical plant.

It can be a single piece, for example tablet compression, weighing machine.

Equipment is an integrated system that is, group of equipment come together to perform single activity. e.g.: water mineralizing plants, air handling systems.

The quality of the manufactured product much depends on the suitability, and level of the technology of the equipment used since it is major requirement in the manufacture of the pharmaceutical products.

The regulatory literature on GMP in various countries gives enough importance and provide guide lines on the management of equipment in pharmaceutical plants.

We have a glance on international GMP literature following points coming up, those are:

- Design & Location
- Preventive and breakdown maintenance
- Construction
- Size and adaptation
- Cleaning and cross contamination
- Maintenance and calibration
- Qualification and validation
- Automatic, mechanical, electronic equipment

LIFE STAGES OF EQUIPMENT

Equipment management in the pharmaceutical industry has a life cycle, and the GMP requirement cover the life cycle of equipment. It starts with decision to purchase equipment and ends with scrapping or elimination of equipment from operation.

Decision to purchase equipment is primarily need based.

It consists of following stages:

- ✓ decision to purchase equipment
- ✓ purchase of equipment

- ✓ qualifying, installing and validating equipment
- ✓ using the equipment

Selection of Equipment

1. Availability of spares and servicing.

2. The frequency and ease of maintenance will significantly impact on productivity and even quality.

3. Equipment breakdown during processing could adversely affect quality. Included in the maintenance evaluation should be the cleanability of the equipment. This will involve accessibility to the parts to be cleaned and the relative ease of disassembly and reassembly process.

4. Environmental issues are important constraints. Is the design of the equipment conductive to the application? Such attributes as the ability to contain toxic products, the ability to maintain aseptic conditions, etc. need to be reviewed.

5. Construction materials and design.

6. The type of process controls such as automatic weight adjustment on tablet temperature recorders on ovens.

Purchase Specification

This primarily helps the user requirement specification for the equipment.

Following questions may arise in relation to design, size, location, adaption and construction of the equipment.

- ✓ Why the need arises for the purchase of equipment? e.g. Creation of new facility, increasing capacity, Adapting to new and improved technology.
- ✓ Which operations we want perform with proposed equipment? For example, equipment capability analysis, granulation, sterilization.
- ✓ What capacity the equipment should have in terms output and holding? E.g. ten lakh tablets per shift or ten thousand litters of liquid.
- ✓ How the equipment will be cleaned? And also need to consider that do we face any problem in validating the cleaning process of the equipment?
- ✓ Do we have trained operators to operate this equipment? Or whether the manufacturer helps in training our existing operator.
- ✓ What will be the starting and stopping time of the equipment?

WHO-GMP Guidelines on Equipment

INSTALLATION AND LOCATION

While installing equipment points mentioned below should be kept in mind.

- Equipment should be located in such a way that contamination of substances by other materials used in the same area is minimized either by dust carried in air or by spillage of liquid.
- One equipment should be located at sufficient distance from the other to avoid congestion and also to ensure that products being processed do not get admixed or confused with each other.
- All open mechanical belts and pulleys should be covered with safety guards.
- Water and other utility service lines should be so installed as to be easily accessible during all phases of operation. These should have colour scheme and should be marked so that these are recognized easily.
- If there are fixed pipelines, these should be labelled to indicate the contents and the direction of flow.
- For dangerous gases and liquids there should be dedicated pipelines.
- All pipes, tanks and jackets which handle steam or coolant should be properly insulated so that risk of injury to workers and energy loss are minimized.
- In case of newly purchased equipment, IQ, OQ, and PQ should be performed.

EQUIPMENT CONSTRUCTION

- Equipment shall be constructed such that the surfaces that come into contact with components, in-process materials, or drug products shall not be reactive, additive, or absorptive.
- Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

EQUIPMENT CLEANING AND MAINTENANCE

Purpose of equipment cleaning is to remove product residues of previous product or batch and to clean and sanitize the equipment for next batch.

Equipment should be cleaned regardless of their size. However large equipment which are fixed or are too heavy to move should be cleaned on location. Detachable parts and small equipment should be taken to cleaning area assigned for the purpose.

Written cleaning procedures or SOP should be prepared for all the equipments. These should be in the language that is understood by the workers & be available in the section.

These procedures shall include, but are not necessarily limited to, the following:

1. Assignment of responsibility for cleaning and maintaining equipment;
2. Maintenance and cleaning schedules, including appropriate sanitizing schedules wherever required;
3. A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as it is necessary to assure proper cleaning and maintenance;
4. Removal or obliteration of previous batch identification;
5. Protection of clean equipment from contamination prior to use;
6. Inspection of equipment for cleanliness immediately before use.

For guidance, some common steps for equipment cleaning are given below.

(i) For Dry Products:

- Remove labels with the help of brush, remove product residues from previous batch;
- Disassemble and clean disassembled parts further with the help of brush.
- Wash parts with soap and jet of water using a scrubber, then wash with sufficient clean water;
- Drain out water and dry in clean area;
- Where necessary, sterilize with 70 % isopropyl alcohol or other suitable disinfectant.
- After drying the parts, assemble the equipment.

(ii) For liquid products-filling equipments:

- Drain out holding tank of left overs, it any;
- Fill the holding tank with water and start filling machine, collect water coming out of filling machine and discard it (Run the machine for appropriate time);
- Now open drain valve of the holding tank;
- Disassemble nozzles and washers;
- Remove tubings;
- Clean all parts with jet of water;
- Soak parts and flexible tubing in antiseptic solution for 30 minutes. (0.5 % cetrimide solution can be used for this purpose);
- Wash these parts and tubing in running tap water;
- If steam is available, subject the parts to live steam, if steam is not available, use 70 % isopropyl alcohol, and allow to dry;
- Flexible tubings should also be cleaned in similar way;
- Cover ends of clean tubings with polyethylene sheet;

- Clean holding tank with hot water, if steam is available subject it to live steam if steam is not available, treat with hypochlorite solution.
- Assemble the equipment.

Whenever there is product change over, final rinse water should be tested for active ingredient(s) of the last product processed. The test for active ingredient(s) could be limit tests and could be performed by colour development or by UV spectrophotometer.

Before use equipment should be inspected for cleanliness and should be cleaned by person responsible for the job.

Tags with words like 'Equipment cleaned', 'Cleaned' or 'Ready for use' can be used for lean equipment. Cleaned equipment should be covered to protect from extraneous contamination. Recording equipment should be calibrated at scheduled intervals and records should be maintained.

SOP should be prepared for cleaning & sanitization of major equipments in production area. Some of the important points in preparing SOP are:

- Selection of cleaning agent;
- Concentration of cleaning agent;
- Where equipment is to be washed with running water time period should be specified in SOP;
- Where equipment is washed/rinsed with water, volume of water to be taken for each rinse should be specified in SOP;
- Quality of final rinse water/solvent should be specified in SOP;
- Selection of sanitizing agent;
- Concentration of sanitizing agent;
- Cleaning implements like brushes, scrubber etc. should be specified in SOP.

MAINTENANCE AND CALIBRATION

- All equipment and instruments are to be provided with unique identification. This can be of any format, but usually is an alphanumerical identifier, which can be easily utilized by a computer planning system.
- All preventive, maintenance, and calibration tasks and regimes are required to be documented as standard operating procedures (SOPs).
- The maintenance and calibration programs are to address both PM activities as well as corrective maintenance activities and they should be documented in SOPs. The frequencies of conducting these activities are to be placed in a scheduling system.
- There is to be a process of entering new equipment and instrumentation items into the maintenance or calibration system. These processes are to be documented in SOPs. The

processes are to identify what information is required before an equipment item can be entered. Information such as, but not limited to:

- unique identifier
- equipment assessment or instrument classification
- URS
- procurement specification
- recommended spare parts
- recommended lubricants
- vendor manuals and drawings

- A history of maintenance and calibration work is to be kept for each equipment and instrument item.

- Process to report abnormal situations, that is, out of tolerance for instruments, unapproved parts for maintenance. The system procedures are to identify the conditions that are considered abnormal.

- Supporting these systems is a spare parts program. This program is to address the specification, acquisition, storage, and issuance of spare parts. How spare parts are approved and how "like-for-like" replacements that are made need to be included in the system SOP.

Name of Company : _____

Address of Company : _____

Name of Machine : _____

Identification No. of Machine : _____

Location : _____

Date of last PM	Date of PM	Time		Maintenance work performed by	Attended by	Checked by
		From	To			

Raw Material

Since a finished product is the result of processing of starting materials, purchasing of starting materials is an important operation.

Purchase Specification

Written guidelines that precisely define the operational, physical, and/or chemical characteristics, as well as the quality and quantity of a particular item to be acquired.

1. Generic and chemical name of material;
2. Trade name and product code established by manufacturer;
3. Description;
4. Name of pharmacopoeia (if official in pharmacopoeia) in which monograph appear or name of any other recognized book of standard, in which monograph appears or international non-proprietary name.
5. If not official in pharmacopoeia or any other book of standards, monograph to be employed for testing containing tests and limits for identity, purity, physical and chemical characteristics microbiological standards and assay.
6. Approved suppliers.
7. Frequency of testing of stored materials.
8. Special precautions to be taken during storage including safety aspects.
9. Date of issue of specifications.

Mode of purchasing:

- By inspection
- By sample
- By description of brand
- By grading

Steps involved in purchase procedure:

1. Purchase requisition
2. Selection of supplies
3. Inviting Quotation
4. Placing the order
5. Receiving the material
6. Checking of invoice or bill
7. Recording of bills in books
8. Releasing the payment to the supplier

Purchasing should involve persons who have knowledge of materials and suppliers. There should be written procedures for receipt, identification, storage, handling, sampling, testing and approval or rejection of raw materials.

Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers.

Maintenance of stores

1. Storage Area Specifications

- Sufficient Capacity
- Clean, Dry and Maintained within acceptable temp. limit
- Designed and equipped reception area
- Ensuring of quarantine status
- Separate sampling area
- Segregation for storage of rejected, recalled or returned material
- Safe and secure area for narcotics and highly active, dangerous and risky material
- First in First out rule (FIFO)
- First expiring First Out (FEFO)

2. Storage conditions

- Room temp. Should be 30° C and R. H. 60%
- A.C storage (25± 2 ° C & R.H. 45 – 55%)
- Low temp. Storage 2 – 8 ° C
- Separate area for Sterile product storage in A.C
- Light sensitive material in amber color container
- Hermitically sealed container

3. Labeling of material in storage area

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

During fully computerized system used, labeling with all above information need not be necessary.

It is beneficial for all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, to be contractually agreed between the manufacturer and the supplier.
The following guidelines will be useful to develop the system.

1. On receipt, each delivery of starting materials should be visually examined for labels, damage to containers, spoilage and possible deterioration during transit. Containers should be cleaned if necessary and if required the damaged containers should be labelled with the requisite particulars.

2. Particulars on the delivery challan/invoice should be tallied with labels on containers of the materials. A goods-in inspection report may be prepared and filed along with delivery challan or invoice. A format which can be used for guidance is printed below:

(Name & Address of Company)

Goods-in Inspection Report

*Date of Receipt*_____

Delivery Challan/invoice No _____ *Dated*_____

Name & Address of Supplier _____

_____

Name of items mentioned in Delivery challan/invoice (D/C/Inv.)

1._____

2._____

3._____

A. Check the following:

(a) Whether total number of containers mentioned in DC/Inv. tallies with the number of containers received? — Yes/No (State total number of containers)

(b) What is the break-up of items and number of containers — Name of items / Number of of containers

(c) Do the following particulars on label of containers and DC/Inv. tally?
Name of item .....Yes/No
Name of Manufacturer .....Yes/No
Batch No. .....Yes/No
Date of Exp., If any .....Yes/No

B. Inspect all the containers & record the observations

(a) Are all containers undamaged? Yes/No

(b) If no (i) No. of containers damaged_____

(ii) Name of item along with B. No._____

C. Extent of damage:

(a) Is damange to outer covering only? Yes/No
If no, to what extent has the container been damaged? _____

(b) Has the material been contaminated with dust, fibres, pieces of packaging materials? Yes/No

D. Put conspicuous identification mark on damaged containers.

Signature

Name of person who carried out inspection _____

Date _____

Signature with date of Stores in-charge

3. Starting materials, then should be transferred to quarantine area and labels over printed with words 'under test' should be pasted on the containers of the materials. Where it is not possible to post labels, paper tags may be used.

4. Request should be made to In-charge, Quality contract for sampling.

5. Quality control personnel, on receipt of request, should draw samples from the raw materials so quarantined. While sampling, points that should be kept in mind are:

   - Samples for identification should be taken from every container of active ingredient as well as excipient;
   - Samples should be representative of the batches of materials from which they are taken;
   - All sampling equipment which come in contact with the material must be clean;
   - Containers which have been sampled should be released after sampling;
   - Appropriate precautions should be taken during sampling of hazardous or toxic materials;
   - Sterile equipment and aseptic techniques should be used wherever necessary;
   - If it is necessary to sample a starting material from top, middle and bottom, sample should be drawn accordingly, but such sub-divisions should not be composited for testing;

6. On receipt of 'approval' or 'rejection' as the case may be, the starting material should be transferred to area marked for approval materials or rejected materials according to the status of material.

7. Labels indicating status of the material should then be attached to the material by person authorized by Quality Control Department.

8. Those materials which require special storage conditions (e.g. controlled temperature and humidity) should be stored in special storage area provided for the purpose.

9. Starting materials in boxes and bags should be stored off the floor and be suitably spaced to permit cleaning and inspection.

10. Stocks of starting materials should be inspected in intervals to ensure that containers are properly closed and labelled and are in good condition.

11. If a material has been lying in the store for too long a period, it should be submitted for retesting.

12. All materials should be stored under appropriate conditions in such a manner that will permit batch segregation and stock rotation by a 'first in-first expiry-first out" (FIFO) principle. Where the material is having expiry date the principle of "First Expiring-First Out" (FEFO) should be used.

13. Segregated dispensing areas suitably equipped to avoid cross contamination should be provided, weighing and measuring equipment should have the capacity, accuracy appropriate to the material to be weighed and measured. These should be calibrated at regular interval.

14. Every time clean equipment should be used for dispensing of different materials.

15. Starting materials should be issued against written demand from production department.

16. Material issued against written demand (requisition) for each batch of finished product should be identified and replaced together.

17. Each dispensed material and its weight/volume should be checked by another person & such check should be recorded.

18. Only those materials which have been released by quality control department and have adequate shelf life should be used in the manufacture of drugs. If one delivery consists of different batches each batch must be considered as separate for sampling, testing and release.

19. Inventory of all starting materials should be maintained as per Schedule U to the drugs & Cosmetic Rules.

20. Raw materials in the storage area should be labelled with the following particulars:
    - Designed name and internal code
    - Analytical reference number
    - Manufacturer's name, address and batch number
    - Status of the contents (e.g. quarantine, approved rejected)
    - Manufacturing date, expiring date and re-test date

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