Name of Unit	Complaints and document maintenance in pharmaceutical industry
Subject /Course name	Quality Assurance
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Learning Outcome of Unit-4

LO	Learning Outcome (LO)	Course Outcome Code
LO1	ıts will able to know about the importance of documentation.	BP606.5
LO2	Students will able to understand the cGMP aspects in a pharmaceutical industry	BP606.5
LO3	To Understand the scope of quality certifications applicable to pharmaceutical industries	BP 606.5

Module Content Table

Topic
• Complaints: Complaints and evaluation of complaints • Handling of return good • Recalling and waste disposal. • Document Maintenance in Pharmaceutical Industry: Batch Formula Record, • Master Formula Record, • SOP, • Quality audit, • Quality Review Quality documentation, • Reports and documents, distribution records.

COMPLAINTS

- All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.
- A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or recall.
- There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
- Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the review of such investigations.
- If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.
- Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.
- The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, counterfeiting or any other serious quality problems with a product.

Complaints and Adverse Reactions

All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated /evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.

Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority.

There shall be written procedure describing the action to be taken, recall to be made of the defective product.

Product recalls

- There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.
- The authorized person should be responsible for the execution and coordination of recalls. He/she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.
- There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.
- An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.
- All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.
- The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.
- The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including reconciliation between the delivered and recovered quantities of the products.
- The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

Recalled products

Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

Returned goods

Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or re-labelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

Waste materials

Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

BATCH PROCESSING RECORDS

A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

a. The name of the product;
b. The number of the batch being manufactured;
c. Dates and times of commencement, of significant intermediate stages, and of completion of production;
d. The name of the person responsible for each stage of production;

e. The initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. Weighing);
f. The batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
g. Any relevant processing operation or event and the major equipment used;
h. The in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
i. The amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
j. Notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

A batch packaging record should be kept for each batch or part batch processed. 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. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

a. 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 that will be obtained, the quantity actually obtained and the reconciliation;
b. The date(s) and time(s) of the packaging operations;
c. The name of the responsible person carrying out the packaging operation;
d. The initials of the operators of the different significant steps;
e. The checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

f. Details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;

g. Whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;

h. Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;

i. The quantities and reference number or identification of all printed pack aging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

MASTER FORMULAE RECORD

A formally authorized master formula should exist for each product and batch size to be manufactured. The master formula should include:

1. The name of the product, with a product reference code relating to its specification;
2. A description of the dosage form, strength of the product and batch size;
3. A list of all starting materials to be used (if applicable, with the inns), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
4. A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
5. A statement of the processing location and the principal equipment to be used;
6. The methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. Cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
7. Detailed step-wise processing instructions (e.g. Checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
8. The instructions for any in-process controls with their limits;
9. Where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
10. Any special precautions to be observed.

Standard Operating Procedures (SOPs) and Records

Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- Equipment assembly and validation
- Analytical apparatus and calibration
- Maintenance, cleaning and sanitization
- Personnel matters including qualification, training, clothing and hygiene
- Environmental
- Pest control
- Complaints
- Recalls
- Returns

There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material. The records of the receipts should include:

- The name of the material on the delivery note and the containers;
- The "in-house" name and/or code of the material if different from (a);
- The date of receipt;
- The supplier's name and, if possible, manufacturer's name;
- The manufacturer's batch or reference number;
- The total quantity, and number of containers received;
- The batch number assigned after receipt;
- Any relevant comment (e.g. State of the containers).

There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Standard operating procedures should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment. There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

The sampling instructions should include:

- The method of sampling and the sampling plan;

- The equipment to be used;
- Any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
- The amount(s) of sample(s) to be taken;
- Instructions for any required subdivision of the sample;
- The type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
- Any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number. The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.

There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

Analysis records should include at least the following data:

1. The name of the material or product and, where applicable, dosage form;
2. The batch number and, where appropriate, the manufacturer and/or supplier;
3. References to the relevant specifications and testing procedures;
4. Test results, including observations and calculations, and reference to any specifications (limits);
5. Date(s) and reference number(s) of testing;
6. The initials of the persons who performed the testing;
7. The date and initials of the persons who verified the testing and the calculations, where appropriate;

8. A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.

Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

QUALITY AUDIT

It may be useful to supplement self-inspections with a quality audit. A quality audit 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.

Quality audit may include questionnaires on 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. (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.

DOCUMENTATION & RECORDS

Documentation is an essential part of the Quality assurance system and, as such, shall be related to all aspects Good Manufacturing Practices (GMP). Its aim is to define the specifications for all materials, method of manufacture and control, to ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a bath of drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch

Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General

- Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.
- Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.
- Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.
- Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

- Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.
- Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
- Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.
- Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked.

Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents required

Labels

Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).

All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

- The name of the drug product;
- A list of the active ingredients (if applicable, with the inns), showing the amount of each present and a statement of the net contents (e.g. Number of dosage units, weight, volume);
- The batch number assigned by the manufacturer;
- The expiry date in an uncoded form;
- Any special storage conditions or handling precautions that may be necessary;

- Directions for use, and warnings and precautions that may be necessary;
- The name and address of the manufacturer or the company or the person responsible for placing the product on the market.

For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

Specifications and testing procedures

Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

Each specification should be approved, signed and dated, and maintained by quality control, quality assurance unit or documentation centre. Specifications for starting materials, intermediates, and bulk, finished products and packaging materials are referred to the following sections.

Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

Specifications for starting and packaging materials

Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:

a. The designated name (if applicable, the INN) and internal code reference;
b. The reference, if any, to a pharmacopoeial monograph;
c. Qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice other data may be added to the specification, such as:

- The supplier and the original producer of the materials;
- A specimen of printed materials;
- Directions for sampling and testing, or a reference to procedures;
- Storage conditions and precautions;
- The maximum period of storage before re-examination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

Specifications for intermediate and bulk products

Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

Specifications for finished products should include:

- The designated name of the product and the code reference, where applicable;
- The designated name(s) of the active ingredient(s) (if applicable, with the inn(s));
- The formula or a reference to the formula;
- A description of the dosage form and package details;
- Directions for sampling and testing or a reference to procedures;
- (f) the qualitative and quantitative requirements, with acceptance limits;
- The storage conditions and precautions, where applicable;
- The shelf-life.

DISTRIBUTION RECORDS

- Prior to distribution or dispatch of given batch of a drug, it shall be ensure that the batch has been duly tested, approved and released by the quality control personnel. Pre-dispatch inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched. Detailed instructions for warehousing and stocking of Large Volume Parenterals, if stocked, shall be in existence and shall be complied with after the batch is released for distribution. Periodic audits of warehousing practices followed at distribution centers shall be carried out and records thereof shall be maintained. Standard Operating Procedures shall be developed for warehousing of products.
- Records for distribution shall be maintained in a manner such that finished batch of a drug can be traced to the retain level to facilitate prompt and complete recall of the batch, if and when necessary.

QUESTION BANK

Short Questions (2 marks)

1. What do you understand by pharmaceutical complaint?
2. Define Recall.
3. Define market withdrawl.
4. What are primary reasons for product recall?
5. What are the different types of pharmaceutical waste?
6. Name the common types of documents that are maintained in GMP facility.
7. What is quality audit?
8. Define master formula.
9. Define BMR.
10. What is SOP.

Long Questions (5marks)

1. Explain the complaint handling system
2. Explain different types of recalls.
3. Describe different types of pharmaceutical waste.

Very Long Questions (10 marks)

1. Describe the format of technical SOP.
2. Write a detail note on batch manufacturing record.