UNIT-IV

Complaints

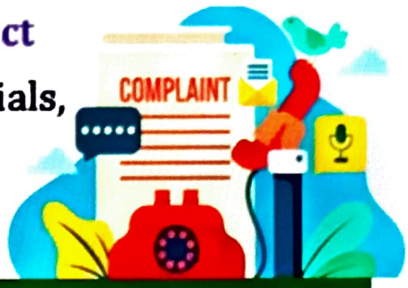
Points to be covered in this topic

- ❖ Complaints & evaluation of complaints
- ❖ Handling of return good
- ❖ Drug Recalling and waste disposal

Complaints

❖ Introduction

- Complaint is defined as Statement that is something wrong or not good enough, **which shows customer dissatisfaction about the company and the product**
- Example: Complaint about packaging materials, Concerning about the product etc.
- Customer Could be **internal** or **external**.



Internal Customer is someone within your company who uses your product or services like warehouse, quality Control.

External customer is an outside organization that receives a product or service from Company like Hospitals, pharmacies, drug stores.

- It can be two forms of complaints they are **written** or **Verbal**
- The written complaints are received in written.
- The verbal complaints are received by oral and must be document by appointed person.

❖ Types of Complaint

1. Quality complaints

- Originate at **consumer level** and concern with **physical, chemical** and **biological properties** or condition of labeling and /or packaging of the product.

2. Adverse reaction complaints

- Due to **allergic reactions** of any other untoward reaction or fatal reaction or near fatal reaction.

3. Other medically related complaints

- Include complaints such as **lack of efficacy or clinical response.**

❖ Steps involved in handling of complaints

- Handling of complaint is done in four basic steps:

(a) Receiving complaints

(b) Technical investigation

(i) Documentation based investigation.

(ii) laboratory analysis phase.

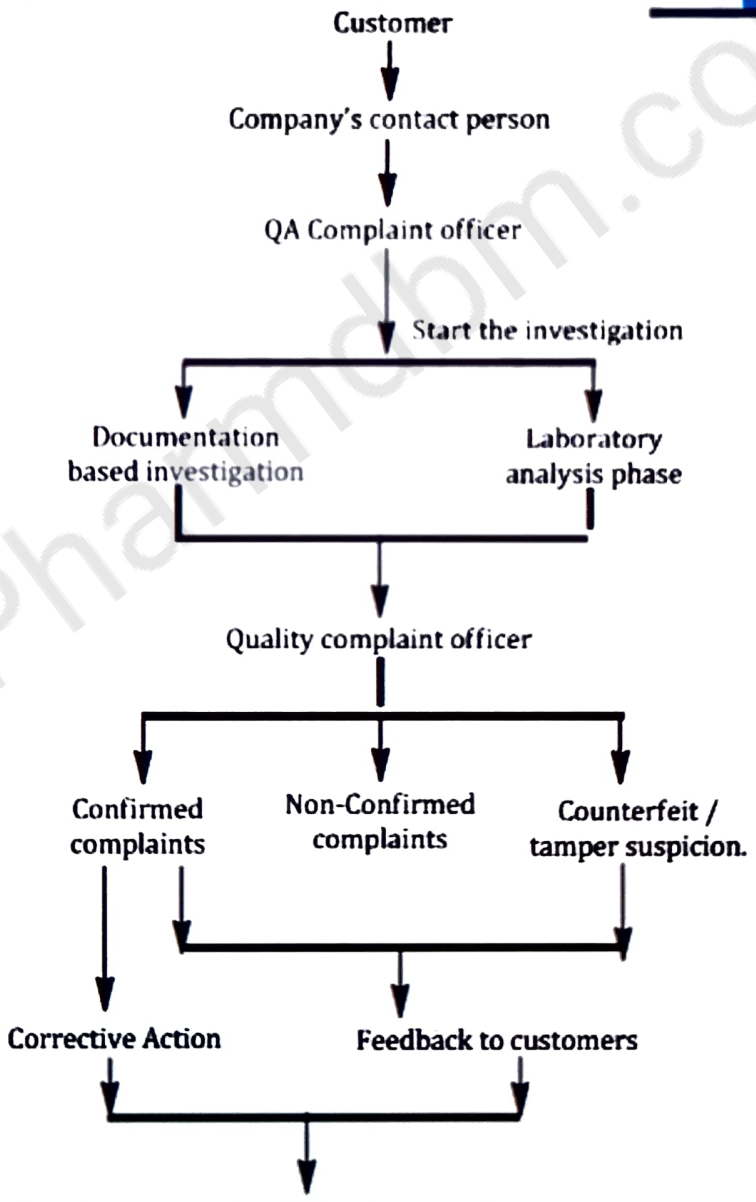
(iii) Confirmed Complaint

(iv) Non-conformed complaint.

(v) Counterfeit / tamper suspicion.

(c) Correction Action & feedback to customers

(d) monthly reports & Trend analysis.



❖ Evaluation of complaint

1. A person shall be designated responsible for **handling the complaints.**
2. Head of Quality Assurance, Quality Control Shall be involved in all actions taken:
   - Including investigation to find the **root cause, checking of retention samples & batch related documents.**
   - The eventual decision made shall be **recorded.**
3. All investigation, root cause & action taken shall be recorded complaint could be on:
   - **Products manufactured by legitimate Company**
4. All decisions & measures taken as a result of a Complaint shall be **recorded** and **referenced** to the corresponding batch records
5. For re-occurring problem, a trending shall be established in order to identify the possible Systemic defects.

❖ Handling of returned goods

- Pharmaceutical products can be returned from market for **various reasons.**
- Once a product recall has been initiated, the process must be **monitored** to ensure that the recall is completed within the stipulated timeframe.
- A check must be performed to evaluate the **effectiveness of the recall.**
- An investigation must be carried out to study the reason for the recall and **remedial action** must be worked out to ensure the defect does not reoccur.
- When stock of recalled drugs is received, it must be placed under quarantine, in a segregated place, with no chance of being mixed up with other products.
- Entry to this area must be restricted to **authorized personnel only.**
- Samples must be drawn and testing performed to identify the **root cause of the defects.**
- Once this has been established, **corrective and preventive actions (CAPA)** must be drawn up and implemented.

- Based on the results of the investigation, the defective product may be **re-processed** or **destroyed** after due **authorization**.
- Generally, reprocessing is permitted only if it is sure to produce a product that will meet the same **quality requirements** after the **re-working**.
- Reprocessed batch details **must be carefully** monitored throughout their shelf life and the records must indicate the **identity as a reprocessed batch.**

❖ Drug Recall

- Drug recall refers to the **action of removing** or withdrawing a batch of product from distribution or use, to be returned to the **manufacturer**.
- This action is generally done in cases where **deficiencies are discovered** in the **safety, quality or efficacy of drugs.**
- It is important to note that product recall does not include the normal removal of products that have passed their **expiry period.**

The Organization of Pharmaceutical Producers of India (OPPI) defines recall as, **"An action taken to resolve a problem with therapeutic goods for which there are established deficiencies in quality, efficacy or safety."**

❑ Types of Recall

Product recall may be of two types:

(a) Voluntary recall:

- This refers to **situations** when the **manufacturer** decides on their own initiative to recall products where the **safety, efficacy and quality of a batch is in question**. For example:

1.	Batch does not comply with regulatory requirements during stability study done in the post-marketing phase.
2.	An in-house investigation reveals a failure (cross-contamination or mix-up) that may have an adverse effect on the quality of a batch of product that has already been released for distribution.
3.	Market complaint investigations show that the entire batch of distributed product is defective.

4.	Visual inspection of retained samples show evidence of deterioration that has an impact on product quality.
5.	Pharmacovigilance reports indicate a serious safety risk to those taking the medication.

(b) Statutory recall

- These are recalls mandated by drug regulatory bodies at Central or
- State levels for one of the following reasons:

1.	The product violates the law – Example, it is not of standard quality.
2.	The formulation contains banned drugs.
3.	The labeling of the product or promotional material violates the law.
4.	Product is found to contravene provisions of Schedule J (it claims to cure a disease/disorder that no drug can claim to do)

❑ Reasons for Product Recall

1.	Potentially dangerous/serious product quality issues have come to light through complaints or other means.
2.	Mandatory regulations have been violated and come to the notice of regulatory agencies, who then order a recall.
3.	New information that comes to light after distribution of a product indicates it is unsafe or ineffective or dangerous

Most common reasons for drug recalls:

- ✓ cGMP violations.
- ✓ Microbial contamination in non-sterile products.
- ✓ Failing dissolution test requirements.
- ✓ Degradation products/impurities.
- ✓ Lack of efficacy.
- ✓ Labeling errors (declared strength).
- ✓ Lack of assurance of sterility.
- ✓ Misbranded drug (therapeutic claims that are unapproved in promotional literature).

- ✓ Lack of drug stability.
- ✓ Incorrect outer packaging (correct label on product, packed in incorrect carton).

❑ Recall Classification

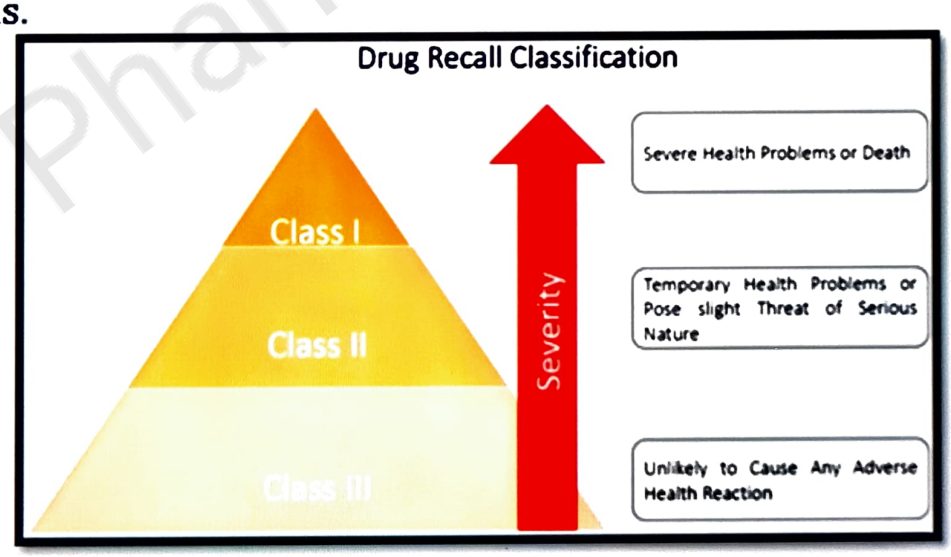
- According to FDA classified the product recall depending on the health hazard caused by the product:

1. Class I

- Class I is a situation in which there is a **reasonable probability** that the use of or exposure to a violative product will cause **serious adverse health consequences or death.**
- Example- pathogen in ready to eat , Salmonella, High level of heavy metals.

2. Class II

- Class I is a situation in which there is a reasonable probability that the **use of or exposure to a violative product will cause serious adverse health consequences or death.**
- Example- pathogen in ready to eat , Salmonella, High level of heavy metals.



3. Class III

- It is a situation in which the **use of, or exposure to, a defective product is not likely to cause any adverse health consequences.**
- Here, recall is executed until the wholesaler level, and a time limit of upto 30 days is permitted.

❑ Product Recall System

- Recall strategy details must include information regarding:

1. **Authorized person** who will initiate the recall.
2. **Nature of communication** that will be used to initiate recall (telephone, email, letters etc.).
3. **Depth of the recall** to be instituted (recall from distributor/wholesaler/hospital/retailer/general public).
4. **Manner of receiving,** segregating and secure storage of the recalled product.
5. **Reconciliation reports** to be prepared, at what frequency.
6. **Verification of success** of recall and report submission to regulatory authorities.
7. Steps to be taken to **avoid re-occurrence** of the same issue with the product.
8. Dealing with **recalled product – reworking or destruction** as may be appropriate.

❖ Waste Disposal

- Pharmaceutical industry generates a lot of waste during the **manufacturing** and **testing** of drugs. It is important to ensure that this waste is appropriately treated to prevent it from polluting the environment.

❑ Types of Wastes

- Waste in the pharmaceutical industry may be of different types

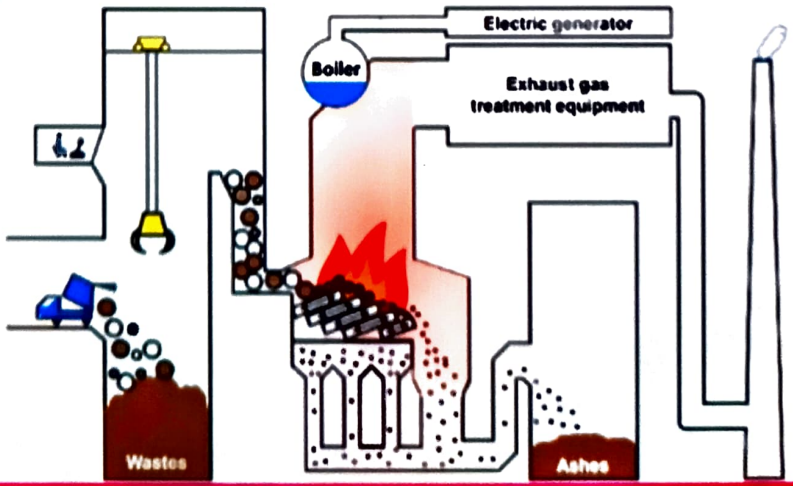
1. **Hazardous wastes**
2. **Non-hazardous wastes**
3. **Inert substances**
4. **Biomedical wastes**

Hazardous wastes	• These are wastes that are potentially dangerous to human health or the environment. • They may be solid, liquids, gas containing or sludgy in nature. • Such waste contains chemical products that may be ignitable ,corrosive ,reactive and toxic
Non-hazardous wastes	• These are materials that do not present a significant hazard at the levels in which they are present.
Inert substances	• These are materials that do not have any therapeutic effect, but they are used for supportive nutrition, for example, dextrose or sodium chloride solutions.
Biomedical wastes	• These are wastes generated during treatment or diagnosis of human beings or animals, or during biological material production and testing. Hospital waste is a major example of this type.

❑ Disposal of Pharmaceutical Waste

1. Incineration or thermal treatment:

- In this method, solid organic waste materials are **incinerated** or **burnt** to convert them into **gaseous products and a solid residue** in the form of ash.
- This is one of the most effective methods, and can be used for disposal of solid, liquid as well as gaseous wastes.



2. Chemical disinfection:

- This method involves treating **waste materials** with some chemicals that will inactivate the chemicals or biological materials that may be present in liquid waste.
- The **effectiveness** of the process depends on the type of chemical used, its concentration, and nature of contact between the disinfectant material and the wastes.

3. Microwaving

- **Microwaving involves the use of microwave radiation** and can destroy the infectious materials in biomedical waste.
- It is advantageous because the electricity requirement is less; steam is not needed either.

4. Autoclaving:

- Here, **saturated steam is passed through the waste in the autoclave** for a duration and at a temperature sufficient to destroy pathogens.
- This is most commonly used for biomedical waste disposal and also waste generated from the microbiological testing laboratory.
- The waste produced after autoclaving must be disposed by landfilling.
- Autoclaving is not the best method for chemical or pharmaceutical waste.

5. Secure land filling:

- Here, the wastes are disposed by **burying** in a landfill that has been designed to contain the **hazardous wastes.**
- Unless properly designed and operated, the landfill may lead to liquid leaching into the ground water, attraction of vermin and other such problems.

6. Sewer treatment:

- Liquid drug products can be largely diluted by mixing with water and flushed down the sewer very slowly in small quantities.
- Small quantities of very diluted medicines may be flushed down fast flowing water bodies too.

7. Waste immobilization – inertization

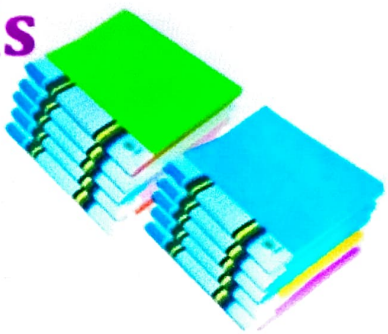
- Inertization involves grinding of **pharmaceutical products** after removing them from the packing materials.
- The ground product is mixed with cement, water and lime and made into a paste.
- **This paste is transported to a landfill and poured into normal waste where it sets as a solid mass.**

UNIT-IV

Document maintenance in Pharmaceutical industry

Points to be covered in this topic

- ❖ Batch formula record
- ❖ Master formula record
- ❖ SOP
- ❖ Quality audit
- ❖ Quality review & quality documentation
- ❖ Reports and documents
- ❖ Distribution records



Document maintenance in pharmaceutical industry

❖ Introduction

- Method of preparing a written material, which describes the process in terms of **specifications** and **instructions** etc.
- Proper documentation is the backbone of **current Good Manufacturing Practices (cGMP)** and in the regulatory world, it is commonly held that "If it isn't documented, it wasn't done!"

❑ Importance of Documentation in Pharmaceutical Industry

- Documents are evidence of all **manufacturing** and **testing activities** and provide traceability to verify if certain actions were performed or not.
- Written procedures provide **clarity** and ensure there are **no errors** that may arise during spoken communication.
- **Records, documents** and **reports** give a clear picture of what has been done and is ongoing work, and it also helps to plan better for the future.
- A **comprehensive review** of the documents maintained in a pharmaceutical facility is often the key used by regulatory bodies to assess the quality function of the facility.
- **Accurate** and **clear records** allow the critical reviewing of processes, which can help to improve quality and create cost-saving measures too.
- **Good documentation** is a must to attain ISO certification and any other industry specific certifications.

❑ Types of Documents

1.	Primary records	Contracts, production formulae, packing instructions, supply source documents etc.
2.	Procedures or supporting documents	SOPs, instructions, manuals, guidebooks
3.	Subsidiary records	Equipment/instrument printouts, calibration reading reports etc.

4.	Quality control records	Test methods, test results, investigations, internal audit reports, Corrective and Preventive Action (CAPA) reports, recall files etc.

❖ Batch manufacturing record (BMR)

- A batch manufacturing record is a **written record** that documents the entire **manufacturing process** and the **history** of a product batch.
- In other words, it tells you how to produce a product and records the way that happens.
- A batch is a **specific quantity of a chemical, food, drug or other material** that, according to the FDA, "has a uniform character and quality, within specific limits, produced according to a single manufacturing order during the same cycle of manufacture."
- BMRs are used in **chemical** and **process manufacturing** to ensure health, safety and quality while meeting FDA requirements.
- These regulations apply to companies that make consumable products or those that go on the body, including pharmaceuticals, packaged foods, nutritional supplements and personal care products such as deodorant and shampoo.
- But before creating the BMR, chemical and process manufacturers must create another document: the **Master formula record (MFR).**

❑ Contents of BMR

✓ Name of the product.
✓ Date and time of commencement and completion of important stages in the processing.
✓ Name of persons responsible for each critical stage, with initials of operators handling each operation and persons who checked these operations.
✓ Name and quantities of each raw material actually weighed with the batch number from which the material was drawn (including details of any re-processed materials added).
✓ Major equipment used in the processing.

✓ Results of readings for critical processing parameters.
✓ Details of samples drawn.
✓ In-process testing reports.
✓ Actual yield obtained at critical phases.
✓ Any deviations from procedure, with signatures to authorize the deviations; their evaluation and investigation if conducted.
✓ Packaging material and label description, with representative material attached.
✓ Results and reports of QC testing of final product for approval of the batch.

❖ Master Formula Record

- A Master Formula Record is defined as an **approved master document,** with instructions of how the entire manufacturing process must be performed for each batch size of each product to be manufactured.
- This document ensures that there is **uniformity** across batches of the same product.
- The MFR must be **prepared, signed** and **dated** by one competent individual, and independently checked, signed and dated by another competent person in the quality department.
- All processing of a given batch must proceed as per its MFR.

❑ Contents of MFR

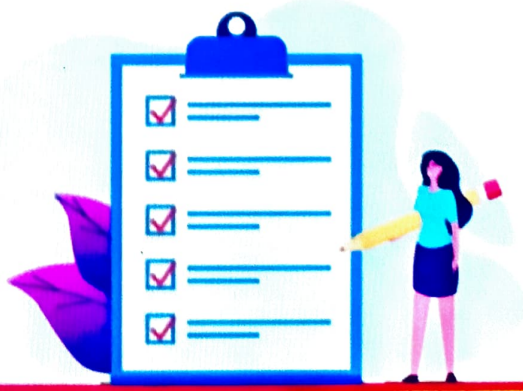
✓ Name of product, its strength and dosage form description.
✓ Name and measure/weight of each active ingredient per dosage unit or per unit weight or per measure of drug product.
✓ Statement of total weight or measure of a dosage unit.
✓ List of component names and their weight or measure using same weight system.
✓ Statement of theoretical weight or measure where necessary in the processing phase.

✓ Description of containers, closures and packaging materials to be used for the drug product packing.
✓ Specimen or copy of each label/labeling material with date and signature of authorized person who has approved the labeling.
✓ All manufacturing and control instructions in detail.
✓ Procedures for sampling and testing
✓ Specifications for raw materials, intermediates and finished products.
✓ Instructions for storage of intermediates and finished products.

❖ Standard Operating Procedure (SOP)

- A standard operating procedure (SOP) is a **written** set of instructions describing **step-wise** how a routine activity is to be performed.
- An SOP must contain a **straightforward** description of the task to be carried out, in simple language, and cover all the major steps in **performing the task.**
- SOP must be written by persons who have **sufficient knowledge** and **experience** with the task being described.
- SOPs must be written in **clear language using the active tense.**
- Any **abbreviations** or acronyms used in the SOP must be explained at the beginning of the SOP.
- SOPs must be prepared by the **respective departments**, and then reach QA for a review for checking if it complies with cGMP.
- After QA approval, the SOP must be **signed, dated** and **authorized** for issue by senior personnel of the concerned department.

❑ Contents of SOP



- **Title page**
- **Table of contents**
- **Procedures**
  - Scope
  - Method summary

- Definitions
- Health and safety warnings
- Cautions
- Interferences
- Personnel qualification/responsibility
- Equipment / supplies
- Procedure in steps
- Calibration/standardization
- Sample collection, handling and preservation
- Troubleshooting
- Data entry, calculation and report writing

- **QA/QC section**
- **References section**

❖ Quality Audits

- A quality audit is an **independent evaluation** performed to review if activities are performed in a manner to comply with set objectives defined in the company's quality system
- In the pharmaceutical industry, audits are an **effective means** of verifying if the different departments comply with **cGMP regulations.**

❑ Purpose of the Audit

- Audits serve to verify if the **production** and **control systems** are operating as intended.
- Regular audits help to provide confidence that the **organization** is **functioning** under effective control.
- Audits performed in problem situations such as **product recall** or repeated market complaints is useful to identify non-compliance with cGMP and to drive initiatives to take the necessary corrective actions.

❑ Audit Types

- Quality audits may be of three types – **internal audits** or **self-inspections, external audits** for contract manufacturing/testing and regulatory audits performed by regulatory bodies.

INTERNAL AUDITS	• are done by auditors within the company to assess cGMP compliance, identify problem areas and take corrective action, and to prepare for audits by regulatory bodies.
EXTERNAL AUDITS	• are carried out by a company at the sites of its vendors or contract manufacturers or testing laboratories. • This type of audit helps to assess if the outside party understands the contract-giver's requirements and adheres to the quality system to reduce failure risk.
REGULATORY AUDITS	• are performed by regulatory bodies to check for adherence to statutory requirements. These audits are a must to ensure data quality and integrity in respect of products that seek regulatory approval.

❖ Quality Review & Quality Documentation

- It is **regular periodic review** & **documentation** of all licensed medicinal products.

❑ Objective

- Verifying the **consistency** of the existing process, appropriateness of current specification for both starting materials & finished products.
- To **highlight** any trends.
- To identify product & process improvement.
- It is an **effective quality control improvement tool** to enhance the consistency of the process and overall quality of the product.
- Determine the need to make changes the **manufacturing process,** process control, in process tests, product specification
- Verifies **compliance** with market authorization.
- Verifies **consistency** of manufacturing process.
- Determines the need for **re-evaluation** of existing processes.

- Identification the product & processes improvements
- Identifies any Adverse trends & need to take Corrective & preventive action.

❖ Reports & Documents

- Report is defined as it gives a **spoken** or **written account** of Something that one has observed, heard, done or investigated.
- "Documents is defined as a piece of written, printed or electronics matter that provides information or evidence or that series As an official Record.

❑ Objective

- To define the **Specification** & **procedures** for all materials and manufacture & control methods.
- To ensure that the **personnel associated** with manufacturing know their work & time of doing it.
- To ensure the availability of data required for **validation**, **review** & **Statistical analysis.**

❑ Contents of Reports and Documents

1. **Name**
2. **Subject.**
3. **Purpose.**
4. **Date & time**
5. **Scope**
6. **Contents**
7. **Background**
8. **Summary**
9. **Any figures & illustration**
10. **Conclusion**
11. **Name & signature of authorized person.**

Signature

❖ Distribution Records

- **Batches** are released for distribution by the QC department only after thorough **testing and approval.**
- The **warehousing department** must maintain records of batches released for distribution in a systematic manner.
- For every batch of product, it is important to maintain **distribution records** in sufficient detail to be able to trace to which places the product has been sent.
- This is critical in the event of a problem with the product batch that necessitates a product recall from the market.

❑ Distribution record details

Some of the important details required include:

- **Name** of the product, its strength, and description of dosage form.
- **Batch number/lot number** of shipped product.
- **Name** and **address of consignee.**
- **Shipping date and quantity shipped.**
- Besides warehouse inventory records, distribution records also include **invoices, receipts from customers and bill of loading.**