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

B.PHARM

(SEMESTER –VII)

SUBJECT NAME: QUALITY ASSURANCE

SUBJECT CODE: BP706TT

UNIT 04 (b): DOCUMENT MAINTENANCE IN PHARMACEUTICAL INDUSTRY

Content

Document maintenance in pharmaceutical industry: Batch Formula Record, Master Formula Record, SOP, Quality audit, Quality Review and Quality documentation, Reports and documents, distribution records

Documentation

Document is a written report or record that provides information especially of an official or legal nature.

Documentation is a method of preparing a written material, which describe the process in terms of specification, instructions etc.

Documentation is the most important part of the quality assurance system. Documents must be approved, signed and dated by the authorized person.

CHARACTERISTIC OF DOCUMENT

For effective use of documents, they should be designed and prepared with utmost care. Each document shall:

- Have a clear title, nature and purpose
- Have a format which can check easily
- Clear and legible
- Have an identification number.
- Be approved by authorized person.
- Have the date of issue
- Have a due date of revision.
- List to whom it has been issued.

Purpose of Documentations

- Defines specifications and procedures for all materials and methods of manufacture and control
- Ensures all personnel know what to do and when to do it
- Ensure that authorized persons have all information necessary for release of product
- Ensures documented evidence, traceability, provide records and audit trail for investigation
- Ensures availability of data for validation, review and statistical analysis.

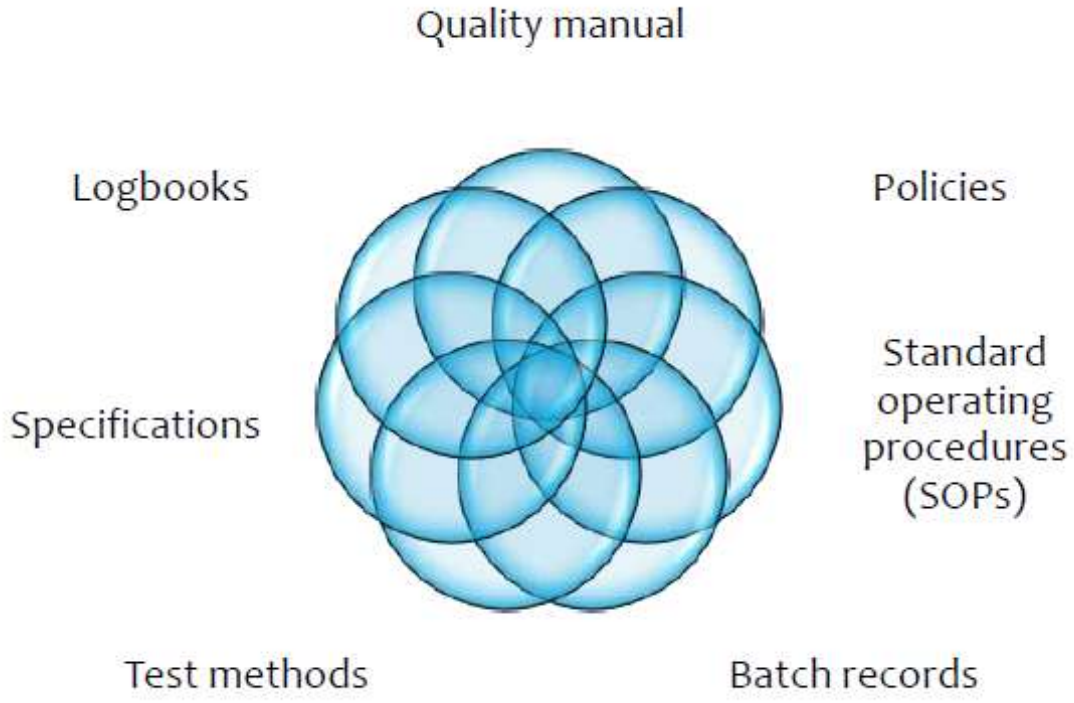
Importance of Documentation

- It provides necessary working details.
- Reduces the risk of mistake.
- Help in tracing the deviation from the expected yield.
- They help in decreasing the batch to batch variation so that quality of product is kept within the limits of acceptability.
- Considered as the history of batch operations.

- Self-inspection of procedure.

Following are the classification of Documents

- For organization & Personnel.
- For Buildings & facilities
- For Equipments.
- For Handling of R.M.& P.M.
- For Production & process control.
- For Packaging & Labeling control.
- For Holding & Distribution
- For Laboratory Control.
- For Records & Reports.
- For Return & Salvaged finished products.



Batch Formula Record

The batch production and control record follows every production batch through the plant. It provides a detailed description of all processing operations and controls, when they are performed, by whom, and where.

Batch processing records are required to be maintained for each batch of the product manufactured. These should be based on master formula records. Methods of preparation of batch processing records should be such that transcription errors do not occur.

Before any processing begins, check shall be performed and recorded to ensure that the equipment and work station are clear of previous products, documents or materials not required for the planned process are removed and that equipment is clean and suitable for use.

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

1. Name of the product
2. Batch number
3. dates and time of commencement, of significant intermediate stages and of completion of production,
4. name of the person responsible for each stage of production,
5. initials of the operator of different significant steps of production and where appropriate, of the person who checked each of these operations,
6. quantity, batch number, quality control report number of each ingredient actually weighed and amount of any recovered material added,
7. any relevant processing operation or event and major equipment used,
8. a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained, signature of person who performed,
9. the amount of product obtained after different and critical stages of manufacture (yield),
10. comments or explanations for significant deviations from the expected yield limits shall be given,
11. notes on special problems including details, with signed authorization, for any deviation from the master formula,
12. addition of any recovered or reprocessed material with reference to recovery or reprocessing stages.

Usually flow-sheets are prepared by the pharmaceutical industry for different pharmaceutical dosage forms. Formats for some commonly manufactured dosage forms are printed below which can be used as guide for preparing flow sheets.

FOR TABLETS

M/s (Name & address of the company)

_____

_____

Name of the product _____

(Trade Name, if any)

_____

(MFR No.)

_____

Batch No. _____ Batch Size_____

Date of Expiry_____

Date of commencement_____

S. No.	Ingredients in order of mixing	Stan-dards	Q/C Report No.	Label Claim	Quantity Required	Quantity actually used	Remarks % overages etc.
1	2	3	4	5	6	7	8

Total

Raw materials intially weighed or measured by _____
(attach requisition/issue slip duly signed by store personnel)

Weights/Measures counter-checked by

_____

I certify that I have checked all equipment and machinery to be used and same have been found clean.

Sign. _____

Mixing

Equipment used _____

Date	Time	Duration

Result of uniformity of mixing (in case of tablets, containing small quantity of active medicament) _____

(attach analysis report)

Wet Granulation

Equipment used _____

Date	Time	Duration

Drying

Equipment used _____

Date	Time	Temp. at which dried	Duration

(if tray dryer has been used, use this chart):

Time	Temperature

Moisture content of granules _____

Actual yield of granules _____

Theoretical yield of granules _____

Whether within permissible limits _____

Lubrication

Equipment used _____

Date	Time	Duration

Actual yield of lubricated granules _____

Theoretical yield of lubricated granules _____

Whether within permissible limits _____

Compression

Compression machines used _____

Punch size _____

Appearance _____

Humidity (in case of moisture sensitive products) _____

Hardness _____

Disintegration time _____

Friability _____

Weight of tablets _____ Average weight per tablet _____

Date(s) of compression _____

Results of test/Analysis of tablets _____

(attach QC report)

Coating

Nature of coating _____

Materials used for coating _____

S. No.	Ingredient	QC Report No.	Quantity used

Date(s) of coating _____

Date(s) of Polishing _____

Name of coater _____

Result of test/analysis of bulk finished product _____

_____

(Status, Report No. & Date)

Packaging

Packaging Description _____

Precoding of labels and printed packaging materials examined & verified by _____

(attach specimen)

No. of precoded

(i) Labels received _____

(ii) Printed packaging material received _____

Date	Start. time	Clos. time	Name of persons responsible for		
			Stripping		Other packg.
			Stripping	Checking	Counting & filling in boxes

Total Quantity packed _____

Date of completion _____

Quantity collected as samples by Q/C Department _____

Reconcilation of Labelling & Packaging Materials

Labels	Foil	Printed cartons
Requisitioned		
Received		
Used		
Returned		
Destroyed		
Destroyed on (date)		
Destroyed by		

Actual yield _____

Theoretical yield _____

Whether within limits _____

Q/C Report of finished product _____

Status No. & date and release order _____

Sign. of Supervisor _____

(approved technical staff)

Date of release _____

Quantity released _____

Date of transfer of finished product to warehouse _____

Counter signed _____

HEAD OF QUALITY CONTROL/QA DEPARTMENT

In-process Control sheet
Average weight

Name of Product _____
B. No. _____
Date _____

S. No.	Time	Weight of 20 tablets	Remarks

Test performed by _____

Signature _____

In-process Control sheet
Uniformity of weight

Average weight of tablet	Percentage deviation
80 mg or less	10.0
more than 80 mg but less than 250mg	7.5
250 mg or more	5.0

Date _____
Time _____

S. No. of tablet	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Weight of tablets																				

Weight of 20 tablets _____
Average weight _____

In-process Control Sheet
Uniformity of content

No. of Tablets taken _____
(These should be same as specified in assay procedure)
Amount of powder taken for testing _____

Protocol of test

content per tablets found	claim	limits

Note: Proceed with test further only if content of active ingredient(s) is within stipulated limits

S. No. of tablet	Content found
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

Limits

Not more than one of the individual values is outside the limits 85 to 115 % of the average value and none is outside the limit 75 to 125% of the average value. If two or three of the individual values are outside the limits 85 to 115% of the average value and none is outside the limits 75 to 125% repeat determination using 20 tablets

Repeat test

S. No.	Content per tab
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

Limits

The tablets comply with the test if in the total sample per tab of 30 tablets not more than three of individual values are outside the limits 75 to 125 % of the 2 average values

Result: _____

_____

_____

Test performed by _____

Signature _____

In-process Control Sheet

Disintegration test

Name of Product _____

B. No. _____

Date _____

Limits _____

_____

Run Time: ___

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	

Run Time: ___

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	

Run Time: ___

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	

Run Time: ___

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	

Run Time: ___

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	

Run Time: ___

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	

Repeat test, if applicable.

Uncoated tablets

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

Limits

Not less than 16 tablets out of 18 should disintegrate within specified limits

Coated Tablets
Medium: Water
For repeat test, it is 0.1 M hydrochloric acid.

Run Time _____

S. No. of tablet	Time taken to pass through sieve
1 2 3 4 5 6	

Limits

For coated tablets other than film coated ones, if any of them has not disintegrated repeat the test on further six tablets replacing water with 0.1 M hydrochloric acid. Tablets pass the test if all tablets have disintegrated in acid medium.

Enteric coated tablets
Date _____
Time _____

Acid Medium
0.1 M hydrochloric acid

Run time _____

S. No. of tablet	Time taken to pass through sieve
1 2 3 4 5 6	

Mixed phosphate buffer (pH 6.8)

Run time _____

S. No. of tablet	Time taken to pass through sieve
1 2 3 4 5 6	

Limits
Enteric coated tablets pass the test if (i) no tablet shows signs of cracks that would allow the escape of the contents of disintegration, apart from fragments of coating in acid medium; (ii) all six tablets have disintegrated in phosphante buffer

Dispersible & soluble tablets
Date _____
Time _____

Medium: Water at 24° to 26°C

S. No. of tablet	Time taken to pass through sieve
1	
2	
3	
4	
5	
6	

Limits

Disintegrate within 3 minute unless otherwise stated in the individual monograph

Uniformity of dispersion
No. of Tablets taken _____
Volume of water taken _____
Pass through sieve no 22 (710 µm) observation.

In-process Control Sheet
Dissolution test

Sample	Replicates	
	1	Medium Temperature RPM Dissolved active ingredient
	2	Medium Temperature RPM Dissolved active ingredient
	3	Medium Temperature RPM Dissolved active ingredient
	4	Medium Temperature RPM Dissolved active ingredient

5	Medium Temperature RPM Dissolved active ingredient
6	Medium Temperature RPM Dissolved active ingredient

Acceptance Table

Stage	Number Tests	Acceptance criteria
S_1	6	Each unit is not less than D + 5%
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than D and no unit is less than D – 15%
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than D, not more than 2 units are less than D – 15% and no unit is less than D – 25%

where,
D = amount of dissolved active ingredient specified in the individual monograph, expressed as percentage of the stated amount.

Limits: If results do not conform to the requirements at stage S_1 given in the acceptance table, continue testing with additional tablets through stage S_2 and S_3 unless the results conform at stage S_2.

Result _____

_____

In-process Control Sheet
Uniformity of container content

This test is applied to containers containing not more than 1000 units, limits for containers containing more than 1000 units limits given in the standards of Weights & Measures (Packaged commodities) Rules 1977 apply

Name of Product _____

B. No. _____

Date _____

Time _____

Sample Size : 10 Containers

Master Formula Record

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

The Indian and WHO GMPs require a manufacturer of the drugs to maintain master formula records for each product. These records should be prepared by competent technical staff and should be reviewed by the heads of production and quality control departments.

Units which have research and development department should associate this department also and master formula records should be reviewed by the heads of these three departments. Master Formula Records should describe the following.

- Name and strength of the product along with dosage form (if it is a pharmacopoeial product under trade name, both names will be given) and batch size.
- the name of the product together with product reference code relating to its specifications;
- The name and weight/measure of active ingredients per dosage unit or per unit weight/measure of the product and total weight/measure of any dosage unit.
- A complete list of all the ingredients to be used in the manufacture of the product indicating any special quality characteristics.
- An accurate statement of weight/measure of each ingredient required as per formula of dosage form and the weight/measure actually to be used.
- a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- A description of containers, closures and packaging materials to be used.
- A description of all vessels, equipment to be used in their preparation and methods or reference to the methods to be used for preparing and operating critical equipment.
- Processing and packaging procedures.
- detailed stepwise processing instructions and the time taken for each step;
- the instructions for in-process controls with their limits;
- the requirements for storage conditions of the products, including the container, labelling and special storage conditions where applicable;

- any special precautions to be observed;
- packing details and specimen labels.

A format, which may be used as guideline for preparing master formula records, is printed below:

M/s (Name & address of the company)

Name of the product _____

Trade Name, if any_____

Master Formula Record No. (MFR No.)_____

Effective Date _____

Approved by

Sign
Q.C. Manager

Sign.
Production Manager

*Specification of Raw Materials:

Name of Raw Material	Specification

*Specifications of Containers, Closures, Labelling and Packaging Materials:

Name of Item	Specification

Weighment Sheet:

S. No.	Ingredients (in order of mixing)	Specifications	Labelled claim per dosage unit	Qty. required as per label Claim	Qty. to be used	Overages	Remarks
1	2	3	4	5	6	7	8

Dispensing instructions:

List of Equipment and Machinery (may be appended as annexure):

Manufacturing Instructions including in-process controls to be exercised

Packaging Material Requirements (requisition and issue formats):

Packaging instructions:

Precautions to be taken

Finished product specifications

Expiry date

Review due on

Note: In-process control and theoretical yield/actual yield should be indicated at appropriate stage of manufacture.

SOP

One of the important activities in the implementation GMPs is preparation of SOPs. One may very well ask why should there be SOPs. One of the objectives of GMP is consistency in quality. Consistency in quality can be achieved by minimizing sources of quality variation. Lin, Lachman and Senkowski's have classified sources of quality variation into four major sources.

Sources of variation	Sources of quality variations
1. Materials	a) Variation between supplier of the same substance b) Variation between batches from the same supplier c) Variation within a batch
2. Machines	a) Variation of equipment for same process b) Difference in adjustment for same process c) Ageing and improper care
3. Methods	a) Inexact procedure b) Inadequate procedure c) Negligence by chance
4. Men	a) Improper working conditions b) Inadequate training and understanding c) Lack of interest & emotional upheavels d) Dishonesty, fatigue & carelessness

These sources of quality variations are required to be controlled. Preparation of SOPs is a step in this direction.

SOPs can be defined as written documents specifying the procedures that must be followed to carry out operations. One of the purposes of SOPs is to reduce the introduction of errors and variation in the operation. The other purpose of SOPs is of historical perspective i.e. how an operation was carried out.

Preparation of SOPs and their use is beneficial to an organization in many ways. Some of the ways in which these are beneficial are outlined here:

- Since SOPs outlines critical aspects of procedure, they help to assure that these aspects are appropriately emphasized while carrying out the procedure.
- Individual need not rely on memory or word of mouth communication procedure. This helps to prevent introduction of errors and variations.
- SOPs can be used to train personnel. Personnel under training can clarify the aspects which have not been clearly understood by them. This helps to prevent misunderstanding.
- Preparing an SOP will require an individual to think the whole operation and the procedure to be described. In doing this, he can identify the potential problems and their solutions. Thus, SOPs improve planning and organization.
- SOPs eliminate need to redevelop the procedure every time an operation is performed.

Some guidelines are given below to prepare SOPs. These guidelines will be helpful in preparing SOPs.

i. Give a clear & descriptive title to each SOP.

ii. Provide sufficient details. The SOP should meet the need of an individual, all the same, it should be general enough for more than one user.

iii. Flexibility should be written in the SOP wherever appropriate but it should not be made too general for, it may be useless in meeting its intended purpose.

iv. Organize SOPs according to order of sequence of events involved in performing the operation. Write the text in straight forward and easy to follow manner.

v. After drafting SOP, use it in performing the operation to ensure that it has sufficient details to perform the operation in intended manner.

vi. Take into account the instructions from the manufacturer of the equipment which is employed in performing the operation while drafting SOP.

vii. Indicate total number of pages so that user is certain that he is performing the complete operation.

viii. Indicate the effective date of the SOP.

The best way to prepare SOPs is to involve at least one person from each work area. The person selected should be asked to write down the procedure of the operation with details and the precautions should be taken.

The written down procedure should be discussed by a group of persons intimately connected with the operation. Modifications, if any, should be made. This should be handed over to the person who has been designated as co-ordinator. The co-ordinator should rewrite it, it is needed to bring uniformity in style & format.

It will be advisable to first prepare SOP for SOP. The following explanatory notes will be useful in preparing SOP for SOP.

- Design a format for SOP. This will maintain uniformity in writing SOPs.
- Device a system of assigning number to SOP. This may include a code for the department, activity to which it is related & version. For example, SOP for equipment cleaning in production department may be numbered as PR/EC/01/V1 or PR.EC.01.V1.
- Device a date format. Date format could be: DD/MM/YY or DD/MM/YYYY.
- Define elements of SOP, usually the following elements are included in a SOP:
  - SOP number;
  - Title of SOP;
  - Department;
  - Supersedes
  - Effective date, review date

- Prepared by, Approved by, Authorized or Issued by;
- Page No.
- Purpose/Object;
- Scope;
- Responsibility;
- Procedure;
- References;
- Distribution.

How to write SOP?

Supersedes: It is the Ref. No. of the earlier version. (In capital letters of font size 12)

Effective Date: It is the date from which the SOP shall be put in use. The date format has to be DD/MM/YYYY, where DD indicates the date, MM indicates the month & YYYY indicates the year (e.g. 01/11/2007). Date shall be written with blue indelible ink pen.

Review Date: It is the Month & Year during which the SOP shall be revised e.g. 21/2013, written with blue indelible ink pen. It shall be maximum 2 years from the effective date.

Page No.: It is like X OF Y. Where X is the individual page number and Y is the total number of pages.

Title: It shall be clear and descriptive. (In bold capital letters of font size 12).

Signature Block: It shall be below the header and only on the first page of the SOP.

(Titles in the rows & columns shall be in bold letters & other text in normal letters of font size 12. Name and designation shall be typed. And signature and date shall be put in blue indelible ink pen)

Prepared by: Signature with date, name and designation of the person from user department who has drafted the SOP.

Verified by: Signature with date, name and designation of the HOD or the person from user department who has verified the draft of the SOP.

Authorized by: Signature with date, name and designation of the person authorizing SOP, DGM QA or HOD QA.

Body: It shall contain the subject matter, which is written in the following Manner. (Subtitles in capital bold letters and text matter in normal letters of font size 12).

Objective: It shall define the purpose of the SOP.

Scope: It shall define the area of application.

Responsibility: It shall specify the person responsible for carrying out and monitoring the activity as per the SOP.

Procedure: It shall give all steps required by the process in a proper sequence and instructions to be followed while carrying out the activity so as to achieve the desired goals.

Procedure shall be:

a) Logically lay out.
b) Written in the imperative (authoritative) tense.
c) User friendly.
d) Simple to understand and in plain unambiguous English.
e) To the point with no unnecessary information.
f) In standardized terminology.

Abbreviation: This shall include list of abbreviations used and their meaning.

Annexure: This shall include list of annexure attached.

Reference: This shall include list of reference documents.

A blank format given on next page may be seen for guidance. It will be useful if a history page is attached with every SOP. The history page has record of revision(s) to that SOP. This page may contain the following information:

- Version number;
- Reasons for revision;
- Nature of revision;
- Revised by;
- Retrieval and distribution of obsolete copies.

SOP PROCESS

1. Sop Preparation:

The organization should have a procedure in place for determining what procedures or processes need to be documented.

SOPs should be written by an individual who performs the tasks routinely or someone who is directly responsible for the performance of the task.

2. SOP Review and Approval

SOPs should be reviewed by one or more individuals with appropriate training and experience with the process especially helpful if draft SOPs are actually tested by individuals other than the original writer before the SOPs are finalized.

3. Frequency of Revisions and Reviews

SOPs need to remain current to be useful. Therefore, whenever procedures are changed, SOPs should be updated and re-approved. If desired, modify only the pertinent section of an SOP and indicate the change date/revision number for that section in the Table of ontents and the document control notation.

SOPs should be also systematically reviewed on a periodic basis, e.g. every 1-2 years, to ensure that the policies and procedures remain current and appropriate, or to determine whether the SOPs are even needed.

4. Implementing SOP

The most important step for implementing the SOP is in working area, train or retrain the user. Everyone should follow the procedure exactly with each and every step in detail, it is very important to train the user otherwise individual may interpret meaning in different ways.

While training the user trainer should share the reason WHY, SOP must performed correctly. People are much more to follow when they understand importance of procedure.

Trainer should explain and demonstrate how each step in the SOP will be performed and should assure them this will increase Quality of product by providing safety and accuracy which will ultimately increase the confidence of the user.

5. Management of SOP

Organization shall have SOP on Preparation, approval, revision and control of standard Operating Procedure for better control and management of SOPs.

Generally, administrative aspects of the SOP system such as distribution and filing are well managed. On the other hand, overall system management, frequently characterized by the lack of a system owner, is generally poor. If a system owner exists at all, his or her responsibilities are limited.

Blank Format for SOP

Name of company: _____

Site: _____

SOP No. _____ Total pages: _____

Title: SOP FOR _____

Department _____

Effective date _____ Review date _____

Prepared by:

Approved by:

Authorized or issued by:

Purpose:

Scope:

Responsibility:

Procedure:

Step 1
Step 2
. .
. .
. .
. .

References:

Distribution:

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.

The purpose of quality audit is to find out whether the company is complying with all aspects of GMPs in production and quality control.

Definition:-

Quality audit is defined as a systematic and independent examination of a quality system carried out by an internal or external quality auditor or an audit team to determine whether activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

Quality audit means a systematic examination of a quality system.

Quality audits are typically performed at defined intervals.

Reasons for quality auditing:

- Determine the level of compliance
- Build confidence (hopefully) in GMP and the QC system
- Build interdepartmental trust, understanding, and communication (if the audit is done properly and tactfully)
- Determine measures necessary to improve, e.g.,: Premises, equipment, environment Operations, actions, procedures
- Personnel/training
- Provide a stimulus for improvement
- Recommend corrective action
- Monitor improvement

Types of Quality Audit

1. **Internal audit:** The Company performs audits by its own system, procedures and activities in order to ascertain whether they are adequate and being complied with.

2. **External audit:** External audits are audits carried out by a company by its own vendors or subcontractors.

3. **Regulatory audit:** These audits are carried out by regulatory bodies against relevant regulations for the manufacture and supply of pharmaceutical products.

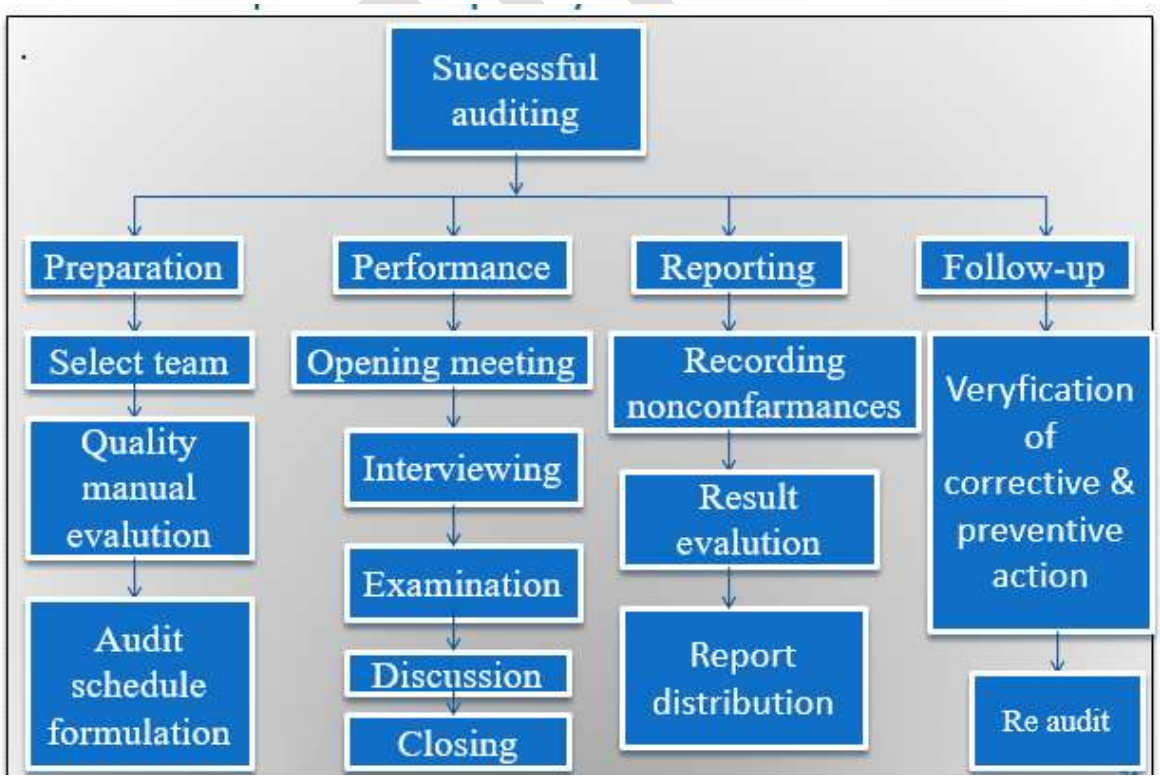
National regulatory bodies, such as the Medicines Control Agency (MCA) in the UK and Food and Drug Administration (FDA) in the USA, are statutorily responsible for carrying out such audits.

4. **Product audit:** This type of audit is an examination of a particular product or service, such as hardware, processed material, or software, to evaluate whether it conforms to requirements.

5. **Process audit:** This type of audit verifies that processes are working within established limits. It evaluates an operation or method against predetermined instructions or standards to measure conformance to these standards and the effectiveness of the instructions.

6. **System audit:** An audit conducted on a management system. It can be described as a documented activity performed to verify, by examination and evaluation of objective evidence, that applicable elements of the system are appropriate and effective and have been developed, documented, and implemented in accordance and in conjunction with specified requirements.

STEPS TO PERFORMING A QUALITY AUDIT



1. **Audit planning and preparation:**
   Audit preparation consists of planning everything that is done in advance by interested parties, such as the auditor, the lead auditor, the client, and the audit program manager, to ensure that the audit complies with the client objective.

Following Audit Preparation Checklist may be set down:

- Agree date and time of audit
- Clarify and communicate objectives and the standard, regulation, or guideline against which audit will be performed
- Decide type of audit and auditing strategy
- Define areas or systems to be covered
- Inform auditee

It is important to learn as much as possible (and to think as much as possible) about the site or area to be audited, in advance.

Obtain and review details of site or area to be audited, e.g.:

- Site or area plans or drawings
- Personnel organization charts
- Products manufactured
- Quality Manual, or Site Master File (if available)
- Any available records of complaints and recalls
- Any reports of previous audits and follow-up records

Prepare a structure for note taking, or devise a checklist

Hold final team briefing meeting

2. Audit Execution and performance:

It is the data-gathering portion of the audit. It consists of multiple activities including in-site audit management, meeting with auditee, understanding the process and system controls and verifying that these controls work, communicating among team members, and communicating with the auditee.

After all above things done, examination is to be carried out. Generally whole process, performance of authorized person and all facilities are inspected according to GMP.

3. Audit reporting:

The purpose of the audit report is to communicate the results of the investigation. The report should provide correct and clear data that will be effective as a management aid in addressing important organizational issues.

4. Audit follow-up and closure:

According to ISO 19011, clause 6.6, "The audit is completed when all the planned audit activities have been carried out, or otherwise agreed with the audit client." Clause 6.7 of 19011 continues by starting that verification of follow-up actions may be part of a subsequent audit.

Self-inspection:

Self-inspection is basically a method of objective overall review of one's own operation on aspects that may have on quality effect on quality assurance.

- Purpose of self-inspection is to evaluate the manufacturer's Compliance with GMP in all aspects of production and Quality control.
- The self-inspection programmed should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.
- Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is concerned.
- The procedure for self-inspection should be documented.

Self-Inspection Team:

Management should appoint a team from the staff and or from outside. The persons selected should be experts in their fields and should be familiar with GMPs. Members of the team should be from different areas of experience. It is advisable to have them from:

- Quality assurance/quality control
- Production and engineering;
- Production planning and inventory control;
- General affairs

Items for Self Inspection:

To provide a minimum and uniform standard of self-inspection the WHO text of GMPs has prescribed items of self-inspection. Self-inspection should include following items:

- Personnel,
- Premises including personnel facilities
- Maintenance of buildings and equipment,
- Storage of starting materials and finished product,
- Equipment;
- Production and in-process controls;
- Quality control;
- Documentation;
- Sanitation and hygiene;
- Validation and revalidation programmes;
- Calibration of instruments or measurement systems;
- Recall procedure;
- Complaints management;
- Labels control;

- Results of previous self-inspections and corrective steps taken. Self-inspection report and follow up action

Questionnaire can be prepared on the items of self-inspection.

Quality Review and Quality Documentation

QUALITY REVIEW:

Regular periodic or rolling quality reviews of all authorized medicinal products, including export only products should be conducted.

Purpose of this review is to verify the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

Product Quality Reviews (PQRs) are important for communication between manufacturing, quality and regulatory Affairs, to enable quality improvement processes.

Regular reviews of process and quality system performance is necessary to ensure product quality.

All regulatory authorities require "reviews“ which may be called

- "Annual Product Review“ (US GMP term), or
- "Product Quality Review“ (EU GMP term)

Benefits of PQR

- Decrease the risk of out-of-specification results.
- Minimize the risk of rework/reprocessing
- Decrease downtime
- Increase productivity
- Decrease the risk of product recalls
- Meet all regulatory commitments/requirements
- Improve communication between production, engineering, quality and regulatory functions

Requirements:

There should be a written procedures, which must be followed when conducting Product Quality Reviews.

The Product Quality Review should cover a one year rolling period.

The review should normally be completed within sixty (60) calendar days of the period close and must in all cases be completed within ninety(90) calendar days of the period close.

If the production is less than 10 batches per year, an annual product review must still be conducted and this review can include a review performed on the 2 or 3 preceding production years.

The number of batches to be considered is the number of batches manufactured during the agreed annual period. The Product Quality Review must include all batches of product whether they were accepted or rejected or destroyed during manufacture.

The Product Quality Review report must address the assessment of data, documents and electronic records reviewed.

Product Quality Reviews are to take into account previous reviews.

Quality Review must include:

- Review of starting materials (API(s) & Excipients) and primary packaging materials
- Critical in-process controls, finished product results and critical API test results
- Number of batches manufactured, including partially completed batches and corresponding yields
- Number and percentage of batches rejected and related reasons
- Number and percentage of batches reworked or reprocessed and related reasons
- Review of "deviations from the validated state“
- A review of all batches that failed to meet established specification(s) and their investigation
- Out of Specification Results and related failure investigations
- Product quality complaints
- Product Recalls
- A review of the adequacy of all corrective & preventive actions
- Product quality Review must be prepared for each water quality grade produced at each site.
- If one quality of water is only used for one product, the data concerning this water can be included in the PQR of the corresponding FPP.
- For critical utilities it is recommending either to perform a separate PQR or to include a specific chapter in the corresponding PQR.
- Changes effected (change control) and variations during the period (e.g. process, suppliers, equipment, facility).
- Changes of product specifications or methods (e.g. analytical changes as required by regulatory bodies, FPP appears in compendium, etc.)
- Any outstanding validation commitments or corrective and preventive action plans from last PQR and its status?
- Is the qualification status (IQ/OQ/PQ) acceptable for production and QC equipment?

RESPONSIBILITIES

Individual departments, such as, Supply Chain, Engineering, Production, Quality and Compliance, Pharmacovigilance and Regulatory Affairs are responsible for providing data required (if any) and participating in the Product Quality Review process.

QUALITY DOCUMENTATION:

There are many documents are recorded and maintained after quality control tests of raw material, finished products and finished products. Some general documents are listed below.

1. **Specifications:**

   These types of documents covers the all testing parameters of any type of dosage form along with their criteria or limit. These documents should be prepared from pharmacopoeia.

   This document is to be prepared in form of table. Specification is prepared for raw material, excipients, finished product and packaging material.

   This document includes the following details-

   - Title of document
   - Material/Product name
   - Reference standard
   - Material/Product code
   - Sample quantity
   - Specification no.

- Standard testing procedure no.
- Effective date
- Review date
- Page no.
- List of tests with specification
- Name and signature of authorized person who have prepared, reviewed and approved the document

Following is the format for specification for raw material:

RAW MATERIAL SPECIFICATION			
Material Name	Aspirin		
Reference	USP	Page	
Material Code		SPEC No.	
Sample Quantity		STP No.	
Effective Date		Review Date	

Sr. No.	TESTS	SPECIFICATION
1	Description	White to off white coloured powder.
2	Identification	Heat it with water for several minutes, cool, and add 1 or 2 drops of ferric chloride TS: a violet-red color is produced.
4	Loss on drying	Not more than 0.5 % of its weight
5	Residue on ignition	not more than 0.05 %
6	Chloride	not more than 0.014 %
7	Heavy metals	Not more than 10 µg per g
8	Assay	Aspirin contains not less than 99.5 %t and not more than 100.5 % of $C_9H_8O_4$, calculated on the dried basis.

	Prepared By	Reviewed By	Approved By
Name and Designation			
Sign/Date			

Following is the format for specification for finished product:

FINISHED PRODUCT SPECIFICATION			
Product Name	Aspirin Tablets		
Reference	USP	Page	
Product Code		STP No.	
Sample Quantity		SPEC No.	
Effective Date		Review Date	

Sr. No.	TESTS	SPECIFICATION
1	Description	White, round flat tablets
2	Identification	
	Method A	A violet-red color is produced.
	Method B: By IR	Complies
4	Dissolution	Not less than 80% (Q) of the labeled amount of $C_9H_8O_4$ is dissolved in 30 minutes.
5	Uniformity of dosage units	Meet the requirements.
6	Assay	Aspirin Tablets contain not less than 90.0 % and not more than 110.0 percent of the labeled amount of aspirin ($C_9H_8O_4$)

	Prepared By	**Reviewed By**	**Approved By**
Name and Designation			
Sign/Date			

2. Test Methods (Standard Testing Procedure):

These types of documents consists of procedures of all tests to be performed on raw material, excipients, finished product or packaging material. These documents are also prepared from respective monograph only.

This document include following information:

- Title of document
- Material/Product name
- Reference standard
- Material/Product code
- Sample quantity
- Specification no.

- Standard testing procedure no.
- Effective date
- Review date
- Page no.
- List of tests with procedure
- Name and signature of authorized person who have prepared, reviewed and approved the document

Following is the format for Standard Testing Procedure for finished product:

FINISHED PRODUCT STANDARD TESTING PROCEDURE			
Product Name	Aspirin Tablets		
Reference	USP	Page	
Product Code		STP No.	
Sample Quantity		SPEC No.	
Effective Date		Review Date	

Sr. No.	TESTS	TESTING PROCEDURE
1	Description	White, round flat tablets
2	Identification	
	Method A	Crush 1 Tablet, boil it with 50 mL of water for 5 minutes, cool, and add 1 or 2 drops of ferric chloride TS: a violet-red color is produced.
	Method B: By IR	Prepare the test specimen as follows. Shake a quantity of finely powdered Tablets, equivalent to about 500 mg of aspirin, with 10 mL of alcohol for several minutes. Centrifuge the mixture. Pour off the clear supernatant, and evaporate it to dryness. Dry the residue in vacuum at 60 for 1 hour.
4	Dissolution	Determine the amount of C9H8O4 dissolved from UV absorbances at the wavelength of the isosbestic point of aspirin and salicylic acid at 265 ± 2 nm of filtered portions of the solution under test, suitably diluted with Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same Medium.
5	Uniformity of dosage units	**Mobile phase and Diluting solution**—Prepare as directed in the Assay. **Standard solution**— Dissolve an accurately weighed quantity of USP Salicylic Acid RS in the Standard preparation prepared as directed in the Assay, to obtain

		a solution having a known concentration of about 0.015 mg of salicylic acid per mL. **Test solution**— Use the Stock solution prepared as directed for Assay preparation in the Assay. **Chromatographic system**— Use the Chromatographic system described in the Assay. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for salicylic acid and 1.0 for aspirin; the resolution, R, between salicylic acid and aspirin is not less than 2.0; and the relative standard deviation of the salicylic acid peak responses is not more than 4.0%. Procedure— Proceed as directed for Procedure in the Assay. Calculate the percentage of salicylic acid ($C_7H_6O_3$) in the portion of Tablets taken by the formula: $2000(C / QA)(rU / rS)$ in which C is the concentration, in mg per mL, of USP Salicylic Acid RS in the Standard solution; QA is the quantity, in mg, of aspirin ($C_9H_8O_4$) in the portion of Tablets taken, as determined in the Assay, and rU and rS are the peak responses of the salicylic acid peaks obtained from the Test solution and the Standard solution, respectively: not more than 0.3% is found. In the case of Tablets that are coated, not more than 3.0% is found.
6	Assay	**Mobile phase**— Dissolve 2 g of sodium 1-heptanesulfonate in a mixture of 850 mL of water and 150 mL of acetonitrile, and adjust with glacial acetic acid to a pH of 3.4. **Diluting solution**— Prepare a mixture of acetonitrile and formic acid (99:1). **Standard preparation**— Dissolve an accurately weighed quantity of USP Aspirin RS in Diluting solution to obtain a solution having a known concentration of about 0.5 mg per mL. **Assay preparation**— Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 100 mg of aspirin, to a suitable container. Add 20.0 mL of Diluting solution and about 10 beads. Shake vigorously for about 10 minutes, and centrifuge (Stock solution).

		Quantitatively dilute an accurately measured volume of the Stock solution with 9 volumes of Diluting solution (Assay preparation). Retain the remaining portion of Stock solution for the test for Limit of free salicylic acid. **Chromatographic system**: The liquid chromatograph is equipped with a 280-nm detector and a 4.0-mm × 30-cm column containing packing L1. The flow rate is about 2 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not greater than 2.0; and the relative standard deviation is not more than 2.0%. Procedure— Separately inject equal volumes (about 10 µL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of aspirin ($C_9H_8O_4$) in the portion of Tablets taken by the formula:

	Prepared By	**Reviewed By**	**Approved By**
Name and Designation			
Sign/Date			

3. Certificate of analysis:

A Certificate of Analysis refers to an authenticated document that is issued by Quality Assurance Department that ascertains that a product has met its predetermined product release specification(s) and quality.

It is document which includes the report of all analytical testing results after quality control test is carried out. This document is to be prepared for raw material, excipients, finished product and raw material. COA is prepared from specification of that particular material or product only.

Certificates of Analysis can be used to satisfy qualification and/or acceptance activities (e.g. receiving inspection) by customers that are subject to regulatory or governing body

This document includes following details.

- Material/ Product Name
- Batch No.
- Batch size
- Manufacturing Date

- Expiry Date
- Date of analysis
- Release Date
- Page Number
- Pack style
- List of test parameter with test specifications
- Test results
- Signature of person who perform analysis, check the document and approve document.
- Conclusion

FINISHED PRODUCT CERTIFICATE OF ANALYSIS QUALITY CONTROL DEPARTMENT			
Product Name	Aspirin Tablets USP		
Batch No.		Batch size	
Mfg. Date		Expiry Date	
A.R. No.		Date of Analysis	
Effective Date		Release Date	
Pack style		Page Number	

Sr. No.	**TESTS**	**RESULTS**	**SPECIFICATION**
1	Description		White, round flat tablets
2	Identification		
	Method A		A violet-red color is produced.
	Method B: By IR		Complies
4	Dissolution		Not less than 80% (Q) of the labeled amount of $C_9H_8O_4$ is dissolved in 30 minutes.
5	Uniformity of dosage units		Meet the requirements.
6	Assay		Aspirin Tablets contain not less than 90.0 % and not more than 110.0 percent of the labeled amount of aspirin ($C_9H_8O_4$)

	Analysed By	**Checked By**	**Approved By**
Name and Designation			
Sign/Date			

Conclusion:_____

Distribution Records

DISTRIBUTION:

Written procedures shall be established and followed, describing the distribution of drug products. They shall include:

- A procedure whereby the oldest approved stock of a drug product is distributed first.
- A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.
- Distribution record must be constructed and procedures established to facilitate recall of defective product. Manufacturer must maintain record of all distribution transactions involving in process or finished goods.
- All record should be indexed by either manufacturing batch-lot number of the packaging control number as a means of accountability until the shipment passes from the direct control of the manufacturer.
- The distribution process also include other considerations, it must be arranged so that a first in /first out movement of product occurs.
- These requirement is consistent with the intent of the stability and expiration dating policy.

DISTRIBUTION RECORD:

- Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.
- Distribution records shall be maintained in a manner so as to facilitate prompt and complete recall of the batch if necessary.
- Distribution records include a wide range of documentation such as invoices, bills of lading customers' receipts, and internal warehouse storage and inventory records.
- Records for distribution shall be maintained in a manner such that finished batch of a drug can be traced to the retail level to facilitate prompt and complete recall of the batch, if and when necessary.
- Prior to distribution or dispatch of a given batch of a drug, shall be ensured that the batch has been used, approved and released by the quality control personnel. Periodic audits at distribution centers shall be carried out and records shall be maintained.