

**REVIEW: GMP REQUIREMENTS ON DOCUMENTATION WITHIN PHARMACEUTICAL INDUSTRY**

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**ABSTRACT**

Documentation within pharmaceutical industry is an essential part of both the Quality assurance and Quality control system. Documentation describes the specifications for all materials, methods of manufacturing and control. It will allow the personnel to decide whether or not to release batch for sale. And also to permit investigation of history of batch of product through tool of audit trails. The purpose of this work is to specify the GMP requirements on documentation within pharmaceutical industry. In this article firstly Processing of documents like (preparation, issue, use, storage, retrieval, retention, and disposal) and briefly information about the PMD is described. Secondly specification about key documents concerning Manufacturing, testing, packaging and other aspects like (distribution, complaints, and labels) are described.

**KEYWORDS:** - PMD, Specifications, Quality Assurance, Quality Control, Batch, SOP, Record.

**INTRODUCTION:**

The Document is any a written statement or proof. Documentation is an essential Part of Quality Assurance and Quality Control system and it is related to all aspects of Good Manufacturing Practices (GMP). It mainly defines the specification for all materials, method of manufacturing and control. It also ensures that personnel concerned with manufacturing should know information to decide whether to release the batch or not for sale it also provides an audit trail which also allows the investigation of history of any suspected defective batch. These documents should be approved, signed, dated by appropriate and authorized persons. These documents shall specify their title purpose and nature. They should be regularly reviewed and kept up to date and if any alterations are made in their entry shall be signed and dated. For any organization it is very difficult to make a consolidated list of documents, which will meet all requirements of company.

Objectives of Documentation: -

1. It defines manufacturers system of information and control.
2. It will prevent the risk of errors and misinterpretation which are inherent in oral or casual written communication.
3. It allows the calculation to be checked.
4. It also allows the tracing of History of any product.
5. To provide confirmation of performance of task.

**Pharmaceutical Manufacturing Documentation (PMD):**

It is a really complex subject. For a PMD programme one needs to carefully study organizational environment and for this following need to be consider.

1. Manufacturing activities taken under that organization.
2. Which country's requirements of documentation the company needs to fulfill e.g. W.H.O., U.S.A. or any other?
3. Level of computerization available in that organization.
4. Any other consideration.

Steps involved in Total PMD Programme: -

- Step 1- Identify at least 2 knowledgeable persons from production and Q.A/Q.C. who are familiar with organization product profiles and Q.A/Q.C. Activities.
- Step 2- List out the manufacturing formulation departments.
- Step 3- List out the Q.A/Q.C. Activities.
- Step 4- List out the countries where the product is likely to be sold and their PMD requirements.
- Step 5- Categories the documents so as to meet the requirements of step 4.
- Step 6- Design the document.
- Step 7- Explain the document to concerned persons and train them for using same.
- Step 8- Trial run the document, study difficulties, modify if required.
- Step 9- Implement the document.
- Step 10 – Review it by receiving feedback from users at regular intervals.

Table 1: Categorization of Documents.

First Category.	Second Category.
Documents for personal training.	Standard Operating Procedures.
Documents for Quality control	Lists.
Documents for Building/Factory.	Charts/Formats.
Documents for Materials/Stores	Test methods.
Documents for Engineering.	Reports.
Documents for Distribution.	Specifications.
Documents for Market complaints.	MPCR and BPCR.

**Preparation, Issue and Use of Documents:**

Documents should be carefully and logically set out to allow their correct use and easy to check. Each document should include.

1. The name of company.
2. Purpose and title of Documents.
3. The document identity number.
4. Date of its authorization.
5. Date of its expiry or Review.
6. Signature of authorizing person.
7. Page number.
8. The distribution list where copies are distribute.
9. The way in which it is used and by whom.
10. The reason for its revision.
11. References used in its preparation.

Issued documents should not be hand written. Reproduced computer printed documents should be clear and legible. If any corrections are made in entry of document should be signed and dated. Where the documents which bears instructions should be written as imperative. Master documents which have direct bearing on product quality should be authorized by person responsible for Quality Assurance. Documents should allow sufficient space for entry, sufficient space between the entries and should clearly indicate what is to be entered.

**Storage and Retention of Documents:**

The completed documents and records of each batch should be retained for at least 1 year after expiry date of batch if expiry date is not mentioned then they should be retained for at least 6 years from the date of its manufacturing. Master documents should be kept secured from theft loss or alteration of information. Even the storage and retention of documents and records can be done in electronic format in the form of microfilms and microfiche that are photo reduced copies.

**Storage and Retrieval of Documents:** The documents should be stored in such manner that their retrieval is easy and for this purpose a system is adopted in which a list of documents are prepared as per their name, location, person to be contacted for its retrieval. Retrieval of master documents should be possible with proper authorization of Q.A.

**Disposal of Documents:** The expired Documents must be destroyed by Q.A. with proper record and authorization by suitable methods like shredding, burning.

**Type of Documentation within Pharmaceutical industry:**

**Master formula Records:** Such Type of master formula record is prepared for each product and batch size to be manufactured. These shall be prepared by competent technical staff like head of production and Quality control. They are one time documents. These documents are prepared to achieve uniformity within batch to batch. Such type of records shall contain.

1. Name of product along with its reference code which relate to its specifications.
2. The patent or proprietary name of product along with its generic name.
3. Description of dosage form, strength, composition of product and batch size.
4. Specifications for all starting material used.
5. A statement of expected final yield along with its acceptable limits.
6. A statement of processing location.
7. Methods or reference to methods used for preparing and operating critical equipments to be used.
8. Detailed stepwise processing instruction.
9. Instructions for in process controls.
10. Instructions for storage conditions of product including container, labeling and special storage conditions.
11. Any special precautions to be observed.
12. Packing details with specimen labels

M/S (name & address of the company) \_\_\_\_\_

Name of the product \_\_\_\_\_

Trade name, if any \_\_\_\_\_

Master formula record No. \_\_\_\_\_

Effective Date \_\_\_\_\_

Approved by

Sign	Sign
Q.C. Manager	Production Manager

Specification of Raw Material:

Name of Raw Material	Specification
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Specifications of container, closure, labeling and packaging Materials:

Name of item	Specification
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Figure 1: Master formula Record.

**Master packaging records:** - They should contain.

1. Name of the product.
2. Description of dosage form, strength and composition.
3. The pack size in terms of number of doses, weight or volume of product.
4. Complete list of all packaging materials required for standard batch size.
5. Special precautions to be observed including careful examination of area and equipments in order to ascertain line clearance.
6. Description of packaging operation.
7. Details of in-process controls with instruction for sampling.
8. Reproduction of relevant packaging materials and specimen indicating batch number and expiry date of product.
9. Detailed investigation of unexplained events e.g. discrepancy in number of units labeled and packaging units issued.

**Batch production record:** - It is a product and batch specific document designed to provide information on History of any batch of Product. It is a recurring document. It is based on the Master formula record and shall be compiled, checked and approved by competent technical persons responsible for Production, Quality control. The computer printout of such documents should prefer to avoid transcription errors. Such type of documents should contain.

1. Date and time of all activities which are carried out concerning the production and control of batch.

2. Identification of major lines and equipments to be used. Identification of rooms with their unique identification number.
3. Specific identification of in-process materials.
4. Weights and measures of components used in processing.
5. Inspection status of packaging and labelling area before and after it use.
6. A statement of actual yield and percentage theoretical yield at every stage of processing.
7. Complete labelling control records.
8. Description of container and closure system.
9. Any sampling which is performed during production and packaging activities.
10. Identification of persons supervising significant steps of operation.
11. Any investigation made of unexplained events like yield variation.
12. Results of examination made.
13. In-process and laboratory control results.

**Batch Packaging records:** - It should be kept for each batch which is produced/processed. It should be based on relevant parts of packaging instructions. And method of its preparation shall avoid transcription errors. As per the schedule M before any packaging operation begins checks shall be made and recorded that work stations are clear of previous products and equipment is clean and suitable for use. They should contain:

1. Name of product, batch number, and quantity of bulk product to be packed.
2. Date and time of packaging operations.
3. Name of person responsible for carrying out packaging operation.

4. Initials of operator and different significant steps.
5. Check is made for identity and conformity with packaging instructions.
6. Details of packaging operations carried out.
7. Details of sampling.
8. Note on any special problem encountered during operation
9. Identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock

Total quantity packed \_\_\_\_\_

Date of completion \_\_\_\_\_

Quantity collected as sample by Q/C department \_\_\_\_\_

Reconciliation of labeling & packaging material

Label	Foil	Printed cartons
Requisitioned		
Received		
Used		
Returned		
Destroyed		
Destroyed on		
Destroyed by		

Actual yield \_\_\_\_\_

Theoretical yield \_\_\_\_\_

Whether within limits \_\_\_\_\_

Q/C report of finished product \_\_\_\_\_

Status no. & date and release order \_\_\_\_\_

Sign. of supervisor \_\_\_\_\_

Date of release \_\_\_\_\_

Quantity released \_\_\_\_\_

Date of transfer of finished product to warehouse \_\_\_\_\_

Figure 2: Batch Packaging Record.

**Standard Operating Procedures (SOP):**

They shall be prepared by supervisor who supervising the actual performance of the operations of respective departments.

1. Objective: - This section should describe the intended use and applicability of SOP.
2. Responsibility: - This section should describe the designation of persons along with their responsibilities towards the implementation of objective of SOP.
3. Accountability: - This section should describe designation of persons who are seniors to person responsible for compliance of any SOP.
4. Procedure: - This section must include operating procedures in short and in unambiguous sentences. All the process checks must be clearly defined.

5. Implementation of SOP: - it is done after approval of SOP and then Q.A. department ensures that all persons who are user get appropriate training before implementation of SOP. And after its successful completion of training SOP becomes effective.
6. Issuance and Retrieval Of SOP: - The original copy shall be stamped as 'master copy' using red ink to the top right hand corner and the copies of it are distributed to all concerned departments the master copy is duly stamped as 'controlled copy' In blue to top of left hand corner and these master copies should be stored under strict supervision of Q.A.
7. Revision Of SOP: - SOP revision should be carried out as per 'change control procedures' the document change request form should be properly filled signed and attached with SOP and submitted to document section by respective department.

LEVEL	SOP NO		Page No. of
SUBJECT			
Prepared by	Position	Signature	Date
Checked by			
Approved by			
Authorized by			
Change control No.	Effective from Date		Reason for Revision.

Figure 3: Format of SOP.

**Site Master File:**

It is a document which contains specific and factual GMP Information about production and control on pharmaceutical manufacturing preparations carried out at licensed premises. Its format varies from country to country. The document should not be very much massive like running not more than 100 pages. At the same time it should not be very brief. It should be written of A4 size pages. It has total 10 chapters they are:

Chapter 1- General information: - It should include brief information of organization, its manufacturing activities, and other too. Name and address of site, type of product which are manufactured, Description of site, Employee details, Quality management system.

Chapter 2- Personnel: - it includes the organization chart, qualification experience and responsibilities of key personnel, Training, Health requirements, and clothing.

Chapter 3- Premises: - Description of Manufacturing area, nature of construction and finish, description of HVAC, Special areas, water system description, maintenance of premises.

Chapter 4- Equipments: -Maintenance of equipments, calibration, sanitation, major production and laboratory equipments.

Chapter 5- Sanitation: -Written specifications and procedures for cleaning of manufacturing areas and equipments.

Chapter 6- Documentation: - Preparation, revision and distribution of documents, additional documents, and other documents related to product quality.

Chapter 7- Production: - Brief description of Production activities, handling of products and rejected materials, general policy for process validation.

Chapter 8- Quality Control: -Description of quality management system.

Chapter 9- loan license manufacturing: - description of way to asses compliance of GMP by loan licensee.

Chapter 10- Distribution complaint and product recall: - arrangement and recording system for distribution, complaints and product recall.

Chapter 11- Self inspection: - Description of self inspection system.

Chapter 12- Export of drugs: - products exported to foreign countries their complaints, and recalls.

**Distribution Records:**

Records of distribution shall be maintained in such way that finished batch of a drug can be traced to retail level. And It should also allow the prompt and complete recall of batch whenever necessary.

**Complaints and Adverse reaction records:**

All complaints concerning the product quality has to carefully reviewed and recorded as per standard procedures. The complaints shall be evaluated by designated personnel of company and records of action which are taken shall be maintained.

Records concerning the adverse reactions result from the use of drug shall be forwarded to licensing authority.

**Specifications to be include in Documents:**

The GMP has also described the specifications to be included in documents they are:

1. Specifications for starting and packaging materials: - Specifications for starting, packaging, printed materials should provide description of materials which includes the designated name and internal code of reference, the reference to any pharmacopoeial monograph and to a qualitative and quantitative requirements with its acceptance limits. Depending on the specifications of company the other data like supplier information, specimen of printed materials, directions for sampling

and testing, storage conditions which are required and time period of storage are included.

**2.** Specifications for intermediate and bulk products: - These specifications should be similar to specifications for starting materials or for finished products as appropriate.

**3.** Specifications for finished product: - it should include the name of product along with its code reference, the designated name of its API, formula, description of dosage form its packing details, directions for sampling and testing, the storage conditions and shelf life, qualitative and quantitative requirements.

#### **Equipment Cleaning and Use Record:**

Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

#### **Laboratory Control Records:**

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing.

- 1.** A statement of or reference to each test method used;
- 2.** A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;
- 3.** A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
- 4.** A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;
- 5.** A statement of the test results and how they compare with established acceptance criteria;

**6.** The signature of the person who performed each test and the date(s) the tests were performed; and

**7.** The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

#### **Batch Production Record Review:**

Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

#### **Labels:**

Labels who are applied to container, equipments, or premises should be clear and should be in company's agreed format and should also be unambiguous. Labels on finished drug product should contain at least following information:

- 1.** Name of product.
- 2.** A list of API showing amount each present.
- 3.** Statement of net contents.
- 4.** Batch number assigned by manufacturer.
- 5.** Expiry date in uncoded form.
- 6.** Storage conditions and handling precautions.
- 7.** Directions for use, warning, precautions.
- 8.** Name and address of manufacturing company.

For reference standard labels should indicate the concentration, date of manufacture, expiry date, date of closure first open, storage conditions, and control number. All containers and equipments shall also bear labels. Different color coded labels should be used to indicate status of product (under test, approved) prior to release of the product all labels on containers, cartons and boxes shall be examined by Q.C. department.

### **Quality control Documentation:**

As per GMP some important documents should readily available to Q.C. department of company they are as follows;

1. Specifications for R.M, P.M, intermediate and finished product.
2. Sampling procedures for above.
3. Testing procedure and records.
4. Analytical reports and certificates.
5. Data from environmental monitoring.
6. Validation records of test methods.
7. Procedures for calibration of instruments and maintenance of equipments.
8. All Q.C. documentation related to batch record.
9. Trend evaluation data should be maintained for yields, environmental controls, and analytical test results.
10. Complete record should be maintained for any modification in established method of testing.
11. Complete record should be maintained for periodic calibration of lab instruments, apparatus, gauges and recording devices.
12. Complete record should be maintained for stability testing performed.
13. Complete record should be maintained for testing of lab. Standards, reagents, standard solutions.

### **CONCLUSION:**

Documentation is essential to achieve total approach towards GMP. It also ensures the availability of necessary data needed for validation, review and statistical analysis. The design of documents depends upon the manufacturer. Documentation also serves as existence of evidence and allows traceability. It also allows audit trail which will permit the investigations. Master documents like Master Formulae record, batch production record which have direct bearing on the product quality should always protected against theft, loss and alteration of information. Even the design of the PMD depends upon

the manufacturing activities, regulatory agencies certification, and computerization. These documents also serve as written statements and proofs and should be carefully handled and kept up to date. If any alteration is made in their entry should be signed and dated.

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