# DOCUMENTATION AS AN INTEGRAL PART OF QUALITY ASSURANCE IN THE PHARMACEUTICAL INDUSTRY

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**Abstract:** The basic rules in any Good Manufacturing Practice indicate that the drug manufacturer must keep proper documentation and records. The documentation helps to build a detailed picture of the functioning of the processes within the pharmaceutical industry, and thus provides a basis for planning improvements that will be implemented in the future.
Good manufacturing practice (GMP), which is part of quality assurance, ensures that products are consistently manufactured and controlled according to quality standards and according to their intended use. Good manufacturing practice is primarily aimed at reducing risk when performing activities that are involved in pharmaceutical production and control. Good manufacturing practice is a regulatory requirement.
Regulatory bodies during their inspections of production sites, often spend a large part of the inspection time in the review of the documentation and records made by the manufacturer. Documentation provides the route for auditors to assess the overall quality of operations within a company and the final product.
Effective documentation makes good visualization of the quality assurance system. Clearly written procedures prevent errors resulting from spoken communication, and clear documentation permits tracing of activities performed. Documents must be designed, prepared, reviewed, and distributed with care and must be approved, signed, and dated by the appropriate competent and authorized persons.
Records must be kept at the time each action is taken and in such a way that all activities concerning the development, production and the quality control of products are traceable. Storage of critical records must at secure place, with access limited to authorized persons. The storage location must ensure adequate protection from loss, destruction, or falsification, and from damage due to fire, water, etc.
Good Documentation Practice (GDocP) is a pharmaceutical industry term. Good Documentation is an integral part of the Good Manufacturing Practice and it is essential for the integrity of data collection and reporting for supporting development, registrations, commercialization, and life-cycle management of pharmaceutical products. Documents are a mirror to show actual image of any pharmaceutical industry. Such measures that collectively and individually ensure documentation, whether paper or electronic, is attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate.
'If it's not written down, then it didn't happen!'
**Keywords:** documents, records, Good Manufacturing Practice, Quality Assurance

## 1. INTRODUCTION

Documentation is key to compliance with Good Manufacturing Practice and provides traceability throughout development, production and quality control activities of the product. It provides evidence for auditors/inspectors to be able to assess the overall quality of operations within a company, as well as the final product.
Documentation is an integral part of the quality assurance system and as such is related to every aspect of Good Manufacturing Practice.
The goals of the documentation are:
- Establishing communication of information within the company,
- Proof of compliance with regulatory requirements/standards,
- Knowledge sharing among company employees,
- Spreading and preserving the experience within the organization. (Eudralex Volume 4, 2011)

## 2. MATERIALS AND METHODS

The paper presents literary data, which are analyzed and compared with real cases of creation, management and use of different types of documents within the pharmaceutical industry.

**3. DISCUSSIONS**

A document represents any information that needs to be controlled and maintained by the organization and the form/media in which it is contained (paper, electronic, photographic, etc.).

Documented information represents all significant data contained in documents and records/reports (on various media – mainly in electronic or paper form) which defines, describes and maintains the quality system and overall processes within the company.

Documents can be of internal or external origin (internal or external) and are the result of: regulatory requirements, requirements of implemented standards as well as documented information necessary for the operational functioning and effectiveness of the quality system. (WHO, 2014)

Regarding the way of using the documents, they are divided into two groups:

- Instructions (documents that define requirements, guidelines) and
- Records (documents that represent evidence of compliance with requirements).

*Hierarchy of the document system*

The company should provide a hierarchy of the document system. At the top of the pyramid should be all the regulatory documents that the company has to follow. All guidelines are represented here (EU GMP guideline, USFDA, ICH guidelines, PIC/S guidelines, etc.).

Immediately below them in the first level are the documents (eg the Quality Manual) which should provide the correct information for the company for the development, documentation and implementation of a quality system that will be in accordance with the applicable requirements and standards. All documents found at this level are applicable to all organizational units of the company.

At the next second level in the pyramid are documents (eg Quality Policy) that should establish guidelines at all levels of employees, with the aim of alignment and consistency between organizational units. This type of document should ensure the setting of quality objectives and the establishment of employee behavior in relation to quality. Standard operating procedures (SOPs) should be on the next level of the document hierarchy after quality policies. These types of documents provide specific "step by step" instructions that are created to ensure consistency of the process(es) they handle.

Third-level documents are usually specific to a certain organizational unit or a certain process.

The last level 4 of the pyramid contains documents with the highest specificity (eg batch records, forms, validation documentation). They are intended for a specific organizational unit, product, equipment or process. (Patel & Chotai, 2011)

*Site Master File*

The Site Master File is a document that the regulatory authorities require for review, in order to familiarize themselves with the company before conducting an inspection on it. This document was prepared by the drug manufacturer and presents a description of the company and its activities from the perspective of Good Manufacturing Practice.

This main site/plant document is a regulatory requirement that is explicitly described as a requirement in Chapter 4: Documentation of the EU GMP Guide, and its format and structure is described in F.5 PIC/S PE 008-4: Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File.

In April 1993 the Pharmaceutical Inspection Convention (PIC) published Guide PH 4/93, with detailed guidelines for the preparation of a Site Master File (Site Master File), but only as a recommendation. In November 2002 the Pharmaceutical Inspection Co-operation Scheme (PIC/S) published a revision of this document under the new title PE 008-1, where key changes were made to the requirements for this type of document.

The structure of this document consists of several chapters covering information related to the following topics:

- General information about the manufacturer,
- Manufacturer's quality management system,
- Staff,
- Premises and equipment,
- Documentation,
- Production,
- Quality control,
- Distribution, complaints, non-compliant products and withdrawal from the market,
- Self-inspection.

Together with these previous chapters, appendices related to the content of the document are added. (FDANews, 2013)

*Quality Policy*

The quality policy is a statement or principle of action, which describes the company's commitment to the quality of activities and products. Most often this document is interpreted as a short text that is created based on the company's goals and regulatory responsibilities, which describes the continuous commitment to quality improvement. It is a strategic document, which represents a directive from the top management with an emphasis on quality. The policy is publicly shared with employees and is the basis for setting quality goals and establishing employee behavior in relation to quality.

The quality policy is a requirement that is described in the following documents:

- Chapter 2: Personnel from the EU GMP guide
- ICH Q10: Pharmaceutical Quality System
- Chapter 2: PIC/S I GMP Personnel
- ISO 9001 Quality Management Systems – Requirements

It is the responsibility of the company's top management to establish a quality policy that will explain the company's overall quality intentions and directions. It should be shared, understood and applied by personnel at all levels in the company.

The quality policy is revised periodically in order to continue its effectiveness. (ICH Q10, 2008)

*Procedures/Standard Operating Procedures/Working instructions*

Procedures are written documents that define the processes as a whole and the responsibilities for all activities of those processes.

Standard operating procedures are documents that formalize the tasks in the company, by stating the positions of employees who are responsible for the process/s, as well as the resources used in the process/s. In this way, identification of the data about who, what and when is performed during each stage of the process is done.

Working instructions are documents that are elaborated and usually related to a specific Standard Operating Procedure. This type of document describes the activities "step by step" and contains more details about the execution of the tasks, including the method and time of execution. In other words, the work instructions show how the activities should be carried out. Most often, these documents are created based on the user manual from the equipment manufacturer, they contain uncomplicated instructions using simple language, in order to ensure consistency of the process/procedure.

These documents have a workflow that covers several stages:

- initiating/creating a new document/new version of a document,
- production (working version of the document),
- checking and approval,
- obtaining the status of an approved document,
- obtaining the status of a valid document,
- archiving of invalid version/invalid document.

Every workflow starts with a need for a new document or a new version of an existing document. First, the responsible person submits a request for the assignment of a new code or a new version of an existing code, respectively. During this procedure, there should be information about all persons who will appear as authors/verifiers or approvers of the document, as well as for whom it is intended.

In the draft phase, the designated author(s) of the document writes/drafts the document, which represents a draft or working version of the document. After the completion of this phase, the document is handed over to the reviewer(s) for document review.

During the review and approval stages, the document may be returned several times for refinement or corrections by the author(s). After it has been reviewed and approved by all designated reviewers and approvers, the document moves to the next stage and receives the status of an approved document. Approved documents are not yet available for use by end users.

While the document is in the stage of approved document, the responsible persons who are appointed for the preparation and verification of the document should conduct training of all persons who are involved in the process described in the document.

After successfully completed training, the document goes from the status of approved to the status of a valid/effective document, which is now available for end users. The documents are periodically revised, and the document can continue to be used in the same version and in the next period, if the content is still in accordance with the process it describes. If there are changes, a new version of it is issued, and if it is no longer applicable, it moves to the stage of an archived document. (Hollmann et al, 2020)

*Documents for using and cleaning the equipment*

The documents (records) which are used during using, cleaning, sterilization and maintenance of the equipment should contain data on the date and time of the activity, the product batch number for each batch made on the

equipment, as well as the name and signature of the person who performed the activity. These documents should also contain a place for a person who checked the implementation of the activity and the accuracy of the record. These entries should be arranged in chronological order.

If the equipment is used for the production of one product, the records of the various activities such as cleaning, ongoing maintenance, etc. it is not necessary to document those activities in separate forms/logbooks, but the same can be noted in each batch record. (PIC/S, 2009)

*Records of raw materials, intermediates, labeling and packaging*

This type of records should contain the following data: name of the manufacturer of the raw material, name and quantity of each batch of received quantity of raw material, intermediate or packaging materials and labeling of the final product. In addition to these records, information about the supplier/transportation company of the raw material and the date of receipt is required.

After receipt, records are made resulting from the tests for the identification of the raw material or intermediate.

Issuing of the raw materials or packaging and labeling materials should be recorded. Records should also be made of any non-compliant incoming raw materials or packaging and labeling materials.

*Master production instructions/Master production records*

To ensure the uniformity of each batch, master production instructions should be made for each product. This document should be prepared and approved by competent persons from the areas of Research and Development, Production, Quality Control and Quality Assurance. Most often, the preparation of this type of document is combined, where these documents represent both instructions and records. Thus, these documents are known under the name Master production instructions/Master production records. After the approval of this type of documents, controlled copies are made, intended for each product batch.

The main production instructions should contain the following sections:

- the names and codes of all raw materials included in the composition of the final product or intermediate,
- an exact measure of the amount or ratio of each raw material that will be used during production, as well as the unit of measure,
- the premises and equipment that will be used during production,
- detailed instructions for all production and control operations,
- instructions for sampling for process control and acceptance criteria,
- the expected yield of the final product,
- instructions for cleaning the equipment and premises and
- instructions for storing the received product.

*Quality Control Documents*

Records of product quality control should contain complete data from all conducted tests, in order to determine compliance with established specifications and standards. These records should contain the following data:

- a description of the samples taken for testing, including the name and batch number of the product from which they were taken,
- the methods used to perform the tests,
- the mass or volume of sample used for each test, as described in the method,
- a complete record of all raw data generated during the conduct of each test, as well as records of all calculations performed during the test,
- the test results compared with the established criteria for acceptability,
- all these documents that were previously listed should contain dates of execution and signatures of the persons who performed the tests, as well as the persons who performed the data check.

In addition to these documents, quality control laboratories should also keep records of the following activities:

- modifications of established analytical methods,
- periodic calibration of laboratory instruments,
- all product stability testing,
- investigations of cases of results obtained out of specification (OOS).

*Good Documentation Practice (GDocP)*

According to the Good Documentation Practice (GDocP), which is part of the Good Manufacturing Practice, there are rules for managing documentation, which some of them are stated below:

- Ensuring unique signatures for every member of the personnel,
- Every document needs to have numbered pages in format X of Y,
- Every document needs to be identified by its own document code and version,
- Level of authorization to access different types of documents for the personnel. (Kumar, 2017)

## 4. CONCLUSIONS

Documentation is extremely important because of the role of accurate information gathering in the pharmaceutical industry and achieving a complete approach to Good Manufacturing Practice. Company's documents are the mirror of the operations and are giving a right picture of all processes. They are subject to review by regulatory bodies. Good documentation includes the systematic management of documents, including the preparation, review, storage and distribution of documents within a pharmaceutical company.

The main goal of the Good Documentation Practice is to define the company's information system and a control of risks minimization of misinterpretation and errors resulting from non-standardized documentation.

Documentation also provides a trail that can serve as a follow-up investigation in the event of a specific product or process nonconformity.

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