Good Manufacturing Practice (GMP) documentation system for production of homeopathic medicines

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SUMMARY

Continuing consideration of the issues of establishing a system of good manufacturing practice (GMP) in homeopathy shows the role of DOCUMENTATION in this process. All types and forms of documents required by a manufacturing enterprise for the release of a high-quality homeopathic medicinal product (GomLS) are described. The material is of practical use for GomLS manufacturers.

Keywords: GMP, homeopathic medicines (GomLS), documents, standards, instructions, SOPs, timesheet, album of forms.

Documentation is an essential part of the quality management system in good manufacturing practice (GMP) for the production of homeopathic medicines (GomLP). It is precisely the accurate and competent documentation that prevents possible errors and makes it possible to trace the continuity in the production of the GomLS series. The documentation system allows you to:

a) carry out the activities of the enterprise in an orderly, efficient and accountable manner;

b) ensure and document the formation of policy and management decisions;

c) ensure the consistency, continuity and productivity of the enterprise;

d) improve the efficiency of the entire enterprise;

e) ensure the continuity of activities in case of emergencies;

f) comply with legal and regulatory requirements;

g) provide protection and support in litigation, including risk management;

h) protect the interests of the enterprise and the rights of employees;

i) provide documented evidence of the production activities of the enterprise;

j) save information.

A manufacturing plant usually has a 4-tier documentation system in place. The available documents are considered as documents of different levels. Documents of the 1st type - corporate (master file, regulatory documentation of the enterprise (pharmacopoeial articles of the FSP), technological regulations (TR), enterprise standards (STP), general administrative documents. Documents of the 2nd type are developed on the basis of documents of the 1st type. They describe necessary production

actions, requirements for production resources and confirm the implementation of these actions (provisions on departments, specifications, instructions, standard procedures (SOP), samples of filled out forms). The documents of the 3rd type are those that are not subject to change and contain the actual data of the results (actually completed forms, reports, journals, protocols, acts, dossiers). Type 4 documents include informational and external materials: from suppliers of raw materials and materials, design documentation, state regulations, federal laws, government decrees, Administrative regulations, national standards). Since the main concern of the entire system of good manufacturing practices is quality assurance, then the Quality Assurance Department (QAU) is the main division for document management. KLO also provides methodological guidance on the organization of office work and control over the observance of the established procedure for working with documents. The instructions of the OOK are mandatory for all employees of structural divisions.

Responsibilities and authorities for managing records should be clearly defined and declared throughout the organization so that it is clear who is responsible for dealing with specific records. Responsibility for the organization and maintenance of the production documentation system rests with: the quality director; Head of Quality Assurance Department; document controller; heads of departments.

All have powers that are clearly stated in their job descriptions.

Records management

The purpose of maintaining the adopted documentation system is to: establish, monitor and record quality assurance at all stages of production and quality control. The documents of the quality system are documented procedures for managing the work of an organization (STP), a subdivision (Regulations on a subdivision) or an individual performer (job descriptions, SOPs, methods). They also include the current filled in forms (magazines, maps, protocols, acts, questionnaires, etc.).

All regulatory and current documentation of the enterprise (FSP, TR, specifications, instructions, SOPs, completed forms should not contain errors and should be available in writing. Technological documentation that meets the requirements of good manufacturing practice (GMP) can only exist within the entire enterprise documentation systems.

The company's documentation system provides a controlled circulation of documents. All documents defining the procedure and methods are reviewed and approved by management prior to their application in production. Documents are available to all performers, within their competence, and outdated documentation is promptly withdrawn. Not a single document can be changed without the permission of the persons who approved and agreed upon the document earlier.

Documents must:

a) be approved, signed and dated by eligible employees; b) have unambiguous content;

c) have a clear order and are easy to check;

d) be regularly analyzed and updated;

e) it is necessary to take measures to prevent the use of outdated versions of documents;

f) all documents must have a period and place of storage, be available for use, but have restrictions on users;

g) copies of documents must be clear. The way of making copies of documents should exclude the risk of errors;

h) any changes in documents must be approved in accordance with the established procedure at the enterprise;

i) when making any small changes to the documents, it is necessary to indicate the reason, affix the date of the changes and the signature of the person who made the change. Changes must be made so that the original text can be read;

j) if it is necessary to enter data into documents, this should be done clearly, legibly and so that the entered information cannot be erased. For this, you must provide enough space;

k) completeness, accuracy of filling out documents, as well as the accuracy of entering and registering data should be controlled;

l) documents on the performance of any actions that allow tracking all operations for the production of products must be stored in a designated place for at least one year from the date of expiration of the finished product;

m) data can be stored on an electronic medium.

General requirements for maintaining enterprise recordsOrganizations should identify the environment that regulates their activities. All documents of the organization must contain evidence (links) of the compliance of its activities with the regulatory environment, including:

a) laws and regulations in the field of drug circulation and related areas;

b) standards related to practice;

c) recommendatory rules and guidelines. A prerequisite for the development of documents is:

- unification of document texts;
- unification of the location of requisites.

The document has legal force in the presence of requisites (GOST R 6.302003), mandatory for this type of document. In the process of preparation and execution of documents, the composition of the requisites can be supplemented with other requisites, if required by the purpose of the document and its processing.

Updating

Updating the document consists in determining its compliance with the regulatory environment and the current regulatory documents of the enterprise, as well as the mandatory presence of the date and signature on the document. The date on the document is stamped in two ways:

- digital (for example: 03/07/2006 - putting down zero, if the number contains one character, required);
- verbal and digital (for example: April 05, 2006).

Credibility

A reliable document is a document that fully and accurately corresponds to the operations, actions or facts presented, which can be trusted in subsequent activities. Completed document forms are created and / or completed during or immediately after the event to which they relate.

Integrity

The document must be protected from unauthorized changes. Management of changes in documents regulates the circumstances of making additions or changes and the circle of persons authorized to do so. All authorized changes or additions are recorded.

Suitability for use

A document is usable if it can be localized, found, reproduced, and interpreted. At the same time, it must reflect the connection with the type of activity or operation as a result of which it was created. References to documentation at various levels should provide information necessary to understand operations and business activities. It is necessary to maintain links between documents, fixing the sequence of actions.

Reliability

Any system used to manage records must be capable of long-term and correct operation in accordance with the required procedures. The documentation system should: include all documents related to this activity; protect documents from unauthorized use, alteration, withdrawal or destruction; be the main source of information about the actions recorded in the documents; provide access to all questions related to a specific document, as well as to related other documents.

Preparation and execution of documents

The text of the document is usually divided into sections and subsections, which can consist of one or more paragraphs. Sections should be numbered throughout the entire document. A large document contains the content or a list of its constituent documents.

In the text of the document it is not allowed: to use turns of colloquial speech, technicalism, professionalism; apply for the same concept

various scientific and technical terms that are similar in meaning (synonyms), as well as foreign words and terms in the presence of equivalent words and terms in the Russian language; apply arbitrary word formations; apply abbreviations of words, except for those established by the rules of Russian spelling, state standards, or abbreviate the designations of units of physical quantities adopted in this document, with the exception of their use in tables and in the decoding of letter designations included in the formulas.

When setting out mandatory requirements in documents, the words in the imperative mood should be used in the text: "must", "should",“Necessary”, “required”, “permitted”, “prohibited”, etc. When setting outother provisions should apply the words: "may be", "if necessary",“Maybe”, “in case”, etc. This uses a narrative formpresentation of the text of the document.

The documents must to apply scientific and technical terms, designations and definitions established by the relevant standards, and in their absence - generally accepted in the scientific and technical literature, as well as obscure signs and designations, such as>, <, =,%, which must be described verbally, should not be used. As a rule, SI units are used, and, if necessary, the units in which measurements are carried out on devices approved for use are indicated in parentheses. The ranges of numerical values of a physical quantity, their rounding, expressed in the same unit of a physical quantity, must be the same.

Materials supplementing the text of the document may be placed in the annexes. It can be: graphic material, large-format tables, calculations, descriptions of equipment and devices, etc.

Document flow and execution of documents

Corrections in documents are made as follows: most often the document is reprinted with corrections and changes; if this is not possible, then the document is corrected by strikethrough and inscribing the correct text, which is certified by a signature, date and, if necessary, a seal; it is prohibited to use a barcode corrector. Working with internal documents includes two stages:

1st stage - preparation and execution of the document: drawing up a project, checking the correctness of execution, approval and certification of the document, and at the end of its registration;

2nd stage - execution, which includes: transfer of the document to the performer, execution, control over execution and subsequent storage of the executed document.

Registration of documents is carried out within the groups (incoming, outgoing and internal), and is recorded in the corresponding registration logs. When registering each group of documents, uniform methods of assigning numbers (indices) are used.

Documents are registered once in the OOK and are submitted for signature to the management. A backup record of the data (on paper) should be kept,

entered into the computer.

Storage and handling of documents

Decision-making on the retention periods of documents is based on the requirements of legislative and regulatory acts, the requirements for the validity period of the documents of the quality assurance system and risk assessment. Storage of documents is carried out:

- to save already collected information;
- to preserve evidence of past and present activities for compliance with reporting obligations;
- for timely, authorized and systematic destruction unused documents.

Documents must be kept on media that ensure their suitability for use, reliability, preservation for a specified period of time.

Table (List) of documents

The table contains a list of documents of the organization, necessary and sufficient for the implementation of its functions and tasks, a description of each document in terms of its legal status, stages of preparation and passage.

All forms of documents of the organization must be collected in the Table (List) of documents, where they are systematized according to various criteria: functions, tasks, structural divisions, legal grounds of the publication, etc. At the same time, the sequence of actions with the form of the document and the circle of persons involved in its creation and circulation are described. The time sheet is drawn up in tabular form, approved by the General Director and its provisions are binding.

Album of uniform forms

Fill-in forms of documents created at the enterprise are included in the Album of unified forms, which is formed on the basis of the Organization's table of documents and contains the forms of the most frequently created documents (protocols, acts, questionnaires, route maps, analytical sheets, specifications, etc.).

The unified form of a document is a unified text of a document and a set of details determined in accordance with the purpose of the document and located in a certain order on the information carrier.

Forms of documents in the album are grouped by sections, (for example, documents of the production unit, quality control department, warehouse, self-inspection, etc.) Album of forms of documents, as well as changes in document forms are approved by the General Director and is mandatory for employees of the organization.

Control over the execution of documents

All documents in the framework of Good Manufacturing Practice (GMP)

are controlled. Control allows you to fix errors in time and take measures to eliminate them. Control over the execution of the documents of the organization is provided by the QLO, which keeps records, the progress of execution and the status of execution of controlled documents.

Organization of control over the execution of documents includes: determination of deadlines; checking and regulating the course of execution of the document; generalization and analysis of the progress and results of the execution of documents; informing the management about the progress of the execution of documents; the signature of the superior person who checked the document. The deadlines for the execution of documents are calculated in calendar days, indicated by the end date and can be standard and individual.

Typical timing are immutable and are established legislative or other regulatory legal acts. Individual deadlines for the execution of documents are indicated in the text of the document or the resolution of the head. Only the manager who established it can change the individual deadline for the execution of the document.

DOCUMENTATION OF THE COMPANY

Technological regulations

Technological regulations (TR) laboratory, pilot-industrial, start-up and industrial include:

a) product name;

b) a description of the dosage form, dosage and batch size;

c) a list of all used raw materials with an indication of the quantity; d) data on the expected output of finished products with an indication of the permissible limits;

e) data on the place of the process and the main equipment used; f) methods, or references to methods, use of equipment, eg cleaning installation, calibration;

g) technological instructions, describing each stage technological process (control of raw materials, processing, loading of raw materials, temperature conditions, etc.);

h) instructions for each control operation in the production process, indicating the limit values; i) requirements for storage of bulk products, including containers, labeling and special storage conditions, where required;

j) a list of production instructions;

k) all special precautions to be observed (safety, fire safety, industrial sanitation).

Enterprise standards

In accordance with Articles 11, 12 and 17 of Federal Law No. 184FZ "On Technical Regulation", organizations and production enterprises independently develop and approve their Standards to improve production and ensure product quality, fulfill

works, services, etc., in accordance with the procedure adopted at the enterprise. Enterprise standards (STP) should not contradict the requirements of federal laws, technical regulations and national standards, as well as the regulatory documents of the enterprise.

STP is approved by the head of the organization by order in the prescribed manner with the determination of the date of its introduction. If necessary, organizational and technical measures are also approved to prepare for the application of the standard.

Information about the company (Dossier of the company or Master file)Basic data about the enterprise (production site) - a document prepared by the manufacturer and containing specific and specific information about the production and control of production operations performed in the specified production area.

This document is updated by the enterprise before each inspection check (as a rule, at least 1 time 5 years) and is submitted to the supervisory authority no later than two weeks before the start of the inspection check.

Information described in the Information about the company (Master file): 1. General information about the company.

2. The quality management system of the enterprise.

3. Personnel.

4. Premises.

5. Equipment.

6. Documentation.

7. Manufacturing.

8. Quality control.

9. Validation.

10. Contract manufacturing and analysis.

11. Wholesale distribution. Complaints, complaints. Feedback of poor quality products.

12. Self-inspection.

Regulations on the structural unit

The regulation on the subdivision regulates the legal status of the structural subdivision of the organization and establishes its tasks, functions, rights, responsibility, relationships and communications, the procedure for organizing work. The regulations on the structural unit include the following sections:

1. Policy and objectives of the structural unit in the field of quality.

2. General provisions.

3. The main tasks.

4. Functions.

5. Rights and responsibilities.

6. Organization of work.

7. Interaction.

As applications, you can develop: an organizational chart

subdivision structure; matrix of distribution of responsibilities and authorities at the level of departments; a description of the products, materials and information received; the scheme of information flows during the interaction of the subdivision.

Job descriptions

Each employee, including the Director General and his deputies, should have job descriptions that establish specific job responsibilities for the employee in accordance with the position held.

The name of the profession for the production of GomLS is taken from the Unified Tariff and Qualification Reference Book of Work and Occupations of Workers (ETKS), issue No. 29 "Production of medicines, vitamins, medical, bacterial and biological preparations and materials", put into effect by the Order of the Ministry of Health and Social Development of Russia dated 05/29/2009 No. 286. Tariff and qualification characteristics for the positions of healthcare workers in the Russian Federation are set out in the decree of the Ministry of Labor of Russia dated August 27, 1997 No. 43 (as amended on December 22, 2003). It is necessary to use the Labor Code of the Russian Federation (Article 21 sets out the rights and obligations of the employee, in Article 22 - the rights and obligations of the employer).

Job descriptions contain the following sections: 1.
General provisions.
2. Main tasks and functions.
3. Job responsibilities.
4. Rights.
5. Responsibility.
6. Relationships (connections by position).
7. Procedure for revision.

Job descriptions for employees are approved by the General Director and agreed with the employee.

Dossier for finished medicinal product (product)

The product dossier contains information about the development, production, fate in the market of each specific product and includes the following documents:

- reports on the problems of the current production;
- list of documents;
- reports on development, tests, experimental industrial regulations, start-up regulations;
- report on the problems that arose in the process of mastering production;
- specifications for raw materials, auxiliary, packaging and printed materials, instructions (procedures) for the main and auxiliary operations of the technological process, a link to the location of the document Dossier for the series;
- specifications for premises, equipment, engineering systems, staff, etc .;
- validation reports;
- protocols for registering complaints, reports on complaints and recalls from

market;

- annual quality report.

Dossier (protocols) for the series

The batch dossier is the main document that records the production of each batch of each drug.

The data included in the protocols for each batch of products should contain information on all the main parameters of the respective filling stages. Batch records should contain the following information:

- Name of production;
- date and time of operations;
- used equipment;
- the name of active and auxiliary substances with reference to relevant specifications;
- intermediate operations of the technological process;
- volume of the series;
- the surname and initials of the persons who carried out all stages of the production process;
- surnames and initials of the persons who controlled all stages production process;
- the main controlled parameters, confirming the correctness standard process conditions;
- sample label and packaging with batch number;
- control of changes, difficulties, unusual cases, violations, marriage, arising in the course of the technological process;
- acts of transfer of finished products for quarantine storage.

The batch dossier is kept for at least one year after the expiration date of the finished product.

Standard Operating Procedure (SOP)

A standard operating procedure is a detailed written instruction of standard procedures and / or operations carried out in an enterprise, and drawn up in a uniform format. Mandatory information for SOP:

- SOP name, number of pages, version, by whom it was developed, issued, the effective date approving the signature;
- the purpose of the SOP;
- interpretation of terms and definitions;
- application area;
- responsibility for implementation and control;
- materials and equipment used for implementation;
- description of the procedure method,
- sequential operations, final procedures, technique security;
- reporting procedure;
- links to sources of information;
- signatures of the contractor and controller.

The enterprise compiles a List of Standard Operating Instructions. SOPs are kept in the documents of the manager, and copies are sent to the Document Controller of the Quality Assurance Department. When compiling these documents, the regulatory documents of the enterprise of various levels are analyzed: enterprise standards, technological regulations, FSP, rules for the operation of equipment and devices, and a list of all types of work and control procedures provided for in them is drawn up. General instructions regarding sanitation and hygiene, safety, handling, insect and rodent control, etc. are also taken into account.

SOPs for the acceptance of raw materials, auxiliary and packaging materials include:

- the name of the material on the consignment note and on the container;
- date of receipt;
- the name of the supplier and, if possible, the manufacturer;
- manufacturer's batch number;
- the total number and number of packaging units received;
- any notes related to the case (for example, on the condition of the container). There are SOPs for in-plant labeling, quarantine and storage of raw materials, packaging materials and other materials. There are SOPs for each instrument and each piece of equipment, which are located in the immediate vicinity of the equipment.

Technological instructions

For each workplace, operational or technological instructions are developed that regulate the specific actions of the employee performing the technological operations of the procedure.

Technological instructions (and not technological regulations) are located where the production process is carried out.

Technological instructions include:

- Name of production;
- a description of the dosage form, dosage and batch size;
- a list of all used raw materials;
- data on the expected output of finished products with an indication of the permissible limits;
- data on the place of the process and on the main used equipment;
- methods or references to methods, preparation of the necessary equipment;
- instructions detailing each action;
- instructions for each control operation in the production process with indication of limit values;
- requirements for storage of bulk products, including containers, labeling and special storage conditions;
- all safety precautions to be observed.

Fillable forms

The completed form is an integral part of all documentation that exists in the enterprise to document all actions carried out by personnel to ensure the quality of products manufactured. The completed forms represent the following documents of the enterprise: protocols, dossiers, route maps, operational sheets, analytical sheets, magazines, reports, acts, questionnaires, etc. They are kept for the implementation and control of various stages of production, packaging, acceptance of raw materials, auxiliary, packaging and / or printed materials, on sampling, quality control, qualification of equipment (systems, etc.), validation of processes and methods, cleaning of premises and equipment, training, self-inspection, etc.

Filling out forms carried out v mode real time, directly at the time of the production procedure, and serve solely to register and save the history of all actions carried out. When maintaining records in the completed forms, omissions of paragraphs and lines are not allowed, and the presence of surnames, signatures and dates is required.

Completed forms contain the following information:

- place, date and time of the action or control;
- an object or type of action or control;
- the name of the operation;
- controlled parameters;
- an indication of the normative document according to which the action is carried out, control;
- the results of an action, operation or control.

Magazines

Certain types of forms to be filled out at the enterprise are journals that are kept to collect and save data on the processes of verification, calibration and maintenance of equipment, indicating the date and persons who performed these works. Types of magazines at the enterprise:

- on registration of incoming raw materials and auxiliary materials;
- accounting for the components of packaging materials and labels;
- accounting for cleaning and equipment use;
- accounting for inspection and cleaning of industrial premises;
- assignment of a series number;
- accounting for processed semi-products and series of finished products;
- accounting for rejected components, packaging materials and closures funds;
- accounting for the condition of the equipment (with an indication of the planned repair);
- calibration and verification of instruments;
- accounting for the distribution (sale) of each batch of each type of product (if necessary, recall the series).

Specifications

Specification - a document that specifies all the criteria for an object

(materials, products, premises, personnel, equipment, systems), by which its quality is controlled. Objects to be specified:

- raw materials, auxiliary and packaging materials;
- semi-finished products and non-prepackaged products;
- finished product;
- production areas and premises;
- personnel;
- equipment and engineering systems.

A drug product specification is a list of tests, references to analytical procedures, and associated acceptance criteria, which are numerical limits or ranges for the tests described. The specification establishes a set of criteria that an active ingredient or drug must meet in order for it to be considered suitable for its intended use.

Compliance with the specifications means that the active substance and / or medicinal product will meet the specified acceptance criteria, provided that the tests are carried out according to the analytical methods specified in these specifications. Each specification is approved and approved by the quality control department, which also revises the current specifications. There should be specifications for water, solvents and reagents used in production.

Labeling documentation

A marking system (labeling) is used to identify the status of an object.

Labels are used to mark all objects (premises, equipment, containers, etc.) that may affect the quality of products. The text of the labels should be clear, unambiguous, and their shape, both in text and in color, should be unified. Objects are marked with labels:

- premises and their status;
- equipment and its status;
- the status of raw materials, starting and intermediate materials;
- containers and equipment for sampling;
- reagents, materials and media used for quality control;
- comparison standards;
- finished products: primary, secondary and transport packaging, finished GomLS.

Finished Product Release Notice

Upon completion of the production process of a batch of a finished product and sending it to quarantine storage at a warehouse, the Authorized Person reviews the batch Dossier produced by GomLS and issues this Notification. The notice contains the following information:

a) product name; b) series number;

c) date of manufacture;

d) expiration date;

e) date of issue;

f) the number of the analytical passport and the date of the analysis.

Validation documents

One of the most important components of validation is carefully designed and completed documentation, complete set, which includes the following:

- STF for validation;
- general validation plan;
- validation protocols defining the validation procedure;
- validation reports;
- attached documentation to the report (SOPs, measurement data, reports on calibration, equipment placement diagrams and work step diagrams, complete analytical and measurement protocols, environmental control protocols, etc.).

All documents (protocols and reports) are checked and approved by the quality assurance department.

Literature

1. Federal Law of the Russian Federation of 22.06.98, No. 86-fz "On medicinal means ".

2. Federal Law "On Technical Regulation" dated December 27, 2002 No. 184FZ.

3. OST 4251098 "Rules for the organization of production and quality control Medicines (GMP) ".

4. OST 91500.05.00100 “Quality standards of medicines. Basic Provisions ".

5. GOST R 6.302003 “Unified documentation systems. Unified system of organizational and administrative documentation. Requirements for paperwork ".

6. GOST R 522492009 "Rules for production and quality control medicines ".

7. GOST R 1.42004 “Standardization in the Russian Federation. Standards organizations. General Provisions ".

8. GOST R 525052006 “Manufacture of medicines. Organizational and technological documentation ".

9. GOST R 525372006 “Manufacture of medicines. System quality assurance. General requirements".

10. GOST R ISO 1548912007 "System of standards for information, librarianship and publishing. Document management. General requirements".

11. GOST R ISO / TO 100132007 "Management of the organization. Guide documenting the quality management system ".

12. MU 64040022002 “Production of medicines. Documentation".
13. MU 64040032002 “Production of medicines. Documentation. General requirements. Sample forms and recommendations for filling them out "
14. MU 64020022002 "Organization and procedure for conducting metrological examination of regulatory documents ".
15. MU 64010012002 “Production of medicines. Terms and definitions ".
16. Guidance on Good Manufacturing Practice for Medicinal Products means for a person: Methodical recommendations / Ed. N.V. Yurgel. - M., 2009.

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