**Procedure of determination of manufacturers’ compliance with requirements of medicinal products good manufacturing practice (GMP).**

For organizing and carrying out of the inspection of the medical products manufacturers on the conformity to the requirements of rules of good manufacturing practice (GMP) and for issuing of the conclusions on conformity of the medical products manufacturers to the mentioned requirements the following documents shall be submitted:

1. Application for conclusion issuance (Appendix No. 1)
2. The following documents shall be attached to the application:

a) a copy of the document confirming the authority of the authorized representative of a manufacturer or a foreign manufacturer;

b) a copy of the main dossier of the production site;

c) information about detected discrepancies between quality of medicines and the requirements, including the recall of medical products from civil circulation, for a period of at least 2 years before the application*;(Appendix No. 2*)

d) the list of medical products manufactured at the production sites of the manufacturer, for which the inspection is carried out (*Appendix No. 3*);

e) a copy of the license issued by the authorized body of the country of foreign manufacturer (or a document based on which the foreign manufacturer operates on the production of medicines) and its translation into Russian language, duly certified (if the presence of such a document is provided the legislation of the country of the foreign manufacturer);

f) a letter about the consent of a foreign manufacturer to conduct inspections*. (Appendix No. 4)*

3. If the production of the medical products is carried out at the production sites located at different addresses, the applications and the documents referred to in paragraph 2. Shall be submitted for each manufacturing site *( Appendix No. 5).*

4. Information about the issuance of conclusion on appropriate decision shall be entered in the state register of conclusions of compliance of manufacturer of medicinal products with the requirements of good manufacturing practice (GMP).

*Appendix No. 1*

|  |  |
| --- | --- |
|  |  Attn: The Ministry of Industry and Trade  of the Russian Federation |

**APPLICATION
on issuing of the conclusion on conformity of the manufacturer (foreign manufacturer) of medical products for the medical purposes to the requirements of the rules of good manufacturing practice**

I hereby ask to issue the conclusion on conformity of the manufacturer (foreign manufacturer) of medical products for the medical use to the requirements of the rules of good manufacturing practice.

|  |
| --- |
| 1. **Manufacturer (foreign manufacturer) of medical products**
 |
| Name |  |
| Address of the location |  |
| Location of operations address |  |
| Tel. No.: | Fax.: | e-mail:  |
| License of production of medical products (or a document based on which the foreign manufacturer operates on the production of medicines) for medical use | Number |  |
| date of issue |  |
| period of validity |  |
| Authorized body which issued the license (or a document based on which the foreign manufacturer operates on the production of medicines) | name |  |
| Location address  |  |
| Tel. No.: | Fax.: | e-mail:  |
| Authorized person  | Full name: |  |
| Position:   |  |
| Tel. No.: | Fax.: | e-mail:  |

|  |  |  |
| --- | --- | --- |
| Contact person | Full name: |  |
| Position:   |  |
| Tel. No.: | Fax.: | Tel. No.: |
| Details of the document confirming the payment for issuing a conclusion on compliance of the manufacturer (foreign manufacturer) of medicinal products for medical use with requirements of the rules of good manufacturing practice |  |

|  |
| --- |
| **B. Authorized representative, acting on behalf of the manufacturer (foreign manufacturer)** *(in the presence)* |
| Name |  |
| Address of the location |  |
| Post Address |  |
| Tel. No.: | Fax.: | Tel. No.: |
| Contact person | Full name: |  |
| Position:   |  |
| Tel. No.: | Fax.: | Tel. No.: |
|  |  |  |  |  |  |  |  |  |  |  |
|  |
| **On behalf of the manufacturer (foreign manufacturer) certify, that** |
| 1)  the information contained in this application is correct; |
| 2) when changing the addresses, email addresses and phone numbers of the contact persons and authorized representatives referred to in this application, the new details shall be submitted to Ministry of Industry and Trade of the Russian Federation no later than 5 working days after the date of change.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Position, full name of the head  |  |  | Signature |  |  |
| Of the manufacturer (foreign manufacturer) | Place for seal |  |   |
| Or their authorized representative  |  |  | (in the presence) |  |  |  |  |
|  |  |  |  |  |  |  |  | Date |  |   |

  |

*Appendix No.2*

**Information about the nonconformity of medical products quality to the established requirements**

At \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*(name of the manufacturer )*

**for 20\_\_\_ and 20\_\_\_**

*(data for the last two years, counting from the date of application, should be provided)*

|  |  |  |  |
| --- | --- | --- | --- |
| **№ in order** | **Information about the complaints, (claims) and recall of medical products** | **Number of series** | **list** |
| **name of medical product, dosage form, dosage (if any)** | **Number(s) of series** |
| 1 | Number of justified complaints (claims) to the quality of products: |   |  |  |
| 1.1 | based on the results of state control |   |  |  |
| 1.2 | Based on the appeals of citizens |   |  |  |
| 2 | Number of product series have been withdrawn from the sales network in Russia: |   |  |  |
| 2.1 | Based on the requirements of state control bodies |   |  |  |
| 2.2 | Based on the decision of the manufacturer |   |  |  |

Date of preparation «\_\_\_\_\_\_» \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ 20\_\_\_\_

|  |  |  |
| --- | --- | --- |
| Head of the company(position) | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |
|  | (signature) | Place for seal | (signature deciphering) |
|  |  |  |  |

*Appendix No.3*

**List of medical products manufactured at the production sites of the manufacturer or foreign manufacturer, in relation to which the inspection is carried out**

|  |  |  |  |
| --- | --- | --- | --- |
| **Stage of production** | Trade name of the medicinal product / name of the pharmaceutical substance | **dosage form, dosage (if any)** | Certificate of registration, date of issue,expiration date / registry entry, the date of inclusion in the register for the AFI(in the presence) |
| All stages |  |  |  |
|  |  |  |
|  |  |  |
| Manufacture of fabricated dosage forms |  |  |  |
|  |  |  |
|  |  |  |
| Packaging (primary and (or) secondary) |  |  |  |
|  |  |  |
|  |  |  |
| Quality control of finished medicinal product |  |  |  |
|  |  |  |
|  |  |  |
| Other (specify) |  |  |  |
|  |
|  |

Date of preparation «\_\_\_\_\_\_» \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ 20\_\_\_\_

|  |  |  |
| --- | --- | --- |
| Head of the company(position) | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |
|  | (signature) | Place for seal | (signature deciphering) |
|  |  |  |  |
| Authorized person | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |
|  | (signature) | (signature deciphering) |

*Appendix No. 4*

Attn: The Ministry of Industry and Trade

 of the Russian Federation

**A letter about the consent of a foreign manufacturer to conduct inspections**

Manufacturer\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |  |
| --- | --- |
|  | Full and short name *(in the case of presence)*, inclusive of trade name, and the legal form of legal entity - producer medicines |

Represented by\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |  |
| --- | --- |
|  | Full name of the Head |

Acting on the basis of\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |  |
| --- | --- |
|  |  Charter, provisions, power of attorney (a notarized copy shall be attached)*1* |

In accordance with point “f” of the paragraph No. 5 of the Rules of the organizing and carrying out of the inspection of the manufacturers of the medicines products on their conformity to with requirements of the rules of good manufacturing practice, as well as of issuance of conclusions on the conformity of the manufacturer of the medical products to the mentioned requirement, approved by the resolution of the Government of the Russian Federation as of December 03, 2015 No. 1314 “On the determination of the conformity of the manufacturers of the medical products to the requirements of the rules of good manufacturing practice”, expresses their consent to conduct the inspection of the mentioned manufacturer at the address of the location of operations on production of medicines.

 \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |  |
| --- | --- |
|  | address of the location of operations |
| 1 Appendix: 1. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Position, full name of The head of the manufacturer |  |  | Signature |  |  |
|  |  Place for seal |  |   |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  | date |  |   |

*Appendix No. 5*

**I RECOMMENDATIONS FOR PREPARING THE MAIN DOSSIER OF THE MANUFACTURING SITE**

**Introduction (1)**

1. (1.1) The main dossier of the manufacturing site is the document which is drawn up by the manufacturer. It shall contain the information about the police and activities of the manufacturer on quality management, about technological process and (or) the quality control when performing the operations on the medical products production, carried out at the manufacturing site, as well as about any closely related works in adjacent and nearby buildings. If at this manufacturing site only part of the manufacturing operations is carried out, the Main dossier of the manufacturing site describes only these operations, for example, analysis, packaging. It is allowed to prepare the main dossiers on separate operating units.

2. (1.2) When submitting the Main Dossier of the manufacturing site to the authorized body, clear information on the activities of the manufacturer to comply with the Rules of the organization of production and quality control of medicines, approved by Order of the Russian Federation Ministry of Industry and Trade as of June 14, 2013 No. 916 (registered ин the Russian Federation Ministry of Justice on September 10, 2013, registration number: 29938), which may be useful for obtaining by the authorized body of the general overview of the manufacturing site as well as for planning and performing of the checks on compliance with the Rules of production and quality control of medicines (hereinafter referred to as the Rules) shall be mentioned.

3. (1.3) It is recommended that Main dossier of the manufacturing site contains the sufficient information, but it is desirable that its volume, as possible, does not exceed 25-30 pages, exclusive of appendices. The schematic form of the exposition is more preferable than descriptive. The main dossier of the manufacturing site (including the appendices) shall be legible when printed in A4 format.

4. (1.4) The main dossier of the manufacturing site is part of the documentation relating to the quality management system of the manufacturer; it should be regularly updated. In the Main dossier of the manufacturing site it is recommended to specify the version number, the date of entry into force, as well as the date on which the dossier is to be actualized. The main dossier is reviewed regularly to ensure its relevance and reflect the current activities of the manufacturer.

Each appendix can have its own date of entry into force, what will enable to carry out its review independently from other appendices.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\*Here and hereinafter in the text of the Recommendations in brackets the numbering of structure units of the text, corresponding to the rules of СМР ЕС is mentioned.

**The purpose (2)**

5. The purpose of this chapter is to give recommendations for the manufacturers on the drawing up of the Main dossier of the manufacturing site.

**Application area (3)**

6. Provisions of this chapter shall be applicable when preparing and keeping the Main dossier of the manufacturing site. The manufacturer shall draw the Main dossier of the manufacturing site up in the cases, provided by the normative legal acts of the Russian Federation.

7. It is recommended to apply the Provisions of this chapter in spite of the types of operational activities carried out at the manufacturing site, inclusive of production itself, packaging and marking, conducting the tests, repackaging and re-marking of all types of medicines. The main provisions of this chapter can be used when preparing the Main dossier of the manufacturing site or other appropriate document by the manufacturers of medicines from donated blood or tissue, as well as by manufacturers of pharmaceutical substances.

**Contents of the Main dossier of the manufacturing site (4)**

8. When determining the form of the main dossier of the manufacturing site, it is recommended to specify in it the following information:

8.1. (1) General information about the manufacturer:

8.1.1. (1.1) Contact information of the manufacturer: name and legal address of the manufacturer;

Name and post address of the manufacturing site, buildings and production units, located at this site;

Contact information of the manufacturer, including the around the clock working phone number, which can be contacted in case of defected products or product recalls;

an identification number of the manufacturing site, for example, data of geo-location system;

8.1.2. (1.2) Information on licensed production activities at the enterprise:

a copy of a valid license for the production of medicinal products, issued by the authorized body (provided as the appendix No. 1 to the Main dossier of the manufacturing site);

a brief description of the activities of production, import, export, wholesale trade, permitted by corresponding authorized bodies, including the authorized bodies of a foreign country, with an indication of the allowed dosage forms and (or) activities, if it is not covered by the license for the production;

types of products manufactured at the manufacturing site (the list shall be provided as the appendix No.2 to the Main dossier of the manufacturing site), if it is not mentioned in the appendix No. 1 to the Main dossier of the manufacturing site;

a list of the production site inspections on its compliance with the requirements of the Rules over the last 5 years with dates and names of the authorized bodies, who conducted the test. In the presence, the copy of the current conclusion on the conformity of the manufacturer with the Rules (shall be provided in the appendix No. 3 to the Main dossier of the manufacturing site);

8.1.3. (1.3) Any other manufacturing activities carried out at the manufacturing site:

description of the production activity, which is not related to the production of medicinal products or pharmaceutical activities at the manufacturing site, if it is carried out;

8.2. (2) Quality Management System of Manufacturer:

8.2.1. (2.1) Quality Management System of Manufacturer: a brief description of the quality management system of manufacturer and references to the documents, containing the requirements to the production and the quality of products;

responsibility for the operation of a quality management system, including management responsibility;

information about the activities, in relation to which the manufacturer shall be accredited and certified, including the dates and the contents of the documents on accreditation (certification), names of the accreditation bodies (certifying bodies);

8.2.2. (2.2) Procedures of issuance of authorization for production of finished products:

detailed description of the qualification requirements (education and experience) to authorized person(s) responsible for the assessment of conformity for a series of established requirements for issuance of authorization for production;

a general description of conformity assessment of a series with the established requirements and procedures for the issuance of authorization for production;

functions of the authorized person in the quarantine procedure and issuance of authorization for production of finished products, as well as in the assessment of compliance with the requirements of the registration dossier;

document defining procedure of interaction between the authorized persons, if several persons interact;

an indication of the fact, that control strategies use the process-analytical technology and (or) the issuance in real time or issuance by parameters (if used);

8.2.3. (2.3) Suppliers and contractors management:

Short resume, containing the information about the supply chains, as well as about the programs of external assessment of the suppliers and executors, involved by the manufacturer under the contract;

Short description of the system of assessment of the executors, performing the works under the contract, manufacturers of pharmaceutical substances (PS) and other suppliers of critical materials;

Actions, aimed at confirmation of compliance of products to the requirements of the normative legal acts of the Russian Federation in relation to the spongiform encephalopathy;

Measures, taken in cases of suspicion or identifying of counterfeit and (or) falsified products, bulk products (for example, unpackaged tablets) pharmaceutical ingredients or excipients;

use of external scientific, analytical or other technical assistance in the production and analysis;

the list of executors (including the laboratories), performing the works under the contract, including the addresses and contact information, as well as the schemes of organizing of the relations with the executors, performing the actions on the production and (or) quality control, for example, sterilization of primary packaging material for aseptic processes, feedstock testing (shall be provided as the appendix No. 4 to the Main dossier of the manufacturing site);

a brief overview of the allocation of responsibility between customer and executor for the fulfillment of the requirements of the registration dossier (in the case when this information is not provided in the subparagraph No. 8.2.2 of these Recommendations);

8.2.4. (2.4) Risk management for the quality (MUV\*):

A brief description of the methodology used by the manufacturer MUV; the scope and orientation (}1Ш, including the brief description of any activity, performed on the level of the company as well as on the local level, moreover, it is recommended to specify cases of application MUV system to assess continuity of supply;

8.2.5. (2.5) Reviews of the quality of products: a brief description of the methodology used;

8.3. (3) Personnel:

organizational scheme indicating the positions of employees, who take part in the activities on the quality management, production and quality control, including the administration and authorized person(s) (shall be provided as the Appendix No. 5 to the Main dossier of the manufacturing site);

the number of personnel engaged correspondingly in quality management, production, quality control, storage and sale;

8.4. (4) Facilities and equipment:

8.4.1. (4.1) Facilities:

a brief overview of the manufacturing site, including its size and the list of facilities. If the production of products for different markets (for example, the Russian Federation, European Union, the United States of America) carried out in different buildings of the manufacturing site, it is necessary to submit the list of these buildings, specifying the markets, which this production is aimed to (if it is not specified in the paragraph No. 8.1.1 of these Recommendations);

a simple plan or image of the manufacturing site with an indication of the scale (architectural and engineering drawings are not required);

plans and schemes production areas (shall be provided as the appendix No. 6 to the Main dossier of the manufacturing site), where the classification of facilities and and pressure differentials between adjacent areas, as well as manufacturing operations (for example blending, filling, storage, packaging), conducted in the facilities, are mentioned;

plans for warehouses and storage areas with the designation of special areas for storage and handling of highly toxic, hazardous and sensitizing materials, in the presence;

a brief description of non-mentioned in the plans special conditions of the storage, if necessary;

8.4.1 1. (4.1.1) A brief description of the heating, ventilation and air conditioning (НVАС):

principles for determining the supply of air, temperature, humidity, differential of pressure and air exchange multiplicity, the level of air recirculation (%);

8.4.1.2. (4.1.2) Brief description of water treatment systems:

an indication of the quality of produced water;

schematic drawings of water treatment systems (shall be provided as appendix No. 7 to the Main dossier of the manufacturing site);

8.4.1.3. (4.1.3) Brief description of other support systems, such as the delivery system of steam, compressed air, nitrogen;

8.4.2. (4.2) Equipment:

8.4.2.1. (4.2.1) A list of the main technological equipment and

control laboratory equipment with the designation of critical units (shall be provided as appendix No. 8 to the Main dossier of the manufacturing site);

8.4.2.2. (4.2.2) Cleaning and disinfection:

a brief description of methods of cleaning and disinfection of surfaces in contact with the product (eg, manual cleaning, automatic system "cleaning in place");

8.4.2.3. (4.2.3) Computerized systems, critical from the point of view of the requirements of the Rules of good manufacturing practices and quality control of medicines:

Description of the computerized systems, critical from the point of view of the requirements of the Rules of good manufacturing practices and quality control of medicines, exclusive of equipment with special programmable logic controllers;

8.5. (5) Documentation:

Description of documentation system (for example, electronic, manuscript);

If the documents and records are stored or archived outside the manufacturing site (including data on monitoring of safety of medicines, if available): a list of documents and (or) records, name and address of a manufacturing site where the documentation is stored, as well as the approximate time required to obtain documents from the archive located outside the manufacturing site;

8.6. (6) Technological process:

8.6.1. (6.1) Types of products:

(The reference to the appendix No. 1 to the Main dossier of the manufacturing site or to the appendix No. 2 to the Main dossier of the manufacturing site is possible)

8.6.1.1. Types of products, including:

The list of dosage forms as medicinal products for medical use, as well as medicinal products for veterinary use, produced at the manufacturing site;

The list of dosage forms of medicinal products for clinical studies conducted at the manufacturing site. It is necessary to provide the information about the production areas and personnel, if they differ from those involved into serial production;

8.6.1.2. Working with toxic and hazardous substances (for example, a substance with high pharmacological activity and (or) sensitizing properties);

8.6.1.3. Types of products produced in specially designed areas or on the basis of principle of campaigns (production cycles), in the presence;

8.6.1.4. The use of process and analysis technology (Ргосess Analitical Тесhnology - РАТ) in the presence: a general description of the relevant technologies and related computerized systems;

8.6.2. (6.2) Validation of processes:

a brief description of the general principles of process validation; principles of reprocessing and recycling;

8.6.3. (6.3) materials management and warehousing: measures for the handling of the raw material, packaging

materials, bulk and finished products, including sampling, quarantine, issuing permits for the production and storage;

measures for the handling of rejected materials and products;

8.7. (7) Quality control:

description of the quality control activities carried out at the manufacturing site in terms of physical, chemical, microbiological and biological tests;

8.8. (8) Wholesale, claims, defect products and recalls of products:

8.8.1. (8.1) Wholesale (the part which the manufacturer in responsible for):

Types of companies (for example, organization of wholesale, manufacturer), to which the products of the manufacturing area are supplied, and their location (for example, the Russian Federation, the European Union, the United States of America);

Description of the system, applicable for the approval of the fact that every buyer shall have the right to obtain medicinal products from the manufacturer;

A brief description of the system of the ensuring of appropriate conditions during transportation (For example, monitoring and (or) control of the temperature);

contracts on the sale of products and methods that provide traceability;

measures aimed at preventing the manufacturer of products of falling into the illegal supply chain;

8.8.2. (8.2) Claims, defect and recall of products:

A brief description of the work with the claims, defect products and recalls of products.

8.9. (9) Self-inspection:

a brief description of the self-inspections system, including criteria for the selection of scheduled inspected areas, practical activities and further actions.

9. The list of the recommended appendices to the Main dossier of the manufacturing site:

appendix No. 1. A copy of a valid license for manufacture of medicinal products;

appendix No. 2. The list of manufactured dosage forms, including international nonproprietary names (INN) or usual names (if any) used by the pharmaceutical substances (PS);

appendix No. 3. A copy of the current conclusion on the conformity of the manufacturer to the requirements of the Rules of organization of production and quality control of medicinal products;

appendix No. 4. The list of performers carrying out work under the contract, including laboratories, their addresses and contact information, as well as the scheme of the organization of relations with the performers;

appendix No. 5. Organizational schemes;

appendix No. 6. Plans for production areas with indication of feed streams, packaging materials and personnel, the general scheme of the production processes for each type of product (dosage form);

appendix No.7. Schematic drawings of water treatment systems;

appendix No. 8. A list of the main technological and laboratory equipment.