Ministry of Industry and Trade Russian Federation
State Institute of Drugs and Good Practices

THE RUSSIAN GMP INSPECTORATE. INSPECTION EXPERIENCE AND REVIEW OF INSPECTIONS

GMP Symposium by JPMA
November 16, 2019
TOKYO, JAPAN

TABLE OF CONTENTS

TABLE OF CONTENTS

Medicinal Drugs Circulation in Russia

Ministry of Health

State policy and regulatory control for medicinal drugs circulation:

- Medicinal drugs registration;
- Permissions for clinical trials.

Federal Service for Surveillance in Healthcare

- Pharmacovigilance;
- GLP, GCP, GSP, GDP, GPP inspections;
- Medical devices registration.

Scientific Centre for Expert Evaluation of Medicinal Products

Expert evaluation upon:

- Pharmaceutical products registration (including quality control);
- Issuing permissions for clinical trials.

Ministry of Industry and Trade

Department of Pharmaceutical and Medical Industry Development

- Licensing of drug products manufacture;
- Issuing GMP-certificates to pharmaceutical manufacturers.

FSI "SID & GP"

- GMP inspections of foreign pharmaceutical manufacturers;
- GMP / GEP training programs.

Ministry of Agriculture

State policy and regulatory control for circulation* of pharmaceuticals for veterinary use (GLP, GCP, GSP, GDP, GPP)*.

Federal Service for Veterinary & Phytosanitary Surveillance

- Registration*;
- Clinical trials*;
- Manufacture licensing;
- Pharmacovigilance.

Russian State Center for Animal Feed and Drugs Standardization and Quality

Expert evaluation upon:

- Registration*;
- Clinical trials.

Legal basis for the need to determine compliance of drug manufacturers with regulatory requirements (GMP)

1. Article 45. Production of medicines. Federal Law of April 12, 2010 No. 61-FZ “On the Circulation of Medicines”

2. Article 18. Filing and consideration of an application for state registration of a medicinal product for medical use. Federal Law of April 12, 2010 No. 61-FZ “On the Circulation of Medicines”

3. Article 30. Amendment of the documents contained in the registration dossier
for a registered medicinal product for medical use
Federal Law of April 12, 2010 No. 61-FZ “On the Circulation of Medicines”

4. Article 34. Inclusion in the state register of medicines and exclusion from the state register of medicines of a pharmaceutical substance produced for sale
(as amended by the Federal Law of December 22, 2014 N 429-FZ)
Federal Law of April 12, 2010 No. 61-FZ “On the Circulation of Medicines”

Legal basis for the need to determine compliance of drug manufacturers with regulatory requirements (GMP)

1. **Article 45. Production of medicines. Federal Law of April 12, 2010 No. 61-FZ “On the Circulation of Medicines?**

- “The production of medicines must comply with the requirements of the rules of good manufacturing practice, approved by the authorized federal executive body. The issuance of certificates on the conformity of the pharmaceutical manufacturer to the requirements of the rules of good manufacturing practice is carried out based on the results of the inspection of pharmaceutical manufacturers in the manner established by the Government of the Russian Federation.
- “The production of medicines in the Russian Federation is carried out by manufacturers of medicines that are licensed to manufacture medicines. Confirmation of compliance of the licensee with the rules of good manufacturing practice is carried out in the framework of licensing control in accordance with the legislation of the Russian Federation ... "

Rules for organizing and conducting inspections of drug manufacturers (Rules)

Approved by the Resolution of the Government of the Russian Federation of December 3, 2015 N 1314

"ON DETERMINING THE CONFORMITY OF DRUG MANUFACTURERS REQUIREMENTS OF RULES OF GOOD MANUFACTURING PRACTICE «

These Rules establish the procedure for the organization and conduct of inspections of drug manufacturers for compliance with the requirements of the Rules of Good Manufacturing Practice, as well as for issuing opinions on compliance of the drug manufacturer with the requirements of the Rules of Good Manufacturing Practice (hereinafter referred to as the Conclusion).

Rules for organizing and conducting inspections of drug manufacturers

The main provisions of the inspection rules:

- Inspection is carried out on the basis of an application for the issuance of a report submitted to the authorized body by the drug manufacturer / foreign drug manufacturer or their authorized representative
- If the production of a medicinal product is carried out at production sites located at different addresses, applications and submitted documents referred to in these Rules shall be submitted for each production site.
- A certificate is issued for each production site.
- The validity of the Certificate is 3 years and is calculated from the day the inspection is completed.
- Inspection should be carried out in a period not exceeding 160 working days from the day of decision by the authorized body to conduct an inspection.
- The inspection period may not exceed 10 working days, excluding travel time to the inspection site.
- Based on the results of the inspection, the authorized body issues certificates in the form approved by it.

GMP Pharmaceutical Inspectorate Structure

* According to the Order by the Ministry of Industry and Trade of the Russian Federation No. 877 as of 07 June, 2013

** According to the Order by the Ministry of Industry and Trade of the Russian Federation No. 4184 as of 21 December, 2015, FSI "SID & GP" was authorized to carry out GMP inspections of medicinal drugs manufacturers with manufacturing sites located outside the Russian Federation, as well as to be involved in inspections of Russian manufacturers as an expert organization and a co-inspecting agency.

Russian GMP Inspectorate Structure

*(*to the previous slide):

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Structure of the Russian State GMP Inspectorate

- The body authorized to inspect local drug manufacturers and issue Certificates on the compliance of the drug manufacturer with the requirements of the rules of good manufacturing practice is the **Ministry of Industry and Trade of the Russian Federation** (MPT).

- The department responsible for the inspection and issuance of Certificate on the compliance of the manufacturer of medicines with the requirements of the rules of good manufacturing practice is the **Department for the Development of the Pharmaceutical and Medical Industry of the Ministry of Industry and Trade of the Russian Federation**

* (in accordance with the order of the Ministry of Industry and Trade of the Russian Federation No. 877 dated June 7, 2013 “On approval of the administrative regulations of the Ministry of Industry and Trade of the Russian Federation on the provision of state services for licensing the production of medicines for medical use”).

Structure of the Russian State GMP Inspectorate

- *** The Federal State institution "State Institute of Drugs and Good Practices" (FSI "SID & GP") is a subordinate institution of the Ministry of Industry and Trade of the Russian Federation.*

- *Since 2014, SID & GP has been accredited as an expert organization involved in licensed control of pharmaceutical sites as part of a commission of the Russian Ministry of Industry and Trade.*

- *Since 2015, SID & GP has been authorized to inspect foreign manufacturers of medicines for medical use for compliance with the requirements of the GMP Rules with the aim of issuing conclusions on the compliance of the manufacturer of medicines with the requirements of the rules of good manufacturing practice (Order of the Russian Ministry of Industry and Trade dated December 21, 2015 No. 4184), as well as participate as an expert organization and co-inspector during the inspection of Russian manufacturers.*

Russian GMP Inspectorate Specialization

- Inspections of Russian medicinal drugs manufacturers for compliance with GMP requirements
- Inspections of foreign medicinal drugs manufacturers for compliance with GMP requirements
- Inspections of Russian medicinal drugs manufacturers within the licensing procedure

Current Russian GMP

- **Existing up to date Russian GMP were approved on June 14, 2013** as per Order No. 916 of the Ministry of Industry and Trade of the Russian Federation (hereinafter **Russian GMP)** and registered in the Ministry of Justice of the Russian Federation on September 10, 2013 under No. 29938.

Also use in during inspections:

- part III "Recommendations on organization of production and quality control of medicines" approved by order of the Ministry of Industry and Trade of Russia

of December 12, 2013 № 1997.

Current Russian GMP

These regulations were based on the European GMP regulations effective at that time. They were adapted and developed for the Russian Federation. In terms of structure and content, they did not differ much from the European regulations effective at the time that contain:

- Part I (9 chapters)
- Part II (basic requirements for pharmaceutical substances used as raw materials - 20 parts), 18 Annexes).
- Part III is presented in a separate document (Order of the Ministry of Industry and Trade of the Russian Federation No. 1997 "Approval of Recommendations in organization of manufacturing and quality control of medicines" dated December 12, 2013).

Almost every point of Russian GMP corresponds to a certain point of European GMP and on the text of the regulations, there are brackets that contain the numbering of structural units of the text (points) given in the European GMP regulations.

Current Russian GMP

The Differences:

- Since the approval to the present time, there were no changes in the text of the Russian GMP, except for one change №4148 from December 18, 2015, related to the name of the " Russian GMP " (earlier "Rules of manufacturing and quality control of medicines").

- Since 2013 to the present time, **a number of changes has been made to the European GMP, which are not included in the Russian GMP. In addition, the main difference is precisely in this *(these changes are not reflected in the current Russian GMP.***

- Order No. 916 (in the edition of Order No. 4148 of the Ministry of Industry and Trade of the Russian Federation dated 18.12.2015) there have been a number of changes in the EU GMP, which were reflected in the new versions of the GMP sections:

Current Russian GMP

Review of the main changes in EU GMP as of June 2018 in comparison with the current Russian GMP.

Key changes were made in the following sections of the European GMP regulations:

Part 1:

- Chapter 2 (Personnel)
- Chapter 3 (Premise and Equipment)
- Chapter 5 (Production)
- Chapter 6 (Quality Control)
- Chapter 8 (Complaints and Product Recall)

Part 2 – minor changes of references in the text due to EU regulations' changes

Annex 15 - Qualification and validation

Annex 16 - Certification by a Qualified Person and Batch Release

Current Russian GMP

In Russia:

Federal Law No. 61 dated April 12, 2010 "Circulation of Medicines" established the obligation for manufacturers of medicinal products to comply with the requirements of the GMP regulations.

In Europe:

relevant EU Directives are required to follow, and the GMP requirements are of a recommendatory nature, allowing flexibility in application.

General Procedure for Inspections Organization

Collection of a package of documents needed to submit an Application for Issuance of a Medicinal Drug Manufacturer GMP Compliance Statement

Carrying-out the inspection
(not more than 10 days)

Actions taken by a foreign manufacturer after a decision is made by RF Minpromtorg to refuse issuance of a Medicinal Drug Manufacturer GMP Compliance Statement

Report elaboration
(30 calendar days)

Decision to issue a GMP Compliance Statement

Preparation of Documents for GMP Inspections

A pack of documents needed to submit an Application for Issuance of a Medicinal Drug Manufacturer GMP Compliance Statement (GMP Certificate)

- A manufacturers or its authorized representative shall submit to Minpromtorg of Russia **a paper-based** Application for Compliance Statement Issuance directly or **by registered mail**, or **an electronic version** of **the Application** for Compliance Statement Issuance with an electronic signature, specifying the details of **the document supporting payment of the state duty for compliance statement issuance** and **the package of documents**, according to the RF Government Decree No. 1314 as of 03 December, 2015

Preparation of Documents for GMP Inspections

Collection of a pack of documents needed to submit an Application for Issuance of a Medicinal Drug Manufacturer GMP Compliance Statement (GMP Certificate)

- **An Application for Compliance Statement Issuance (Form 1);**
- A copy of the document to confirm powers of the authorized representative of a manufacturer or a foreign manufacturer;
- **A copy of the Site Master File;**
- The information about non-conformities of the drugs quality with the established requirements discovered, including recall of drugs from civil circulation for at least the last 2 years (Form 2);
- **The List of Drug Products Manufactured at Manufacturer's or Foreign Manufacturer's Production Site Subjected to Inspection** (Form 3);
- A copy of the license issued by the authorized agency of the country of a foreign manufacturer (or the document permitting drug manufacturing activities of a foreign manufacturer) and its duly certified translation into Russian (if such a document is required by the legislation of the country of a foreign manufacturer);
- A Letter from a Foreign Manufacture with a Consent to Host an Inspection (Form 4).

Carrying-out GMP Inspections

Inspection preparation:
Appointment of inspectors.
Estimating the timeframe.
Concluding the agreement.
Paying the invoice.

Inspection plan
(10 calendar days before the inspection)

Opening meeting

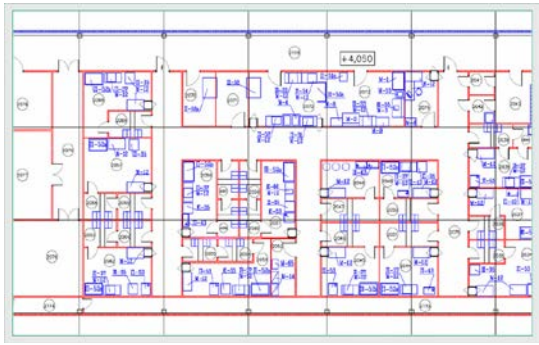
Inspection carrying-out
(not more than 10 business days)

Closing meeting

Report elaboration
(30 calendar days)

Report submission
(3 calendar days)

Assessment of the complexity of the site under inspection and preparation of the Inspection Plan



A risk-based approach based on site complexity assessment is used to determine the scope of the inspection and prepare the inspection plan. To estimate site complexity, use:

- Production Site Master File (SMF):
- Information submitted by the Applicant in the package of documents for inspection.

Assessment of the complexity of the site under inspection and preparation of the Inspection Plan

There are 3 different types of valuation/difficulty indicator 3:

- Site Complexity
- Complexity of processes
- Product Complexity

Preparation for Carrying-out GMP Inspections. Site Evaluation.

Complexity indicators:

- Site complexity
- Product complexity
- Process complexity

- Site size;
- Variety of manufacturing processes: - number of processes
- Level of utilities dedication: - shared utilities for different types of manufacture
- Number of site personnel – number of persons employed
- List of products manufactured for different markets – product distribution scope
- Whether the manufacturing site is used as a contract manufacturer or a laboratory

Preparation for Carrying-out GMP Inspections. Process Evaluation.

Complexity indicators:

- Site complexity
- Product complexity
- Process complexity
- Sterile and aseptic processes
- Large amount of process control points
- Product types: manufacture of high-potent agents, modified release forms
- Number of sub-processes in non-sterile manufacture
- Presence of repackaging processes
- Presence of reprocessing/rework processes
- Extensive use of contract manufacturers/laboratories
- Products of biological origin

Preparation for Carrying-out GMP Inspections. Process Evaluation.

Complexity indicators:

- Site complexity
- Product complexity
- Process complexity
- Results of measures to eliminate inconsistencies identified during the previous inspection/
- Products requiring special storage and distribution conditions: for example, for products stored in cold conditions or for radiopharmactic preparations, the complexity is higher.

Preparation for Inspection Carrying-out

Taking into account the conducted evaluation of all indicators:

- Appointment of the Lead Inspector
- Determination of the number of inspectors
- Estimation of the number of inspection days
- Determination of the inspection scope
- Drafting an Inspection Agreement (with the cost estimate attached)
- Invoice issued
- Working out the itinerary (logistics)

Preparation for Inspection Carrying-out

- **Guidelines for inspection carrying-out:**

Order by the Ministry of Industry and Trade of the Russian Federation

- **Inspection goal**: to assess compliance of the manufacture of the requirements of Good Manufacturing Practice
- **Inspection scope:** drug manufacturing activities at the site on the whole

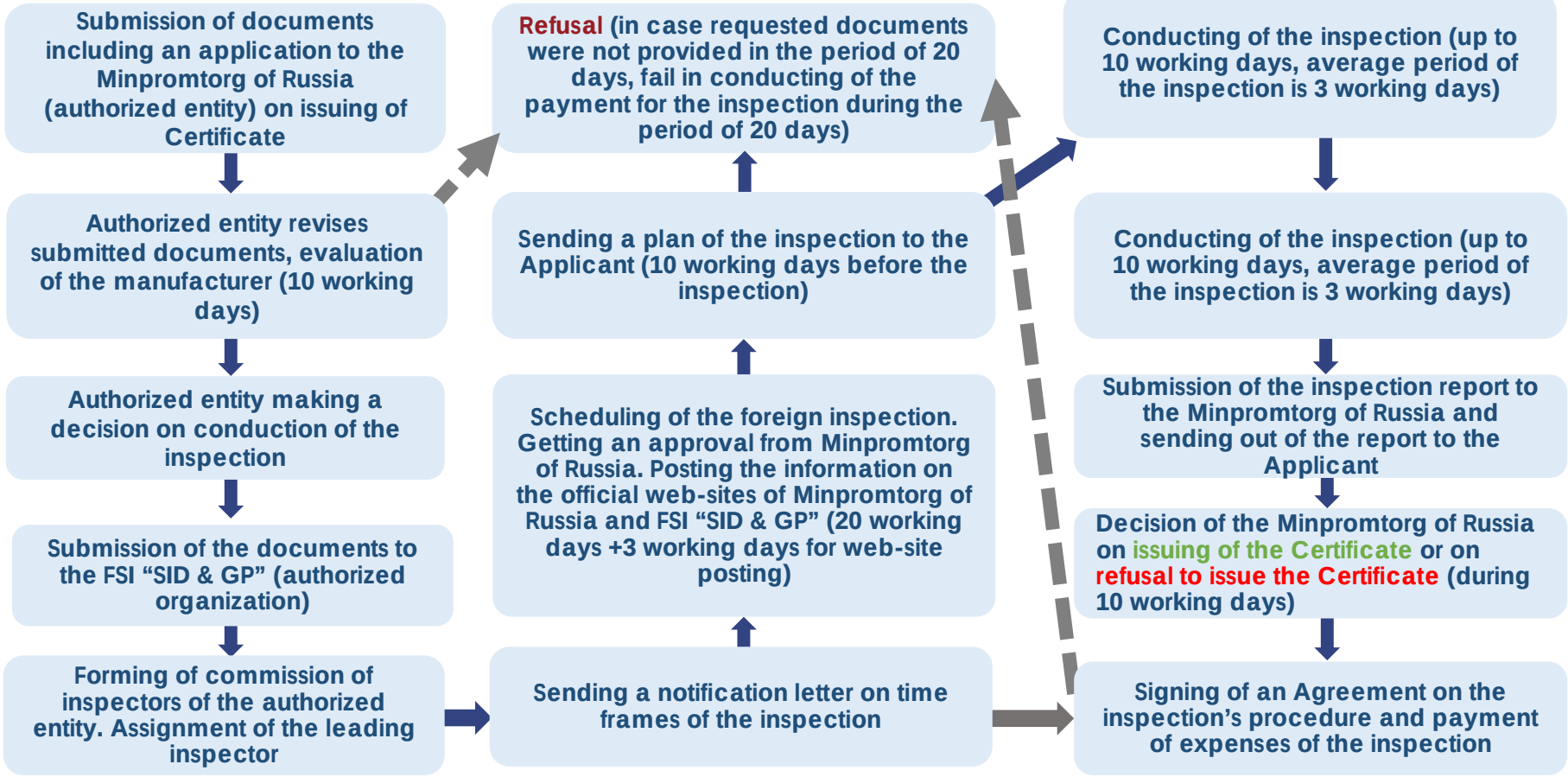
- **Inspection date and time:**
- **Inspection group members:**
- **Regulatory documents:**

  - Order by Minpromtorg of Russia No. 916 as of 14 June, 2013 “On Approval of Good Manufacturing Practice Guidelines”, amended by the Order by Minpromtorg of Russia No. 4184 as of 18 December, 2015

Conducting inspection

- Introduction meeting
- Representation of parties (education, work experience)
- Discussion of the objectives, tasks of the inspection, procedure for its conduct
- Changes since previous inspection
- Presentation of the enterprise (optional)

Consequence of Actions During GMP Inspection Block-Scheme



Conducting of the Inspection

- Inspection of warehouse areas
- Inspection of manufacturing areas
- Inspection of engineering systems and supporting area
- Inspection of quality control areas
- Verification of pharmaceutical quality system documentation
- Verification of production documentation
- Validation Documentation Verification
- Verification of Corrective Action Plan
- and Preventive Action (CAPA).

Closing Meeting

Existing Inspection Practice-

- Existing inspections practice – all the non-conformities found during an inspection are presented by the Lead Auditor at the closing meeting.
- No final categorization of all the non-conformities found is presented at the closing meeting
- The procedure for elaboration, review and check of implementation of the Corrective and Preventive Actions (CAPA) Plan

Министерство промышленности и торговли Российской Федерации
(Минпромторг России)

Федеральное бюджетное учреждение
«ГОСУДАРСТВЕННЫЙ ИНСТИТУТ ЛЕКАРСТВЕННЫХ СРЕДСТВ И НАДЛЕЖАЩИХ ПРАКТИК»
(ФБУ «ГИЛС и НП»)

ИНСПЕКЦИОННЫЙ ОТЧЕТ № 60/16024/19-16
по результатам инспектирования производителя
(иностранного производителя) лекарственных средств
для медицинского применения на соответствие требованиям
правил надлежащей производственной практики

I. ОБЩИЕ ПОЛОЖЕНИЯ

Производитель (иностранный производитель):

Общество с ограниченной ответственностью

наименование, адрес места нахождения производителя (иностранного производителя);

адрес производственной площадки

Виды деятельности:

Производство фармацевтических субстанций	-
Производство лекарственных препаратов (лекарственных форм): паста для приготовления суспензии для приема внутрь	X
Производство промежуточных продуктов	X
Производство нерасфасованных лекарственных препаратов	-
Упаковка (первичная/вторичная)	X
Выпускающий контроль качества	X
Прочее	-

Дата(ы) проведения инспектирования:

11.05.2016 - 13.05.2016 г.

Инспекторы:

Иванова Ирина Ивановна	Руководитель комиссии
Смирнова Мария Викторовна	Инспектор
(полностью фамилия имя отчество)	

Нормативная база:

ФБУ «ГИЛС и НП»
Лавров пер., д. 6, Москва, 109044
Тел. (495) 676-43-60; E-mail: info@gilsinp.ru; http://www.gosgmp.ru

Inspection report

- The inspection report is prepared within a period not exceeding 30 calendar days from the date of completion of the inspection
- identified non-conformities are classified by the inspection commission in accordance with the order of the Ministry of Industry and Trade of Russia dated 04.02.2016 No. 261.

Inspection report

- I. GENERAL PROVISIONS
- II. RESULTS OF THE INSPECTION
- Pharmaceutical quality system
- Personnel
- Premises and equipment
- Documentation
- Manufacturing
- Quality Control
- Outsourcing
- Complaints and Product recalls
- Self-inspection
- Manufacturing Site Master File (SMF)
- Results of non-conformities identified during the previous non-conformance inspection
- List of detected observations/inconsistencies with assessment according to GMP Rules requirements and with reference to GMP Rules points. The identified inconsistencies are classified in accordance with Order No. 261 of the Ministry of Industry and Trade of Russia dated 04.02.2016.

Report Elaboration

- Final report version
- Cooperation with Expert Evaluation Department
- Decision about site compliance
- Preparation of documents package
- Cover letter
- Report submission to Minpromtorg of Russia

GMP Compliance Statement

Issuance of a Medicinal Drug Manufacturer GMP Compliance Statement (GMP Certificate)

On compliance of the manufacturer (foreign manufacturer) of medicines for medical application with the Russian GMP rules

МИНИСТЕРСТВО ПРОМЫШЛЕННОСТИ И ТОРГОВЛИ
РОССИЙСКОЙ ФЕДЕРАЦИИ

ЗАКЛЮЧЕНИЕ
о соответствии производителя (иностранного производителя) лекарственных средств для медицинского применения требованиям Правил надлежащей производственной практики

№ GMP-00001/16/SI

Часть 1

Министерство промышленности и торговли Российской Федерации подтверждает, что **Акционерное общество «КРКА, фармацевтический завод, д.д. Ново Место» (АО «КРКА, д.д., Ново место»),**

(полное и сокращенное наименование (при наличии) производителя (иностранного производителя) лекарственных средств для медицинского применения)

находящегося по адресу 8501, Республика Словения, г. Ново Место, Шмарьешка цеста, 6,

осуществляющего производство лекарственных средств для медицинского применения по адресу 9240, Республика Словения, г. Лютомер, ул. Рада Пушеньяка, 10

прошел инспектирование в рамках лицензионного контроля на соблюдение лицензионных требований при осуществления деятельности по производству лекарственных средств в соответствии с лицензией от __ _____ ____ г. № ____ в соответствии с законодательством Российской Федерации *или* прошел инспектирование в части регистрационного(-ых) удостоверения(-ий), указывающего(-их) производителей, расположенных за пределами Российской Федерации,

в соответствии с требованиями **Правил надлежащей производственной практики,** утвержденных приказом Министерства промышленности и торговли Российской Федерации от 14 июня 2013 г. № 916.

Страница 1 из 8

0000007

Updating and improving GMP regulations

Russia has been and is working to update and improve Russian GMP rules.

- In 2015, five countries - Russia, Belarus, Kazakhstan, Kyrgyzstan and Armenia - established the Eurasian Economic Union (EAEU). Russia is an equal member of the EAEU along with other participating countries.
- The EAEU member states signed the Treaty on the Eurasian Economic Union as of May 29, 2014 and intend to develop economic cooperation and expand trade and economic ties.
- Recognizing that medicines are socially significant products, the EAEU members signed an international "Agreement on uniform principles and rules of circulation of medicines within the EAEU" on 23 December 2014.
- The establishment of the EAEU considers:
  - Updated legislation, including in the field of pharmaceuticals based on international standards
  - New regulatory developments
- Meanwhile, there is a lot of work going on to create the EAEU documents in the field of medicines and GMP compliance inspection.
- The creation of the EAEU has led to the need to harmonize regulations in the pharmaceutical sector, including tax legislation and GMP standards.
- More than 60 documents are planned to be approved by the end of 2019.

Updating and improving GMP regulations

- GMP regulations of the EAEU came into force on May 6, 2017 and during 2019-2020, the regulators and the pharmaceutical industry plan to switch to the GMP EAEU.

The basis for the development of the EAEU GMP were the European GMP regulations as amended by 2014.

EAEU GMP = EU GMP v.4 99.99%

- Today, work is underway to update the EAEU GMP in accordance with the current EU GMP. Draft modifications are under consideration by the Working Group of the Eurasian Economic Commission (EEC).

Updating the GMP regulations will help all participants of the pharmaceutical industry to continuously improve their proficiency of creating quality medicines in order to improve the health of patients around the world.

Updating and improving GMP regulations

- The EAEU GMP certificate – is a binding document/component of the registration dossier.
- One of the most important EAEU rules is the confirmation of the EAEU GMP compliance in terms of the inspection of one of the EAEU member states' inspectorates and mutual recognition of the inspections' results by all EAEU member states.
- Until December 31, 2020, when submitting documents for registration, it is possible to submit a national document (GMP certificate) of the Union Member State.
- From January 1, 2021, the EAEU GMP certificates will be the only possible option.

The GMP regulations continue to be updated, which will undoubtedly help all participants of the pharmaceutical industry to continuously improve their proficiency of creating quality medicines in order to improve the health of patients around the world.

CARRYING OUT INSPECTIONS IN ACCORDANCE WITH THE RULES OF GMP OF THE EAEU

- Since October 2017, the Ministry of Industry and Trade of Russia has received the corresponding powers. In order to start inspections in accordance with the rules of the EAEU, it is necessary to introduce additions to the legislative framework.

- Intensive efforts are being made in this regard. Internal procedures were developed, personnel were trained and professional relations were established with colleagues from the EAEU countries.

- Within the framework of the WHO educational program on the basis of GILS and NP, a training course was held for representatives of regulatory bodies of the EAEU (Russia, Armenia, Kazakhstan and Kyrgyzstan) on the organization of GMP-inspection
- In the second half of 2020 in Russia it is planned to switch to inspection according to the rules of GMP EAEU.

Ministry of Industry and Trade Russian Federation
State Institute of Drugs and Good Practices

Russian GMP inspectorate in figures as of 01.07. 2019. Review of typical non-conformities

GMP Symposium by JPMA
November 16, 2019
TOKYO, JAPAN

Geography of inspections

68
Countries
inspected in 2019

390
Inspections
worldwide in 2019

Фармацевтический инспекторат в цифрах

МИНПРОМТОРГ РОССИИ

Первая GMP инспекция с выдачей GMP сертификата

Российского фармацевтического производителя - 2014 год	Иностранного фармацевтического производителя - апрель 2016 года

2014	2015	2016	2017	2018
12 инспекторов	12 инспекторов	34 инспектора	64 инспектора	80 инспекторов
101 инспекция	144 инспекции	348 инспекций	804 инспекции	632/768** инспекций

** на 17 сентября 2018 года/ запланировано на 2018 год

Russian GMP Inspectorate in Figures*

The first GMP-certificate issued
to a Russian manufacturer – January 2015,
to a foreign manufacturer – May 2016.

348 inspections

804 inspections

667** inspections

233**390 inspections

* as of 01.07.2019

** number of foreign inspections

Information about Inspections Carried-out (2016-2019) *

Data as of 01 July, 2019	2016 г.	2017 г.	2018 г.	2019 г.	Total
Total applications submitted to RF Minpromtorg	620	792	639	293	2344
Inspections carried-out	188	521	667	**233**	1609
Compliance statements issued	90	403	489	186	1168
Refusals to issue a compliance statement	39	111	241	120	511

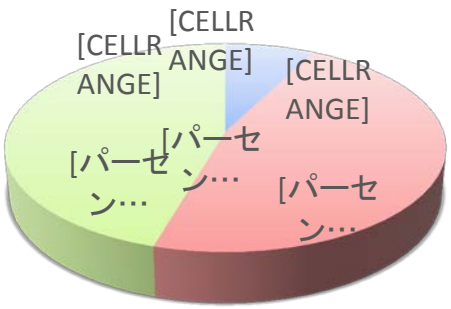
* as of 01.07.2019

Inspection-hosting Countries (2016-2019)

2016		2017		2018		2019 * as of 01.07.2019	
Country	Number of inspections carried-out	Country	Number of inspections carried-out	Country	Number of inspections carried-out	Country	Number of inspections carried-out
India	31	Germany	108	Germany	126	Germany	30
Germany	14	India	81	India	88	Italy	22
Hungary	11	France	45	Italy	54	France	20
Slovenia	10	USA	40	France	56	India	18
Poland	8	Italy	35	USA	45	Japan	12

Non-conformities Found at Foreign Manufacturing Sites in 2017-2019

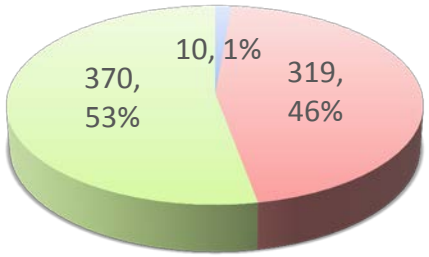
2017



2018

2019

(* as of 01.07.2019)

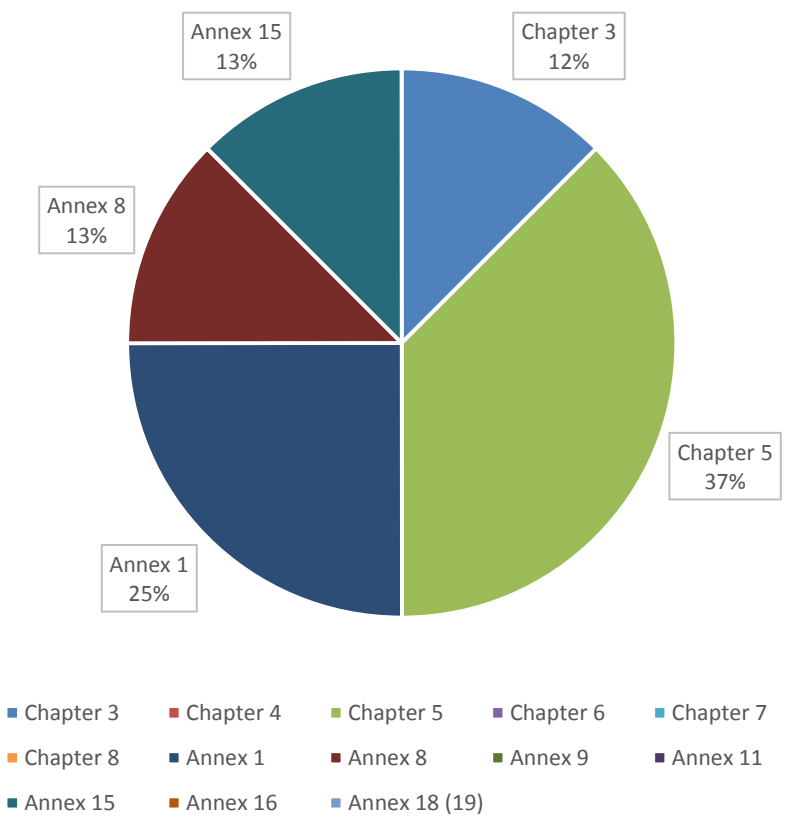


Critical Major Other

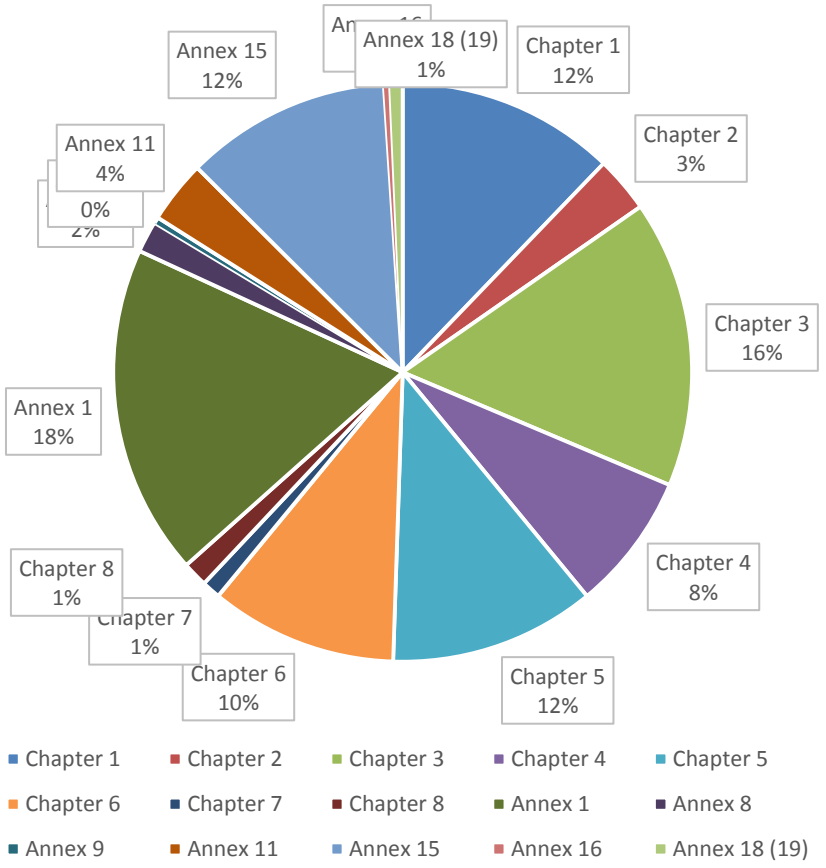
Statistics of Critical Non-conformities Found with Reference to GMP Chapters for 2019

Statistics of Critical Non-conformities Found with Reference to GMP Chapters for 2019

(01.2019 по 06.2019)



Statistics of major non-conformities found with reference to GMP chapters for 2018



Examples of non-conformities

- The tests carried out during the release of the finished product into circulation do not comply with the control methods specified in the regulatory documentation (Chapter 1, paragraph 5.13);
- The integrity of sterilizing filters used in the manufacture of sterile medicines is not controlled (Annex 1, paragraph 118. (111));
- The proof for the shelf life of a thermolabile medicine after lyophilization is not presented, not more than 240 hours in total at room temperature. There is no evidence of the stability of a medicine produced from this product. (Chapter 6. Quality control);
- The maximum allowable storage time of the intermediate product at all stages of the production process (heat-labile preparation) has not been established (Chapter 5. Production, Chapter 6. Quality control) ;.

Re- inspection

Reason	Expiration of GMP Compliance Statement (1 every 3 years)	Additional request by the applicant (E.g. expansion of the List of Manufactured Medicines)	In case of previously received refusal to issue GMP Compliance Statement
Carrying-out the inspection	On the site	On the site / Out of site	On the site

10. Non-conformities Typical of Foreign Drug Manufacturers

Chapter 1

1. Principles, 5, 13 (1.8) GMP

- The tests conducted for finished product release do not correspond with the test methods specified in the normative documentation:

- no testing of sterile drugs for "abnormal toxicity";

- no testing of drugs for "microbial purity". (C)

- The composition and (or) the technology of drug manufacture is different from that specified in the registration file. (C)
- The drug is manufactured at the manufacturing site which is not listed in the Marketing Authorization/registration file. (C)
- Evaluation of the quality of finished product (for solid dosage forms) and issuance of the release permit are done based on quality control of in-bulk products. (Mj)
- The finished product in final packaging is not controlled. No justification was provided for reduction of testing within release control. (Mj)

10. Non-conformities Typical of Foreign Drug Manufacturers

2. 70 (3.23) GMP:

- The rejects area is not isolated and has a contact with other storage areas (e.g., for finished products). (Mj)

Chapter 6. Quality Control

3. 233(6.30)

- The drug product batches manufactured with significant changes and/or major deviations during the manufacturing process are not subjected to post-approval stability studies. (Mj)

Annex 1. Manufacture of Sterile Medicinal Products

4. Annex 1 ,3(1), 4(2), 11(4) ?

- Sampling of raw materials used for manufacture of sterile drugs is performed in a non-classified area.? (Mj)

5. Annex 1, 74(67)

No justification was provided for reduction of the time interval for the media fill test. (Mj)

6. Annex 1, 118(111)

- During aseptic filling, no second filtration via an additional sterile filter is performed to retain microorganisms. (Mj)
- 87. (80),117. (110)

No control of the microbial contamination level before sterile filtration of the drug product N in the form of the lyophilizate for intravenous and subcutaneous solution. (C)

10. Non-conformities Typical of Foreign Drug Manufacturers

- No justification was provided for selection of the sterilization method for the lyophilizate solvent. Sterile filtration of the lyophilizate solvent is performed via a 0.22-µm filter. (C)

Annex 8. Sampling of Starting and Packaging Materials

7. Annex 8.3 -6

- No incoming control of the API is performed for the parameters from the specification, including identity from each tare space (manufacture of parenteral drugs). (Mj)

Annex 15. Qualification and Validation.

8. Annex 15, 36,38

- No documents were provided to support validation of cleaning hold times: dirty hold time and clean hold time. (Mj)

11. Non-conformities Typical of Russian Drug Manufacturers

1. No isolated areas for storage of rejected and recalled products.
2. Temperature mapping in warehouse premises executed in 1 season.
3. No data integrity and security provided in the analytical laboratory (in such computerized systems as Milichrom, Chromateck, Chemstation, no user access levels and passwords established). The computerized systems are not validated.
4. The batch size in process validation for API manufacture does not correspond with the batch size established in the master formula.
5. No monitoring of aerosol particles during the assembly of critical equipment.
6. For the time of the inspection, calibration of control and measuring instruments and laboratory equipment was expired.
7. No justification (risk analysis) provided for selection of the points for microbiological environmental monitoring and monitoring of aerosol articles in A zone of B grade rooms.
8. Within cleaning validation, no time interval between the end of the process and cleaning, as well as between cleaning and the start of the next process established.
9. No mock recall performed, though required by the approved procedure in case of absence of real product recall from the market.
10. No data integrity and security provided in the electronic documentation management system. No limitation of access to the materials and products management computerized system to execute the procedure of changing the material status.

Thank you for the attention!

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