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RUSSIAN GMP INSPECTION. USER'S MANUAL

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ABSTRACT

Development of pharmaceutical industry in Russia requires for a common approach to the qualification and standardization of manufacturing process for drug products. To achieve this goal the package of relevant legal Acts was approved in Russia in 2015-2016. How to obtain RU GMP certificate? What is the role and responsibilities of Regulator? What is the role and responsibilities of drug Manufacturer? What to do if the Manufacturer has received the refusal of RU GMP certificate? This article answers these and other questions.

KEYWORDS: GMP, inspection, EEU.

INTRODUCTION

In 2013 the global pharmaceutical industry has celebrated an important date - the 50th anniversary of publication of the first variation of GMP rules. This abbreviation – GMP - is also deeply included into lexicon of Russian Pharma now.

In Russia the first attempt of harmonization with the European GMP rules was undertaken in 2004 by the introduction of GOST R 52249-2004. Paragraph 4 of this documents said that "this standard is identical with "EC Guide Good Manufacturing Practice for Medical Products". But the Russian legislation available at that time was not allowed to implement GMP inspection as a mandatory action for the drug registration.

Regulatory framework and organizational structure of the Russian Inspectorate

In the period from 2010 to 2016 a package of updated regulatory acts was adopted:[1,2]

- Administrative regulation of the Ministry of Industry and Trade (herein after MIT), approved by MIT's Order no. 1714 dated 26th of May, 2016.[3]
- MIT's Order no. 261 dated 04th of February, 2016 "Forms of Application for GMP inspection".[4]
- MIT's Order no. 916 dated 14th of June, 2013 "GMP Rules" (with update of 18.12.2015).[5]
- Directive of RU Government no.1314 dated 3rd of December, 2015 "Criteria of Compliance to GMP requirements".[6]
- MIT's Order no. 9 dated 11th of January, 2016 "Fee of GMP inspection".[7]

The Ministry of Industry and Trade of the Russian Federation is the authorized body for issuing the Conclusion of compliance with GMP requirements. The Federal Governmental Budget Unit «Governmental Unit Lekarstv Sredstv and Normative Practices» (herein after FGBU), is the authorized body for GMP inspection.[8] As for today the pool of RU GMP Inspectorate is 42 inspectors. All of them are highly qualified specialists with 5-10 years' experience in the pharmaceutical industry. Also they have completed a special training course in College "Farmak", Denmark. In addition to the theoretical course of international principles and rules of GMP, all the Inspectors were directly involved in the real GMP inspections, conducted together with the international inspectors and independently.

All the Inspectors have a State Diploma of post-professional training in theory and practice of GMP inspection, as well as international certificates, confirming the right to perform the functions of the inspector.[9]

Aldo Russia has adopted a Code of Inspector to prevent the possibility of a biased assessment of the situation and doubts about the reputation or authority of the Inspector.

The Inspector must follow to the rules of Ethics and Business Code of conduct, the laws of the Russian Federation, international rules and regulations.

How to obtain a Conclusion of compliance with GMP requirements in Russia

To apply for a Conclusion the Applicant (pharmaceutical manufacturer of its authorized representative - legal entity or civil person, registered in Russia) submits the following documents:[10]

1. Application (Form 1). The information about name and address of the Manufacturer including into the Application must meets the other official documents (i.e. Manufacturing License, GMP Certificate issued by the authorized body of country of Manufacturer, Site Master File etc.).
2. Power of Attorney (PoA) to represent the Manufacturer in MIT (the apostle original with notarized translation OR notarized copy of the translated original). The PoA may have the rights of re-authorization (substitution). The authenticity of the signatures of the Manufacturer is certified by Apostille or Consular legalization.
   NB! In case of re-authorization/substitution the additional PoA must also be notarized.
   I.e. the general PoA is given by Manufacturer to Head of Russian representative office. Then the additional PoA is given by Head to the employee to authorize him to sign the documents and submit the dossier to MIT.
3. Copy of Site Master File (SMF).
4. Form 2 is the information about complaints and recalls concerning inspected drugs for the last 2 year's period.
5. Form 3 is the List of drugs manufactured by the inspected site.
6. Copy of the Manufacturing License issued by the authorized body of country of Manufacturer (with notarized translation into RU).
7. Form 4 is the Letter of Consent for GMP inspection. The Letter must be prepared on the language of country of Manufacturer, signed by the Head of site and notarized. The translation of the Letter can be confirmed by stamp of Russian representative.
8. Confirmation of payment of state fee for Conclusion (7500 RUR).

All the documents must be in Russian, one hard copy and one soft (i.e CD) copy. If document has more than 2 pages, it can be sewn and sealed with the seal and signature of the Applicant / legal representative of the Manufacturer.

Each manufacturing site applied for the GMP inspection must has the own package of the documents.

Terms of review of Application and conducting Inspection

During 10 working days after submission of Application and package of documents Assessors of the Department of Development of pharmaceutical and medical industry of MIT check the completeness and correction of submitted documents. Assessor may require the additional information if the submitted documents are not enough. The Applicant must submit the required documents within 20 working days. If the requested documents will not be submitted during this period MIT may reject the Application. If the documents meet all the requirements MIT then forward it to the FGBU for the next step - inspection. Within 20 working days after decision of the Inspection FGBU discusses Inspection's dates with the Manufacturer and enter it into the List of Planned GMP Inspections.

Then Applicant and FGBU sign an Agreement. After that FGBU calculates the cost of Inspection and prepares the Invoice. Applicant pays for the Invoice within 20 working days from the date of signature of Agreement.

The Inspection must be carried out in a period of time not exceeding 160 working days from the date of decision of MIT on inspection. Duration of Inspection should not exceed 10 working days. The Inspection's Report should be prepared within 30 calendar days, then the Report is submitted to Applicant and MIT.

During 10 working days after receiving of the Report MIT takes a decision and issues the Conclusion of Compliance (or Incompliance) of Manufacturer to GMP requirements.

The validity of RU GMP certificate is 3 years after the date of Inspection.

The cost of Inspection

When the date of Inspection is agreed, Manufacturer should pay for Inspection within 20 working days. The cost calculation is prepared by FGBU according to MIT's Order no. 9 dated 11.01.2016.

The cost of Inspection depends of volume and program of inspection, number of inspected items (warehouse, laboratory of Quality Control, manufacturing lines etc.), no. of involved Inspectors (2 or 3), economically reasonable material and job costs, overhead costs, indirect expenses etc. But the total cost cannot be exceed 2,8 million RUR.

General recommendations to Applicant during Inspection

- During the Inspection any situation which may compromise Inspectors or site employees should be avoided;
- Manufacturer may organize the events only in frame of polite hospitality, for example offer a city tour or visit the historical places;

- It is possible to organize lunches and/or coffee-brakes (it is recommended to organize the lunch out of the territory of the inspected site in the nearest café with a standard business lunches or with the non-expensive national food);
- Manufacturer does not participate with accommodation and/or transportation of Inspectors;
- Manufacturer cannot take from Inspectors or give to Inspectors any costly gifts (including promo materials with logo of inspected site and/or products);
- Manufacturer does not have any additional expenses which are not included into official Invoice from FGBU.

The major objectives/violations during Inspection

The inspections of foreign Manufacturers by RU Authorities are started in April of 2016 (by the Applications received by MIT in December of 2015). And despite 25 years of experience in GMP standards in Europe, the Russian Inspectors detected many violations at European sites, and some of these violations may be considered as critical.

The main objections are concerning of deviations between documents registered in Russia and documents at site. For example:

- Common Technical Document (CTD) registered in Russia, says that it is a full-cycle Manufacturer of the drug. During Inspection it is found that some manufacturing steps are performed by another manufacturer, even in another country.
- Manufacturer implemented some Variations (i.e. Composition, Specification, Analytical methods etc.), but they are not registered in Russia.
- The Normative Document (ND, specific Russian document combined some parts of CTD – Supply chain, Composition, Specification and analytical methods) which is approved in Russia, says that Quality Control testing is performed according to Russian Pharmacopeia. But in real practice site uses Eur.Ph. (or USP etc.).
- The different Manufacturer of Active Product Ingredient registered in Russia.
- In case of Contracting/Third party manufacturing or cooperation (i.e. warehouse, laboratory of Quality Control, any intermediate site) an appropriate Contracts are not available.
- Manufacturer uses expired Standard Operation Procedures (SOPs).

To minimize the risks of rejection, some Manufacturers invite independent (non-state) GMP-inspector and arrange pre-audit to align analytical documentation for the drugs produced for RU market, in accordance with Normative Document, approved in Russia.

This procedure allows Manufacturers to save time and money. Indeed, in the case of a negative Conclusion fees are not refunded and all the documents need to be prepared for the new Application.

Major objections are found – what have to do?

If during Inspection some serious discrepancies are found the serious and responsible Manufacturer has a possibility to develop plan "Corrective Action Preventive Action" (CAPA). If these discrepancies may be corrected by CAPA, they are removed from Inspection's Report. If objections are concerning the documents, the follow-up visit of Inspector is not required (i.e. during Inspection Manufacturer did not submit some required documents or change to the registration dossier is required). If objections are concerning some technical issues (i.e. water treatment or airflow) the follow-up visit of Inspector may be required after improvement.

All the above are concerning not only Manufacturers of drugs, but for Manufacturers of Active Product Ingredients (API) also.

If API is planned to be included into the official Register in Russia, its Manufacturer must be inspected for GMP compliance. If API is a part of drug, its quality is checked by Manufacturer or drug.

EEU perspectives

Currently, the Eurasian Economic Union (EEU) brings together five countries-members: Armenia, Belarus, Kazakhstan, Kyrgyzstan and Russia. In 3rd of November 2016 a common GMP standards were approved by Order no. 77 of Eurasian Economic Committee (EAC). This document has 3 Parts: Part I is for drug manufacturing, Part II is for APIs, Part III has a comments to the GMP rules. In future this document will replace current national GMP requirements of EEU members. Up to the end of transition period (end of 2021) both EEU and national GMP requirements are valid. But if the drug is planned to be registered in EEU by the decentralized procedure (parallel submission in a few EEU members), each Manufacturing site must be complied with EEU GMP requirements.

At the same day November 3rd, 2016 EAC has approved Rules of conducting GMP inspection by Order no. 83. EEU members agreed to mutual recognition of results of GMP inspections, conducted by the Authorities of any EEU member and full rejection of the results of inspections from third countries, including EU, USA, Japan etc.

This decision is based on the fact that these countries also do not recognize the results of the inspections performed by EEU members. Coming into force the Order no. 77 and Order no.83 and conducting of pharmaceutical inspection according to requirements of EEU GMP is planned immediately after the approval of the relevant Administrative regulations in September 2017.[11,12]

In the period from 2022 to the end of 2025 all the national rules and standards will be eventually cancelled excepting procedures controlling the post-registration turnover of drugs.

SUMMARY

March 24, 2017 held its final Board meeting of the Ministry of industry and trade named «About general results in 2016 and future plans for 2017». The Board meeting was opened by Prime Minister of Russian Federation Anatoly Medvedev. In his speech, the Prime Minister noted the necessity of further development of the local manufacturing "not only generics, but modern, innovative medical drugs." Now the share of Russian Manufacturers of the Essential Drugs is about 77%. And the current Russian Federal Program of development of the pharmaceutical industry (so-called "Pharma 2020"), also intends to increase the share of Russian Manufacturers of the Essential Drugs to 90% by 2020.

Despite the economic difficulties, the Russian pharmaceutical market is growing and according to the results of 2016 amounted to $14.7 billion. And the total pharmaceutical market of EEU countries in amounted to $17.2 billion in the last year. And with the development of procedure for mutual recognition of drug registration, it is expected that the EEU market will grow faster.

In these circumstances, the early availability of the Russian GMP is becomes a necessary condition of successful work for foreign companies in Russia and the EEU. As soon the foreign Manufacturer will receive RU GMP certificate, then the more chances he has not only to keep but also to increase its share in this market.

REFERENCES

1. Ministry and Industry and Trade of Russian Federation (www.minpromtorg.gov.ru).
2. Ministry of Health of Russian Federation (www.rosminzdrav.ru).
3. Order of Ministry and Industry and Trade of Russian Federation no. 1714 of May 26th, 2016 “Administrative Regulations “How to perform GMP Inspection”.
4. Order of Ministry and Industry and Trade of Russian Federation no. 261 dated 04th of February, 2016 “Forms of Application for GMP inspection”
5. Order of Ministry and Industry and Trade of Russian Federation no. 916 dated of June 14th, 2013 “GMP standard”.
6. Directive of RU Government no.1314 of December 03rd, 2015 “Compliance of Manufacturer of drug with GMP requirements”.
7. Order of Ministry and Industry and Trade of Russian Federation no. 9 of January 11th, 2016 “How to calculate GMP Inspection service fee”.
8. Order of Ministry and Industry and Trade of Russian Federation no. 4184 of December 21st, 2015 “FGBU “GILS and NP” is an Authorized body for GMP Inspection”.
9. FGBU “GILS and NP” (www.gilsinp.ru).
10. http://minpromtorg.gov.ru/activities/services/licensing/.
11. Eurasian Economic Union (www.eaeunion.org).
12. Eurasian Economic Committee, (www.eurasiancommission.org).