Manufacturers' Preparedness

for Follow-Up GMP Inspections

*Fig. 1. Decisions of the Russian Ministry of Industry and Trade are weekly updated at: **http://minpromtorg.gov.ru** (please choose 'GMP decisions register' in the Lists and Registers folder)*

Current issues of pharmaceutical manufacturers

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During the preparation phase of the 3rd All-Russia GMP conference, the State Institute of Drugs and Good Practices (SID & GP) received more than 100 questions from 34 open and anonymous sources. They were mostly about follow-up inspections and Corrective Action/Preventive Action (CAPA) plans.

SID & GP experts analyzed the received information to determine the number of businesses planning to re-submit applications for follow-up inspections. Tentative assessment revealed 112 companies from 38 countries.

Please note the provisions of Federal Law No. 61 'Pharmaceutical circulation' dated April 12, 2010 (as amended on June 4, 2018) article 45 section 1 'Pharmaceutical manufacture', 'Pharmaceutical manufacture shall comply with the GMP rules approved by the Federal Government Authority. GMP certificates are issued based on the outcomes of pharmaceutical manufacturers' inspections per procedure established by the Government of the Russian Federation… '

In accordance with Decree No. 1314 'Verification of GMP compliance among pharmaceutical manufacturers' dated December 3, 2015, '…an Inspection is a sequence of actions undertaken by the Russian Ministry of Industry and Trade (for human-use pharmaceuticals) and by the Russian Federal Veterinary and Phytosanitary Service (for veterinary pharmaceuticals) – hereinafter referred to as Regulating Authorities – or by the Federal State Institution subordinate to the above Authority (hereinafter referred to as Regulating Agency) – aimed at verification of the pharmaceutical manufacturer's compliance with the GMP rules…'

Section 19 reads, 'Inspections of foreign manufacturers fall under the jurisdiction of the Regulating Agency…'

The State Institute of Drugs and Good Practices has been assigned to conduct inspections of foreign manufacturers of pharmaceutical products for human use.

Decree No. 1314 'Verification of GMP compliance among pharmaceutical manufacturers' issued by the Russian Government on December 3, 2015 prescribes to conduct an inspection within 160 work days from the decision of the Regulating Authority. Presently, an average wait time after the Russian Ministry of Industry and Trade issues an inspection warrant (Order) does not exceed 110 – 112 work days. Upon receipt of the inspection warrant issued by the Russian Ministry of Industry and Trade, SID & GP arranges for a follow-up inspection of the production site in a timely manner.

The Russian Ministry of Industry and Trade decides on the issuance of GMP-certificates as provided for by Order No. 916 of the Russian Ministry of Industry and Trade dated June 14, 2013 (as amended by Order No. 4148 of December 18, 2015) 'Approved GMP rules' registered by the Russian Ministry of Justice under No. 29938 on September 10, 2013 (hereinafter referred to as GMP Rules). Decisions of the Russian Ministry of Industry and Trade are weekly updated at: *http://minpromtorg.gov.ru,* please choose 'GMP decisions register' in the Lists and Registers folder (fig. 1.).

The Inspection procedure was established by Decree No. 1314 'Verification of GMP compliance among pharmaceutical manufacturers' issued by the Russian Government on December 3, 2015. The same procedure is equally applicable for both initial and follow-up inspections.

A follow-up inspection is conducted in the following events:

- Expiration of the GMP certificate; in accordance with Decree No. 1314 'Verification of GMP compliance among pharmaceutical manufacturers' issued by the Russian Government on December 3, 2015, a GMP certificate remains valid 3 years.
- Request from the manufacturer to adjust the valid GMP certificate (for example, in case of expanding the Production List) to make sure that deviations revealed during the previous inspection have been eliminated.

If the adjustment happens during the validity of the current GMP certificate issued for pharmaceutical products manufactured at the same facility and in the same conditions specified in the GMP certificate, the Regulating Authority releases a new one with the same expiry date without conducting an inspection.

In order to determine that the conditions of pharmaceutical manufacture remain unchanged, experts of the State Institute of Drugs and Good Practices analyze every submission following the internal procedure and taking the risk-based approach to evaluate quality of the drugs:

- joint production on the same production lines, with the same equipment, in the same premises, using the same engineering systems, as well as the previously approved flows of stock, raw materials, finished products, and personnel, paying special attention to risks of cross contamination;
- launching new production lines,

using new equipment, in new premises, using new engineering and introducing new flows of stock, raw materials, finished products, and personnel;

- adding new dosages of manufactured pharmaceuticals, changing the commercial name of the product, changing the name of the manufacturer, etc.

Based on the findings, it is decided whether an on-site visit is necessary, or the Production List can be extended without an inspection.

Another reason calling for a follow-up inspection is making sure that the deviations revealed during the previous visit have been removed.

If the previous inspection revealed deviations, the manufacturer should provide documentary evidence of corrective measures along with a request for a follow-up inspection.

Experts of the State Institute of Drugs and Good Practices review each application. Their analysis is based on the risk-based approach in line with the SOPs and evaluation of risks pertaining to the detected deviation. The review focuses on paperwork that can demonstrate elimination of identified GMP deviations. First, it is expected that all previous deviations have been cleared, and corrective and preventive actions (CAPA) have been fully implemented.

In case of well-grounded doubts in reliability of the information presented, or if the information does not prove elimination of the identified deviations by the manufacturer, a follow-up inspection is deemed necessary.

Preparation steps for a follow-up inspection on the manufacturer's end include:

- analysis of the previously revealed deviations;
- investigation of the root reason of the said deviations;
- development and enforcement of a CAPA plan, evaluation of its efficiency;
- request for a follow-up inspection, including submission of paperwork for evaluation.

The risk-based approach cannot be underestimated in analyzing the revealed deviations. Deviations are categorized by Order No. 261 issued by the Russian Ministry of Industry and Trade on February 4, 2016. The categories are harmonized with respective regulations used by inspectorates in the EAEU countries, Europe, Canada, Australia, and others.

It is important to realize that an individual inspection is organized for each separate applicant with all deserved confidentiality. A plethora of factors should be considered, e.g. drug characteristics, equipment, technology, manufacture process, documentation (including the drug registration dossier, the list of products to be inspected), the pharmaceutical quality system, etc. Deviations revealed at different manufacturers may belong to the same GMP Rule, however – depending on the above listed factors – they could mean different levels of risk in product's quality, and consequently, will be categorized differently in each particular case. For one, it is obvious that the degree of risk in product quality cannot be the same in manufacture of sterile and non-sterile products exposed to contamination.

Inspectors' responsibility for protection of confidential information about the applicant is part of the Inspection Agreement signed between the applicant and the State Institute of Drugs and Good Practices. Each inspector signs a confidentiality statement to be able to proceed with the site inspection.

A CAPA dossier for a follow-up inspection should demonstrate documented evidence of all actions within the pharmaceutical quality system aimed at eradication of the detected deviations. The dossier should include documentation of all involved systems:

- quality risk management;
- deviations management, including documented investigation and establishment of the root/genuine cause or the most likely cause;
- change control management;
- staff training;
- CAPA management, including performance evaluation of the undertaken measures.

A CAPA dossier reflects the quality system at the pharmaceutical facility. The following principles should be observed in its preparation:

1) Documentation culture:

- structure. The documents should be filed by the type of deviations in a logical and chronological order;
- consistency. The documents should not bear contradictions;
- visibility. The attached photographs should be of high quality to demonstrate the mended deviations;
- correct translation.

2) Relevance. The presented paperwork should be relevant and provide evidence of the measures undertaken to reconcile the deviations.

3) Traceability. It is necessary to ensure traceability of data in various types of documentation, i.e. registration records and reports.

4) System approach. There should be presented an evidence of measures undertaken to prevent the risk of deviations in similar circumstances. For instance, if a deviation is connected to insufficient training of the process manager it might be worth considering a new training course for all the team in charge of this particular process.

When submitting a request for a follow-up inspection the manufacturer should be able to prove during the follow-up visit all corrections of the previously detected deviations:

- If positive, then the previously revealed deviations will be lifted;
- If not, it deems impossible to evaluate performance of the planned actions. In this case, the deviations will again show on the inspection report.

Per existing procedure – governed by Decree No. 1314 'Verification of GMP compliance among pharmaceutical manufacturers' issued by the Russian Government on December 3, 2015 – no CAPA plan can be reviewed during preparation of the report immediately after the inspection was completed. An opportunity exists – however – to submit additional paperwork that was not produced during the site inspection for objective reasons. Please visit the web-page of the State Institute of Drugs and Good Practices to find out what documents can be additionally submitted: *https://gilsinp.ru* (fig. 2.).

In the future, with introduction of the EAEU GMP certificates (Decision No. 77 issued by the Eurasian Economic Commission Council on November 3, 2017) CAPA materials can be reviewed immediately after the inspection, which is provided for in Decision No. 83 issued by the EEC Council on November 3, 2017.

In accordance with Decree No. 1011 of the Russian Government dated August 25, 2017, the Russian Ministry of Industry and Trade is assigned to act as Regulatory Authority for coordination of pharmaceutical circulation, including the manufacture and sharing with the EEC information on pharmaceutical manufacture inspectors in order to open a register of EAEU inspectors. Apart from that, the Russian Ministry of Industry and Trade is in charge of the database of the issued and recalled GMP certificates; conducting GMP inspections; and issuance, suspension or cancellation of EAEU GMP certificates of pharmaceutical manufacturers.

Fig. 2. Please visit the web-page of the State Institute of Drugs and Good Practices to find out what documents can be additionally submitted ***https://gilsinp.ru***

The State Institute of Drugs and Good Practices is preparing to conduct inspections by Eurasian Economic Union rules. SOPs have been finalized and the staff is taking relevant training.

In April 2018, the FSI & GP hosted a WHO Global Learning Opportunities course for GMP inspectors from EAEU countries, i.e Armenia, Kazakhstan, Kyrgyzstan, and Russia.

In anticipation of joint GMP inspections, mock inspections are conducted in cooperation with the inspectorates of the EAEU regulating authorities.

Two Work Groups operate in the Eurasian Economic Commission to establish common pharmaceutical market in the Eurasian Economic Union:

- Work Group for common approach to pharmaceutical products circulation in the EAEU. The WG operates under the Board of the Eurasian Economic Commission (Decision No. 204 issued by the EEC Board on October 30, 2012. The WG composition is regulated by Resolution No. 52 updated by the EEC Board on June 9, 2015). The WG's main task is to draft blueprints of EEC regulations for the common EAEU pharmaceutical market. The WG meets on a monthly basis.
- Work Group for GMP inspections in the Eurasian Economic Union. The WG was initiated by the State Institute of Drugs and Good Practices with the support of the Russian Ministry of Industry and Trade. The WG operates on an ongoing basis; the EEC Board has not yet issued an institutionalizing decision, but it is on the way; the WG convenes every three months, starting 2018. The group focuses on articulation and application of unified technical and practical approaches in GMP inspections to be conducted on the common pharmaceutical market of the Eurasian Economic Union.

The EEC Work Group for pharmaceutical manufacture inspections not only pursues cross-country relations between their Regulatory Agencies, but it also strives to find practical solutions to guarantee a transparent, efficient, and productive functioning of the common EAEU market.

The EEC inspectorates encounter a number of particular issues in certain areas of the common pharmaceutical market, i.e.

- conducting pharmaceutical inspections in line with the unified EAEU rules;
- mechanisms and principles of interagency communications between the EAEU member-states during pharmaceutical inspections by the unified EAEU rules;
- unified rules of pharmaceutical inspections;
- a range of specific questions pertaining to filling out and design of registration documents by the unified EAEU rules.

Per internal procedure, the State Institute of Drugs and Good Practices sends an advance notification to the Regulating Authority of the host country with the dates of the planned inspection of the foreign manufacturer. Should the inspection reveal critical deviations, the Russian Inspectorate relays this information to the host country Regulating Authority with a reference to the relevant GMP Section without specification of the deviation for facility's confidentiality. Representatives of local regulators are invited and in many cases show up for the inspection of foreign manufacturers.

Above said, in submitting a request for a follow-up inspection special attention should be given to preparedness of the production site after all deviations have been cleared and necessary changes introduced. The developed and implemented CAPA plan must be properly evaluated, relevant, and exhaustive. Evaluation of the site preparedness for the inspection includes production capacity (staff, premises, equipment, drug quality control, etc) as well as proper documentation. ■

We wish you all successful inspections!