Remote GMP inspections by Russian authorities

Experiences and guidance

Edelgard Rehak, Ph.D.[1] and Matthias Kobro (M.A.)[2]

[1]Edelgard Rehak Consulting, Berlin, [2]GMP language support, Munich

GMP inspections of production facilities of foreign manufacturers by Russian authorities were introduced in 2016 by Federal Law N 61-FZ dated 12.04.2010 (as amended) [1]. A valid GMP certificate is a prerequisite for new registrations of medicinal products as well as for the maintenance of existing registrations (renewals, variations) in Russian Federation. Without GMP certification of the manufacturing site, the regular import of medicinal products into the Russian Federation is not permitted. Due to the COVID-19 pandemic and the travel ban on Russian inspectors, the continuation of GMP inspections was endangered, as on-site visits to the manufacturing sites were simply not feasible.

In order to avoid a shortage of medicinal products, the Russian government issued several anti-crisis laws in Apr/May 2020, including Decrees #789 and #440, which directly influence the timing and mode of GMP inspections.

This article presents the current Russian legislation regarding GMP remote inspections, describes the process of remote inspections, which is officially implemented by Russia's State Institute of Drugs and Good Practices (SID&GP), and outlines first experiences in this field. Although GMP remote inspections are to be prepared as meticulously as regular on-site inspections that have been carried out in the past, they require prior clarification of a number of additional questions, e.g. which means of communication and online systems are to be used, how the translation is to be organised and how confidentiality is to be ensured. The most important pitfalls are described here by the authors, who were both part of a manufacturing plant team.

1. Introduction

GMP inspections of foreign manufacturing facilities by Russian authorities have been mandatory for new drug applications since 2016, and for variations and renewals since 2017. This is regulated by Federal Law N 61-FZ "On medicines circulation", dated 12.04.2010 (as amended) [1,2]. The production of active pharmaceutical substances (API) is exempted from GMP inspections, unless the API is imported to the Russian Federation for further processing.

Since 2018, conditions for GMP inspections have been facilitated and the filing of a positive vote of the Russian Ministry of Industry and Trade (MoIT) on the conduct of a GMP inspection has been introduced as a prerequisite of dossier submission. Furthermore, minor administrative variations and safety updates have been exempted from the duty of GMP inspection.

A GMP certificate issued by the Russian authorities is normally valid for three years and has to be renewed by re-inspection of the manufacturing sites. This is a considerable additional workload for manufacturers, Russian inspectors and the team involved in preparing and conducting inspection at the site. Travel costs and fees burdening the budget should not be underestimated either.

The legal responsibility for GMP certification of foreign manufacturing facilities lies with Russian MoIT [3]. In practice, the responsibility for conducting GMP inspections lies with the State Institute of Drugs and Good Practices (SID&GP) [4].

From 2016 (the beginning of inspections of foreign manufacturers carried out by the Federal State Institution (FSI) "SID & GP") until 15.09.2020, MoIT databases list 2 272 inspections with a positive outcome and 630 with a negative one.[5]

As a result of the COVID-19 pandemic situation, on-site audits were prohibited due to a travel ban imposed since Apr 2020 by the Russian government.

To avoid a shortage of medicine, the Russian government very quickly passed several anti-crisis laws.

Among others, the following decrees made a significant contribu-

tion to ensuring drug supply to the Russian Federation:

(1) *Decree #440* [6] of 03.04.2020 "On renewal of permits and other characteristics of permits in 2020"
Decree #440 could lead to a postponement of GMP inspections for a maximum of 12 months, as well as to the automatic extension of the validity of registration certificates for medicinal products for human use expires within a defined period of time (15.03. to 31.12.2020).

(2) *Decree #789* [7] of 29.05.2020, amending Decree #1314 "On determining the compliance of pharmaceutical manufacturers with the requirements of the GMP roles" [8]

This decree legalized the conduct of GMP inspection *"using means of remote interactions (including audio and video communication) in case of the emergence, occurrence or liquidation of an emergency situation and/or in the event of a threat of the spread of a disease posing to danger to others* [...] *in which inspection of manufacturing sites is not possible for a period of three years."*

Russian inspectors now regularly practice GMP remote inspections. Since May 2020, a considerable number of audits have already been conducted by SID&GP [5]. It can be assumed that these inspections have been carried out remotely. By implementing the legal framework, Russia has taken a leading role in conducting remote inspections. In general, remote GMP inspections are not prohibited by common international GMP practice, but are performed only rarely and under certain specific circumstances.

2. Procedure of remote GMP inspections

In principle, remote GMP inspections were already practiced in the Russian Federation prior to the release of Decree #789, but they were limited exclusively to the follow-up of on-site visits or the extension of valid GMP certificates through the additional listing of products manufactured on the same production lines under identical conditions as those previously inspected on-site. The evaluation was a risk-based approach based on the review of documents and other materials (e.g., photos, official statements).

With the implementation of Decree #789, initial and re-inspections following failed inspections of production facilities under remote conditions are now legalized.

The application procedure for GMP remote inspections does not differ from that of on-site inspections, as the decision on how the inspection – remote or on-site – is carried out is made by the authorities.

The applicant has to submit the following documents for review by MoIT [9]:

- application form
- letter of consent of the manufacturing site to be inspected
- list of products to be inspected
- manufacturing licence
- list of complaints
- site master file

In case of cooperation with a local partner, a power of attorney (PoA) is mandatory. PoA, manufacturing licence and letter of consent must be notarized and provided with an apostille. All documents have to be translated into Russian.

After positive review of the documents by MoIT, the ministry instructs SID&GP – through an official confirmation letter of acceptance of the application – to conduct a GMP inspection of a manufacturing site within 160 working days.

This letter of agreement temporarily replaces the GMP certifi-

AUTHOR

Edelgard Rehak, Ph.D.

has more than 30 years of experience in the development and registration of medicinal products. She is an expert on regulations in the Russian Federation and the states of the former Soviet Union. From 2012 to 2015, she headed the Regulatory Department of Sanofi in Moscow and, from 2007 to 2010, the Regulatory/QA Department of Novartis in Kiev, Ukraine. She participated in several GMP inspections of production sites located in Russia. Since 2015, she has offered consultancy services for international companies, primarily with regard to the registration of medicinal products. Furthermore, she has successfully supported several European manufacturing sites (incl. API production) in preparation for the GMP inspection by Russian authorities.

AUTHOR

Matthias Kobro

has over 10 years of experience in professional interpreting (simultaneous and consecutive) and technical translation, with over 500 conference days in Germany, Europe, Asia and overseas. His core competencies include assisting clients with GMP audits and inspections by authorities from Russia, Belarus and Kazakhstan, providing teams of interpreters, and supplying technical translations in the pharmaceutical sector. He has gained GMP interpreting experience in more than 30 GMP inspections, incl. several GMP Remote Inspections undertaken by the Russian authority GILS & NP.

Pharm. Ind. 83, Nr. 7, 943–949 (2021)

cate for the submission of new drug applications and other regulatory activities. The regulatory activity is not finally approved by the Ministry of Health (MoH) before the GMP certificate is accepted, but this letter could help to save time during the registration procedures.

The exact date for the inspection is proposed by SID&GP and agreed with the manufacturing site. In order to perform the inspection, SID&GP is obliged to obtain the consent of the authorized representative of a foreign manufacturer.

Two weeks (10 working days) before the start of the inspection, the inspection team will inform the manufacturer's representative about a list of documents to be provided by manufacturing site. It is the duty of the manufacturer's site to provide the listed documents electronically before the inspection starts.

Shortly before the inspection starts, the inspection plan will be handed out, with a detailed list of areas to be inspected and strict time schedules with time slots for video conferencing. The walk through the plant is to be realized virtually. Simple video-clips about special production areas can be requested and should be actively offered.

The duration of a remote inspection is up to 5 working days, depending on the complexity of the manufacturing site and process, the status of inspection (e.g., initial inspection/reinspection), and the complexity of the quality of the medicinal product.

On day 1 of an inspection, an opening session in the form of a video conference is scheduled. A short presentation of the manufacturing site and an introduction of the team members is expected. Any special features of the product, preaudit results or contractual issues should be clarified to avoid misunderstandings in the future.

At the end of each inspection day, the inspectors determine a list of additional documents and further questions. The requested documents and answers should be made available as soon as possible. Delays might be considered incompetence.

At the closing meeting on the last day of the inspection, the inspectors summarize all violations found during the inspection. Only critical violations are evaluated as such, all others are merely announced. Findings and assessments are listed and recommended in the final inspection report [10].

The classification of violations is defined as follows.

"Critical deficiencies – violations (discrepancies) of the requirements of Good Manufacturing Practice or of the requirements of the registration dossier of the medicinal product for medical use, which have resulted or may result in the manufacture of a substandard-quality medicinal product for medical use that has caused or may cause harm to human health or life.

Major deficiencies – violations (discrepancies) of the requirements of Good Manufacturing Practice that have resulted or may result in the manufacture of a substandard-quality medicinal product for medical use, which cannot cause harm to human health or life, or violations (discrepancies) of the requirements of the registration dossier of the medicinal product for medical use or a complex of several insignificant violations (deficiencies), none of which can be classified as significant, but which taken together are significant violations (discrepancies) and shall be deemed as such.

Other deficiencies – violations (discrepancies) of the requirements of Good Manufacturing Practice that are not classified as either critical or major violations."

The clarification process takes another 15 calendar days after the final meeting. Discussions between the manufacturing site and the inspection team are no longer explicitly scheduled.

Since Oct 2020 the provision of a CAPA (corrective and preventive action) plan 60 days after receipt of inspection report receive was implemented. This is regulated by amendment no. 1361 to Decree 1314 [11]. The re-implementation of CAPA provision might lead to a reduction of number of refusals of GMP certifications.

The signed inspection reports will be handed over by the inspection team within 30 calendar days after the last day of the inspection, if no CAPA was agreed.

3 copies of the report are to be created. One copy of the report is submitted to the applicant, while the second copy is sent to the MoIT.

In case of positive decision MoIT will issue a GMP certificate within another 15 working days (Fig. 1).

3. Preparation of manufacturing sites for remote inspection

■ 3.1 Russian particularities

Besides to "normal" preparation of an international GMP inspection on-site, the inspection by Russian authorities in remote mode has its own peculiarities.

- The absolute prerequisite for every successful GMP inspection is compliance of the production process with the dossier. The core document is the currently approved normative document (ND). All ongoing variations to the ND (and other parts of the dossier) submitted to authorities must be communicated to the inspection team in advance. It is strongly recommended to consult an expert familiar with the Russian Pharmacopoeia and European standards.
- All documents must be available in electronic format and, ideally, in Russian & English language. The Russian GMP roles are defined in the regulation N 916 (revision dated 18.12.2015) dated

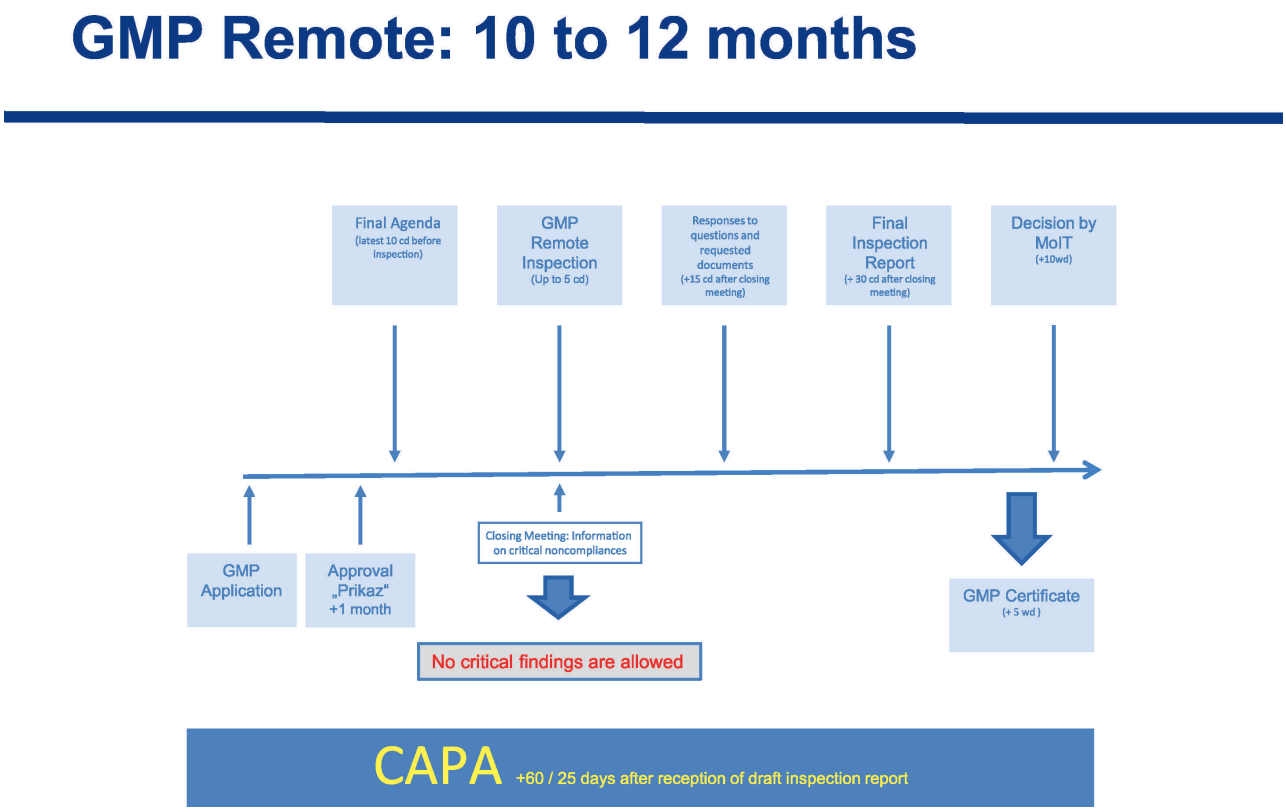

Figure 1: The process of GMP inspection of foreign manufacturing sites by Russian authorities (source: Edelgard Rehak Consulting).

14.06.201 [10]. Russian GMP has its own specificities. The manufacturing site should be aware of this and prepare in advance a justification for any deviations.

- For the preparation of the audit, the inspectors normally use the information from the application dossier provided by the manufacturer's representative, from Russian registration databases (GLRS) and also from international databases, both closed and open. The databases should be checked by the manufacturing site prior to the GMP inspection. All gaps should be known.
- Inspectors should be notified in advance of any changes to the application documents since the application was submitted.
- All documents listed specified in the inspection plan as well as the documents requested by the inspection team during the inspection shall be submitted by the applicant to the FSI "SID&GP" in the form of certified paper copies. An electronic format of these documents may also be acceptable. All submitted documents must be in Russian or English (exceptions might be possible based on alignment with the inspection team). If the documents are available in other languages, a translation into Russian should be provided.
- The preparation of remote inspections takes much more time than an on-site inspection. The team should be prepared for it.

■ 3.2 The team at the manufacturing site

A key factor for a successful GMP inspection is a strong collaboration of the team at manufacturing site.

A local partner or subsidiary, which acts as the authorized representative of the manufacturer and is located in Russia, plays a crucial role in the communication between the manufacturing site and the inspection team before, during and after the inspection. All correspondence goes through this partner. He is responsible for application filing, negotiating the date of the GMP inspection and clarifying organisational issues.

The main actor in a GMP remote inspection is a defined person from the manufacturing site who is the direct communication partner for inspectors in video conferences. For specific questions, the defined person can delegate this function to any internal or authorized external expert.

It is highly recommended to invite a person with detailed knowledge of the registration dossier as part of the team.

For the preparation of the audit and the preparation of the application dossier, an expert should be consulted who is familiar with specifics of Russian and European legislation, GMP roles, the Russian Pharmacopoeia and the Russian normative document preparation. This expert could also provide support in finding the right local part-

Pharm. Ind. 83, Nr. 7, 943–949 (2021)

ner in Russia and, if necessary he could build bridges between European and local Russian understandings and interpretations.

Effective communication with the inspectors is very important for a successful inspection. Therefore, communication during video conferences is also supported by professional interpreters who are familiar with pharmaceutical terminology and experienced in GMP inspections.

The support provided by the IT department should not be forgotten either. Colleagues should be always ready to support the team.

Another challenge could be dealing with the differences in time zones.

Despite the pandemic situation, the core team should be available on-site following the strict rules of social distancing.

■ 3.3 Communication via electronic tools

Prior to the start of the inspection, the inspection team and the applicant shall coordinate the procedure for the submission of the manufacturer's documentation in electronic format.

Shortly before the inspection starts, the inspection team sends a list of documents to be shown during inspection. A detailed inspection plan is also provided.

The manufacturer ensures the availability of all documents requested for the document list on the day of inspection by storing them in a cloud storage, or by another method agreed with the inspection team.

Method 1: cloud storage

The manufacturer collects all requested documents of the pharmaceutical quality system in electronic form and loads them into a cloud storage. Raw data should also be uploaded in electronic form. Various cloud solutions have already proven themselves in practice. The most important criteria are data security and confidentiality. When storing documents, it is advisable to find a suitable folder structure so that inspectors can find their way through the large volume of documents. Once the manufacturer has received the final agenda, the uploaded documents can be sorted, for example by inspection days. A table of contents for each inspection day is highly recommended.

Method 2: document camera

In addition to uploading all documents, the Russian authorities might allow the use of a document camera with live transmission via desktop sharing. This method is particularly suitable for the submission of large amounts of raw data, such as batch records, to substantiate certain facts. With the 1st method, the inspectors need more time to review the documents themselves, while the 2nd method is close to an on-site inspection.

During an on-site inspection, the premises are usually inspected. During the remote inspection, especially during an initial inspection, short video films provide a remedy. These video films can be requested by the inspection team to confirm the existence of facilities and rooms and to illustrate critical production steps. The following areas can be requested as video material: weighing, mixing, filling, sealing, secondary packaging, storage, receiving area, sampling and quality control. The video films should be stored in the cloud together with the documents, so that the inspectors can view the films if necessary. The facilities and procedures shown should be commented on, either when the films are recorded or during play back during video conferences.

Before the inspection begins, the inspection team is given access to the cloud, which should be tested and confirmed in advance. During the inspection, communication takes place via video conferencing. This communication channel should also be tested in a test call a few days before the inspection begins, in order to minimize possible technical difficulties in advance.

On the first day, the inspection starts with the sending of an introductory presentation of the Russian authorities. In return, the inspected manufacturer sends an initial presentation to the inspectors which can be presented in the first video conference.

The inspection plan specifies time slots for video conferencing, which may vary depending on the scope of the questions and answers. During the video conferences, questions are asked about the documents viewed, which are answered by the respective experts from the specialist departments in the same way as during on-site inspections. Documents such as standard operating procedures (SOPs) or raw data are either scanned or released via document camera via the screen.

When all documents are stored in the cloud, a typical remote inspection day looks like this: In the morning, the documents are reviewed by inspectors in the cloud, while in the afternoon the questions and answers are discussed in a video conference.

At the end of each day of inspection, the inspection team shall send a list of questions arising from the day and a list of additional documents required for verification in the form of a checklist; at the end of the last inspection day, the inspection team shall send the final list of questions and additional documents required for verification. On the last day, preliminary observations may also be communicated orally during a final meeting.

4. Conclusions

Russia passed the legalisation of anti Covid-19 crisis very quickly in order to avoid a shortage of Russia's drug supply.

Pharm. Ind. 83, Nr. 7, 943–949 (2021)

The legalisation of GMP remote inspections ensures the continuity of GMP inspections. First inspections are carried out in remote mode.

Remote GMP inspections are a risk-based approach based on document evaluation, interviews with responsible employees and virtual information exchange.

The key factor of success is a qualified internal team accompanied by experienced external experts who support the manufacturing site before, during and after the GMP inspection.

The preparation time for remote inspection is much longer than for on-site inspections. Translation costs and IT infrastructure costs must be taken into account.

In general, GMP inspections by the Russian authorities have their own particularities, which also reflect the Russian national GMP roles.

It is expected that remote GMP inspections will be used in the future as an additional tool to on-site inspections after COVID-19.

REFERENCES

[1] Federal Law dated 12.04.2010 N 61-ФЗ (as amended on 29.12.2015) "On Circulation of Medicines"

[2] Federal Law dated 12.04.2010 N 61-ФЗ (as amended on 03.07.2016) "On Circulation of Medicines"

[3] *http://minpromtorg.gov.ru*

[4] *http://gosgmp.ru/?page_id=24*

[5] *http://minpromtorg.gov.ru/docs/#!reestr_zaklyucheniy_gmp*

[6] Decree #440 "On renewal of permits and other features regarding permits in 2020"; *http://publication.pravo.gov.ru/Document/View/0001202004060049*

[7] Decree #789; *http://www.consultant.ru/document/cons_doc_LAW_354050/*

[8] Decree #1314; *http://www.consultant.ru/document/cons_doc_LAW_190256/*

[9] Decree; *https://rulaws.ru/acts/Prikaz-Minpromtorga-Rossii-ot-04.02.2016-N-261/*

[10] Decree N 916 (revision dated 18.12.2015), dated 14.06.20132013; *https://gmpreg.com/sites/default/files/2019-09/2013_06_14%20RUSSIAN%20GMP%27s.pdf/*

[11] *http://government.ru/docs/40364//*

All links accessed 14.12.2020.

Correspondence:

Dr. Edelgard Rehak
RM Beteiligung GmbH
Robert-Koch-Str. 16
15859 Storkow (Germany)
e-mail: Edelgard.Rehak@web.de

Matthias Kobro
Kobro Kommunikation GmbH
Prinzregentenstr. 66
81675 München (Germany)
e-mail: info@mkobro.de

Editor-in-Chief: Claudius Arndt. Managing Secretary's office: Valentina Krinizki. Publisher: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Phone: +49 (0) 75 25 940 0, Fax: +49 (0) 75 25 940 127. e-mail: redaktion@ecv.de. www.ecv.de. Typesetting: rdz GmbH / Printed by Holzmann Druck GmbH & Co. KG.