Points to Consider for Virtual GMP Inspections – An Industry perspective

Introduction

The 2020 COVID-19 pandemic has resulted in governments imposing temporary measures such as confinement, quarantine orders and travel restrictions that are impacting National Regulatory Authorities (NRAs) in their capacities to perform on-site GMP inspections. Consequently, a number of NRAs have adopted temporary measures such as performing virtual (or remote inspections) to sustain the supply of high-quality medicines to patients.

This paper is based on the biopharmaceutical research-based industry’s experience to date of conducting and receiving remote inspections. It consolidates industry lessons learned from these remote inspections and proposes shared best practices. It is meant to complement efforts ongoing in other industry organizations such as EFPIA¹ and PhRMA². These practices can assist in carrying out an efficient and effective remote inspection and can be developed further as more experience is gained and more data is collected.

Definitions

Different options exist to allow a NRA to verify compliance of site operations with applicable laws and regulations. During conventional on-site inspections, inspectors are physically present at the manufacturing facility to assess the site’s conformity with regulatory expectations and related GxP requirements.

¹EFPIA position paper, 28 May 2020: Alternative GMP/GDP Inspection Practices in a Pandemic Situation (COVID-19) and Beyond. (link)
²PhRMA paper(draft), unpublished: COVID-19 Response: Inspections & Records Requests Proposal (link to be provided soon)
Inspections can also be carried out on the basis of a **remote (desktop) review**, which means confirming GMP compliance without undertaking an on-site inspection\(^1\)\(^2\) (i.e., a combination of a formal examination of information available to an inspector or auditor). It consists of the evaluation of information obtained from several sources, including documentary evidence provided by companies without a physical inspection and can include a “**paper-based inspection**”, as outlined in Figure 1 (ref: EFPIA\(^4\), PIC/S\(^5\); WHO\(^6\)). The option to undertake a remote (desktop) review does not preclude an on-site inspection if the outcome of the assessment does not confirm compliance with the expected practices or there are doubts with integrity. Sometimes elements of a remote (desktop) review can be performed prior and in addition to an on-site inspection.

In this paper, the term ‘**virtual inspection**’ applies to inspections that are performed off-site through the use of enhanced communication and information technology to fulfil a legal requirement of an on-site inspection. The only difference is that the inspector is not physically present. The term “remote/distant inspection” is used as alternate terminology.

**Considerations on the use of technology enablers for virtual inspections**

Remote inspections heavily rely on supporting Informational Technology (IT) to replace the physical presence of inspectors on site. It is therefore critical to carefully manage all technology aspects to allow for a faultless virtual inspection. Key elements to consider besides technical feasibility are privacy, security and confidentiality of remote connections. Legal concerns and understanding of requests to perform recordings need to be addressed upfront. Alternatively, the conventional approach using scribes to take notes has proven to be suitable. A system that allows all participants to know who is connected and is able to visualise the content being shared is also recommended.

**Technology support and redundancy**

It is highly advisable to have an IT professional engaged in the preparation, and available to support technology aspects during virtual inspections. IT support staff at the NRA is highly recommended. In some cases, when agreed upfront by both parties, companies may be available to support the local NRA conducting the virtual inspections by providing office space and IT support at the company country affiliate.

An IT Redundancy and Back-up Plan in case of unforeseen issues should be planned (e.g. problems with WiFi connections and the use of mobile phones). Efforts should be made to secure the highest speed broadband and that this be available in all areas that may need video, i.e. be virtually observed. Secure and unique communication channels should be established to assure only those who are deemed necessary are granted access. For example, new meeting invitations should be created on a daily basis, in addition to separate meeting sessions for multiple parties with the NRA, or internally.

**Video technology**

Video connections enable better personal interaction during virtual inspections. A secure video platform should be used upon agreement between the company and the NRA. One challenge can be bandwidth of the connection. This can be successfully remediated by turning off cameras for interveners that will not be speaking during video conferencing discussions.

---

\(^3\) GMP-Inspection reliance, PIC/S guideline PI 048-1, 1 June 2018 [link](#)

\(^4\) EFPIA position paper, 26 June 2019: Request for Optimising the GMP paper-based Inspection Process by Regulatory Authorities [link](#)

\(^5\) PIC/S guideline PI 048-1, 01 June 2018: GMP Inspection Reliance [link](#)

\(^6\) WHO TRS 1010 (2018), Annex 9: Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions [link](#)
Document sharing technology
Secure pathways for sharing documents, transferring files and information should be identified, agreed upon and installed. These might follow the same rules as those established for sharing documents in advance or in lieu of an onsite inspection (ref: FDA\textsuperscript{7}). Establishing a secure pathway for information exchange also includes establishing the inspectorate NRA as a “secure” email client and using a shared web-based portal with appropriate capability for file type and size. Lastly, the retention/period of access and availability to documents needs to be defined and agreed upon.

Pre-Testing IT systems and inspection site selection
Once everything is in place, pre-testing of IT and connection is recommended e.g. one week before inspection. The test should include any remote sites of the company/MAH. The feasibility study should include testing of the following elements:

- Security/Access to the Online Portal
- Telephone or Video Conference Capacity
- Screen-Sharing Capability
- Wi-Fi Signal Strength
- Computer Hardware and Connectivity

Final considerations
The COVID-19 Pandemic continues to have profound health, social and economic impacts around the world. Measures put in place by governments to prevent the spread of the virus (e.g. restrictions on travel, movement, border closures or measures on supply chain) can all directly or indirectly affect patients ability to have access to the therapies they need at the right time. The R&D-based biopharmaceutical industry is working to prevent and mitigate any shortages through close coordination with national regulatory authorities and other global stakeholders, including the World Health Organization.

Digital alternatives to standard practices that are an integral part of the regulatory process for ensuring quality and efficacy of medicines and vaccines are an emerging trend that has gained even more traction within the COVID-19 environment. This is the case for inspections normally carried out at manufacturing sites by NRAs to ensure compliance with the relevant standards and norms. Where adequately prepared, remote inspections can prove to be a useful alternative; when compared to traditional on-site inspections, they can decrease travel time and costs while enabling business continuity during challenging times. It also provides additional flexibility to inspectors and inspectorates, as they can be carried out on non-consecutive days and NRAs can review the relevant documentation at their own pace and through an extended time frame. There are also more opportunities for both parties to exchange information, and SME’s from different locations can participate in real-time. On the other hand, we also acknowledge that virtual inspections have their own limitations such as working between different time zones, the lack of body language and context, increased possibility of technical issues impeding/delaying inspections and the need for additional preparation associated with training.

As technology advances, the use of digital tools will in all fields of regulatory science will become more and more prevalent, and time will allow further evidence to be collected regarding safety and efficacy of such processes. In the meantime, onsite inspections remain the golden standard for the industry: IFPMA and its member companies and associations are in favour and support onsite inspections by the local NRA. Virtual inspections should be preferably used if an inspection in a 3\textsuperscript{rd} country is necessary and the inspectorate cannot conclude on the compliance status with other tools out of the remotes (desktop) review pool.

\textsuperscript{7} FDA staff manual, 31 August 2017: POLICY AND PROCEDURES FOR REQUESTING RECORDS IN ADVANCE OF OR IN LIEU OF A DRUG INSPECTION (link)
Annex: Tools & Best Practices

Preparing for a virtual/remote inspection

The preparation of a virtual inspection is not different to an on-site inspection with the exception of Pre-testing IT Systems. A set of steps to be followed in preparing for a virtual inspection is listed below:

1. The NRA identifies the name and contact information of their staff member(s) organizing and requesting records/documents.
2. The inspected site/firm identifies the company name, address, and the name and contact information of the individual(s) at the firm responsible for hosting and facilitating regulatory requests during the inspection.
3. The NRA requests documents in advance, taking the following into consideration
   a. Use of standardized list of pre-request documents, potentially developed by PIC/S or other collaboration (note: a standardized list of typical pre-requests would provide efficiency for both parties)
   b. Document type and detail descriptions (i.e. Standard operating procedure, example dataset, and/or summary reports)
   c. Scope the request and considers the volume and scale of documentation, which would be determined by such thing as timespan (i.e. 1 to 2 years), volume of product manufactured over a set period, number of products manufactured at the site, retention requirements and type of inspection.
   d. A clear indication of when the documents are to be provided. The timeframe between request and receipt would need to take account of the situation in hand for staff access (e.g. limited numbers on site during high risk epidemics). At a minimum the firm should have 15 calendar days to respond or 30 calendar day when language translation is requested.
   e. The requirements for document translation, as well as the need to receive the records in the original language. (For security reasons Google translate or other publicly available translation tools should not be used).
   f. A mutually agreed upon method and identification system for document sharing/transfer to assist with organization and ease of transfer and review, such as a shared secure web-based portal. The established portal should be maintained for pre-requests, during the virtual inspection, and for any follow-up requests.
4. The inspected site provides the documents requested, seeking clarification where needed. In addition:
   a. for documents that cannot be provided, a statement to that effect and justification/rationale.
   b. The regulatory authority provides confirmation of receipt of the requested documents, thus ensuring transfers are occurring between the parties.
5. Following review of the pre-inspection documents by the NRA, the need for virtual inspection may be revisited. If it proceeds if, the following activities occur
   a. Secure technology to conduct further communications that works for regulatory authority and firm is agreed. The section on Information technology outlines the considerations. A feasibility study and test runs should be performed in advance of inspection. (Feasibility items to consider are Security/Access to the Online Portal, accessibility due to NRA and the inspected site’s computer systems firewall protection, Telephone or Video Conference Capacity, Screen-Sharing Capability, Wi-Fi Signal Strength, Computer Hardware and Connectivity, IT Redundancy and Back-up Plan)
b. The number of days required to complete the review process should be outlined, allowing the regulatory authority and the firm ability to cover the scope of inspection, plan and adhere to a schedule.

c. The schedule for the inspection can be very helpful to ensure availability of staff at the appropriate time, both for logging into tele-meetings and/or being on site.

d. The number of regulatory inspectors involved should be no more than two to allow for efficient and dedicated responses. In addition, this reduces the risk of problems with teleconference infrastructures.

e. If the virtual inspection is occurring across multiple time zones, a mutually agreed upon time for receipt and delivery of documents and virtual interactions will be needed to arrange work schedules and accommodate the process.

f. If a translator will be needed during the discussions, identify practical logistics including their remote access or on-site if needed.

g. If remote tour or “observing of any process or activity” is anticipated, this should be discussed and the technology agreed and tested before the inspection begins.

**Inspection Conduct**

The inspection schedule and timing should be agreed upon prior to the inspection to take into account differences in time zones. If any party wishes to record any part of the inspection (both audio or visual), this should be agreed to up front and any notification should be given so all parties have an opportunity to make duplicate recording should it be necessary.

If needed, translators should be scheduled and be available to provide whatever translation services is needed for discussions. It is optimal the limit regulatory inspectors to two individuals because of the nature of video conferencing and logistics of the number of people that need to be conferenced in for discussions.

The virtual inspection should mimic, as much as possible, the general process of an on-site inspection. This should include the following as it relates to conference room discussions:

- An opening meeting to authenticate and introduce inspectors and site staff and clarify and logistical plans and issues for the conduct of the virtual inspection.
- Daily debrief or wrap up meetings that allows the inspectors to share their initial thoughts and any issues that may need follow up activity.
- In order to facilitate an efficient and effective inspection it is suggested that inspectors provide a list of documents and areas to be reviewed during the inspection such that a schedule can be established to best coordinate site personal and logistics. This schedule should be updated on a daily basis during the inspection to ensure a site coordination and timely response.
- Site subject matter experts should be available to the inspectors for providing both an overview and specific aspects of programs and processes as requested by inspectors.
- A close out meeting should be conducted that clearly communicates with the site personnel the areas of concern by stating specific observations and express the level of severity of any noncompliance. The site should be allowed to question and provide additional information to fully understand the nature and criticality of the issues.

Virtual inspections have more challenges mimicking facility tours and observing actual manufacturing processes. The following should be considered:
• Inspectors should clarify either prior to the inspection or at the opening meeting their desire to see certain areas or processes. The specific areas and/or processes should be communicated and scheduled to allow IT and logistical considerations.
• Remote tours or observing processes maybe facilitated by either pre-recorded video or if required, a “real time” video transmission. The privacy, security, safety and confidentiality requirements must be established as part of the pre-inspection discussions.
• Special considerations should be addressed with regard to the potential for product issues (both viable and non-viable contamination) and potential safety issues (explosion triggers and preventing human safety and ergonomic issues).

Similar to an on-site inspection, opening, closing and daily debrief meetings ensure expectations and potential concerns are clearly communicated. Technical and logistical matters can be raised and resolved. A document request reconciliation performed daily between the regulatory inspectors and firm ensures that record flow is occurring as it should, given the extended use of technology to transfer files and the number of transfers occurring during a typical day.

**Inspection Follow-up**
Identify when the formal non-compliance report will be issued, and the timeline and expectations for follow-up actions or written response by the site/firm.

• When writing the response and committing due dates for remediation actions, sites should be aware of potential challenges, including limited skills and resources available onsite and off-site (i.e. Vendors), due to COVID-19.
• Ensure this is communicated and agreed with the NRA. Remediation actions may need to be aligned to the site’s change management to address COVID-19, or at minimum with a COVID-19 mindset. Consider Legal, Regulatory and other Quality Leadership review of the inspection responses if the inspection is/or may be mutually recognized by FDA, MHRA, EMA.
• This review will need to be factored into the inspection response submission timeline. If possible, limit extension to review of already collected documents and not to provide additional document requests.
• The challenge is that frequently the paper-only review is a very lengthy process and there is no acknowledgement that the documents were reviewed and acceptable.