HOSTING REMOTE INSPECTION AT PHARMACEUTICAL FACILITIES

A Good Practice (GxP) inspections during the COVID-19 pandemic outbreak

Abstract

COVID-19 pandemic has put manufacturers, affiliates and inspectors in a new and challenging situation where it is in the public interest to continue to supply medicines while ensuring demonstrated compliance. Regulatory agencies coming with the idea for conducting remote inspection across foreign manufacturing site.

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FROM THE AUTHOR'S DESK

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We know most of the information's now a days are easily available over web media, but I am always trying to collate best information based on my industrial experience in a single article.

Once again, I would like to thank my readers, followers and seniors, who has encouraged me a lot.

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Introduction

The COVID-19 pandemic presents an unprecedented challenge to healthcare, the pharmaceutical industry's supply chain and personnel movement. Globally different support functions like API, excipient and packaging patterners to this industry are not able to respond with in pre-defined time frame. Apart from the third-party services like calibration and annual maintenance also impacted due to travel and transportation restriction. Currently, it was big challenge for industry to serve for the society with affordable and quality medicines. Even regulators are concerned with the standard of the medicines produced and supplied across globe during this pandemic as currently it is not possible for conduct onsite inspection for international travel restriction. COVID-19 pandemic has put manufacturers, affiliates and inspectors in a new and challenging situation where it is in the public interest to continue to supply medicines while ensuring demonstrated compliance.

Background

Major regulatory agencies are coming up with the strategy to audit/or inspect facility remotely to ensure continues regulatory compliance and patient safety. Here we will discuss regarding the new regulation coming up with this new strategy by few major regulatory bodies like US FDA, MHRA, TGA and European medicines agencies (EU).

Due to the COVID-19 pandemic, FDA announced that agency is temporarily postponing all domestic and foreign routine surveillance facility inspections. These facility inspections are assigned biannually using a risk-based Site Selection Model. FDA confirmed that they will continue the quality assessment of all applications per normal assessment operations for all disciplines, where all manufacturing facilities will be evaluated using risk-based approach as per existing guidelines. During this interim period, agency will be utilizing additional tools to determine the need for an on-site inspection to support the application assessment such as reviewing a firm's previous compliance history, using information sharing from foreign governments as part of mutual recognition and confidentiality agreements, and requesting records "in advance of or in lieu of" on-site drug inspections. [5]

Nevertheless, there may be many challenges on an organization to support remote inspections. It is fundamental to assess whether the inspectee meets the technical requirements to provide remote access to electronic systems and maintain communication with and support to inspectors. The technical nuances of these systems as well as the IT policies (of the inspectee and regulatory authority(ies) performing the inspection) are likely to cause additional challenges and need to be duly taken into consideration.

However, there will be a preintimation from the regulators to make sure all the readiness can be done in well advance. Expectation to set up a common cloud platform between inspectee and inspector, where organization can upload all

requested documents before start of inspection. Organization managing electronic documentation can directly provide authorization as viewer or auditor (read only) to review manufacturing, validation, testing or any development reports.

Remote inspection will take quite longer time related to routine inspection at your site. The initial success of the inspection will be built up based on the flawless communication and compatibility between inspectee and inspector. Both team members are setting together to understand well the process and practices and ensure patient safety; hence the objective of the remote inspection will be the as onsite inspection.

Inspection Preparation

There will be a possibility where agencies will provide a detailed agenda with the name of auditor for inspection well in advance. Addition to this prior inspection agencies can ask to provide few relevant documents to understand better. Similarly, it may possible regulators can ask for consolidated list of SMEs from your organization, to whom they need to interact. So, be ready with the SME list with primary contact and mentioned if secondary or additional SME is required to support.

For example, suppose clean utility review is going on, where firm need to explain few questions regarding **Compressed Air (CA)** system.

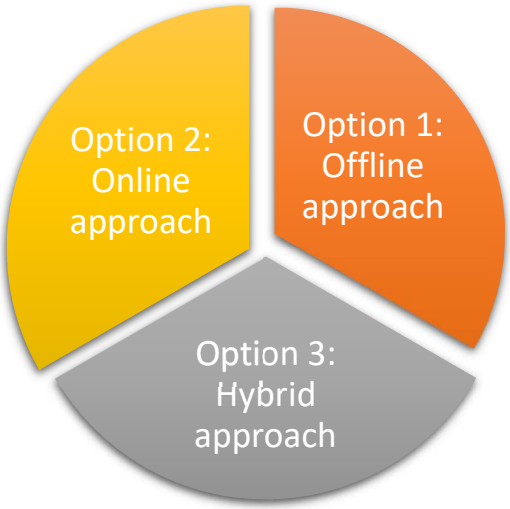
Question	Validation	Engineering	Quality Control	Production
How many sampling points are available? Share and explain current P&ID of compressed air system	Secondary SME: Validation can play a support role in this.	Primary SME: Engineering will be the primary contact for the query.	N/A	N/A
Explain the qualification of compressed air system.	Primary SME	Secondary SME: Engineering can play a support role in this.	N/A	N/A
What is the frequency of chemical and microbial testing?	N/A	Few firm engineering performed chemical testing with third party.	Microbiology team can respond regarding the microbial testing frequency.	
Are user points of the compressed air are conned with 0.2 µ air filter? If yes, what is the integrity/or replacement frequency of the compressed air filter connected with product processing/formulation?	N/A	Engineering can support as secondary SME.	N/A	As the discussion regarding the production user point. Production will be the primary SME.

#Note: Quality and Plant head can intervene based on the requirement to connect the dots

Time zone between inspectee and inspector can be concern, if immediate feedback not possible to provide that need to be indicated to inspector deliberately. IT personnel will be an important part of remote inspection process to fix any kind of technical glitch.

There are several software applications (apps), video conferencing systems, interactive tools for document sharing, instant messaging apps, whiteboarding apps and meeting platforms providing the users with more real time interactive communication tools that could enhance remote working. [1]

Any recording (audio / video / screenshots) during the inspection process should be notified and agreed upfront between all involved parties. [1]



Option 1- Offline inspection: Agency will ask document and review offline. Query can be resolved through telecommunication/ email or web-based call.

Option 2-Online inspection: Agency conduct web-based inspection program by using video conferencing.

Option 3- Hybrid approach: It will be combination of online and offline review and inspection process. Will be conduct by agencies as per predefined plan mutually agreed by agency and firm.

Figure 1: Remote inspection strategy during pandemic

[6]TGA clearly explained few requirements of remote inspection process and urge to firm to make it available during inspection.

- The manufacturer should organize to have pre-recorded videos of the site and operations so that the inspectors can be presented with a virtual tour of GMP relevant areas.
- If the manufacturer has electronic systems for QMS databases such as complaints, deviations, OOS/OOT and other GMP relevant areas then it is requested to organize guest remote read only logins to the QMS databases for inspectors' use at the time of inspection.
- The manufacturer must have the ability to participate in and/or host virtual communication on a suitable and agreed IT platform, with timely IT support during the remote inspection. This should include the ability to live stream video if required.

- Where time zone differences need to be taken into consideration staff including subject matter experts should be made available at the pre-agreed real-time communication timeslots.
- The manufacturer should address any other requests during the remote inspection in a timely manner to ensure a smooth process flow.
- Any information requested by inspector's post-inspection should be provided by the manufacturer within the requested timeframes.

However, we cover all the points in this articles and expectation of all the regulatory agency at this moment is same. Regulators are quite flexible at this time to received positive response /or suggestion from firm as well.

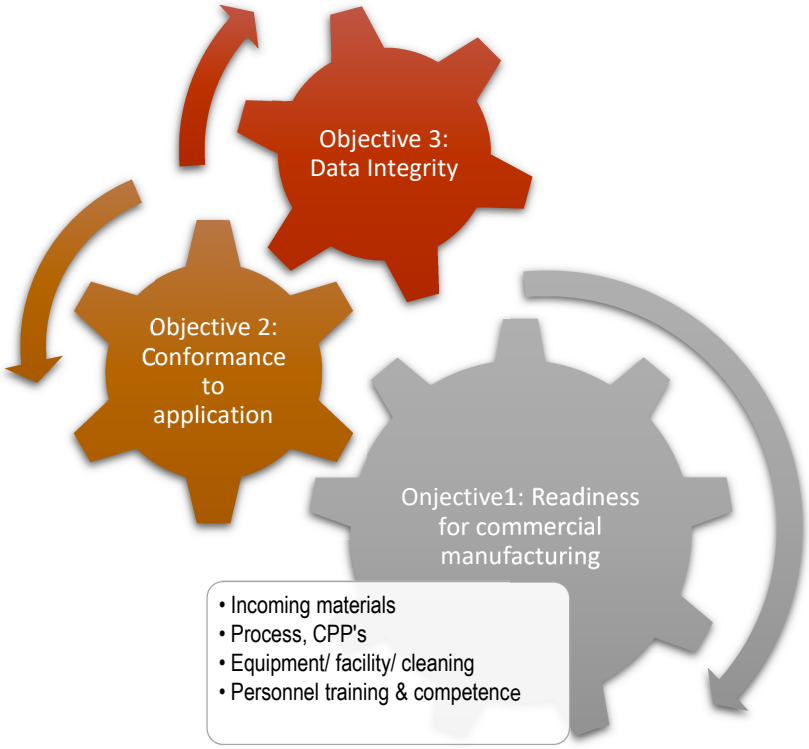


Figure 2: Pre-approval inspection goal; USFDA

During Inspection

The inspectee should provide a list of attendees for the opening meeting. This process should be followed for any subsequent meeting / session. Firm should follow their respective procedure for providing access to auditor and indicate that the validity of the authorization will be valid till the completion of inspection. Any further extension of authorization to be evaluated based on the additional request. Try to conclude every day meeting with meeting minutes (MOM), if

you leave any query or concern it can be consider as ignored /or not attended. Feel free to discuss /or clarify in case you have any doubt.

MHRA aims to monitor the inspection by requesting electronic copies of documents and other information for review off-site. Any follow-up will be conducted via email and teleconferences.[2]

PIC/S is a confidentiality arrangement between 53 global inspectorates, mutual recognition partners and other regulators. The MHRA will rely on inspection information shared by the network to monitor international organizations and their supply chains' compliance.[2]

Discussion

Anyhow the reduction in inspectorate on-site presence, the Agency expects organizations to maintain GxP compliance and be prepared to take "flexible and pragmatic approaches" to ensure the protection of public health. For organizations awaiting licenses that usually require an on-site GxP inspection, it is not clear whether the agency will issue licenses without an on-site inspection or if considerable delays should now be expected. As the situation evolves, the agencies will continue to update organizations and their supply chains on its proposed approach.

Definition

[7]Remote audit:

Audit performed off-site through the use of information and communication technology. [Synonyms: eAudit, virtual audit]

Communications

FDA:

For additional questions about manufacturing changes, please email CDER-OPQ-Inquiries@fda.hhs.gov. Please include “COVID-19 inquiry” in the subject line of the email.

MHRA:

If you have any questions to MHRA on GxP-related issues, please email to below mentioned email:

- Good Laboratory Practice: gxplabs@mhra.gov.uk
- Good Clinical Practice: ctdhelpline@mhra.gov.uk
- Good Manufacturing Practice: gmpinspectorate@mhra.gov.uk
- Good Distribution Practice: GDP.Inspectorate@mhra.gov.uk
- Good Pharmacovigilance Practice: gpvpinspectors@mhra.gov.uk

TGA:

The TGA is committed to working with Australian sponsors during this time. Our staff are available to assist via the contact information below:

- For domestic and overseas inspections and general GMP enquiries, contact the Licensing and Certification Section: GMP@health.cov.au
- For overseas GMP Clearance desk-top assessments and extensions to GMP Clearances, contact the GMP Clearance section: GMPClearance@health.gov.au

Reference

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9. Drug Compliance Programs; https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs
10. Approaches to GMP inspection; CDER Small Business - Regulatory Education for Industry (REdI); https://www.fda.gov/media/89231/download
11. GMP inspection reliance, https://picscheme.org/docview/2475

Annexure 1:

A comprehensive list of documents from Pharmaceutical quality system

1. Site Master plan with following additional enclosure,
    - manufacturing site license and site GMP certificate (issued by local Authority)
    - Description of the product XYZ , production flow – name, address and manufacturing stages for each involved site.
    - Information about quality agreements between involved sites and agreements status.
2. CA/PA for observations from the previous inspection and closure statement
3. Quality Management Review report (current)
4. Current Annual Product Review (APQR) for product to be inspect (should considered mentioned sections: review of finish drug product quality, review of complaints, review of deviations, review of changes).
5. List of standard operating procedure from all departments
6. Procedure for product release. List of persons who performs product release.
7. Procedure for change control management and list of major changes for the Product form current to last 2 year
8. Procedure for deviation management (planned/ unplanned) and list of deviations for the Product form current to last 2 year
9. Self-inspection procedure. List of persons who perform self-inspection. Information about self-inspections for the production facility (rooms) used in Product manufacturing process with status of self-inspections (dates, conclusions, responsible auditors)
10. Procedure for complaints management. List of complaints for the Product form current to last 2 year
11. Procedure for recalls management. List of recalls for the Product form current to last 2 year
12. List of approved suppliers of materials for Product
13. Job description for key personnel: Head of manufacturing, Head of Quality Control
14. Detailed layout of manufacturing facility with indication of rooms AHU's, classification, pressure differential, personnel & material flows, equipment location, indication of manufacturing line used for manufacturing of Product *(current)*
15. Detailed layout of QC laboratories (chemical and microbiology) used for Product testing
16. Detailed layout of warehouses involved in Product manufacturing
17. Procedure for handling of intermediate and finished products on warehouse (receiving, storage)
18. Copy of Master Batch Record for product

19. In-process controls of Product manufacturing process (procedure that defines performing of In-process controls)
20. SOP for Storage conditions for Product
21. List of planned validation and qualification activities for current and last 2-year 24 Report and protocol of qualification of production rooms used for Product XYZ manufacturing
22. Current qualification documents (Report and protocol) for all critical equipment / instrument / and clean utilities (purified water, WFI, pure steam or compressed gases) involved in Product manufacturing.
23. SOP deals with laboratory instrument calibration and periodic verification.
24. SOP deals with access control, backup, audit trial, password management and disaster management of equipment's.
25. Handling and assessment of Breakdown and preventive maintenance
26. Specification for intermediate and finish product
27. Stability study report for Product including data along all product shelf life.
28. SOP deals Procedure for products stability study. Stability planner
29. Analytical methods validation (or methods transfer report) for Product XYZ (methods will be selected after specification receiving)
30. Procedure for OOS management. List of OOS for last 2 year. Arrange a list here OOS invalidated based on the identification of laboratory error.

Annexure 2:

A comprehensive list of documents for clean Utilities

Water:

- Diagram containing purification steps: A clear diagram is required showing each step for purifications.
- Distribution system, using and sampling points: All the sampling point details. System maintenance.

Pure Steam:

- Points of use, Specification,
- Routine Monitoring Program (Micro and Chemical) and
- Last Annual Review. System maintenance.

Water system documentation:

- Specifications of the different water grades used by the company.
- Routine monitoring procedure and results obtained last year.
- Trend analysis.
- Sanitization procedures and records.

HVAC:

- AHU distribution,
- Pressures differential;
- diagram showing rooms classification and
- Activities performed in every room.
- System maintenance.

Environmental monitoring:

- Frequencies,
- Sampling points,
- Sampling techniques,
- Testing,
- Evaluation and results obtained within last year.
- Specifications for viable and non-viable contamination.
- Trend analyses.
- Periodical Re-qualification approach and records.

Gases for pharmaceutical purposes:

- List of Gases that are in direct contact with products.
- Specifications and Routine Monitoring Program (Microbiological and Physicochemical).
- System maintenance.

Annexure 3:

Example- Declared List of products to be considered for inspection

Sr. No.	Product Name	Strength	Manufacturing line	Formulation	Validation document reference No.
1.	ABCD	2 mg	Line 1	Tablet	Process: Cleaning: APQR: Stability: IP/FP specification:
2.	ABCD	1 mg	Line 1	Tablet	Process: Cleaning: APQR: Stability: IP/FP specification:
3.					

Annexure 4:

Example- Identify Subject matter list

Topic	SME_1	SME_2	SME_2
APQR			
Site Master File			
Validation Master Plan			
Cleaning validation plan			
Process validation			
Media fill			
Facility Layout			
Water System			
HVAC			
Batch manufacturing and packaging record (BMR/BPR)			
Environmental monitoring			
Gases for pharmaceutical purposes			
<mentioned topics here>			

Annexure 5:

Example- Detailed list of critical equipment's product wise

Product Name:

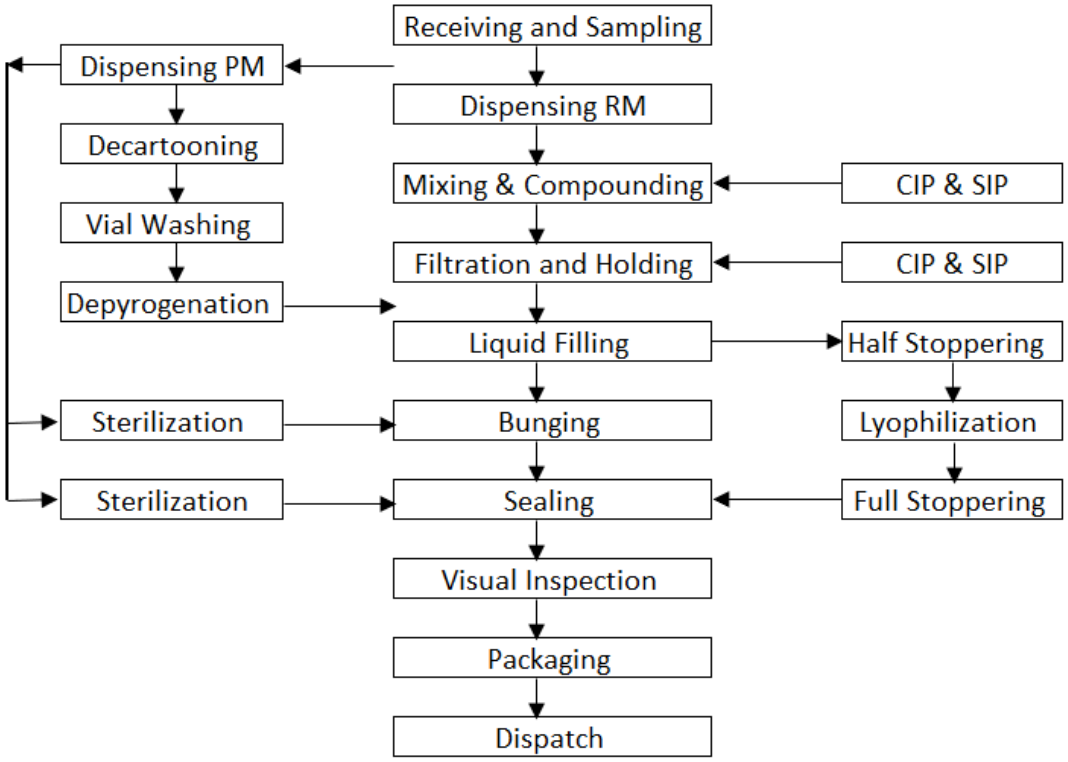
ABCD, 2 mg

Equipment list:

Sr. No.	Equipment Name	Equipment No.	Make	Model	Serial No.	Capacity	Installed at	Validation details

Annexure 6:

Example- Manufacturing flow of Product XXXX



Note: Flow demonstrated liquid/lyophilized injectable process flow

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