European Federation of Pharmaceutical Industries and Associations

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Alternative GMP/GDP Inspection Practices in a Pandemic Situation (COVID-19) and Beyond

Author: MQEG inspection topic team

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✱ Reflection Paper

Executive Summary

Complying with regulatory processes and ensuring continuous supply can be a challenge during crises such as the COVID-19 pandemic. EFPIA companies are currently gaining valuable experience with approaches alternative to on-site inspections. EFPIA sees added value in retaining these practices beyond the pandemic situation, as enabler for reliance and recognition, while utilizing local inspectorates and manufacturing sites resources for on-site inspections.

Tools available from the Pharmaceutical Inspection Co-operation Scheme (PIC/S) provide the basis for performing Remote Desktop Reviews as distant assessments in a coordinated way. This includes using relevant information from other departments within the agency, information from other inspectorates and paper-based and/or e-technology enabled inspections, as appropriate.

EFPIA recommends implementation of lessons learned for both pre-approval and routine inspections which could be permanently implemented, in compliance with existing legislation e.g.,

1. Inspectorates make decisions about the compliance status of manufacturing and distribution facilities using remote desktop review to complement the on-site inspection by an acknowledged local supervisory inspectorate.
2. Foreign inspectorates to conduct on-site routine inspections only in exceptional circumstances.
3. A commonly accepted set of documents to be submitted by the inspected sites in conjunction with evaluations using electronic technology (e.g., video conferencing).

1. Introduction

Legal requirements mandate inspections confirming compliance with Good Manufacturing practices (GMP) and Good Distribution Practices (GDP) as part of the authorisation procedures and surveillance. This can be a challenge in crises situations such as the COVID-19 pandemic and EFPIA acknowledge the options provided by regulators[1].

Based on experience to date from before and during the current crises, EFPIA sees added value in applying alternative approaches to on-site inspections, such as remote desktop reviews, beyond the pandemic situation, while utilizing local inspectorates and manufacturing sites resources for on-site inspections.

Tools available from the Pharmaceutical Inspection Co-operation Scheme (PIC/S) provide the basis for performing such Remote Desktop Reviews.

2. Principles on Inspections

In countries, where GMP/GDP inspections are regulated, procedures are well established. They follow this general process i.e., 1. Inspection planning, 2. Gathering of information, 3. Assessment of the outcome and 4. Legal decision on the compliance status.

PIC/S[2] provides inspectorates with definitions that contribute to harmonising the classification of observed deficiencies across inspectorates. EFPIA understands that a site can rely on the statement provided by the inspectors at the close out meeting, pending the final legal statement.

3. Inspection Planning

EFPIA companies promote using the PIC/S guidance on risk-based inspection planning[3]. This tool facilitates the planning of regulatory inspections / certifications performed by regulators including notified bodies as well as delegated bodies and industry when planning internal and supplier audits.

The major elements to consider include the knowledge of the history of the GMP/GDP compliance status of the inspected body, the past footprint of critical and major deficiencies and the type of inspection to be envisaged i.e., routine, for cause, pre-approval. The following risks are assessed:

a. Intrinsic risk (e.g., complexity of site, processes and products, criticality to availability), and
b. Compliance-related risk (including e.g., GMP/GDP, CMC/regulatory compliance status, number of deficiencies, reported events to the agency since the previous inspection)

The output of the risk-based inspection planning provides a risk ranking of the sites (some jurisdictions also include 'Quality metrics'), inspection frequency, scope, focus, depth and duration of the next routine inspection as well as a suggestion for the number of inspectors and competence / expertise for the next inspection.

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[1] E.g., **Questions and answer on regulatory expectations for medicinal products for Human use during the covid-19 pandemic**, EC, HME, EMA, 10. April 2020 and further version(s) https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf, accessed 05.05.2020.

[2] **Classification of GMP Deficiencies**, PIC/S guideline PI 040-1, 1 January 2019

[3] **Risk-based inspection planning**, PIC/S guideline PI 037-1, 1 January 2012


EFPIA Brussels Office
Leopold Plaza Building ✱ Rue du Trône 108
B-1050 Brussels ✱ Belgium
Tel: + 32 (0)2 626 25 55 ✱
www.efpia.eu ✱ info@efpia.eu

4. Leveraging Previous Inspections

Routine and For Cause Inspections

To ensure continuous supply during crisis e.g., the COVID-19 pandemic, EFPIA member companies welcome that GMP/GDP and ISO certifications as well as and Certificate of Pharmaceutical Product (CPP) issued by recognised authorities (e.g., PIC/S members, Notified Bodies) were broadly accepted, even where is no formal Mutual Recognition Agreement is in place. Despite differences in legal terminology we observed that expectations on practical implementation of GMP/GDP requirements are to a significant extent similar across the different jurisdictions. Thus, recognition of inspections in 3rd countries as well as extending other MRAs in this regard can be possible.

Consideration for Pre-Approval Inspections (PAI)

Some countries require individual Pre-Approval-Inspections (PAI) for launching every single product. Such PAI serve two purposes: 1. Confirm integrity of the data provided in the submitted dossier, and 2. Confirm that Quality Systems (QS) at the site are suitable for this purpose. The data collected in the EFPIA annual inspection survey 2018 and 2019 demonstrates evidence that the quality system compliance part of PAI mirrors the depth and content of routine inspections.

Therefore, it should be considered whether quality systems inspected in a PAI had been recently inspected as part of a routine inspection and efforts can be reduced for this reason. Companies experience communicated in the EFPIA inspection survey demonstrate that clarification of dossier integrity can be concluded in about one day of a PAI and reference the results from the related inspection for the QS part. Thus, we conclude, there is an opportunity for referring to a previous inspection at that site; preferably performed by the inspectorate in the country where the manufacturing site is located.

5. Remote Desktop Reviews as Enabler for Efficiency

Based on a robust local inspection system, EFPIA supports the global implementation of the harmonised PIC/S reliance guideline[4] to perform remote assessment of GMP compliance of facilities. Elements to be considered as part of remote desktop review, include:

1. Information from inspectorates,
2. Other relevant information and / or
3. Paper-based inspectional elements

Thus, EFPIA would welcome, if this guidance[4] could be added to the regulatory framework for inspectorates e.g., in the Compilation of Community Procedures (EMA/572454/2014 Rev 17).

Information from inspectorates

Inspectors can collect existing GMP/GDP-certificates and inspection reports. The pandemic situation demonstrated feasibility of this approach. Furthermore, EFPIA member companies are prepared to share inspection reports, usually redacted. Full information can be shared upon request, where confidentiality is preserved.

[4] **GMP-Inspection reliance**, PIC/S guideline PI 048-1, 01. June 2018

EFPIA Brussels Office
Leopold Plaza Building ✱ Rue du Trône 108
B-1050 Brussels ✱ Belgium
Tel: + 32 (0)2 626 25 55 ✱
www.efpia.eu ✱ info@efpia.eu

Reliance on inspections performed by inspectorates in other countries could follow the principles of the PIC/S guidance 'GMP Inspection Reliance'[4]. Beside the current situation, there are successful examples of remote desktop inspections replacing duplicated on-site inspection by either formal Mutual Recognition Agreements or by joint audit programs. EFPIA member companies understand it is a prerequisite that high-quality standards are embraced and supported by the local government. Evaluation and surveillance of national regulatory systems (e.g., PIC/S member inspectorates, WHO Global Benchmarking Tool, Medical Device Single Audit Program (MDSAP)) should be recognized. The advantage of an assessment / inspection / certification by a local inspectorate includes knowledge of the site-specific history, insight on culture, the optimisation of resources and the benefit from improved inspection logistics (e.g., no language barrier, less travel). This facilitates transparency on implementing Corrective and Preventive Actions (CAPA). Local inspectors will take this task equally professional following their legal obligation to protect public health. They do not want their reputation to be jeopardised.

Other relevant information

Inspectorates performing Remote Desktop Reviews have access to additional supportive information about the site and products e.g., Site Master File, Annual Product Reviews including complaints, recalls, variations, validation status, quality defects.

Paper-based inspectional elements

EFPIA promotes using paper-based inspections as one tool in a remote desktop review replacing onsite-inspections to gain efficiency in the inspection process. Therefore, we are in favour of a constructive dialogue using electronic technology rather than different loops of questions and answers exchanged between the manufacturing site with representatives of affiliates and the inspectorate, as applicable.

EFPIA member companies are aware that inspectorates apply different procedures for conducting paper-based inspections as element in the remote desktop review supplementing the compliance decision on a manufacturing site. Documentation requested for paper-based reviews is not harmonised currently. Requests to submit documents might even appear prior to an on-site inspection. EFPIA summarised which documents could be valuable as part of such a paper-based inspection[5] to provide comprehensive view of the site. This includes general information as provided from the Site Master File (SMF), product knowledge (Annual Product Quality Reviews[6]), Quality Management System knowledge (Site Quality Manual). Additional information can be limited to the list of the results of regulatory inspections and audits and the status according to the assessed risk in the last inspection[7]. Such a procedure will also limit traveling and therefore frees resources and supports the environment footprint as requested by the EU 2025 priorities.

Opportunity of using electronic technology

Videocall technology can be a substitute for physical presence of an inspector aiming for a virtual[8] discussion including performing interviews, documentation review and/or walking around. Depending on

[5] **Enhanced GMP/GDP Inspection Efficiency**, EFPIA, Position Paper, 19. May 2014.
[6] This includes among others information on **complaints, recalls, deviations and out of specifications**
[7] **Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries,** Compilation of Community Procedures, EMA/572454/2014 Rev 17, 3 October 2014:
[8] Virtual = no physical presence as such but made by software to appear to do so


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B-1050 Brussels ✱ Belgium
Tel: + 32 (0)2 626 25 55 ✱
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the number of inspectors on tour at the same time there may be the need for multiple videocall transmissions. Similar to an on-side inspection the need for interpreters should also be taken into consideration. Utilization of video technology may have significant privacy issues. Company's and regulators security standards and Environmental Health and Safety (EHS) principles e.g., cautiously access of electronic equipment in explosive zones needs to be addressed. The parties need to align on details e.g., no recording is taken for granted.

6. Call for actions using lessons learned

The existing PIC/S guidance are established and reviewed by more than 50 participating inspectorates. These consensus approaches are practical and demonstrate how reliance can ensure quality and compliance, before and during times of this crisis.

Thus, EFPIA is calling regulators to consider the following course of action to further support GMP compliance assessments:

1. Increasing reliance though appropriate use of remote desktop review
    a. Sharing experience among regulators and discuss opportunities with industry
    b. Agreeing on a commonly accepted set of documents to be submitted by a site in the context of an inspection. This should be a component in the decision-making process that an on-site inspection can be limited in the scope and duration or in best case might not be necessary after the assessment of these documents.
    c. Enabling the GMP compliance decision for supporting local registration and licencing processes

2. Clarifying in the compilation of community procedures and/or a Q&A that GMP/GDP certificates are valid if available in the EU GMDP-Data base.

3. Optimizing MRAs
    a. Implementing recognition of the Quality System compliance inspected previously in a compliance decision of a PAI
    b. Recognising compliance decisions on a manufacturing site located in the territory of a recognized issuing authority (e.g., PIC/S member)
    c. Continuing the discussion on the extension on the scope of MRAs


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B-1050 Brussels ✱ Belgium
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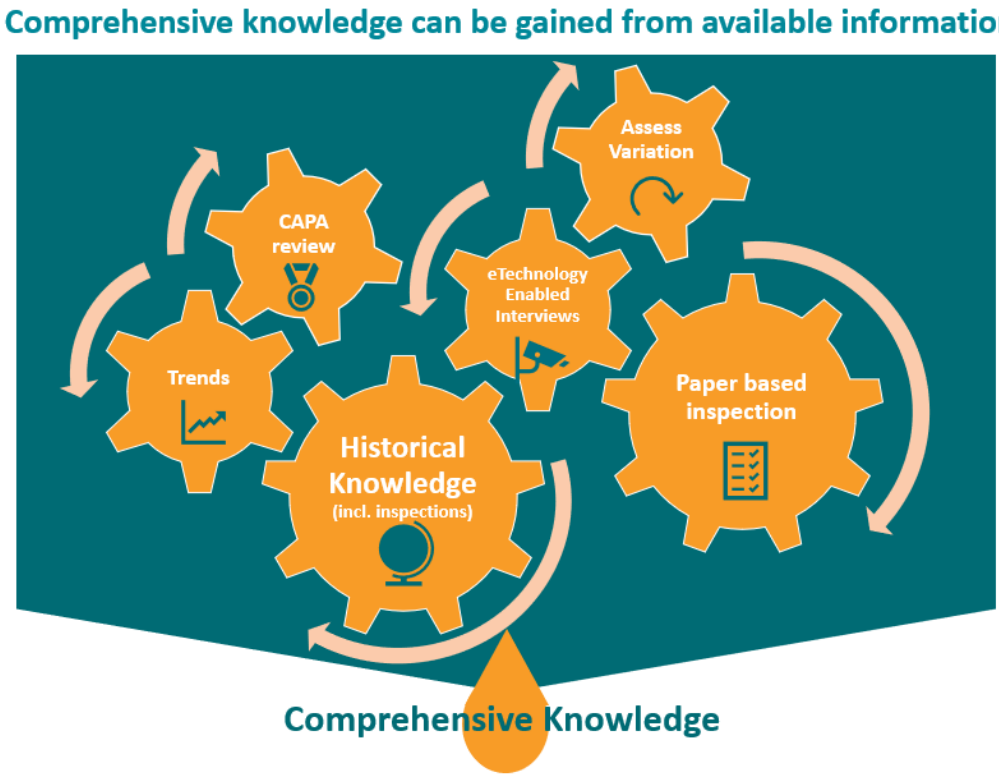
7. Conclusion

There are different ways to manage the legal requirements to perform an inspection. These can be managed either by an on-site inspection performed by the own agency, if anticipated to be required by the local law or with tools summarised as 'Remote Desktop Review':



Reflecting on the public health crisis, EFPIA sees an opportunity to continuously improve the inspection process. We seek broad implementation of the concept of remote desktop review and bring attention to some elements that have already been implemented - but are not considered as remote desktop review elements (e.g., Corrective and Preventive Actions (CAPA) review on observations, remote process for US-FDA issuing Establishment Inspection Reports (EIR)).

Inspectorates and industry can benefit from harmonised guidance e.g., by PIC/S. EFPIA would welcome PIC/S, in collaboration with stakeholders, to develop a guidance on an efficient paper-based inspection process specifying a reasonable set of documents to be submitted.

The legal requirements for GMP/GDP inspection or ISO certification can be fulfilled with increasingly applying reliance approaches[9] soon. This should be supported by considerations on an appropriate fee structure facilitating flexibility for inspectors performing remote desktop reviews.

[9] Convergence of Good Manufacturing Practice (GMP) standards and Related Inspections, IFPMA Position, January 2020

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