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Request for Optimising the GMP paper-based Inspection Process by Regulatory Authorities

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✱ Position Paper

Executive Summary

Results from annual surveys amongst EFPIA member companies on GMP inspections worldwide reveal that Japanese inspectors are conducting many paper-based inspections that are felt to be time- and resource-consuming for the industry.

The following options to optimise the process could be considered:

a. Reliance on available information,
b. Harmonisation of forms, and/or
c. Focus on domestic inspections and sites in third countries that have not previously been inspected.

EFPIA members suggest to use the recently expanded Mutual Recognition Agreement (MRA) between the European Union and Japan as an opportunity to discuss possibilities for simplification of the inspection process.

1. The situation

According to the Pharmaceutical Inspection Cooperation Scheme (PIC/S), remote (desktop) review consists of the evaluation of several components, including information provided by companies. The review of this information is referred in this document as "paper-based" inspections (Figure 1).

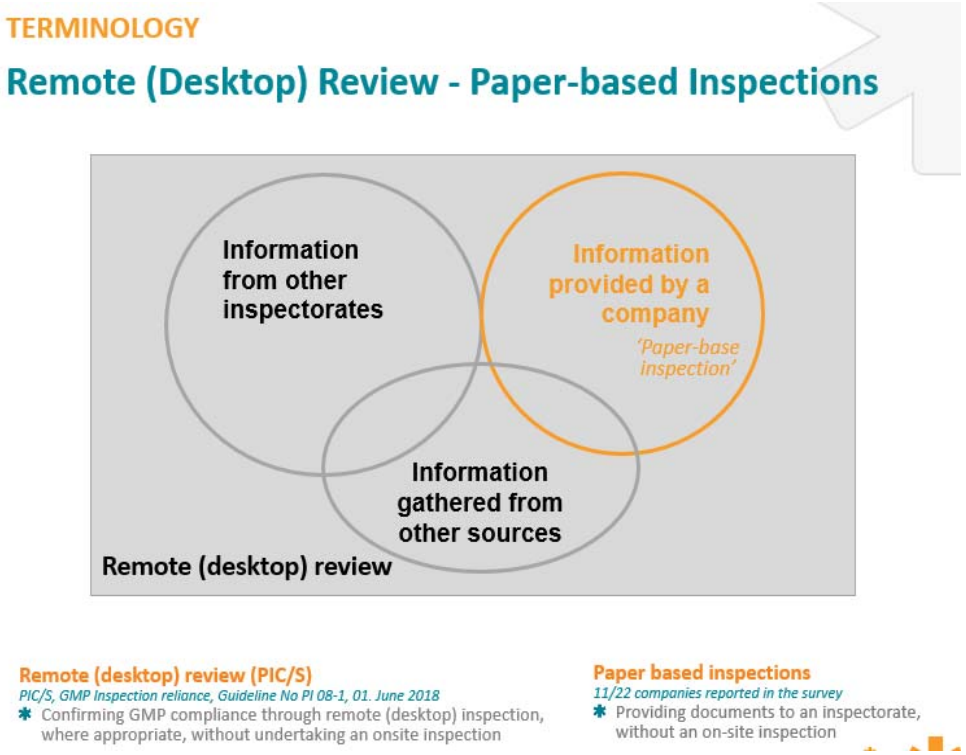

Figure 1: Remote (desktop) review includes evaluation of information provided by other inspectorates, companies and other sources.

EFPIA's annual inspection survey of 2019 amongst member companies looking at inspections that occurred in 2018 indicates that Japan[1] performs 61% of all reported paper-based inspections, compared to South Korea and Turkey with 4% each and USA, Australia, Russia, Brazil and China with 2% each[2]. Paper-based inspections can be conducted both for domestic and foreign located manufacturing sites for regulatory/accreditation purposes. In this document, we are referring to all types of GMP (Good Manufacturing Practice) inspections, which in the case of Japan include:

[1] Pharma Medical Device Act Art. 14.6, relating to the procedure for GMP inspections either on-site or via desktop (Section2.1)

[2] Publication of the annual Regulatory GMP/GDP Inspections surveys: https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/annual-regulatory-gmpgdp-inspection-survey/; Link to the 2018 assessment: https://www.efpia.eu/media/412840/efpia-2018-reg-inspection-survey_v2-public.pdf


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- Pre-approval GMP compliance inspections before a new drug application (NDA) is approved;
- Pre-approval GMP compliance inspections before a partial change application (PCA) is approved;
- Periodic GMP compliance inspections (every 5 years) for all products manufactured at a site for Japan;
- Site Accreditation (corresponds to a Manufacturing License; renewal every 5 years; subject to strict change control requirements).

Before starting an inspection there is paperwork required providing knowledge about the manufacturing site, the products and the Quality System at the site (e.g., as described in the Quality Manual[3]).

EFPIA appreciates that waivers are increasingly established for sites located in an MRA (Mutual Recognition Agreement) member country or in an MoU (Memorandum of Understanding) country for both on-site and paper-based inspections. For instance, to apply for a Periodic GMP Compliance Inspection, exemption from submission of further documents may be granted by providing a copy of the most recent GMP certificate or the certificate number to search for in EudraGMDP[4]. The submission of Product Quality Reviews (PQRs)[5] during the past two years is a standard requirement, but can also be exempted as explained above. The format of a Site Master File[6] can be used to provide certain information of manufacturing sites. However, EFPIA member companies report to the inspection survey that even if an MRA or MoU is applicable, additional paper documentation is requested by Japanese inspectors (33 paper-based and 5 onsite inspections in 2018 reported by 10 companies[2]).

The information required by the Japanese Pharmaceuticals and Medical Devices Agency, PMDA, is readily available by companies in line with harmonised requirements, e.g. by PIC/S, which Japan respects as a member country. However, this available information has a different format than needed for the completion of the forms for the paper-based assessment. Some companies report that under certain circumstances it can take the time of one person and the involvement of about 10 additional experts for 5 full working days to convert the available information into the right format to fulfil regulatory expectation, without any obvious additional benefit to the quality of the data or to the information provided.

2. Proposal of the following points to consider for optimisation and harmonisation

EFPIA ask the European Commission to seek a dialogue with their Japanese counterparts to raise awareness about the provision of information and communication for the paper-based inspections and to find a solution to simplify and harmonise them. It is strongly believed that such simplification will not

[3] PIC/S GMP Part 1 Chapter 1.7, equivalent to EUDRALEX Vol.4 (EU-GMP) Part I, chapter 1.7

[4] http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do;jsessionid=63YcZBkj9L7oj2GFft2HOkLvY4IPYSMcY3N8lxP_prdx3iSooIPq!-1649922705

[5] PIC/S GMP Part 1 Chapter 1.10, equivalent to EUDRALEX Vol.4 (EU-GMP) Part I, chapter 1.10

[6] PIC/S procedure PIC/S PE008, equivalent to EUDRALEX Vol.4 (EU-GMP) Part III, document No SANCO/C8/AM/sl/ares(2010)1064603


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impose any risks on patients; on the contrary, it shall lead to eventual benefits for patients such as earlier access. EFPIA members suggest the following options for consideration:

a. Reliance on available information

We suggest that available GMP certificates that have been issued by recognised inspectorates, e.g. issued by countries, where the inspectorate is a PIC/S member, shall be accepted and replace the information package that companies otherwise have to compile. With this procedure, time and resources can be saved for both inspectors and companies.

To apply for a Periodic GMP Compliance Inspection (every 5 years) companies are requested to submit amongst others the following documentation: PQRs (issued during the past 2 years), Site Master File (SMF) if it includes any of the information required. If the site is located in an MRA member country or MoU member country, the submission of these documents can be waived by providing a GMP certificate or the certificate number to search for in EudraGMDP[4]. EFPIA support this approach and suggest applying similar waivers also for the other types of GMP inspection/accreditation.

b. Optimisation of forms

A practical solution to simplify the filling of the forms for paper-based inspections is, for instance, to add the opportunity to use existing recognized formats (e.g. Site Master File; SMF). This means that Japanese inspectors would still receive all information as required, but time and resources can be re-allocated as re-formatting available information is omitted. Potential differences in terminology could be overcome by using harmonised definitions as agreed e.g. by PIC/S.

c. Focus on domestic inspections and on sites previously never inspected

Paper-based inspections are currently a routine step in enhancing the efficiency of GMP inspections. They often can substitute on-site inspections and thus avoid duplication of inspections. However, EFPIA suggest that under the EU-Japan GMP MRA, both parties should prioritise domestic inspections, which could then be relied upon by the other party and would make repeated inspections unnecessary. The resources can be used to inspect sites, which have not been inspected by another authority before. By sharing knowledge on their domestic and foreign inspections both parties will benefit from the increased amount of information on more manufacturing sites in total. In line with this proposal, GMP inspections would be performed on a manufacturing site basis, instead of a product-basis, as it is done today. If this new system is introduced, the total number of inspections will be reduced and resources saved.

Such harmonisation of GMP inspection procedures can be adopted in the sense of the scope of the recently broadened GMP MRA between the EU and Japan even as they are not explicitly mentioned. EFPIA member companies suggest that optimising the process would be a win-win for the Japanese authorities and industry, as it will make the processes more robust by avoiding sources of mistakes that might occur by re-entering available information in modified formats into forms, and enable the best use of resources for inspectors, who do not need to re-evaluate information that has already been checked and approved.

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3. Conclusion

Despite potentially different terminology in the respective laws in the EU and Japan, the principles and expectations are comparable and can be specified in the local guidance for inspectors, as applicable. That means, we believe that making our suggestion a reality, the available guidelines may be interpreted in a different way, no change of the legislation would be needed. Therefore, EFPIA member companies are convinced that enhanced collaboration between inspectorates and industry, as appropriate, could lead to reliance based on acceptance of generally recognised expectation on implementation of GMP requirements, related enforcement systems and international accreditation for regulatory inspectorates under the umbrella of an internationally recognized body such as PIC/S. It is expected that PIC/S will further facilitate building trust amongst inspectorates.

Annex: Background on Enhanced Good Manufacturing (GMP) Inspection Efficiency

EFPIA supports effective regulatory inspection systems for overseeing compliance with regulatory standards and medicinal products' quality, and to ensure that patients have confidence in the medicines they take. The pharmaceutical industry has become increasingly global and new risks have emerged such as falsification of medicines. Consequently, there has been an increased level of oversight. We are pleased to see cooperation between regulatory agencies with respect to implementation of risks-based approaches by sharing intelligence, inspection activities and results. Despite this cooperation, an increase in duplication of inspection oversight at manufacturing sites[2] has been observed. The EFPIA survey of 2019 shows that one manufacturing site had been expected by 12 different inspectorates in 2018, and all of them accepted the site as GMP compliant. This creates potential shortage of inspection resources to focus on inspecting all sites and higher risk areas of the supply chain and distribution.

EFPIA proposes that effective and balanced risk based regulatory oversight, allowing for improved resource utilisation, can be further enhanced by:

a. Continued regulatory agency collaboration

- To drive harmonisation and optimise use of global inspection resources;
- By mutual recognition of each other's systems or reliance on inspection outcome, enabling domestic inspectorates to act as the primary overseeing body.

b. Harmonised GMP standards

- To support consistent interpretation of regulatory requirements.

c. Harmonised regulatory inspection processes including:

- Inspectorates certification process;
- Inspection planning and documentation: standard data packs for on-site and paper-based inspections for faster provision of information and better use of resources;
- Risk based approach to inspection;
- Inspection findings and reports: standard terminology for the categorisation of observations and standard reporting template;
- Sharing of inspection results in database;
- Globally accepted GMP certificate format to document compliance of an inspected site.

The EMA and PIC/S already provide guidance on elements of this in the Compilation of Community Procedures on Inspections and Exchange of Information, including the ´*Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers*´. Full utilisation of the process by regulatory agencies together with continued collaboration globally will allow GMP inspections to be increasingly focused and optimise the use of resources.

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