



PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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GUIDANCE

GMP INSPECTION RELIANCE

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1 DOCUMENT HISTORY

Adoption by the PIC/S Committee of PI 048-1	17-18 April 2018
Entry into force of PI 048-1	1 June 2018

This guidance has been initially drafted by the International Coalition of Medicines Regulatory Authorities (ICMRA) GMP Inspection Reliance Framework and taken over by PIC/S at the request of ICMRA.

2 INTRODUCTION

- 2.1 With the complexity of global supply chains, the demand for inspecting pharmaceutical manufacturing facilities far exceeds what any one National Competent Authority (NCA) can accomplish and a framework is required to assist regulators in managing product quality risks posed by the increasingly complex pharmaceuticals global supply chain.
- 2.2 Informed decisions on the GMP compliance of a manufacturing facility can be made, in certain circumstances, based on the outcome of work by another regulatory authority or authorities. Consequently, it is possible (outside the established framework of Mutual Recognition Agreements, or equivalent and where legal requirements allow) for Inspectorates to identify specific instances where an onsite inspection of a manufacturing facility in an overseas territory is not required because an acceptable level of GMP compliance has been confirmed and assured by another regulatory authority or authorities.
- 2.3 Confirming GMP compliance through remote (desktop) inspection, where appropriate, without undertaking an onsite inspection avoids duplication of work between regulatory authorities, reduces regulatory burden on manufacturing sites, and allows more efficient deployment of global inspection resources.

3 PURPOSE

- 3.1 This document outlines a process for remote assessment of GMP compliance of overseas facilities to identify instances where an acceptable level of GMP compliance can be confirmed and assured from the activities of another regulatory authority or authorities without the need for an onsite inspection.
- 3.2 High level guidance is provided to facilitate this assessment process. The details of the process will vary from regulatory authority to regulatory authority and it is recommended that the details are defined at a national level in local procedures. Some regulatory authorities already have established processes for identifying instances where an onsite inspection of an overseas facility is not necessary which can be continued under the framework described in this document.
- 3.3 This procedure, supplemented by national procedures detailing local processes, will also help Inspectorates to make optimal use of inspection resources.

4 SCOPE

- 4.1 The procedure is limited to manufacturing facilities in territories where assurance has been gained of the capability of the hosting NCA (i.e. the regulatory authority in the territory in which the site is based). That is, either:
- a) the facility is situated within the territory of a PIC/S Participating Authority; or
 - b) the hosting NCA has been assessed, typically within the last 5 years utilising a robust assessment tool (typically aligned with the Joint Audit Program (JAP) / Joint Reassessment Programme (JRP) harmonised framework), that resulted in a positive outcome;
 - c) There is a Mutual Recognition Agreement (MRA) in place between the two countries that covers GMP; each partner of the MRA reserves the right to conduct an inspection for reasons identified to the other Party, as an exception or if for example the product is not included in the operational scope of the agreement.
- 4.2 Whilst not within the scope of this procedure, NCAs may decide to use the principles of the framework and adapt them into local procedures so as to support their risk based inspection programmes where manufacturing facilities are based in territories where assurance has not been gained of the capability of the hosting NCA, however, the relevant manufacturing facility has been inspected by a regulatory partner that the NCA does have confidence in.
- 4.3 It should be noted that some NCA conduct inspections solely to confirm compliance with the details as listed in the Marketing Authorisation/Product Licence and they may deem this work to be outside of the scope of this framework given the specific nature of their inspection.
- 4.4 This procedure can equally be used by non-PIC/S members to support their inspection programmes and make more efficient deployment of inspection resources.

5 PROCESS

5.1 Introduction

- 5.1.1 The process for assessing whether satisfactory levels of GMP compliance of an overseas facility can be confirmed remotely without an onsite inspection is outlined in the following sections.
- 5.1.2 It is recommended that regulatory authorities use this framework to establish their own procedures containing details of the assessment process:
- 5.1.2.1 The procedure should include the information that is needed to make an informed regulatory decision about site compliance, triggers and risk factors that would result in an inspection being required, and how the assessment and outcome should be recorded.
 - 5.1.2.2 Any procedure should also detail who should perform/authorise the assessment, typically a GMP Inspector or technical personnel who have been trained on the relevant GMP requirements.

5.1.2.3 Regulatory authorities may define any types of products which are to be excluded from the process and those that are deemed to always require the regulatory authority to conduct an onsite inspection.

5.1.3 Regulatory authorities could establish these procedures at either a national or regional level depending on national legislation and how they operate with the global regulatory landscape.

5.2 Establishing country reliance

5.2.1 The regulatory authority performing the assessment (the requesting NCA) should first gain assurance of the capabilities of the hosting NCA. This can be done by:

- a) confirming that the hosting NCA is a PIC/S Participating Authority: <https://picscheme.org/en/members> or
- b) the regulatory authority performing the assessment (the requesting NCA) undertaking an assessment of the hosting NCA using the JAP/JRP process or a similarly robust assessment tool. There would be no expectation on this assessment being conducted by PIC/S for the purposes of GMP reliance framework.

5.2.2 If the regulatory authority performing the assessment (the requesting NCA) gains assurance of the capabilities of the hosting NCA then an assessment of site compliance can be performed by the requesting NCA.

5.3 Assessment of site compliance

5.3.1 Gathering information

If a GMP certificate has been issued by the hosting NCA, the regulatory authority performing the assessment should obtain this document as a minimum. This document may be obtained from a central repository (e.g. EudraGMP) or the manufacturing site and verified with the hosting NCA if necessary.

If the hosting NCA does not issue GMP certificates, it is recommended that the inspection report from the most recent inspection of the manufacturing site by the hosting NCA is obtained as a minimum. This will allow an assessment if the report includes a clear statement on the GMP status of the site. So, as to keep requests to the hosting NCA to a minimum this information could be obtained from the manufacturer and verified with the hosting NCA if necessary.

Additional information should be requested from the manufacturing site, as required. This may include:

- Information relating to the latest inspection by the hosting NCA. For example: dates on site, inspection scope and outcome, inspection report, company response/corrective and preventative action (CAPA) plan, and planned re-inspection date (if known).
- Post inspection information provided by the hosting NCA on justified request
- Information relating to inspections by other regulatory authorities in a defined time period (e.g. previous 2 years or since the previous inspection by the regulatory authority performing the assessment). For example: name of regulatory authority, dates on site, inspection scope and outcome, and

planned re-inspection date (if known/applicable). Inspection reports and company responses could also be requested, as appropriate.

- Site master file (typically this will be in the EU-PIC/S format).
- Information to aid in an assessment of risk. For example, changes since the last inspection by the hosting NCA to key site personnel or personnel numbers, company ownership, and processes and products (e.g. changes in the types or numbers of products manufactured/handled, previously outsourced activities that have been brought back in house).

When requesting information from the manufacturing site, an explanation of why the information is being requested should be included in the covering email or letter. For example:

"I am contacting you regarding the next GMP inspection of your facility by <name of regulatory authority performing the assessment>. We have initiated a process for performing a remote GMP assessment of your operations. If the outcome is successful, it will result in confirmation of the GMP compliance status without the need for an onsite visit.

"In order to perform the assessment, we require the following information to be provided:"

Additional information may also be obtained from other sources, as appropriate. This may include warning letters (or similar), rapid alerts and information on recalls.

Depending on the information obtained, and the time since the last inspection, it may be appropriate to obtain the date of the next planned inspection by the hosting NCA. This may be obtained from the hosting NCA or from centralised scheduling information (where available).

5.3.2 Assessment and outcome

The aim of the review of information is to gain assurance that GMP compliance has been established by the hosting NCA (evidenced by a GMP certificate or equivalent information contained in an inspection report or information defined in 5.3.1) and that there are no new gathered evidence that would warrant an onsite inspection by the regulatory authority performing the assessment.

An assessment should be made of whether an appropriate level of GMP compliance can be confirmed from the available information and whether an onsite inspection is not required (this is the default position for eligible sites under this procedure), or whether further information or an onsite inspection are necessary.

The assessment of site compliance should be recorded according to national or regional procedures. This may be in the format of an inspection report. It is recommended that this includes the following minimum information: what documentation was reviewed and by whom, the outcome of the assessment, and the rationale for the decision. Further guidance on the suggested content of the written assessment is provided in Appendix 1.

The outcome of the assessment should be communicated to the manufacturing site and if possible also be communicated to the hosting NCA.

Where a decision has been made that an inspection is not required, Inspectorates may choose to issue a GMP certificate (if legislation permits) that contains a statement regarding the basis on which it has been issued; that is, referencing the process of remote (desktop) review and the information that was taken into account to establish that the level of GMP compliance was assessed as acceptable.

5.3.3 Triggers and risk factors for an onsite inspection

The following are examples of possible triggers or risk factors for an onsite inspection:

- Failure of the site to supply the requested information.
- There is no inspection history for the site.
- The site is not licensed by the hosting NCA.
- The GMP certificate / available inspection report does not cover products or processes that are of interest to the regulatory authority performing the assessment.
- There is evidence that another regulatory authority has not approved the manufacturing facility, or even aspects of it (e.g. sterile vs non-sterile areas)

This is not an exhaustive list and decisions on whether or not to perform an onsite inspection should be made on a case-by-case basis taking into consideration the available information and triggers and risk factors defined within national/regional procedures.

If an onsite inspection is considered to be required, this should be scheduled and conducted in accordance with relevant national/regional procedures. Consideration may be given to performing a joint inspection with the hosting NCA if appropriate.

5.3.4 Additional considerations

Where documents that have been obtained to assess site compliance require translation, this is the responsibility of the regulatory authority performing the assessment to undertake and it could be by request of the manufacturer to perform this task.

Regulatory authorities performing assessments under this procedure should have processes to protect the confidentiality of information shared under this process.

Questions targeted to the hosting NCA should be kept to a minimum, so as not to add to the regulatory burden. It may be appropriate, in certain instances, to verify information provided by the manufacturing site with the hosting NCA to ensure its authenticity.

5.4 Monitoring and review

- 5.4.1 Where a decision is made not to perform an onsite inspection of the overseas facility, the regulatory authority, which has undertaken the assessment, should maintain the site within their inspection programme to ensure periodic review (e.g. review on an annual basis of whether the decision not to inspect still applies or whether an onsite inspection is required in light of new triggers, intelligence or identified risks), unless the decision is to not authorise the overseas facility to supply product to the domestic market.
- 5.4.2 There may be circumstances in which a manufacturing site is approved on the condition that an inspection be conducted within, or at the end of the approval period. The circumstances may include past history of low level compliance, or non-compliance, with manufacturing standards.

6 REVISION HISTORY

Date	Version number	Reason for revision

7 APPENDICES

Appendix 1: Recommended Content of GMP Inspection Reliance Assessment Report

Site information	<ul style="list-style-type: none">• Name and address of the manufacturing site under assessment• Further details, if available/applicable such as building number/GPS location/UFI.• Name and contact details of site contact
Regulatory authority performing the assessment	<ul style="list-style-type: none">• Name of the regulatory authority performing the assessment• Name and job title of the person performing/responsible for the assessment• Date of the assessment• Signature of the person responsible for/endorsing the assessment
Scope of assessment	<ul style="list-style-type: none">• A statement that the assessment of GMP compliance is being performed under the PIC Scheme• Specific products/dosage forms that are within the scope of the assessment• Activities that are within the scope of the assessment (e.g. manufacture of API/non-sterile finished product/sterile finished product/biological finished product; packaging; importation etc.).
Hosting national competent authority	<ul style="list-style-type: none">• Name of the hosting NCA• Basis on which country reliance has been established. Either:<ul style="list-style-type: none">○ Confirmation that the hosting NCA is a PIC/S Participating Authority, or○ If the hosting NCA is not a PIC/S Participating Authority, confirmation of a positive outcome from an assessment of the hosting NCA using the JAP/JRP process or a similarly robust national assessment tool and date the assessment was undertaken.

Basis for the assessment (Review of documentation)	<ul style="list-style-type: none"> • A list of documents reviewed as part of the assessment including versions/dates • Date, scope and outcome of the last inspection by the hosting NCA • Confirmation that the GMP certificate (where available) or inspection report covers the products and activities that are of interest to the regulatory authority performing the assessment • Information related to possible involvement of the hosting NCA in the assessment (e.g. verification of the translation of documents provided by site)
Assessment outcome and rationale	<p>For example:</p> <ul style="list-style-type: none"> • “Based upon the collected information, along with the oversight of the operations by the PIC/S Participating Authority in the country in which the site is based, no onsite inspection by <name of regulatory authority performing the assessment> is considered to be required at this time. A new GMP certificate can be issued.” (If legislation permits) • “Due to the following <summary of risk factors / triggers to be inserted>, an onsite inspection is considered to be required.”