EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 October 2020
EMA/335293/2020

Guidance related to GMP/GDP and PMF distant assessments

A. GMP/GDP distant assessment guidance (version 1)

1. Introduction & Scope

1.1. Introduction

During national or international crises such as the COVID-19 pandemic, on-site GMP/GDP inspections may not be possible for a number of reasons such as travel restrictions, risk to health, or other restrictions/guidance issued by local or national authorities. During these situations, the obligation of manufacturers, importers and distributors to comply with GMP/GDP is not waived and the ongoing verification of compliance by Supervisory Authorities is important to ensure the protection of public health.

In these circumstances, taking into account national and European legislation, distant assessments can represent a suitable means of determining compliance with the principles and guidelines of GMP/GDP and the purpose of this document is to provide supplementary guidance and points for consideration to inspectors relating to the particulars of performing distant assessments.

If a member state decides to use this guidance beyond the current COVID-19 pandemic, the IWG should be informed.

1.2. Scope

In the context of this guidance, "distant assessment" can be defined as follows: "Assessment of the compliance of a site with the Union GMP/GDP principles performed by officials of Union Competent Authorities on the basis of documents and interviews and supported by technology for communicating, accessing systems, sharing and reviewing documents and other information, without the inspectors being physically present at the sites where the activities subject to the assessment have taken place and where the inspection would ordinarily be hosted".

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This guidance is applicable to manufacturers, importers, distributors and quality control laboratories based in the EU/EEA and manufacturers and quality control laboratories in third countries, and is relevant to Human and Veterinary Medicinal Products, Investigational Medicinal Products, and Active Substances.

This guidance is not intended for use or to replace on-site inspections outside of crisis situations.

2. Planning/Feasibility Assessment

2.1. Manufacturing site/dosage form considerations

Distant assessments can be considered for all types of inspections as necessary and can be performed for all types of sites and dosage forms following a careful case-by-case evaluation, taking into account the criticality of the manufacturing activities and the product(s) concerned.

On-site inspections should be conducted when circumstances permit following the distant assessment; the scheduling should be based on risk management principles and priority should be given to sites which have never been inspected on-site before by an EEA inspectorate or by an MRA partner authority, and to sterile manufacturing processes.

2.2. Distant assessments requested by the CHMP/CVMP and coordinated by EMA

The Supervisory Authority and inspectorate (if different) together with EMA should make a case-by-case decision on whether a distant assessment is considered appropriate and feasible. For pre-approval distant assessments, the Rapporteurs should also be informed, and the criticality of the product should be taken into consideration.

Distant assessments should follow the applicable procedures that already exist for coordinating, preparing and conducting GMP inspections requested by the CHMP or CVMP, respectively, and should take into consideration the present guidance.

If it is not deemed feasible to carry out or continue with a distant assessment, the inspection team shall communicate this to EMA without delay and the most suitable course of actions should be determined in each case together with the EMA product team and the Rapporteurs (e.g. adjust procedure timelines to facilitate an on-site inspection when restrictions are lifted).

2.3. Distant assessments coordinated by member states

Individual National Competent Authorities (NCAs) can determine on a case-by-case basis whether a distant assessment is required, feasible and appropriate for sites on their national inspection programmes.

2.4. IT and other practical considerations

Following a decision to perform a distant assessment, early contact should be made with the site to determine the feasibility. Although it is envisaged that manufacturers, importers, and distributors generally have the necessary resources and IT capabilities to support distant assessments, there are a number of practical items that require consideration in order to determine the scope of the distant assessment, and to ensure it is a suitable means of assessing the required areas to allow for a decision to be made regarding GMP/GDP compliance. At a minimum, the following should be considered:

- The use of appropriate platforms to allow for the timely provision of data such as large electronic documents (e.g. access to secure cloud servers or the use of Eudralink or other secure NCA platforms).
- The use of teleconference/videoconference or alternative to allow for real time discussions with company personnel and Subject Matter Experts (SMEs).
- The capability for the live sharing of screens displaying computerised systems used at the site, or the feasibility of providing remote (read-only) access to inspectors to computerised systems.
- The provision of live camera footage or video recordings (e.g. smart glasses, mobile cameras, drones or cameras in place) to allow for a remote review of manufacturing operations, equipment, facilities and relevant documentation such as logbooks, if applicable.
- The time zones of the site and the location of the inspector(s).
- The language of the site. The inspector(s) may require access to a translator for parts of or all of the remote inspection.

The outcome of these considerations may highlight whether any additional resources are required by either the site or the inspectorate(s) conducting the distant assessment.

It is preferable for the site to host and manage the communication platform and consider its security requirements. In cases where the site does not have or cannot obtain the appropriate capabilities, the inspectorate(s) could consider hosting the communication platform.

An example of an optimal communication platform could include the following:

- A live videoconference platform which has the following capabilities:
  - Break-out rooms/conferences to facilitate separate channels of discussion between different inspectors and the site.
  - Screen sharing to display site applications/electronic systems.
- Smart glasses or other mobile cameras which can be interfaced to the videoconference platform to provide live footage of manufacturing operations, facilities and equipment.
- Access to a secure cloud server to share documents.

2.5. Limited on-site inspections

Depending on the circumstances at the time, it may be possible to conduct a limited on-site inspection of sites located in the EEA. This should only be considered if it is compatible with travel restrictions, health measures, and other restrictions/guidance issued by local or national authorities at the time and should be discussed with the site. The inspection could consist of a distant assessment of relevant documentation with a limited on-site inspection of manufacturing operations, facilities and equipment. The on-site inspection and distant assessment should be considered together as parts of the same inspection. A single inspection report and inspection outcome (e.g. GMP certificate) should be produced.

2.6. Distant assessment duration

The principles of the Union procedures *A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers* and *GDP Inspection Procedure (Medicinal Products for Human Use)* should be taken into account, as relevant, when determining the scope and duration required for the distant assessment.

The practicalities and potential challenges associated with distant assessments should also be considered and could result in a longer duration compared to an equivalent on-site inspection. Aspects such as the communication process, site time zone and language, and location(s) of the inspectors should be taken into account.

3. Preparation

Inspector(s) should adequately prepare for the distant assessment and familiarise themselves with the site to be inspected, in accordance with the Union procedures for *Conduct of Inspections of Pharmaceutical Manufacturers or Importers* and *GDP Inspection Procedure (Medicinal Products for Human Use)*, as relevant.

3.1. Distant assessment plan

It is recommended that a plan is drafted in a manner similar to on-site inspections, outlining the areas of the site to be reviewed by each inspector. It is also recommended to share relevant parts of the plan and timetable with the site to facilitate the smooth running of the distant assessment and ensure that site SMEs are available at the requested times.

3.2. Announcement of distant assessment

Notification of the intention to perform a distant assessment should be communicated to the site in accordance with the standard timelines for on-site inspections. In order to prevent any delays during the distant assessment, consideration should be given to requesting that electronic copies of documents and/or lists of documents are provided to the inspector(s) in advance of the distant assessment or, at least, are available for review from the start of the distant assessment.

3.3. Communication process for the distant assessment

The communication platform and process for the provision of electronic copies of documents and other information to the inspector(s) should be defined and agreed with the site in advance of the distant assessment. Consideration should be given to the items listed in paragraph *2.4. IT and other practical considerations*.

If there are significant differences in the time zones of the inspector(s) and the site, it is possible that site personnel may not always be available to respond to inspector queries in real time. In these cases, the inspector(s) should ensure that they have sufficient documentation available for review when site personnel are not online, and related queries should be logged as documents are being reviewed. In these circumstances, efforts should be made to ensure that there is at least a sufficient over-lap time each day to hold discussions in real time.

The communication process between inspectors should also be determined if inspectors are based in different locations. To avoid duplication of review or document requests, consideration should be given to making all requests for documents and other information visible to all members of the inspection team.

It is recommended that the communication platform is tested prior to the commencement of the distant assessment to verify its functionality. If possible, IT support staff should be readily available to respond to any IT issues that may arise during the remote distant assessment. The site should also be aware that if there are any unexpected delays in the provision of electronic copies of documents to the inspector during the distant assessment, the inspector(s) should be informed immediately.

4. Conduct

4.1. Opening Meeting

The distant assessment should start with an opening meeting via videoconference, teleconference or alternative. In addition to covering the relevant items listed in the Union procedures for *Conduct of Inspections of Pharmaceutical Manufacturers or Importers* and *GDP Inspection Procedure (Medicinal Products for Human Use)*, as relevant, the inspector should consider outlining the following:

- A brief overview of the process for communication and the distant assessment plan/timetable.
- Any video/audio recording of the distant assessment by the inspectorate should be agreed between the site and the inspector(s). If part of the distant assessment will be recorded, the site should be given the opportunity to appropriately inform any personnel who may appear in such video footage in accordance with any relevant local legislation.

4.2. Performing the distant assessment

Relevant elements of the Union procedures for *Conduct of Inspections of Pharmaceutical Manufacturers or Importers*, the *Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries* and *GDP Inspection Procedure (Medicinal Products for Human Use)* should be considered to assess the compliance with GMP/GDP and with the terms and conditions of authorisation(s) as applicable.

If a distant assessment of manufacturing operations, facilities and equipment is facilitated through the use of cameras or video footage, it may be useful to have the site schematics, drawings and/or process flow diagrams available for reference, as relevant, to help the orientation of the inspector(s).

In order to facilitate the smooth running of the distant assessment, at the end of each day, the inspector may consider informing the site of the documentation intended to be reviewed the following day to give sufficient notice for the scanning and provision of the requested documents. As the inspector reviews a new topic (e.g. deviations, process validation etc.), it may also be helpful to promptly communicate this to the site.

Inspectors should record notes on the documents being reviewed as per on-site inspections. Relevant documents, emails and other information received should be securely saved or deleted as required.

4.3. Closing meeting

The distant assessment should end with a closing meeting via videoconference, teleconference or alternative and should cover the relevant items listed in the Union procedures for *Conduct of Inspections of Pharmaceutical Manufacturers or Importers* and *GDP Inspection Procedure (Medicinal Products for Human Use)*, as relevant.

5. Post distant assessment activities

5.1. Distant Assessment Report

Distant assessment reports should be written in line with the Union formats of GMP/GDP inspection reports. Appropriate clarifying remarks should be included in relevant sections of the report to make it clear that a distant assessment was performed and to indicate if physical aspects of the facility were assessed and the methods used.

5.2. GMP/GDP certificates

If the outcome of the distant assessment is positive, GMP/GDP certificates should be issued. For GMP distant assessments, the *Type of Inspection* on the certificate should indicate *Distant Assessment*. If a limited on-site inspection as per paragraph *2.5.* was conducted*,* the *Type of Inspection* on the certificate should reflect the on-site inspection and a clarifying remark may be included to indicate that part of the inspection was performed as a distant assessment.

Existing regulatory risk management principles should be used to determine the duration of the validity of GMP/GDP certificates issued following distant assessments.

5.3. Serious GMP/GDP non-compliance

For new sites, including pre-approval distant assessments requested by EMA, if any critical deficiencies are identified during the distant assessment, the relevant application should be put on hold until an on-site inspection can be performed.

For other types of distant assessments, if any critical deficiencies are identified during the distant assessment, existing processes for on-site inspections should be followed and a Statement of non-compliance may be issued if applicable.

5.4. Planning of next Inspection

On-site inspections should be conducted once circumstances permit. The principles of the Union procedures *A Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers* and *GDP Inspection Procedure (Medicinal Products for Human Use)* should be used as relevant when recommending the next interval, scope as well as duration and number of inspectors for the next inspection of the site. A distant assessment may be considered a suitable justification to recommend a reduced interval until the next on-site inspection. The following items could also be taken into consideration:

- The risk and complexity of the dosage form/active substance/manufacturing process.
- The compliance history.
- The type of distant assessment (e.g. for-cause distant assessment or distant assessments to support an application for a new type of product or activity).
- The date of the last inspection.

B. PMF distant assessment guidance (version 2)

1. Introduction & Scope

1.1. Introduction

During the COVID-19 pandemic, on-site PMF inspections of plasma collection sites may not be possible for a number of reasons such as travel restrictions within and between the boarders of countries, risk to health, or other restrictions/guidance issued by local or national authorities.

During these situations, the obligation of Blood Establishments to comply with GMP/GP is not waived and the ongoing verification of compliance by Supervisory Authorities is important to ensure the protection of public health and consequentially the access to essential medicines.

This document provides guidance on conducting distant assessments of new plasma collection centres operated by a parent company/blood establishment that already operates other centres that are included in the manufacturers' PMF during the COVID-19 pandemic to determine compliance of the centre with GMP/GP. In addition, an on-site inspection should be conducted as soon as circumstances permit.

Distant assessments should take into consideration the limitations imposed by using a remote process and recognise that such a remote process cannot completely replace an on-site inspection.

The purposes of this document is to outline the requirements and specificities of distant assessments for PMF plasma collection centres outlining the points to be considered during the preparation, conduct, and reporting phase in this context.

1.2. Scope

In general, Blood Establishments have access to appropriate technologies/platforms, electronic systems and virtual working environments facilitating communication of remote staff. These may enable appropriate communication settings during distant assessments. In these circumstances, distant assessments can represent a suitable means of determining compliance with the principles and guidelines of GMP/GP.

This document is intended to provide guidance on the conduct of distant assessments during the COVID-19 pandemic. It is applicable to new plasma collection centres operated by a parent company/blood establishment that already operates other centres that are included in the manufacturers' PMF (as stipulated in the Notice to Stakeholders issued by the European Commission, Heads of Medicines Agencies (HMA) and EMA and entitled "Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use during the COVID-19 Pandemic"). For centres that have been previously inspected and for which a control measure may already have been performed, the time frame for reinspection can be extended during the COVID-19 pandemic by performing either another control measure in line with EMA recommendation EMA/INS/GMP/534269/2018 "Application of inspection and control measures" or a distant assessment.

This guidance is not intended for use or to replace on-site inspections during normal circumstances which are conducted in line with existing guidance.

2. Planning/Feasibility Assessment

The preparation of a distant assessment will be significantly more demanding compared to on-site inspections. Following a request to perform a distant assessment, the intended extent of the distant assessment should be communicated in a timely manner.

The distant assessment feasibility will need to be assessed by the inspection team (e.g. whether the inspectee meets the technical requirements such as providing remote (read-only) access to electronic systems and maintain communication with and support to inspectors). The inspectee should provide detailed information as requested by the inspectors to allow for the feasibility assessment. In this context, appropriate mitigation strategies (e.g. for poor communication or non-optimal system performances/interruptions) should also be considered.

The practicalities and potential challenges associated with distant assessments could result in a longer duration compared to an equivalent on-site inspection. Aside from aspects such as the communication processes, company time zone, language, and location(s) of the inspection team should be considered. The principles of the EMA Guideline *Application of inspection and control measures to facilitate risk-based inspection planning of sites within the Plasma Master File (PMF) certification system* should be taken into account, when determining the extent and duration required for the distant assessment.

2.1. Distant assessments requested by the CHMP and coordinated by EMA

The inspectorate together with EMA should make a case-by-case decision on whether a distant assessment is considered appropriate and feasible.

Distant assessments should follow the applicable procedures that already exist for coordinating, preparing and conducting PMF inspections requested by the CHMP and should take into consideration the present guidance. Similar to the process for on-site inspections, multiple sites can be grouped for distant assessments under one reference number. Procedure timelines should be agreed between the inspectorate and EMA taking into consideration that grouped distant assessments might require a greater period of time than normally applied for the conduction of on-site inspections.

If it is not deemed feasible to carry out or continue with a distant assessment, the inspection team shall communicate this to EMA without delay and the most suitable course of actions should be determined in each case (e.g. adjust inspection timelines to facilitate an on-site inspection when restrictions are lifted) together with the PMF coordinator. The PMF holder should also be informed.

2.2. Distant assessments coordinated by member states

Individual NCAs can determine on a case by case basis whether a distant assessment is required, feasible and appropriate for sites on their national inspection programmes during the COVID-19 pandemic.

2.3. IT and other practical considerations

There may be many challenges for an organisation to support distant assessments. It is fundamental to assess whether the inspectee has the necessary resources and IT capabilities to support distant assessments not only at the headquarter but also at the collection/processing sites. A number of practical items require consideration in order to ensure the distant assessment is a suitable measure. The following items should be considered:

- The use of teleconference/videoconference or alternative to allow for real time discussions with site personnel, especially at the collection sites.

- The capability for the live sharing of screens displaying computerised systems used at the site, or the provision of remote (read-only) access to inspectors to computerised systems, especially at the collection sites.

- The use of appropriate platforms to allow for the timely provision of large electronic documents (e.g. access to secure cloud servers or the use of Eudralink or other secure NCA platforms). Methods used to share, and transfer information should comply with an adequate standard of security as well as with IT policies of the inspectorate(s) and the site, especially for the exchange of highly confidential donor information.

- The communication process between members of the inspection team, especially when not in the same location.

- The time zones of the site undergoing distant assessment and the location of the inspector(s).

- The language of the site. The inspector(s) may require access to a translator for parts of or all of the distant assessment.

The outcome of these considerations may highlight whether any additional resources are required by either the site or the inspectorate(s) conducting the distant assessment.

It is preferable for the site to host and manage the communication platform and consider its security requirements. In cases where the site does not have or cannot obtain the appropriate capabilities, the inspectorate(s) could consider hosting the communication platform.

An example of an optimal communication platform could include the following:

- A live videoconference platform which has the following capabilities:
  - Break-out rooms/conferences to facilitate separate channels of discussion between members of the inspection team and the site.
  - Screen sharing to display site applications/electronic systems.

- Access to a cloud server and other secure platforms in compliance with IT policies of the inspectorate(s) and the site to share documents including highly confidential donor information.

- A chat / instant-messaging platform should be considered, in case of sound interferences.

3. Preparation

Inspector(s) should prepare adequately for the distant assessment and familiarise themselves with the site to be inspected, taking into account the existing guidance.

A plan similar to an inspection plan for on-site inspections, outlining the areas of the site to be reviewed by each member of the inspection team may facilitate the smooth running of the distant assessment and ensure that site representatives are available at the requested times.

3.1. Announcement of distant assessment

Notification of the intention to perform a distant assessment should be communicated to the site in accordance with the standard timelines for on-site inspections. In order to prevent any delays during the distant assessment, consideration should be given to requesting that electronic copies of documents and/or lists of documents are provided to the inspector in advance of the distant assessment or, at least, are available for review from the start of the distant assessment.

It should be communicated that a subsequent on-site inspection is required in addition to the distant assessment to be conducted when circumstances permit.

3.2. Distant assessment agenda

A detailed agenda similar to on-site inspections should be submitted to the inspectee in advance. The agenda should list all (planned) sessions and anticipated time slots for items that need to be scheduled to facilitate the smooth running of the distant assessment and ensure that relevant site representatives are available at the requested times.

3.3. Communication process for the distant assessment

The communication platform and process for the provision of electronic copies of documents and other information by the site to the inspector(s) should be defined and agreed with the site in advance of the distant assessment. Consideration should be given to the items listed in paragraph *2.4. IT and other practical considerations*.

Duration of daily sessions should be agreed between inspectors and inspectee, especially if there are significant differences in the time zones of the inspector(s) and the site, and in adherence to procedures on both sides. A host should be assigned by the inspectee to coordinate and manage further requests and queries during the distant assessment.

The communication process between inspectors should also be determined if inspectors are based in different locations. To avoid duplication of review or document requests, consideration should be given to making all requests for documents and other information visible to all members of the inspection team.

It is recommended that the communication platform is tested prior to the commencement of the distant assessment to verify its functionality. IT support staff should be readily available to respond to any IT issues that may arise. Any unexpected delays in the provision of electronic copies of documents to the inspector during the distant assessment should be communicated to the inspector(s) immediately.

4. Conduct

4.1. Opening Meeting

The distant assessment should start with an opening meeting via videoconference, teleconference, or alternative.

In addition to taking into consideration the relevant items listed in existing guidance, the inspector should consider outlining the following:

- particularities of a distant assessment setting so that the scope and logistics are understood by all parties involved
- A brief overview of the process for communication.
- The inspectee should provide a list of attendees for the opening meeting
- Video/audio recording of the distant assessment is forbidden. It shall be guaranteed to the inspector to get photos of buildings, rooms and equipment if necessary. This shall be attached to the distant assessment report.

4.2. Performing the distant assessment

Relevant elements of existing guidance should be considered to assess the compliance with GMP/GP and with the terms and conditions of the Plasma Master File.

Essential components of the distant assessment include interviews, presentations (by the inspectee) relating to the topics requested by inspectors in the agenda, and documentation review. Where electronic systems for data management are used, it is necessary to have remote (read-only) access to these systems.

In order to facilitate the smooth running of the distant assessment, at the end of each day, the inspector may consider informing the site of the documentation intended to be reviewed the following day to give sufficient notice for the scanning and provision of the requested documents. As the inspector reviews a new topic (e.g. deviations, process validation etc.), it may also be helpful to promptly communicate this to the site.

4.3. Closing meeting

The distant assessment should end with a closing meeting covering the relevant items taking into account existing guidance.

It should also be communicated that an additional on-site inspection is required when circumstances permit.

5. Post distant assessment activities

5.1. Distant Assessment Report

Distant assessment reports should be written taking into account the Union formats of GMP/GDP inspection reports. Appropriate clarifying remarks should be included in the relevant sections of the report to make it clear that a distant assessment was performed and to indicate that physical aspects of the facility were not assessed.

5.2. Statements of Next Inspection (SONI)

If the outcome of the distant assessment is satisfactory, a SONI should be issued taking into consideration the EMA Guideline Application of inspection and control measures to facilitate risk-based inspection planning of sites within the Plasma Master File (PMF) certification system stating the recommended date of next inspection. The Subject on the certificate should indicate Distant Assessment and a clarifying remark (as per the Questions and Answers issued by the European Commission, HMA and EMA referenced in paragraph 1.1.) that on-site inspections will resume as soon as circumstances permit should be added and any exceptions indicated.