

Provisional Translation (as of August 2022)*

PMDA/CPE Notification No. 0525001

May 25, 2022

To: (applicable stakeholders)

Director of Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency

Procedure for Remote Inspection as a Part of Compliance Inspection on
Drugs and Regenerative Medical Products

Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) conducts the following compliance inspections (hereinafter collectively referred to as “compliance inspection”) under commission from the Minister of Health, Labour and Welfare.

- Document-based inspection and GCP on-site inspection for approval of drugs and regenerative medical products
- Document-based inspection and GPSP on-site inspection for interim evaluation, re-examination, and re-evaluation of drugs
- Document-based inspection and GPSP on-site inspection for regulatory review after conditional and time-limited approval, re-examination, and re-evaluation of regenerative medical products

Procedures for compliance inspection are specified in the following notifications (hereinafter collectively referred to as “Notifications on Procedure”).

- “Procedure for document-based inspection and GCP on-site inspection on application data/documents for approval of drugs as well as that for document-based inspection and GPSP on-site inspection on application data/documents for interim evaluation, re-examination, and re-evaluation of drugs” (PMDA Notification No. 0831001 by Chief Executive of Pharmaceuticals and Medical Devices Agency dated August 31, 2020)

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

- “Procedure for document-based inspection and GCP on-site inspection on application data/documents for approval of regenerative medical products as well as that for document-based inspection and GPSP on-site inspection on application data/documents for regulatory review after conditional and time-limited approval, re-examination, and re-evaluation of regenerative medical products” (PMDA Notification No. 0914001 by Chief Executive of Pharmaceuticals and Medical Devices Agency dated September 14, 2020).

PMDA’s inspectors (hereinafter referred to as “inspectors”) have examined records/documents which form the basis of the inspected trials and studies from PMDA office remotely through the cloud system and video conferencing system (hereinafter referred to “Remote Inspection”) in accordance with “Procedure for Remote Inspection as a Part of Compliance Inspection on Drugs and Regenerative Medical Products” (PMDA/CPE Notification No. 1116002 dated November 16, 2020, hereinafter referred to the “former Notification on Remote Inspection”).

As of May 20, 2022, the Act on Partial Revision of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 47 of 2022) was issued, and in response to this revision, the following notifications were issued, and the former Notifications on Procedure were abolished on the same days as the issuance dates.

- Procedure for document-based inspection and GCP on-site inspection on application data/documents for approval of drugs as well as that for document-based inspection and GPSP on-site inspection on application data/documents for re-examination, etc. of drugs (PMDA Notification No. 0520001 by Chief Executive of Pharmaceuticals and Medical Devices Agency dated May 20, 2022)
- Procedure for document-based inspection and GCP on-site inspection on application data/documents for approval of regenerative medical products as well as that for document-based inspection and GPSP on-site inspection on application data/documents for re-examination, etc. of regenerative medical products (PMDA Notification No. 0525001 by Chief Executive of Pharmaceuticals and Medical Devices Agency dated May 25, 2022)

In association with the above, this notification is issued, and it is effective on May 25, 2022, and the former Notification on Remote Inspection is abolished. Please inform all of the members of your association about this notification.

The method of documentation submission through the Electronic Study Data Submission System specified in 2. (1) [3] (b) in the Annex of this notification (hereinafter referred to as the “Gateway System”) is effective on July 1, 2022.

Major changes from the former Notification on Remote Inspection are made on matters related to the procedure and points to be considered for Remote Inspection as follows:

- Submission through the Gateway System is added as a method of documentation submission
- Points to be considered in preparation of documentation are clarified
- Points to be considered for documentation prepared in a language other than Japanese or English are added
- Points to be considered related to the cloud system and video conferencing system are clarified.

End of Document

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- “Procedure for document-based inspection and GCP on-site inspection on application data/documents for approval of regenerative medical products as well as that for document-based inspection and GPSP on-site inspection on application data/documents for re-examination, etc. of regenerative medical products” (PMDA Notification No. 0525001 by Chief Executive of Pharmaceuticals and Medical Devices Agency dated May 25, 2022).

As described in the Notifications on Procedure, PMDA’s inspectors (hereinafter referred to as “inspectors”) may examine records/documents which form the basis of the inspected trials and studies (hereinafter referred to as “documentation”) from PMDA office remotely through the cloud system or video conferencing system (hereinafter referred to as “Remote Inspection”). Details of the procedures for Remote Inspection are provided in the Annex.

1. Policy of Remote Inspection

A compliance inspection is usually conducted by examining documentation presented by an applicant, marketing authorization holder (MAH), sponsor, sponsor-investigator, clinical trial in-country representative, medical institution, and/or their external contractor (hereinafter referred to as “applicant, etc.”) and interviewing them about inspected trials and studies according to the date and place of the inspection previously notified by PMDA, (hereinafter referred to as “usual compliance inspection”)

In a Remote Inspection, on the other hand, the applicant, etc. present documentation in advance, and then inspectors examine the documentation and interview the applicant, etc. in 2 steps of pre-inspection and main-inspection. In some cases, however, neither the prior presentation of documentation nor pre-inspection is conducted, but only the main-inspection is conducted by examining all documentation and interviewing the applicant, etc.

2. Procedure for Remote Inspection

(1) Prior communication about Remote Inspection

[1] PMDA informs the applicant, etc. of their intent to conduct compliance inspection as Remote Inspection by e-mail or telephone at the time of scheduling as specified in the Notifications on Procedure, in principle. In addition, inspectors may have a pre-meeting about the Remote Inspection with the applicant, etc. where necessary.

[2] PMDA confirms the schedule of pre-inspection and the method of presenting documentation with the applicant, etc. by e-mail preferably 1 to 2 months before the main-inspection.

[3] The applicant, etc. should present documentation to the inspectors by the method indicated in (a). If it is difficult to present documentation by the method indicated in (a), the applicant, etc. should present by the method indicated in (b).

(a) Uploading documentation through the cloud system

(b) Submitting documentation through the Electronic Study Data Submission System specified in III 2 in Annexes 1 and 2 of the Notifications on Procedure (hereinafter referred to as the “Gateway System”)

The applicant, etc. may present documentation by saving it in electronic media (CD, DVD, or Blu-Ray Disc) and sending them to the Office of Non-clinical and Clinical Compliance, PMDA only if it is permitted in III 2 in Annexes 1 and 2 of the Notifications on Procedure. If it is difficult, for some reason, to present documentation either by (a) or (b), or by saving documentation in

electronic media and sending it, the applicant, etc. should consult the inspectors whether paper documentation is acceptable. If the paper documentation is accepted, the applicant, etc. should submit this as specified in 3. (4) [2].

[4] If the applicant, etc. present documentation by the method indicated in [3] (a), inspectors provide information necessary for setting the cloud system to the applicant, etc. by e-mail as soon as possible.

[5] If the applicant, etc. present the documentation by the method indicated in [3] (a), they should issue an account to each inspector to access the cloud system and also provide a user manual of the cloud system specified in 4. (2) [5] as appropriate.

(2) Presentation of documentation

[1] In usual compliance inspection, inspectors inform the applicant, etc. of the condition/scope (such as subject ID, clinical site, period, etc.) of documentation to be inspected on the day of or one day before the inspection. In Remote Inspection, inspectors inform the applicant, etc. of them preferably by 10:00 am, 13 business days before the main-inspection. If any concern is found at the prior check, etc., inspectors may change the condition/scope to be inspected and request the applicant, etc. to present additional documentation where necessary.

[2] The applicant, etc. should present documentation to the inspectors by a method indicated in (1) [3] by 10 business days before the main-inspection. If the applicant, etc. present the documentation by the method indicated in (1) [3] (a), they should inform the inspectors of having presented the documentation. If it is inevitably difficult to present these by the deadline, the applicant, etc. should consult the inspectors.

[3] If a presentation on the organizational structure is necessary, the inspectors make a request for it to the applicant, etc. by 13 business days before the main-inspection, in principle. However, if the inspectors deem it necessary to request a presentation during the pre-inspection, they request it promptly.

(3) Pre-inspection

[1] Usually, conducting a pre-inspection takes inspectors 10 business days. During this period, inspectors examine the documentation presented by the applicant, etc. and identify concerns. If any concern is found, inspectors send inquiries to the applicant, etc. by e-mail and other means as appropriate.

[2] If requested by inspectors, the applicant, etc. should present the appropriate documentation and respond to inquiries promptly.

[3] Inspectors inform the applicant, etc. of concerns to be examined and

interviewed at the main-inspection by e-mail by noon, 1 business day before the main-inspection (for inspection on a clinical study not involving Japan, 2 business days before the main-inspection). This, however, shall not apply to any case where the response is submitted by the applicant, etc. immediately before the above communication or additional concerns are found after the above communication.

[4] Even if the applicant, etc. respond about concerns to be examined and interviewed at the main-inspection before the main-inspection, they should explain them at the main-inspection.

(4) Main-inspection

[1] Inspectors examine documentation not presented at the pre-inspection through the video conferencing system and interview the applicant, etc. about the concerns identified during the pre-inspection.

[2] If requested by inspectors, the applicant, etc. should present the appropriate documentation and respond to inquiries promptly.

(5) Post-inspection

The applicant, etc. should take actions on the unresolved concerns at the main-inspection according to direction by inspectors as soon as possible. In such a case, the applicant, etc. can explain the concerns through the video conferencing system.

3. Points to be considered for preparation of documentation

(1) General matters

It is not necessary for the applicant, etc. to present all documentation but those to be presented to the inspectors at a usual compliance inspection. Some pieces of documentation may be specified with condition/scope to be inspected, while some pieces are not. After the compliance inspection is determined to be conducted as Remote Inspection, the applicant, etc. should start with the preparation of documentation that are not specified with condition/scope to be inspected. After the condition/scope is specified, the applicant, etc. should proceed with preparing documentation for those specified with condition/scope. In the end, the applicant, etc. should present both type of documentation. If the applicant, etc. have limited experience with compliance inspections or Remote Inspection, or in other necessary cases, the inspectors may request the applicant, etc. to explain the contents of documentation in advance. If there are any unclear points about the method of presenting documentation, or a supplementary explanation is needed on the documentation, the applicant, etc. should proceed with the preparations as soon as possible by requesting inspectors to have a pre-meeting and other approaches.

(2) Points to be considered for presentation of documentation (electromagnetic records)

[1] The applicant, etc. should present all the required documentation at a pre-inspection in principle. If the applicant, etc. want to present documentation through the video conferencing system at main-inspection, they should communicate this matter with the inspectors and do so. In addition, if there are documentation that have been submitted as documents of Annex 2 or 6 specified in the Notifications on Procedure, the applicant, etc. should communicate this matter with the inspectors. If these have to be additionally presented as documentation, the inspectors direct the applicant, etc. to do so.

[2] The applicant, etc. should consider the following points as well so that the inspectors can readily access the target documentation.

- The applicant, etc. should present a document showing the folder structure, etc. with the documentation, and should also submit it by e-mail.
- In the document showing the folder structure, etc., it is desirable to set hyperlinks to electronic files retained in the cloud system.
- If one folder contains many documents and thus it is deemed difficult to find documents, the applicant, etc. should make efforts such as creating lower folders for each category of documents.
- The applicant, etc. should present supplementary documents necessary for the inspectors to access the documentation. The applicant, etc. should include, in the supplementary data/documents, the following information:
 - The name of the written procedure
 - Outline of the procedure
 - Effective date (version number) of the written procedure
 - Names of documents generated
 - File locations of documents

Then, the applicant, etc. should upload the supplementary documents to the cloud system with the documentation. In addition, at the request of inspectors, the applicant, etc. should submit the supplementary documents by e-mail or through the Gateway System to PMDA (excluding information included in a management sheet, etc. separately submitted).

(3) Points to be considered for conversion of documentation from paper into electromagnetic records

[1] The applicant, etc. should establish a procedure for scanning paper documentation and follow it. The applicant, etc. should confirm the following points about the electronic documentation obtained by scanning.

- They are clear with adequate contrast.
- They are consistent with the paper documentation in terms of the number of pages.
- Both sides of each paper have been scanned if applicable.

For files created by scanning paper documentation, it is acceptable that no functions shown in 4. (2) [1] can be used.

[2] Inspectors may request the applicant, etc. to present original paper documentation where necessary.

[3] The applicant, etc. should consult inspectors how to handle documentation for which scanning is difficult.

(4) Points to be considered for mail delivery of documentation

[1] If the documentation is to be submitted in electronic media (CD, DVD or Blu-ray Disc), the applicant, etc. should send documentation in such electronic media to the Office of Non-clinical and Clinical Compliance, PMDA by 10 business days before the main-inspection. PMDA destroys the submitted electronic media upon notification of the inspection result in principle, but not return them.

[2] If the paper documentation is to be submitted, the applicant, etc. should send paper documentation to the Office of Non-clinical and Clinical Compliance, PMDA by mail if applicable. In addition, the following points should be noted as well.

- The due date of submission is determined through communication with the inspectors irrespective of the pre-inspection period.
- The number of days (desirably) from receipt of the documentation to return will be 5 business days. If there is any issue, the applicant, etc. should consult the inspectors.
- If any concern is found, the inspectors send inquiries to the applicant, etc. by e-mail or telephone as appropriate.
- If the applicant, etc. cannot respond to the inquiries without the documentation, they should respond after the documentation are returned.
- The applicant, etc. should bear the expenses for mail delivery (submission and return of documentation).

(5) Points to be considered for documentation prepared in a language other than Japanese or English

[1] The applicant, etc. should consider the following points when presenting the documentation.

- The documentation should be submitted after the document title, section

names, etc. in the document are translated into Japanese or English.

- If inspectors separately request a translation of a specific document, the document should be translated.
- The method of translation is not particularly specified, but the applicant, etc. should check that the contents are understandable.

[2] The applicant, etc. should consider the following points at the main-inspection.

- The applicant, etc. should employ an interpreter and the like to explain the contents of the documentation.
- The applicant, etc. should be careful when employing an interpreter and the like because the time for the main-inspection may be longer than usual and the number of days of the main-inspection may be increased due to the time difference and other reasons.

[3] If there are any unclear points about [1] and [2], the applicant, etc. should make inquiries to inspectors.

4. Points to be considered for the cloud system and video conferencing system

(1) Common points

[1] The applicant, etc. should conclude a contract with a service provider of the system and bear the expenses for use of the system (except for the expenses for PMDA's access to the system).

[2] The applicant, etc. should specify the procedure for setting the system and set the system in accordance with the procedure. If any problem occurs at the time of setting, the applicant, etc. should review the setting procedure so that no problem should occur in the next and subsequent Remote Inspections.

[3] The applicant, etc. should ensure security of the system. If any unauthorized access occurs because of a security vulnerability and communication interception by fault of the service provider, the applicant, etc. should take appropriate actions including stopping use of the system. If there is any point to be considered by PMDA to ensure the security, the applicant, etc. should inform the inspectors in advance.

[4] The applicant, etc. should take appropriate preventive actions for sound leakage and unauthorized access by communication interception on devices and lines used for connections.

[5] If any critical security problem occurs in the system, the applicant, etc. should promptly communicate this incident with PMDA. The applicant, etc. and PMDA should decide to suspend or postpone the Remote Inspection. The timing of re-start and its method should be determined through consultation.

(2) Points to be considered for the cloud system

[1] The applicant, etc. should issue to each inspector an account with read-only access authority that can use the following functions in principle to connect and operate the cloud system.

- Text search
- Text copy
- Sort & Filter function of Excel files

From the viewpoint of preventing erroneous operations, the applicant, etc. should avoid issuing an account with authorities for editing, downloading, etc. wherever possible. If the applicant, etc. issue an account with any other authority for some reason, it should be accepted by the inspectors in advance, and the applicant, etc. should communicate the points to be considered. In this case, if an inspector performs operations such as erroneous downloading, he/she takes actions by deleting and other means.

[2] Even if an applicant, etc. has used the same cloud system as the previous Remote Inspections, the cloud system may take time to re-connect or may be inactivated. Thus, the applicant, etc. should make sure to conduct the connectivity test for each inspection. At the time of the connectivity test, the applicant, etc. should upload a file for which the functions shown in [1] can be tested. For the Sort & Filter function of Excel files, it is acceptable to upload a file within which a filter is set in advance.

[3] If any change or addition of an inspector is made, an additional account should be issued as required. The same account should not be issued to more than one inspector.

[4] The applicant, etc. should retain the documentation in the cloud system and accounts of the inspectors until notification of the inspection result.

[5] When the applicant, etc. use the system for Remote Inspection for the first time, they should provide the inspectors with a user manual of the cloud system. The user manual includes the following contents and should be available for any kind of compliance inspection.

- Operation method
- Account issuance method
- No-operation timeout time
- Log-in method/authentication method (use or non-use of one-time password)
- Other requirements (recommended browser, etc.)

If the user manual is updated, the applicant, etc. should provide the revised

version at the next Remote Inspection.

- [6] The applicant, etc. should consider the following points as well.
- The inspectors without their account will not access or operate the cloud system but may look at the screen that another inspector operates with his/her account.
 - The inspectors access the cloud system through PMDA's network system. For cloud system that cannot be connected through or are not available in PMDA's network system (e.g., a system requiring installation of an application, change of security settings, and/or download of a file), the applicant, etc. should change the method of presenting documentation (electromagnetic records), for example, by utilizing other cloud systems.
 - The applicant, etc. should confirm the file formats accessible through the cloud system (e.g., PDF, Word, Excel) before upload of documentation.
 - Any cloud system which takes a long time to access may not be able to be used for Remote Inspection in the future.
 - The applicant, etc. should consult inspectors about whether folders (including eTMF) containing documents other than those to be presented may be utilized. If hyperlinks to electronic files in the cloud system can be set in the document showing the folder structure, etc., it may be possible to present together with the documents other than those to be presented.

(3) Points to be considered for the video conferencing system

- [1] The applicant, etc. should make appropriate arrangements such as sending the inspectors a meeting invitation for the pre-meeting and main-inspection.
- [2] The applicant, etc. should conduct the connectivity test immediately before the start of the conference especially when there are any concerns about the connection to the video conferencing system.
- [3] The applicant, etc. should inform the inspectors of the name and department of participants in the pre-meeting and main-inspection in advance by e-mail. At the pre-meeting and main-inspection, the applicant, etc. should verify identities of the participants. If an additional person participates in the pre-meeting and main-inspection, applicant, etc. should inform the inspectors about his/her name and department in advance.
- [4] The applicant, etc. should make communication lines (usually 1 or 2 lines) available for the main-inspection as required. At the timing specified in 2. (3) [3], the applicant, etc. should ask the inspectors about the number of communication lines required.
- [5] If the applicant, etc. record video or audio of the pre-meeting and main-

inspection to make internal records, they should obtain permission of inspectors in advance. The recorded video and audio data should be used only internally for compliance inspection and must not be leaked out through external use (presentation at a conference, etc.) or the Internet. In addition, upon notification of the inspection result, the applicant, etc. should delete such data immediately. If inspectors record video or audio in PMDA, they take the same action.

[6] The applicant, etc. should consider the following points as well.

- Any video camera function should be turned off unless required. Any microphone should be muted unless required.
- If the participants need to have an internal meeting during the main-inspection, the applicant, etc. should ask the inspectors for permission in advance.
- If unknown participant is found during the pre-meeting and main-inspection, the applicant, etc. should force unknown participant out, if applicable.
- If the inspection takes a long time or involves an interpreter, the break time should be arranged by mutual agreement.

5. Others

[1] PMDA posts information necessary for efficient and effective implementation of Remote Inspection on the PMDA's website and modifies the content where necessary.

[2] PMDA determines a period of pre-inspection, etc. excluding business days during consecutive holidays and company-wide simultaneous holidays (e.g., summer holidays) requested by the applicant, etc. In addition, PMDA may change a period of pre-inspection, etc. taking account of circumstances of the product.

[3] PMDA makes efforts to understand the implementation status and problems of Remote Inspection and, based on them, revises this notification where necessary.

[4] If conduct of a compliance inspection as Remote Inspection becomes necessary instead of scheduled usual compliance inspection, PMDA informs the applicant, etc. of this matter and consults them about the inspection schedule.

[5] Since it is inefficient to convert paper documentation into electromagnetic records solely for enabling Remote Inspection, the applicant, etc. should consider making efforts to computerize the documentation and utilizing the

computerized data for normal work as well. When promoting computerization of documents, the applicant, etc. should also refer to “Basic Principles on Utilization of Electromagnetic Records in Clinical Trial-related Documents” (PFSB/ELD Administrative Notice dated July 31, 2013).

- [6] When conducting document-based inspection and GPSP on-site inspection for re-examination and re-evaluation of drugs by the method of Remote Inspection, applicable terms in this notification shall be replaced as needed, such as replacement of “clinical trial” with “post-marketing clinical trial.”
- [7] When the Office of Non-clinical and Clinical Compliance conducts various types of consultations in accordance with “Implementation Guidelines for Clinical Trial Consultation and Confirmation of Certification, etc., Conducted by the Pharmaceuticals and Medical Devices Agency” (PMDA Notification No. 0302070 of Chief Executive of Pharmaceuticals and Medical Devices Agency dated March 2, 2012) by the method of Remote Inspection, the provisions of this notification shall apply mutatis mutandis, and applicable terms shall be replaced as needed, such as replacement of “applicant” and “inspection” with “applicant of consultation” and “consultation,” respectively.