PMDA and sponsor GLP inspection conducted in Japan under the pandemic

Shuhei Hagiwara, Ph.D.
GLP Division, JSQA

Contents

- GLP compliance inspection by the PMDA during the COVID-19 pandemic
- Sponsor inspections of contract testing facilities during the COVID-19 pandemic
- Change in Operation of Document based Inspection

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GLP compliance inspection by the PMDA during the COVID-19 pandemic

April 2020

✓ GLP compliance inspections were suspended during declarations of a state of emergency

Declaration of a state of emergency:

- The prime minister requests prefectural governors to take measures
- Requests for cooperation such as voluntary restrictions on going out and restrictions on the use of facilities are issued

July 2021

✓ The policy on GLP compliance inspections was posted on the PMDA website

The policy on GLP compliance inspections was posted on the PMDA website

July, 2021

Reference: Website of the PMDA

To testing facilities undergoing GLP compliance inspections:

- ✓ **Remote systems** are used for part of the inspection
- ✓ **Up to 3 individuals** may be present at the same time
- ✓ The duration of the on-site inspection is **shortened** to the extent possible

Even during state of emergency declarations, the decision was not to **uniformly refrain** from conducting GLP compliance inspections.

Remote systems

- Remote systems were used for part of the inspection
  - Content to be performed via web conference systems
    - Explanation of the purpose of the inspection and the contents of the inspection
    - Discussion regarding the inspection schedule
    - Questions and answers regarding "**materials for GLP compliance checks**"

When undergoing a GLP compliance inspection conducted by the PMDA, testing facilities were to submit the following documents to the PMDA in advance.

1. Site layout
2. Building layout
3. Documents showing the classification and flow diagram for animal care facilities, animal supply facilities, testing operation areas, document storage facilities, facilities for handling test and control substances, etc.
4. Documents on the setting of care conditions in animal care facilities and clean air circulation circuits/equipment
5. List of major equipment
6. Organizational charts, number of employees by qualification, and status of education and training
7. List of titles of standard operating procedures

Materials for GLP compliance checks

Remote systems

- Remote systems were used for part of the inspection
  - Required actions/responses from the testing facility
    - Testing facilities were to set up web conference systems and play the role of the host

Up to 3 individuals

- No more than 3 individuals were to be present to respond to the on-site inspection from the testing facility side
  - Request from the PMDA to testing facilities
    - Allow the conduct of a remote inspection using web conference systems
    - All study audits were conducted through **Self-inspection method**

Study audit methods	Details
 Self-inspection method	• Inspectors summarize questions while reviewing study documents themselves. • Once the review of all documents is complete, study directors are called in to respond to questions from PMDA inspectors.
 Interview method	• Study director is asked to explain the contents of the study. • An inspection method where inspectors ask the study directors to respond to questions as they arise.

The interview method is no longer used in during the COVID-19 pandemic

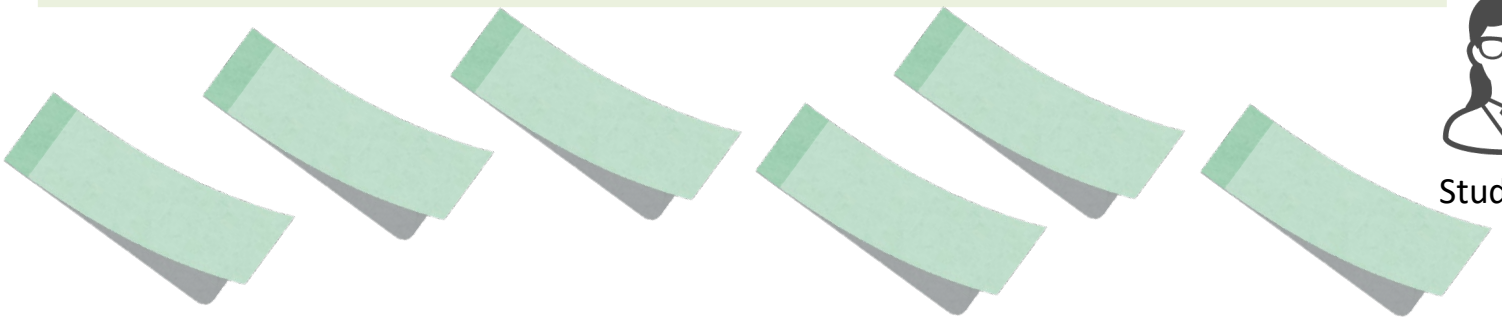
Up to 3 individuals

- Required actions/responses from the testing facility
  - Share the status of progress of the inspection with facility staff using the web conference system
  - In some studies, the PMDA inspector handed **checklists** to the study director.

Checklists

List of key information provided in the final study report

To confirm the location of information on those checklist, the requirement was to place post-it notes on pages containing raw data as evidence (about **100** notes per study)



Study director

The duration of the on-site inspection was shortened

- Request from the PMDA to testing facilities
  - For laboratory tours, inspectors were to be **divided** into several groups to inspect multiple areas at the same time
  - Laboratory tours and study audits were to be conducted simultaneously
  - The PMDA selected laboratory tour areas as necessary
  - Closed interviews and findings **review meeting** were not conducted

- Required actions/responses from the testing facility
  - The time taken daily for the inspection tended to be longer due to the shortening of the inspection period
  - Inspection of similar rooms was omitted for the laboratory tour

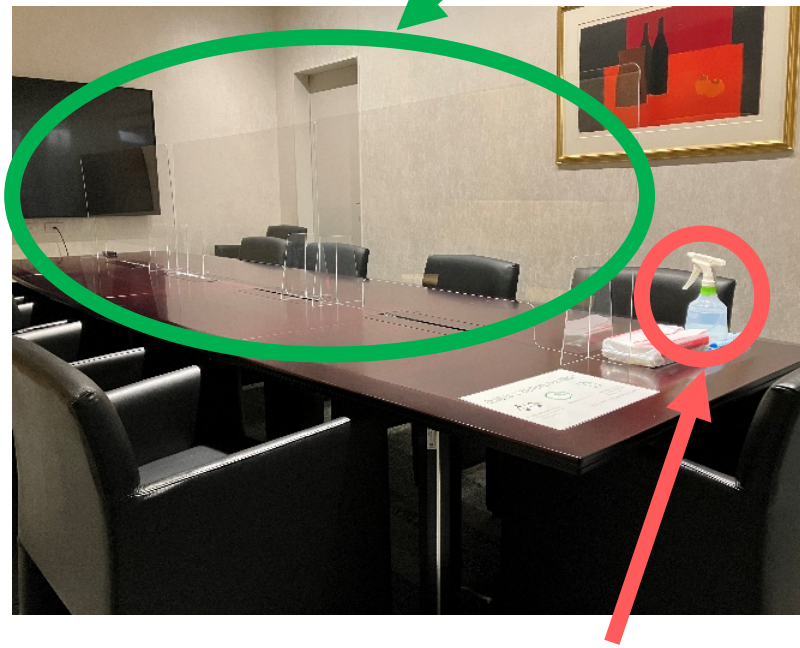
Infection prevention measures

- PMDA side
  - The PMDA inspectors were:
    - to confirm infection prevention measures implemented by the testing facility in advance
    - to take temperature measurements every day
    - to wear masks and face covers
  - If there were any abnormalities in the physical condition of the PMDA inspector(s), the appropriateness of continuing the GLP compliance inspection was to be considered.

Face covers

Infection prevention measures

- Testing facilities side
  - Implement infection control measures at the venue
  - Thorough alcohol spraying for alcohol disinfection
  - Test facility personnel were to wear masks
  - Acrylic plates were to be installed
    - to prevent droplet exposure between PMDA inspectors and testing facility personnel
  - Study audits were to be conducted at spacious and large venues



Changes to the policy on GLP compliance inspections

July, 2023

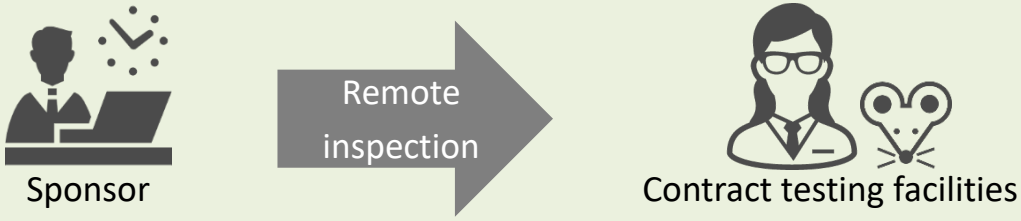
- GLP compliance inspections are performed on-site.
- The policies below are repealed.
  - -Up to 3 individuals may be present at the same time
  - -The duration of the on-site inspection is shortened
- Using remote systems is continued.

Contents

- GLP compliance inspection by the PMDA during the COVID-19 pandemic

- **Sponsor** inspections of contract testing facilities during the COVID-19 pandemic

From here, the presentation will focus on remote inspections of contract testing facilities conducted by the **sponsor** (not the PMDA).



Outline : Questionnaire survey

- Background/Purpose
  - There have been instances where **on-site inspections** of contract testing facilities by the sponsor was **difficult** under the restrictions on travel under COVID-19.
  - **Remote inspections** were considered an alternative to on-site inspections.
  - In order to understand the thinking regarding and the status of remote implementation, a **questionnaire on remote inspections** was administered to sponsors and contract testing facilities in Japan.

Methods: Questionnaire survey

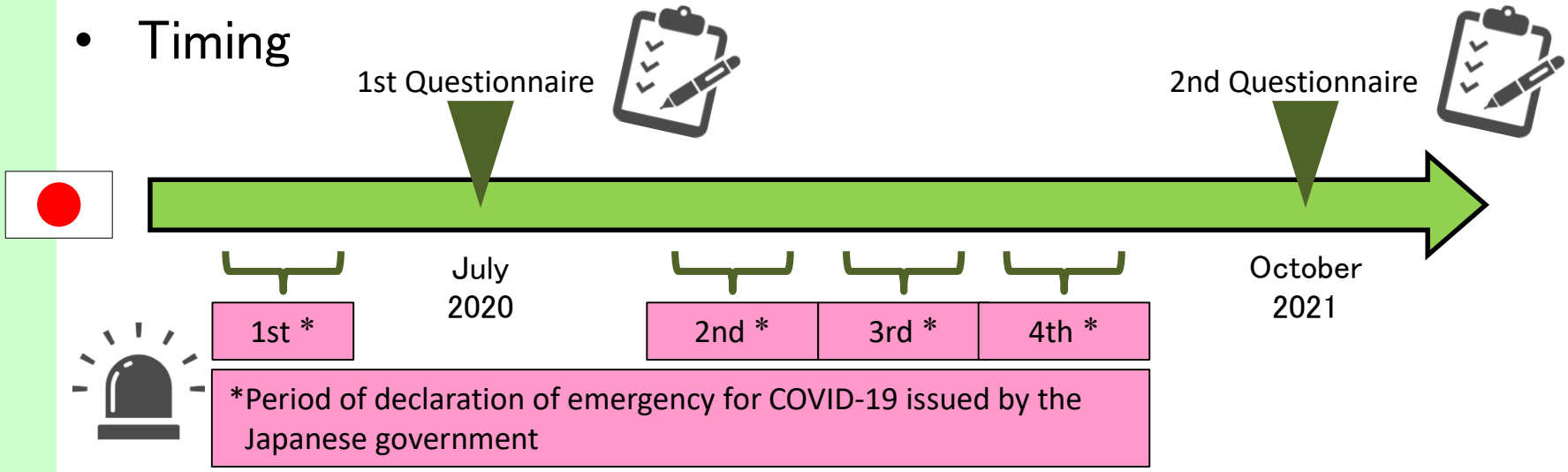
- Target responders
  - Sponsor and contract testing facilities in Japan

    Registered companies under the JSQA GLP committee

No.	Target responders	Question
S-1	 Sponsor	• Whether or not the implementation of remote inspections is being considered?
S-2		• Are there criteria for conducting remote inspections?
S-3		• What are the contents and specific methods of remote inspections being conducted/considered?
S-4		• What are the possible methods for handling study audits?
S-5		• What are the obstacles/concerns in considering remote inspections?
C-1	 Contract testing Facilities	• Were remote inspections anticipated?
C-2		• What are the acceptable contents and specific methods for remote inspections?
C-3		• What methods are acceptable to adopt for the conduct of study audits?

Methods: Questionnaire survey

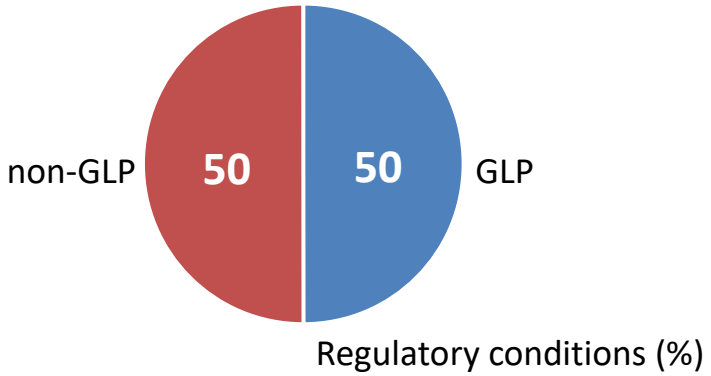
- Timing

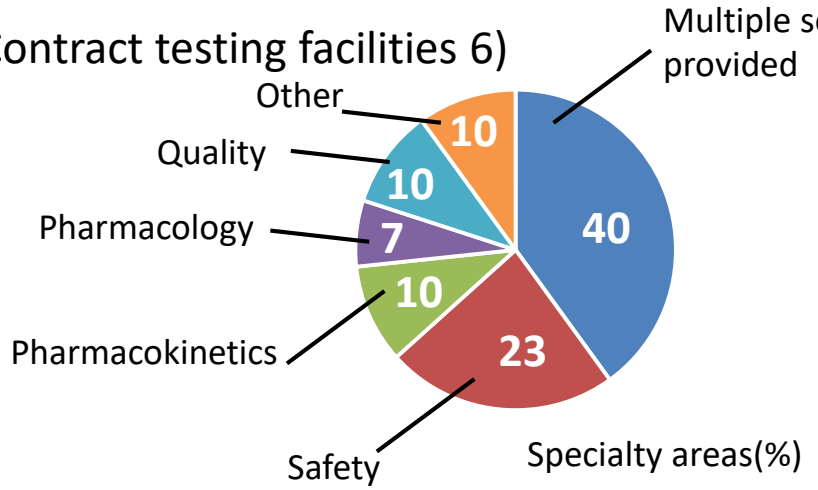


- Based on the questionnaire results, the following content was considered:
  - Changes in the status of implementation of remote inspections
    - First time questionnaire: July 2020 (after the first state of emergency declaration)
    - Second time questionnaire: October 2021 (after the fourth state of emergency declaration)
  - Ongoing issues related to the implementation of remote inspections

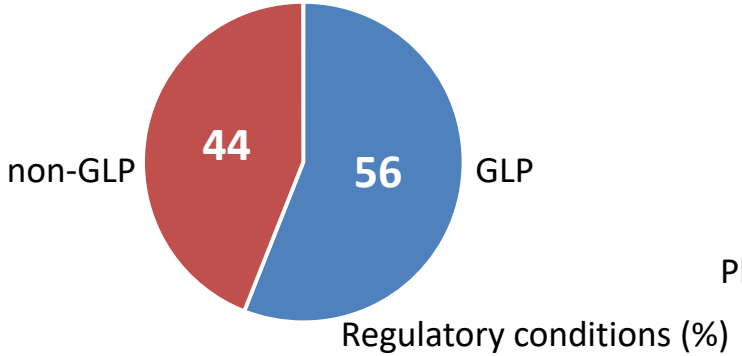
Target responders' institutions and affiliations

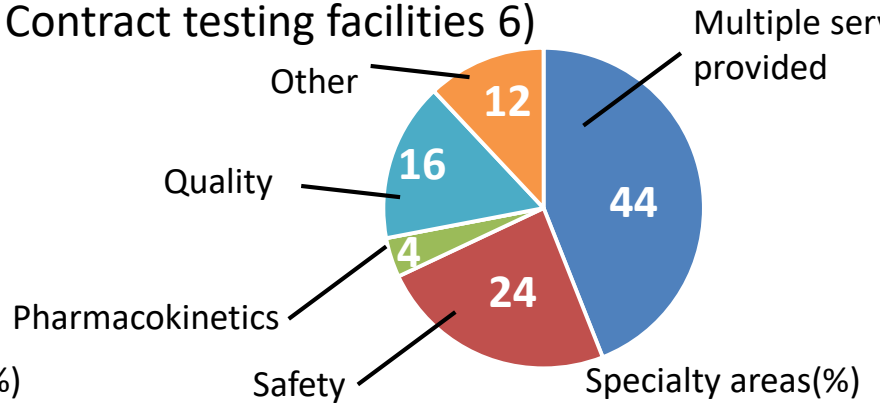
- 1st Questionnaire, July 2020
  - 30 institutions (Sponsors 24, Contract testing facilities 6)





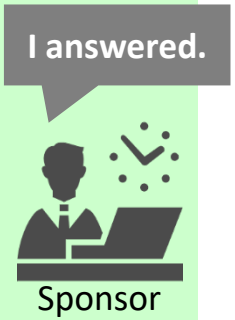
- 2nd Questionnaire, October 2021
  - 25 institutions (Sponsors 19, Contract testing facilities 6)





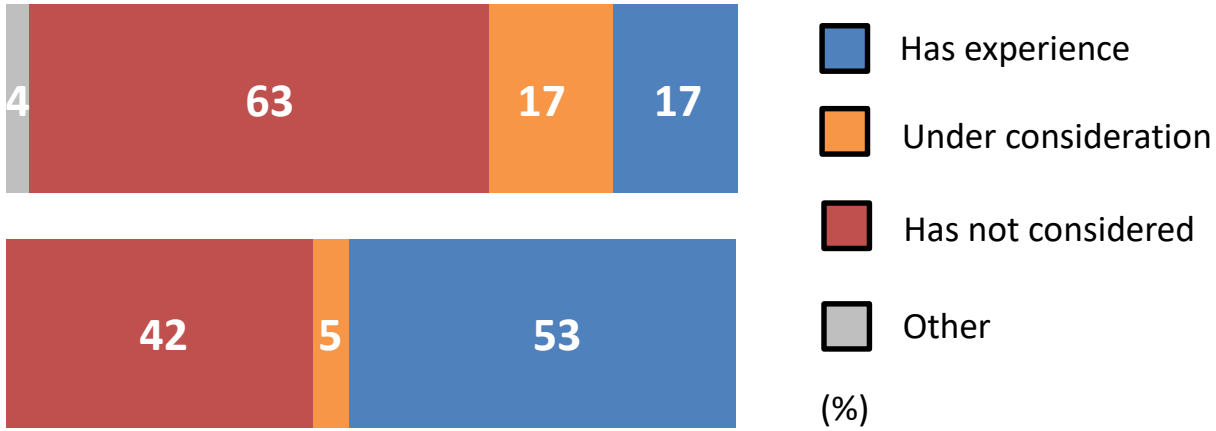
Questionnaire results (S-1)

Q. Whether or not the implementation of remote inspections is being considered?



July 2020
(Number of responding: Sponsors 24)

October 2021
(Number of responding: Sponsors 19)



– From July 2020 to October 2021, the number of sponsors with **experience** in conducting remote inspections increased

Questionnaire results (S-2)

Q. Are there criteria for conducting remote inspections?

I answered.

Sponsor

– **None** of the sponsors had **criteria** for conducting remote inspections

Questionnaire results (S-3)

Q. What are the contents and specific methods of remote inspections being conducted/considered?

Items	July 2020	October 2021
Overview explanation and Q&A	• Facility inspection checklist	• Facility inspection checklist • Web conference system
Findings review meeting	• None	• Web conference system
Laboratory tour	• None	• Webcam broadcast • Recorded videos • Explanation of changes from the past using text and photos through a web conference system

I answered.

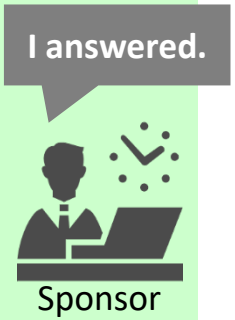
Sponsor

– A **Web conference system** was used to explain the overview, answer questions and provide review comments.
– Laboratory tours have been carried out in **various ways** (through webcams, recorded videos, photos, etc.).

Questionnaire results (S-4)

Q. What are the possible methods for handling study audits?

Number of responses	Methods
At least half of the sponsors responded	• Request to convert raw data into PDF format • Perform on-site audit if the situation allows
A small number of sponsors responded	• Temporary provision and receipt of raw data files • Checklists used to perform a confirmation in the form of an interview • Perform confirmation by having raw data projected using a document camera • Some sponsors did not conduct study audits through remote inspections



- At least half of the sponsors requested:
  - The **conversion** of raw data into PDF format
  - The conduct of a study audit **on-site** rather than remotely
- Some sponsors did **not allow** study audits to be conducted through remote inspections

Responses from July 2020 and October 2021 are presented together

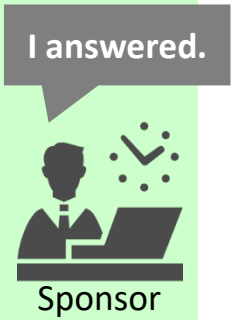
Document camera

- A web camera that allows users to easily take real-time images of items on hand
- Can take images of items below from directly above
- Can be used to take images of items broadcast/shown via the web conference system

Questionnaire results (S-5)

Q. What are the obstacles/concerns in considering remote inspections?

Concerns	Comments
IT environment	• Organizational structure to adopt systems • Handling malfunctions during inspections • Telecommunications environment of both parties
Contracted parties' intent	• Workload on the side of contract testing facilities (large amount of PDF conversion work, etc.) • The time it takes to provide additional materials



Responses from July 2020 and October 2021 are presented together
All of these concerns were reported by at least half of the sponsors

Questionnaire results (S-5)

Q. What are the obstacles/concerns in considering remote inspections?

Concerns	Comments
Ensuring the reliability of laboratory tours	• Limitation of laboratory tour points • Importance of on-site laboratory tours for contract testing facilities being used for the first time
Confidentiality, security and data protection	• What can be inspected and to what extent while maintaining confidentiality • Handling in the event of information leaks (contracts, etc.) • Method of sharing PDF converted data

I answered.

Sponsor

– The IT environment, confidentiality, and **workload** on the contract testing facility were listed as **concerns**

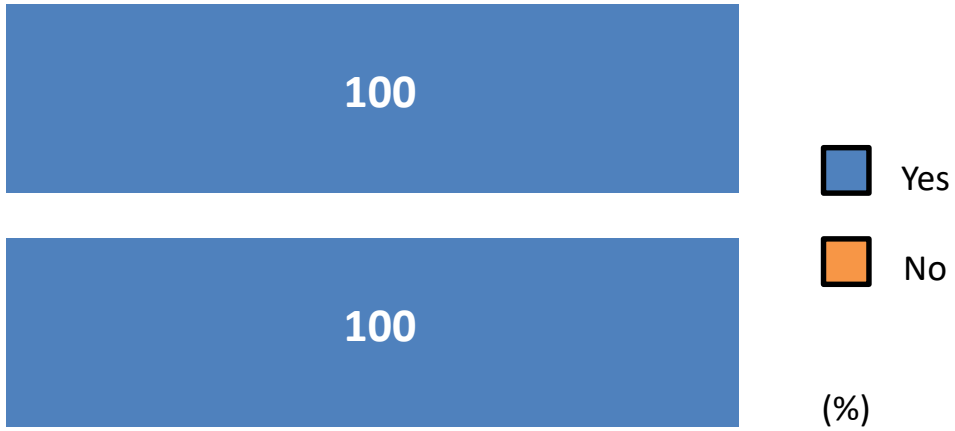
Responses from July 2020 and October 2021 are presented together
All of these concerns were reported by at least half of the sopnsors

Questionnaire results (C-1)

Q. Were remote inspections anticipated?

July 2020
(Number of responding:
contract testing facilities 6)

October 2021
(Number of responding:
contract testing facilities 6)



I answered.

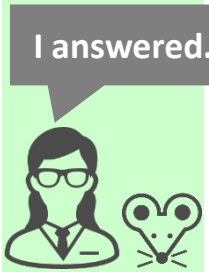
Contract testing facilities

– **All** contract testing facilities assumed remote inspections would be **needed** at an early stage

Questionnaire results (C-2)

Q. What are the acceptable contents and specific methods for remote inspections?

Items	Comments
Overview explanation and Q & A	• Provision of explanatory materials in advance • Web conference system
Findings review meeting	• Web conference system
Laboratory tour	• Webcam broadcast



Contract testing facilities

- Contract testing facilities assumed there would be a need to use **web conference systems** and provide laboratory tours by **webcam broadcast** from an early stage.
- The establishment of a **Wi-Fi environment** (equipment, security) has become an **issue** for broadcasting laboratory tours.
- There was no noticeable difference between the July 2020 and October 2021 questionnaire results.

Questionnaire results (C-3)

Q. What methods are acceptable to adopt for the conduct of study audits?

Number of responses	Methods
At least half of the facilities responded	• Raw data conversion to PDF* • Temporary provision of raw data files** • Use of a document camera to show raw data • Handling on-site if the situation allows

* Heavy workload for PDF conversion

** This depends on the contract. There is a risk of loss/leaks. Raw data files temporarily provided should be returned prior to GLP compliance inspections.

I answered.

Contract testing facilities

- If an SOP for prior confirmation was provided, some facilities **converted** documents to non-printable **PDF format** and obtained a written pledge for handling documents.
- If a self-inspection method was selected for on-site study audits, the facility assumed tasks such as broadcasting the situation with a camera would be required:
  - To prevent removal of unfavorable documents
  - To prevent falsification of documents
- There was no noticeable difference between the July 2020 and October 2021 questionnaire results.

Responses from July 2020 and October 2021 are presented together

Conclusion

- Changes in the status of implementation of remote inspections from July 2020 to October 2021
  - The number of sponsors with **experience** in conducting remote inspections increased.
  - Laboratory tours have been carried out in **various ways** (through webcams, recorded videos, photos, etc.).
- Ongoing issues related to the implementation of remote inspections
  - Burden of **preparation work** on the side of contract testing facilities (PDF conversion work of raw data, etc.)
  - Telecommunications environment of both parties
  - Confidentiality, **data sharing** (temporary lending of files, sharing of PDF files, etc.)

Contents

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Change in Operation of Document based Inspection

https://www.pmda.go.jp/files/000251862.pdf

Future Document-based Inspection
(Quality and Non-clinical Studies)

(1) Change in Operation

February 2023
Office of Non-clinical and
Clinical Compliance, PMDA

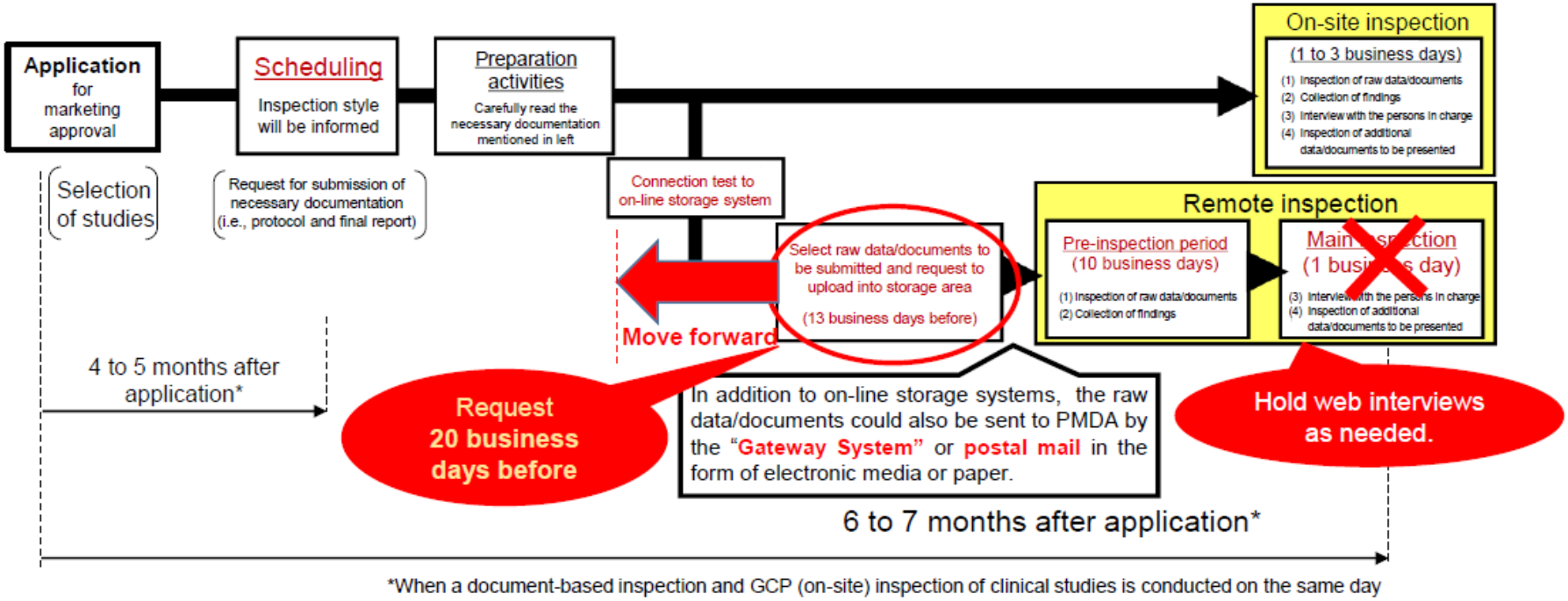
Future Document-based Inspection
(Quality and Non-clinical Studies)

(2) Points to Note
for Remote Inspection

February 2023
Office of Non-clinical and
Clinical Compliance, PMDA

New Remote Document based Inspection process

Remote Inspection Process (After)



NOTE

This change does **NOT** apply to clinical studies, only to quality and non-clinical studies.

Change in Operation of Document based Inspection

- An inspection will be conducted on an equitable basis for data/documents retained in Japan and overseas.
- An inspection style (i.e. remote/on site) will be determined by PMDA as before.
- A web interview* will be requested before the "date of inspection" as needed.

*Attendance of persons in charge of the study concerned is not essential.

How to Upload Raw Data /documents

- On line Storage systems such as Cloud systems

-The applicant shall provide the inspectors permission to (read only) access to the system.

-The following systems are not able to be used under the PMDA s network environment.

e .g.) Systems requiring application installation Systems requiring change of security settings Systems requiring file download.

There are some requirements for word search, word copying, etc.

How to Upload Raw Data /documents

- Electronic Study Data Submission System
("Gateway System")

- Others (electronic media/ paper documents sent to PMDA by postal mail)

File sharing sites such as secure file delivery systems cannot be used.

Types of raw data/documents to be submitted

- Raw data (any records directly linked to study results (such as numerical values) in the application data
- For stability studies, temperature / humidity records
- Deviation records (If applicable)
- Any documents describing QC/QA process employed
- “Description of raw data/documents”

“Description of raw data/documents”

- A list of raw data/documents submitted
- Explanation of the flow of data
- Other information useful for efficient inspection

A list of raw data/documents submitted

(Explains in detail the structure of the raw data/documents submitted)

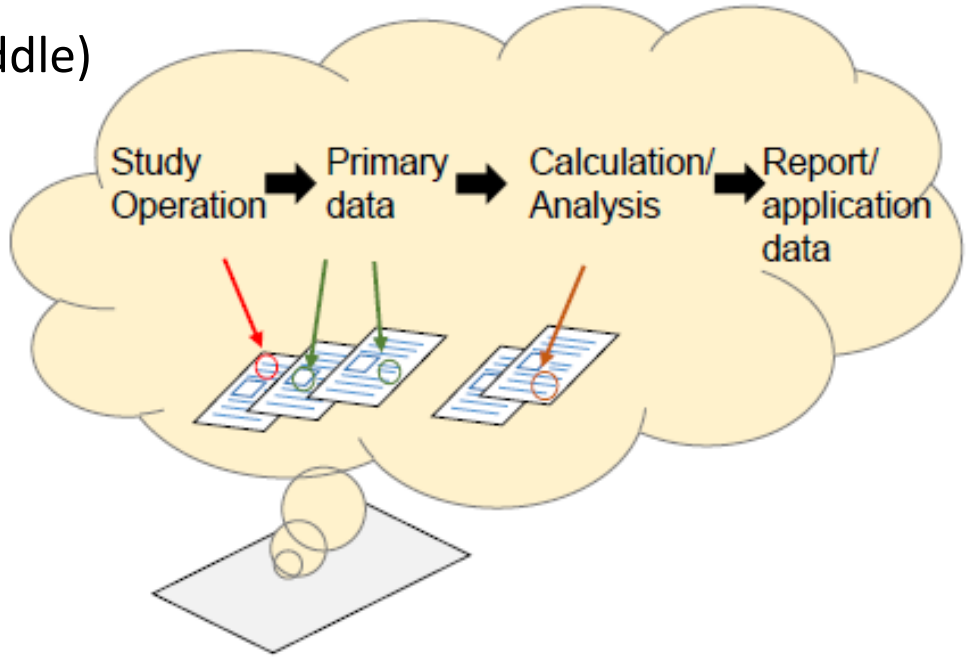
- Organize the data/documents per data/document type listed in the previous table
- Name the data/documents so that the inspectors make it possible to guess the contents

Tier 1	Tier 2	Tier 3	Tier 4	Tier 5
3.2.P.●	Lot No.XXXXX	Measurement raw data	Description	Worksheet.pdf
			Identification	Chromatogram.pdf
				Worksheet.pdf
			Assay	
			..	
		Deviation record	Not applicable	
		QC/QA procedures		
	Lot No.XXXXX	....		
		....		

Explanation of the flow of data

- Explain what part of the raw data/documents corresponds to each step from raw data/documents to the application data

eg.) measurement item “a”
Study operation (Doc A: p. 15 middle)
=> Primary data (Doc B: p. 20)
=> Calculation/Analysis (Doc C)
=> Report/application data



Other information useful for efficient inspection

eg.) If the raw data/documents were recorded in a language other than Japanese and English

-Although do NOT have to translate all of the contents, translate (in Japanese or English) enough for inspectors to be able to follow the flow of data (study items, measurement results, etc. at least.)

-Translation of specific parts of raw data/documents may be requested during the remote inspection period.

Discussion

Question

Are sponsors required to inform overseas test facilities that there is the possibility of requests for overseas test facility personnel to join the PMDA audits?

And whether sponsors will request to an overseas test facility personnel to attend PMDA audits.

Comments of the JSQA GLP division leaders

1-1.

A sponsor usually requests domestic test facility personnel to attend PMDA audits. And it is probably the same with overseas test facilities.

1-2.

Many PMDA audits don't hold web interviews, therefore it is important to request rapid replies to questionnaires given to test facilities.

1-3.

In PMDA policy for Document based Inspection, unclarified issues are generally solved in the pre-inspection period, and web interviews are held as needed, therefore preparations during the pre-inspection period are important.

Question

To reduce the risk of additional translation of the raw data/documents that were recorded in a language other than Japanese and/or English, should sponsors request overseas test facilities to write the raw data/documents in English?

And is it possible to request overseas test facilities to write the raw data/documents in English?

Comments of the JSQA GLP division leaders

2-1.

If there are documents that might need to be translated during the inspection, a sponsor should translate them to English or Japanese before the pre-inspection period.

2-2.

It is difficult to request test facilities in non-English countries to write the raw data/documents in English. However, it is possible to request them to write the report in English.

2-3.

It is possible to translate the raw data/documents to English or Japanese beforehand.

2-4.

It depends on the test facilities, but some test facilities are able write the raw data/documents in English.

2-5.

There are risks with additional translation, if the Data/documents on pharmacological tests are written in the local language.

2-6.

Preparation of unproblematic documents is effective in reducing risks associated with additional translation.

=>These are important for organizing contents of documents and preparation of "Description of raw data/documents".

Japan Society of Quality Assurance

Thank you for your attention