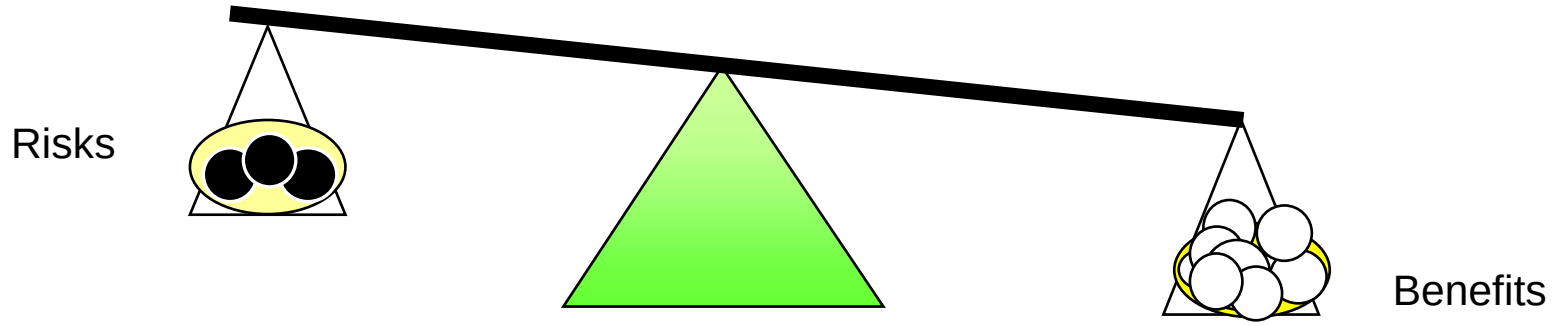
# Compliance Inspection under PMD Act

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

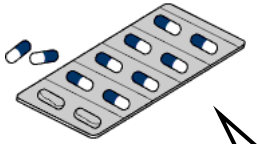
# Relationship between
# Evaluation and Reliability
## for medical products

**Based on the application data submitted, risk-benefit balance of efficacy and safety is evaluated, and then the validity of indications/performance, dosage and administration, and precautions is reviewed.**

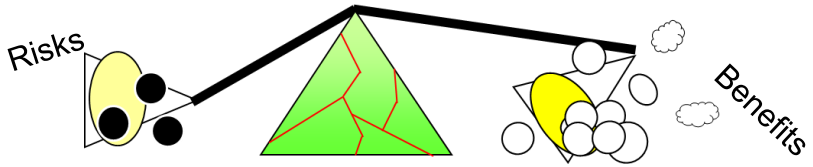


# If data is unreliable…

If correct data were not collected・・・

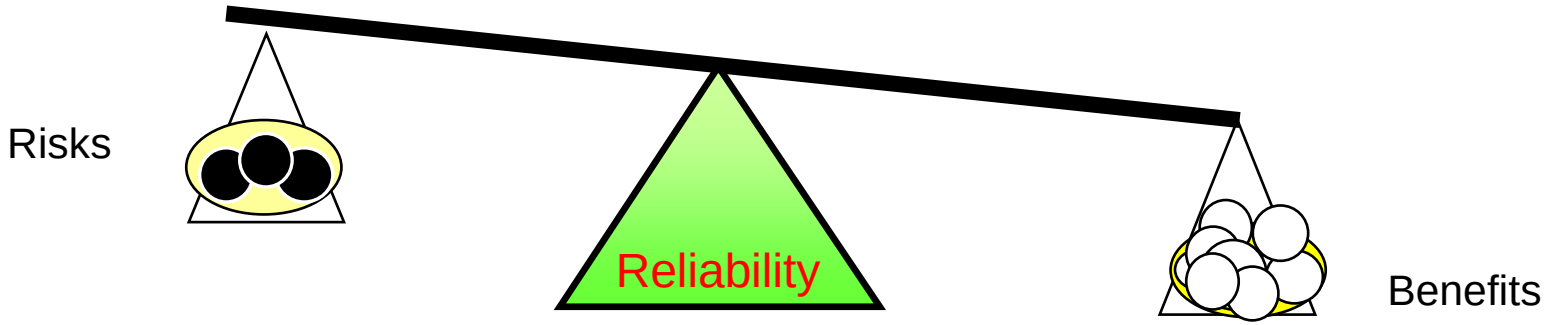
If adverse events were not collected appropriately…




**Efficacy and safety in humans cannot be evaluated!**

# Relationship between
# Evaluation and Reliability
## for medical products

**Based on the RELIABLE application data submitted, risk-benefit balance of efficacy and safety is evaluated, and then the validity of indications/performance, dosage and administration, and precautions is reviewed.**



# A Law for Securing the Reliability of Application Data (1)

**Pharmaceuticals and Medical Devices (PMD) Act*
Article 14, Paragraph 3**

The person who intends to obtain the approval referred to in Paragraph 1 above shall make an application by attaching data/documents related to the results of clinical studies and other data/documents to the application form pursuant to the provisions of the Ordinance of the Ministry of Health, Labour and Welfare（MHLW Ordinance). In this case, if the drug for the application is a drug specified by the MHLW Ordinance, the data/documents must be collected and prepared in accordance with the standards specified by the MHLW Ordinance.

* Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

# What are “other documents/data” in PMD Act Article 14 Para 3?

## Article 40 of the Enforcement Ordinance of PMD Act

The data/documents to be attached to the application form set forth in Article 38, Paragraph 1 or Article 46, Paragraph 1 pursuant to the provisions of Article 14, Paragraph 3 (…) of the Act (…) shall be the data/documents set forth in the relevant items.

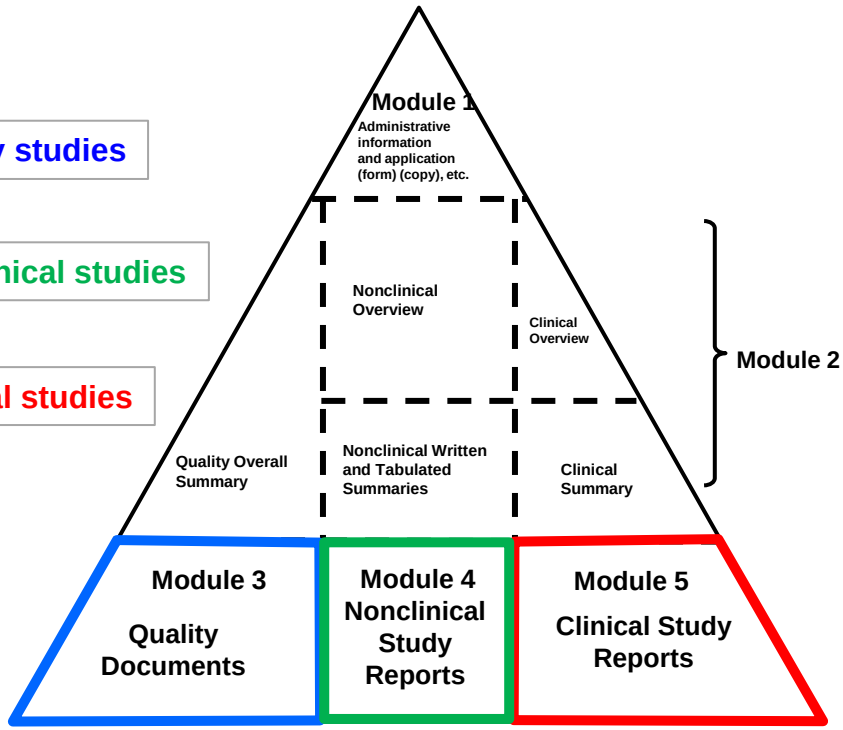
1 Data/documents for approval of drugs:

- **a.** Data/documents on origin or history of discovery and usage conditions in foreign countries, etc.
- **b.** Data/documents on manufacturing process, specification, study methods, etc.
- **c.** Data/documents on stability
- **d.** Data/documents on pharmacological action
- **e.** Data/documents on ADME
- **f.** Data/documents on acute toxicity, subacute toxicity, chronic toxicity, genotoxicity, teratogenicity and other tox
- **g.** Data/documents on study results such as clinical studies (…)

**Quality studies**

**Nonclinical studies**

**Clinical studies**




Common Technical Document (CTD) format is commonly used for application data.

# What are “Standards specified by the MHLW Ordinance”
## in PMD Act Article 14 Para 3?

- **GLP**: **G**ood **L**aboratory **P**ractice
  Standards for non-clinical safety studies

- **GCP**: **G**ood **C**linical **P**ractice
  Standards for clinical trials

- **GPSP**: **G**ood **P**ost-marketing **S**tudy **P**ractice
  Standards for post-marketing studies

The above standards are prescribed in
Article 43 (for drugs) of the Enforcement Ordinance of PMD Act

# Standards of Reliability of Application Data

Quality studies
Non-clinical studies
Clinical studies

## Article 43 of the Enforcement Ordinance of PMD Act

The data/documents as stipulated in the latter part of Article 14, Paragraph 3 of the Act (…) must be collected and prepared according to the following in addition to those specified in the Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (MHW Ordinance No. 21, 1997), the Ministerial Ordinance on Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997), and the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004).

GLP, GCP, GPSP Ordinance

1) The data/documents concerned shall be those accurately prepared based on the results obtained in studies conducted for the purpose of preparing them.

Accurate

2) If any study results that raised a question about the quality, efficacy, or safety related to the drug for the application are obtained in the study in the preceding item, the study results shall be reviewed and evaluated, and the results shall be described in the data/documents.

Complete

3) The raw data that became the basis of the data/documents concerned shall be retained until the date of disposition to the effect that approval of Article 14, Paragraph 1 or Paragraph 15 of the PMD Act is given or not given. However, this does not apply if the storage of data/documents is extremely difficult.

Retain

# A Law for Securing the Reliability of Application Data (2)

## PMD Act Article 14, Para 6 (excerpt)

In the review pursuant to the provisions of Paragraph 2, Item 3, if the product concerned is a drug specified by the MHLW Ordinance provided in the latter part of the same paragraph, a document-based or on-site inspection shall be conducted in advance to determine whether the data/documents related to the product concerned conform to the provisions in the latter part of the same paragraph.

## PMD Act Article 14-2-3, Para 1 (excerpt)

The Minister of Health, Labour and Welfare may have the PMDA conduct a review and inspection for approval of drugs, etc. specified by a cabinet order.

# A Law for Securing the Reliability of Application Data (2)

**PMD Act Article 14, Para 6 (excerpt)**
In the review pursuant to the provisions of Paragraph 2, Item 3, if the product concerned is a drug specified by the MHLW Ministerial Ordinance provided in the latter part of the same paragraph, a document-based or on-site inspection shall be conducted in advance to determine whether the data/documents related to the product concerned conform to the provisions in the latter part of the same paragraph.

**PMD Act Article 14-2-3, Para 1 (excerpt)**
The Minister of Health, Labour and Welfare may have the PMDA conduct a review and inspection for approval of drugs, etc. specified by a cabinet order.

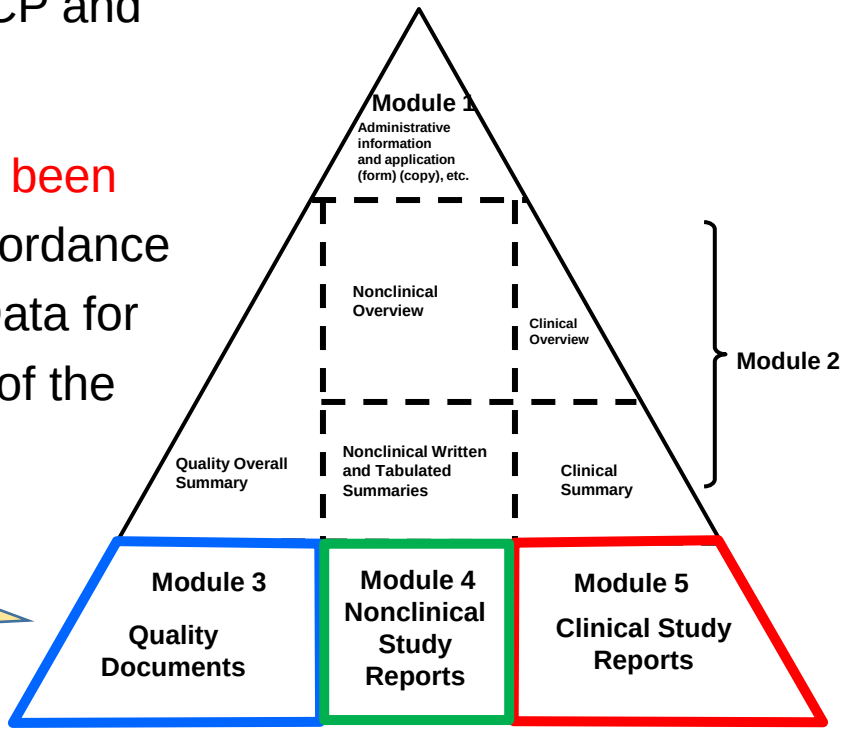
**Describe in detail in terms of "document-based or on-site inspection" specified in Article 14, Para 6 of the PMD Act.**

# What's document-based inspection?

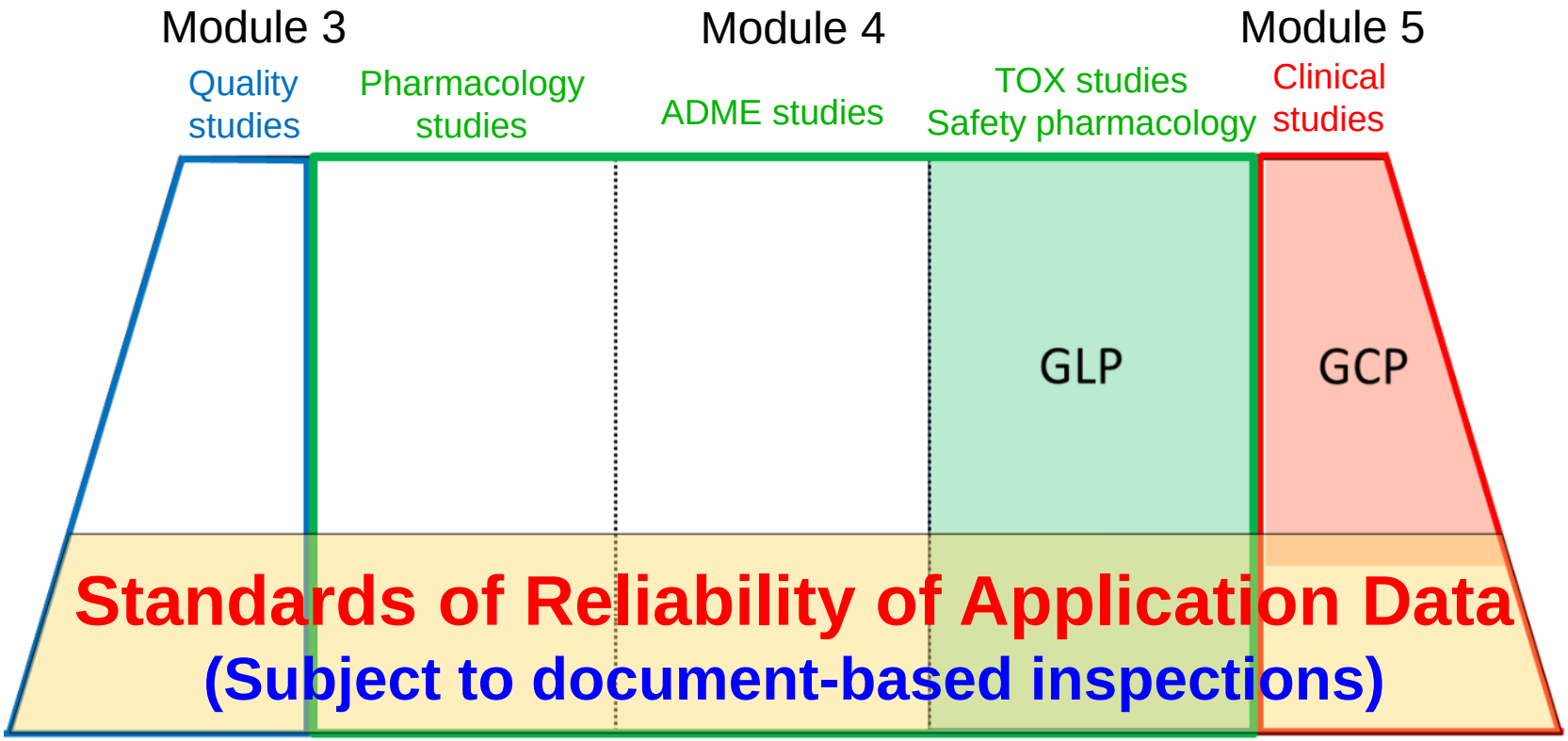
The following should be confirmed by inspecting raw data/documents for quality studies, non-clinical studies, and clinical studies in the application data.

- ✓ Studies in the application data for new drugs have been appropriately conducted in an ethical and scientific manner in accordance with GLP/GCP and the study plan/protocol.
- ✓ Data/documents in the application data have been prepared appropriately and accurately in accordance with "Standards of Reliability of Application Data for application data" prescribed in the Article 43 of the Enforcement Ordinance of PMD Act.

**CTD Modules 3 to 5 are subject to document-based inspection (Article 40, Para 1, Item 1-(b)-(g) of the Enforcement Ordinance of PMD Act).**



# Role of Standards of Reliability of Application Data




- **Unique to Japan**
- **Created as a lesson from drug-induced incidents that have occurred in Japan in the past**
- **Minimum requirements necessary to ensure the reliability of all data/documents (especially non-GxP) in application data**

# ALCOA+ vs Standards of Reliability of Application Data

## International principles for ensuring reliability

Attributable: Identification of the person performing the work

Legible: Maintaining data readability and traceability

Contemporaneous: Recording data simultaneously with the work

Original: Maintaining original format

Accurate: Creating scientifically accurate data

Complete: Ensuring all data without missing data

Consistent: Maintaining consistency throughout the data lifecycle

Enduring: Ensuring maintenance of data for the future

Available: Data can be accessed as needed

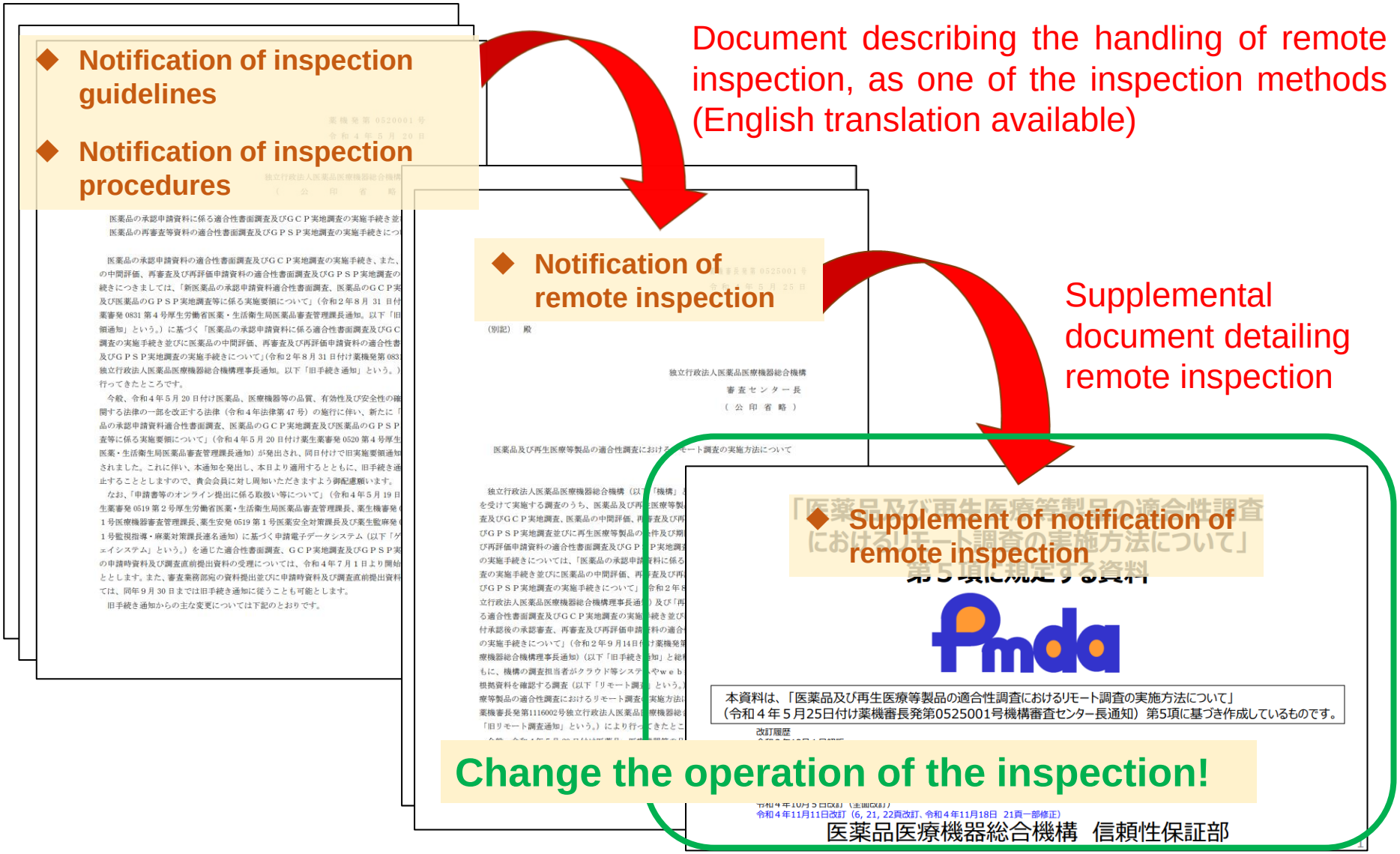
**Requirements in the Standards of Reliability of Application Data for application data are in common with internationally recognized principles!!**

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

# (1) Change in Operation

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

# Notification Series for Implementing Document-based Inspection

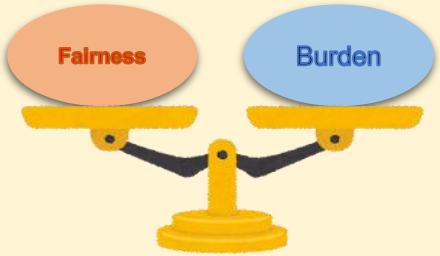


# Change in Operation of Inspection

Basic policy

- 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.
- The following actions will be taken in order to reduce burdens on both the applicant and PMDA.

**Changes in operation from the current practices**




Point 1: Remote inspection process
=>Details to be described later

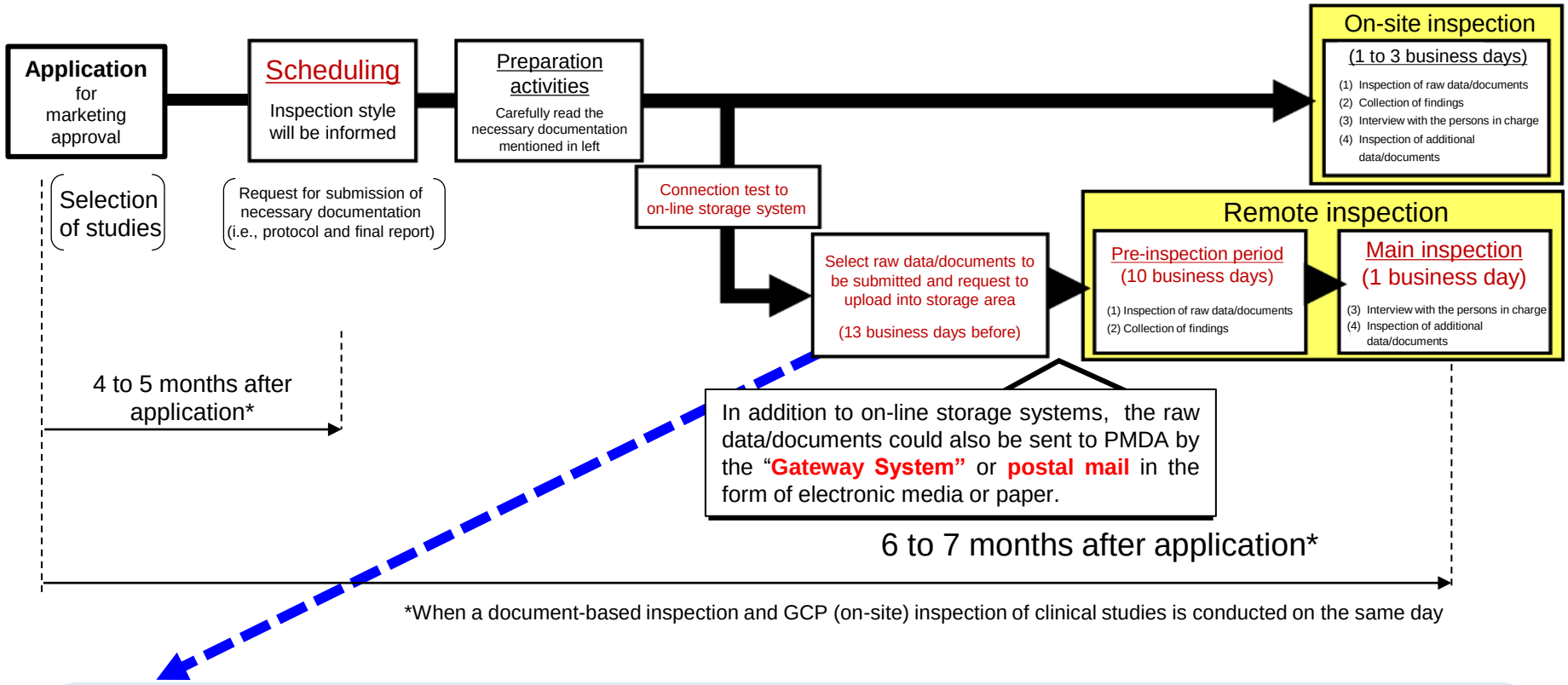
Point 2: Selection of product/selection of study
=>Selection of product subject to inspection in consideration of application category

=>Selection of study subject to inspection in consideration of importance of data

Point 3: Data/documents to be confirmed in the inspection
=>Mainly inspect raw data/documents directly linked to study results

# Point 1

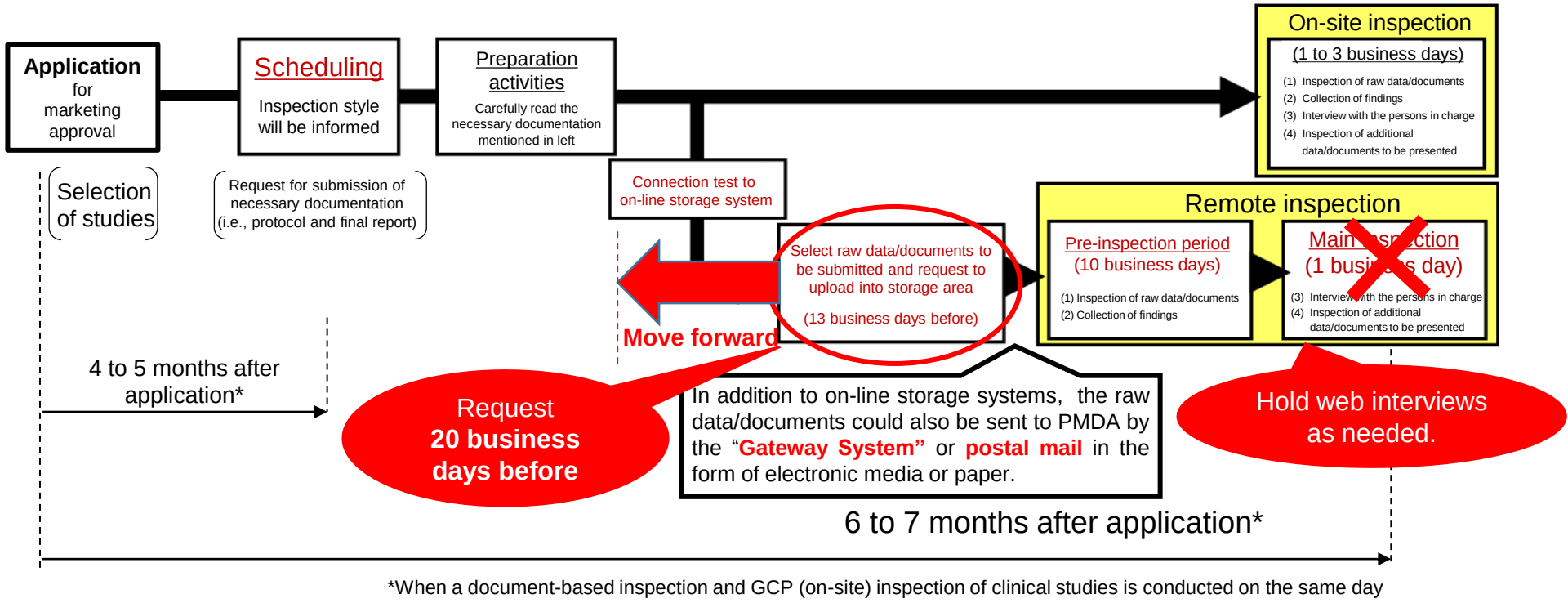
# Remote Inspection Process (Before)




The raw data/documents to be submitted will be selected (e.g., specific lot/time point(s) for quality studies) and be requested to be uploaded into on-line storage system 13 business days before the date of the main inspection.

# Point 1

## Remote Inspection Process (After)




*When a document-based inspection and GCP (on-site) inspection of clinical studies is conducted on the same day

*NOTE*

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

# Point 1

# Remote Inspection Process (Change 1)

(1) Moving forward the date of selection for raw data/documents

- It takes time to prepare raw data/documents to be submitted to PMDA for quality and non-clinical studies because 1) the raw data/documents are often retained as paper documentation at the manufacturing site or CRO, and 2) especially for quality studies, preparations cannot be made until the selection of raw data/documents to be submitted (i.e., target lots, etc.) is done.

- 20 business days before the final day of the remote inspection

  ⇒7 business days extended

- Therefore, this period is changed to 10 business days, while it was necessary to upload data/documents within 3 business days after the selection.

=> Extension of preparation period for raw data/documents selected for remote inspection

# Point 1

# Remote Inspection Process (Change 2)

## (2) Take away with the concept of “main inspection”

- The "date of inspection" written in the notification of conducting inspection used to be the day of the "main inspection" but will be interpreted as the last day of remote inspection.

- A web interview* will be requested before the "date of inspection" as needed.

=> Reduce the burden of arrangement for the “main inspection”

*Web interview

- **Assumed to be held only if issues cannot be resolved by e-mail or telephone.**
- PMDA will request the interview in many cases, but the applicant could request one.
- Attendance of persons in charge of the study concerned is not essential.
- Allowed to answer questions from PMDA after the Web interview.

*NOTE*

Taking into consideration the application category, there may be cases that are NOT required to upload any raw data/documents for remote inspection. In such cases, a web interview will be set up on the "date of inspection“, where the explanation of raw data/documents will be made by the applicant.

# Point 2
# Selection of Product/Selection of Study

## (1) Selection of products

- Taking into consideration the risks associated with the application category, determine products for which raw data/documents for remote inspection are requested to be uploaded into the on-line storage system.

=>Do not consider whether the data/documents are retained in Japan or overseas for selection.

## (2) Selection of studies

- Taking into consideration the importance of data, studies subject to inspection will be further selected and concentrated.

=>Studies to be inspected are selected on a case-by-case basis, taking into consideration the application category, dosage form, intended indication, mechanism of action, study position, study purpose, study design, etc.

# Point 3

## Data/documents to be Inspected

### (1) Presentation of supporting records

- Request to submit raw data/documents, which are directly linked to study results
- Supporting records (records of samples, test/reference items, test systems, etc.) may be requested to be submitted where necessary.

**Important**

For the preparation of remote inspections, electronic copy of raw data/documents will be generated in many cases, which will be then uploaded into on-line storage system. Even so, it is essential that the raw data/documents are retained at the time of inspection and can be presented in the inspection as before. It is the responsibility of the applicant to ensure this prior to application for marketing approval.

### (2) Preparation of “Description of raw data/documents”

- Request the preparation of “Description of raw data/documents”, which explains the structure of raw data/documents and promotes an efficient inspection.

=>Details are explained in the following slides

# Schedule

- **Operation started on April 1, 2023**

  =>The inspection with modified operation will be applied to products for which application for marketing approval is made on or after April 1, 2023*.

*The actual inspection is scheduled to be conducted in the summer of 2023 or later.

# 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

# Topics

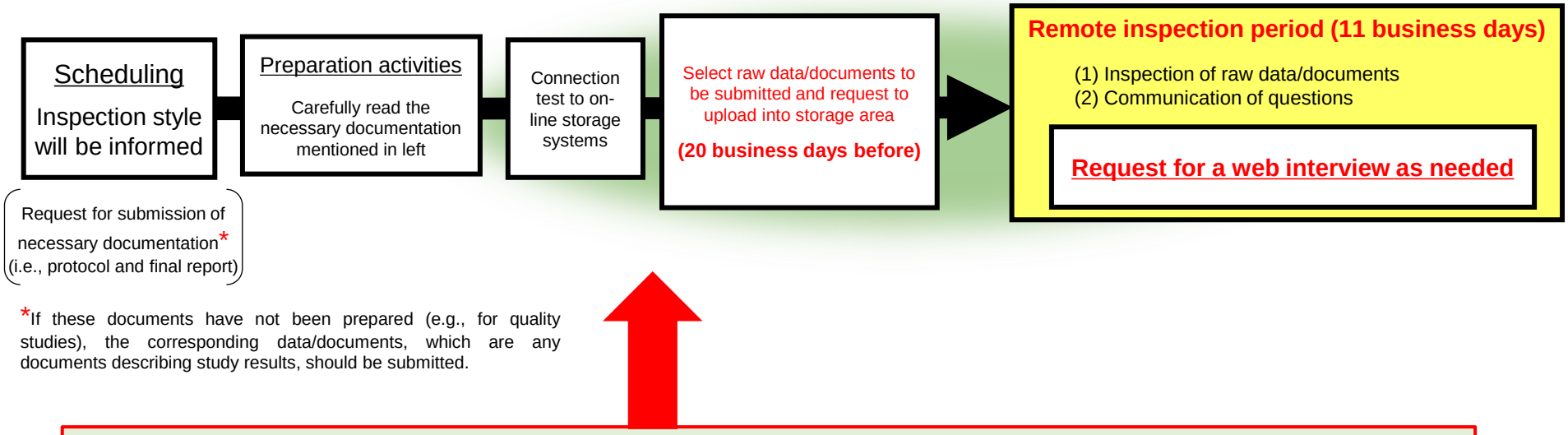
## 1. General information for remote inspection

- How to upload raw data/documents

## 2. Additional information for changes in operation

- Types of raw data/documents to be submitted
- “Description of raw data/documents”

# How to Upload Raw Data/documents




*If these documents have not been prepared (e.g., for quality studies), the corresponding data/documents, which are any documents describing study results, should be submitted.

## ● 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.
- A connection test will be performed prior to uploading the raw data/documents.

**For details, check published documents (Japanese only)!**

## ● Electronic Study Data Submission System ("Gateway System")

- For details, please check the published document

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

- Please coordinate with the inspector individually.
- File sharing sites such as secure file delivery systems cannot be used.

# Types of raw data/documents to be submitted

| Study Type | Data/documents to be submitted as default | Data/documents to be submitted as needed |
|---|---|---|
| Quality studies | • Raw data (any records directly linked to study results (such as numerical values) in the application data)<br>• For stability studies, temperature/humidity records<br>• Deviation records*<br>• Any documents describing QC/QA* process employed<br>• "Description of raw data/documents"<br>*If applicable | • Records on receipt and management of samples<br>• Records on receipt, management and quality of reference standards<br>• Records on maintenance of apparatus/equipment<br>• Other data/documents necessary for inspection |
| Nonclinical studies | • Raw data (any records directly linked to study results (such as numerical values) in the application data)<br>• Deviation record*<br>• Any documents describing QC/QA* process employed<br>• "Description of raw data/documents"<br>*If applicable | • Records on receipt, management and quality of test items (including control items)<br>• Records on receipt and management of test system (cells, animals, etc.)<br>• Records on maintenance of apparatus/equipment<br>• Other data/documents necessary for inspection |

✓ Raw data/documents to be submitted will be selected as follows. It may be further narrowed in consideration of data volume.
Quality studies: Lot number, measurement time point, etc. (could be selected by measurement items)
Non-clinical studies: All raw data/documents, but could be selected by measurement items, treatment groups, etc.

✓ Please coordinate with the inspector individually if the raw data/documents to be submitted are in a file format that cannot be read without specific software (instead, may ask presenting with a screenshot or sharing the screen at a web interview).

✓ The "Description of raw data/documents" should include (1) a list of raw data/documents submitted, (2) explanation of the flow of data, and (3) other information useful for efficient inspection (see the next slide).

# “Description of raw data/documents”

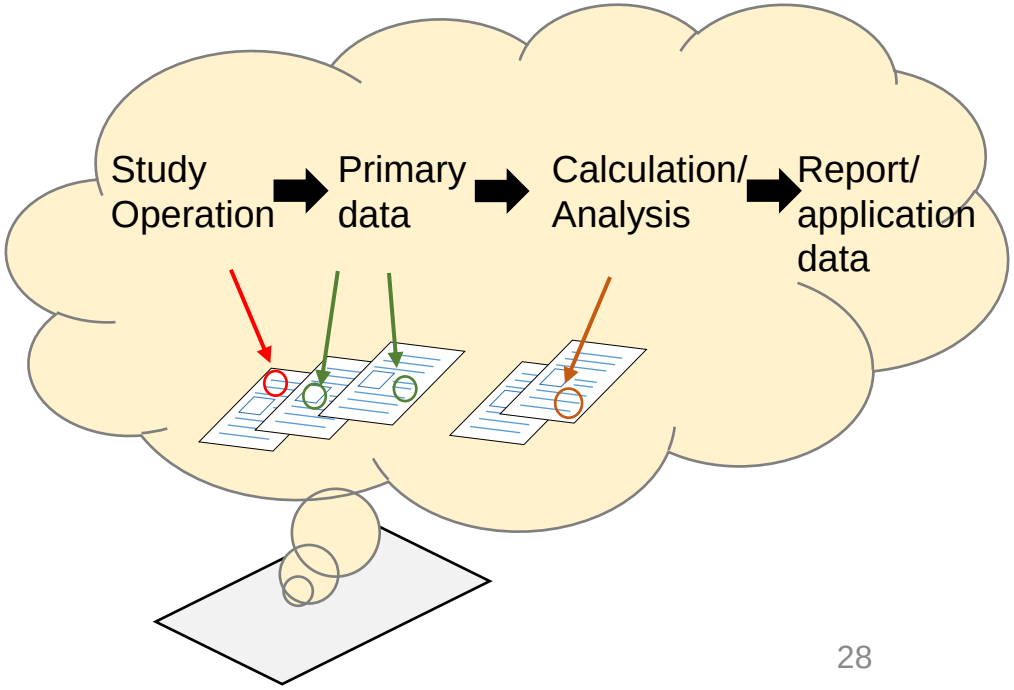
**(1) List of raw data/documents submitted**
(explains in detail the structure of the raw data/documents submitted)

- ✓ 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 | .... | | |
| | | .... | | |
| | | | | |

**(2) Explanation of data flow**

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




E.g.) measurement item “a”

Study operation (Doc A: p. 15 middle)
=> Primary data (Doc B: p. 20)
=> Calculation/Analysis (Doc C)
=> Report/application data

# “Description of raw data/documents”

(3) Other information useful for efficient inspection

e.g.) 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.

**Please submit ”Description of raw data/documents”, as it may lead to an increase in the number of questions or an extension of the inspection period if it is not submitted.**