Considerations in Guidance for Electronically Storing Non-GLP Non-Clinical Study Documents

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Background

- Recently, pharmaceutical companies have begun requiring CROs and academia contracted for non-clinical studies to digitize study-related materials, but some facilities lack the equipment and procedures for this.
- In July 2023, the PMDA, Japan's regulatory agency, notified us that it will remotely conduct investigations into non-clinical trials (including trials conducted outside of Japan) associated with NDA/BLA. For this purpose, digitization of materials is required.
- Under these circumstances, we have considered how to provide guidance to CROs and academia on the digitization of materials.

PMDA: Pharmaceuticals and Medical Devices Agency

Remote Inspection by the Japanese Regulatory Agency

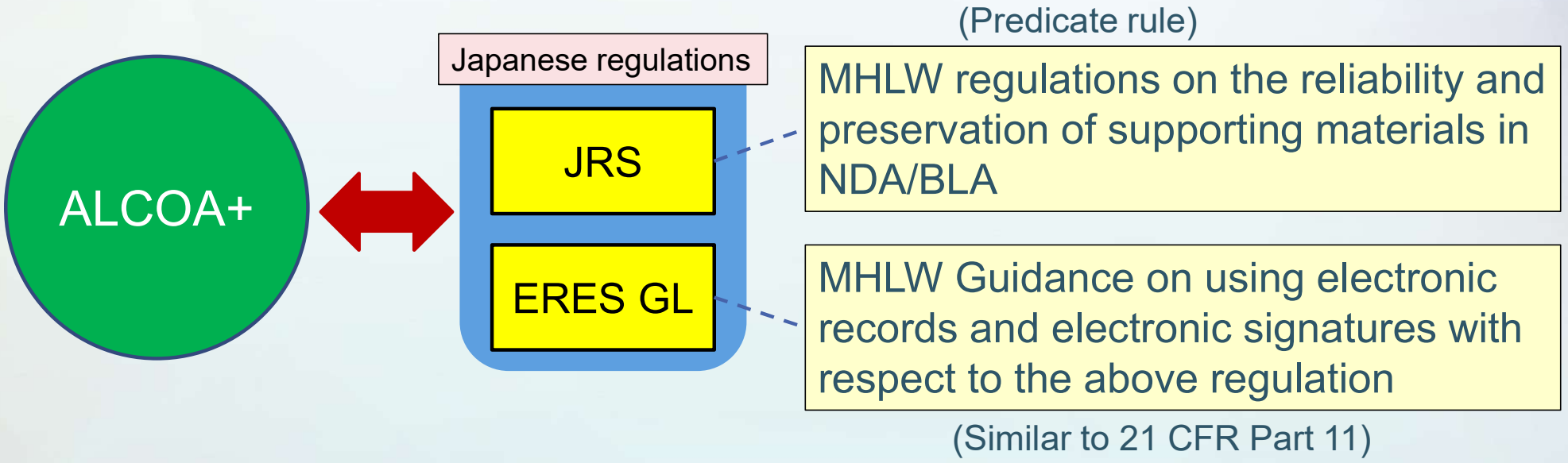
- Japanese regulations require the reliability and archiving of materials on which the NDA/BLA is based.
- PMDA remotely inspects some of these materials, including pharmacological and pharmacokinetic studies conducted inside and outside of Japan, but excluding GLP studies.

PMDA inspection

~ 2 months	~1 month	~2 weeks	
Pivotal studies (1 or 2) are selected for inspection	PMDA will specify the data/records of the selected study to inspect	Applicants should provide PMDA with the required data/records	Applicants should explain the flow of study

Regulations for Electronic Recording

Complying with Japanese regulations for supporting materials for NDA/BLA means achieving the ALCOA+ principles.



JRS: Japanese Reliability Standards in Ordinance for enforcement of Pharmaceutical and Medical Device Act
ERES GL: Electronic record/electronic signature guideline
MHLW: Ministry of Health, Labour and Welfare

Materials/Records

- Materials/Records to be Stored
- Papers or Electronic Files

Materials/Records to be Stored

- Study protocol and Amendment
- Materials that assure the quality of critical reagents such as test substances
- Materials that assure the quality of test systems, such as animals and cells
- Identification information on the equipment used and its qualification records
- Records related to experimental work, such as preparation and operation
- Data output from measuring equipment, including video/images
- Handwritten records for equipment indications or animal observations, etc.
- Analysis records
- Deviation records from the study protocol or SOPs

Papers or Electronic Files

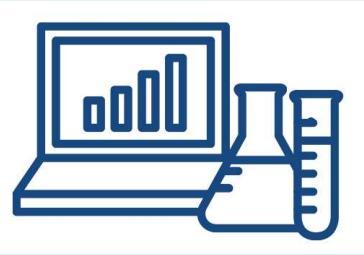
The main forms of evidence include:

Papers

- Handwritten records on paper of observations, activities, and so on
- Direct printouts of measurement results, etc. without electronic storage in equipment or devices

Electronic Files

- Electronically recorded data collected using equipment/devices
- Directly electronically entered records of observations, activities, etc.



Scanning of Papers

- Timing and Preparation for Scanning
- Scanning and Identification
- Checking the Quality of Scanned Data/Record
- Correction of Scanned Data/Record

Timing and Preparation for Scanning

- **Timing**
  - ✓ Paper records are preferably scanned as soon as possible after the experiment is completed to reduce the chance of falsification/fabrication.
- **Preparation**

  - ✓ Separate stapled paper records
  - ✓ Check for potential problems to scanning, such as creases and wrinkles
  - ✓ Check whether both sides are recorded
  - ✓ Remove any sticky notes, if applicable
  - ✓ Confirm whether there are any conditions that would cause information to be lost when scanned, such as fluorescent pens or lightly written text.
  - ✓ Record the number of pages scanned

Scanning and Identification

- **Scanning**
  - Scan and create an image file. Character recognition is not recommended due to the risk of misidentification.
  - We propose recommendation of the following scanning conditions. As needed, the resolution should be increased.

File format	Resolution	Color mode
PDF or TIFF	> 200 dpi	Black and white in principle, color as needed

- **Identification of Scanned Data/Record**
  - Assign an appropriate name to the electronic file to indicate its contents, including the study number, date, record type (preparation, measurement, etc.)
  - It is also useful to classify the files by type, such as data, records or related materials, and store them in appropriately named folders.

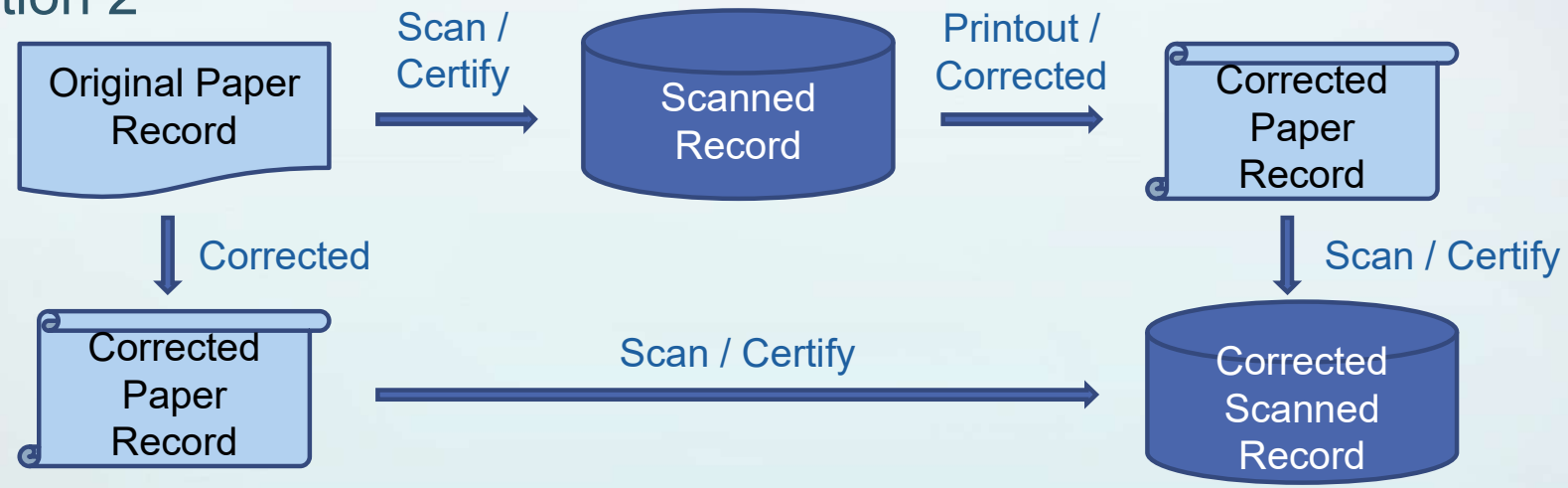
Checking the Quality of Scanned Data/Record

- **Why?** – Confirm equivalence of scanned data and the paper originals.
- **Who?** - The primary responsibility is that of the researcher who studied and scanned the data/record, but third-party confirmation is also useful.
- **What?** - Confirm equivalence based on the following criteria, rescan and reconfirm if there is a problem.
  - The scanned data must be legible, including color that has meaning.
  - Page numbers in paper records and scanned data match.
  - Records written on both sides must be scanned on both sides.
  - The file name must match the content.

Correction of Scanned Data/Record

- Scanned records can be corrected in following two ways:
  - Option 1

  - Option 2



Storage and Transfer of Materials

- Storage Location
- Storage Timing
- Storage Management
- Materials Subject to Inspection by the Regulatory Agency
- Transfer of Materials

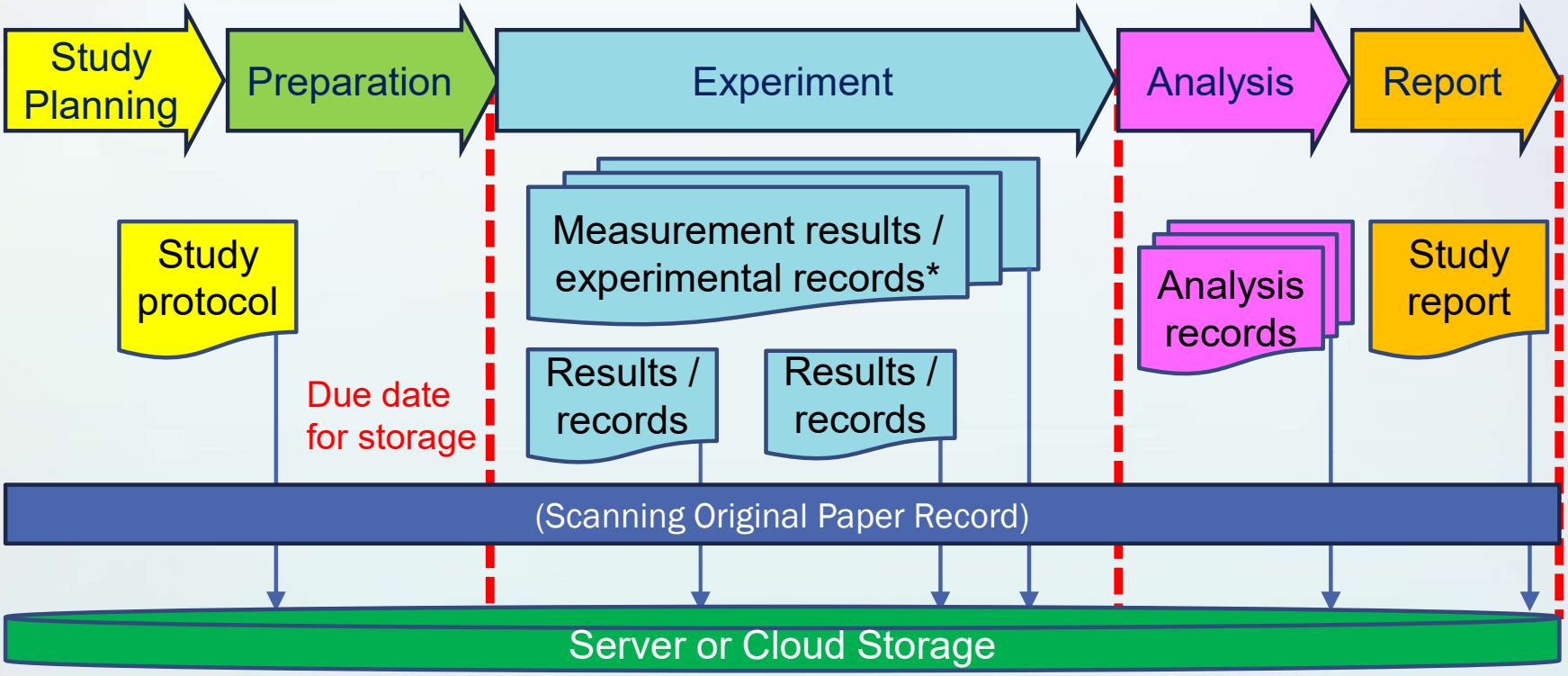
Storage Location

- CROs and academia need to prepare either in-house servers or cloud servers that meet the following requirements:
  - Have functions and procedures that limit the number of staff with access and grant permissions (editable, view-only, etc.) based on their roles.
  - Have a backup function for materials
  - Have audit trail functionality or a mechanism to complement it
  - Assess the provider's QMS, ISMS/BC and services before utilizing the cloud servers (if applicable)
- CROs and academia that are unable to meet the above requirements are recommended to promptly transfer the materials to an appropriate storage provided by the sponsor.

QMS: Quality management system
ISMS/BC: Information security management system/business continuity

Storage Timing

The timing of storing electronic files depends on the type of record.



*: To eliminate the opportunity for tampering/fabrication and to reduce the risk of accidental deletion of files, it is recommended that the files are saved promptly on the experiment date.

Storage Management

- The electronic files obtained from the measuring equipment should be stored intact in a readable condition.
- A list of electronic files is useful.
  - Agreement between sponsors and contractors on materials to be stored
  - Checking by archivist and (if possible) certification by QA that the materials have been stored as listed
- When changes are made to documents stored on internal or cloud servers, the ability to view the before and after changes is needed.
- Access logs for detecting unauthorized access and event logs for detecting falsification and other unauthorized operations are required.
  - If it is difficult to record electronically, it is also possible to keep a paper-based record of the operations and sign it.

Materials Subject to Inspection by the Regulatory Agency

- Documents should be properly stored for the period until inspection by the regulatory agency.
  - Paper original materials
    - Should be digitized and stored at CROs/academia or sponsors based on contract.
    - It is recommended that a certificate be prepared indicating that the digitized materials are equivalent to the original materials. The certificate could be created for a study rather than for each individual document.
  - Electronic original materials
    - Could be stored at CROs/academia or sponsors based on contract.

Transfer of Materials

- Consider prompt transferring materials stored in CROs or academia repositories to appropriate storage provided by the sponsor.
  - Transfer procedures should be documented and properly implemented.
  - It should be stated in the contract that electronic files with ensured reliability will be transferred.
  - A certificate stating that certified copies of all materials have been transferred should be attached at the time of transfer.

Conclusion

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Electronically handling the data and study-related materials/records supporting the NDA/BLA documents:

- Provides certainly that the data/materials/records are stored in appropriate locations
- Is useful in the case of reanalysis of the data
- Facilitates transfer the data/materials/records to the sponsor
- Is useful in dealing with remote inspections by PMDA