Guidance on Ensuring the Reliability of Non-Clinical Pharmacological Studies Conducted in Academia

Group 2 of the Fifth Subcommittee, GLP Division, Japanese Society of Quality Assurance

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1 Introduction

This Guidance was prepared to contribute to ensuring the reliability of non-clinical pharmacological studies conducted in Academia as materials to approve New Drug Applications.

Collaboration with Academia, which has advanced and specialized technologies, is increasingly important for pharmaceutical companies in response to unmet medical needs and in diversifying modalities. Furthermore, considering that the implementation system of the study in Academia differs at facilities, currently it is not easy for Academia to conduct pharmacological study for regulatory submission using guidelines, etc. prepared for the same purpose in the past.

Considering these situations, Group 2 of the Fifth Committee, GLP Division, the Japan Society of Quality Assurance (JSQA) newly prepared "Guidance on Ensuring the Reliability of Non-clinical Pharmacological Studies Conducted in Academia" based on existing guidelines with cooperation of liaison members who participated from Japan Pharmaceutical Manufacturers Association (JPMA).

As mentioned in this document, timely and appropriate communication between Academia and relevant personnel from the Sponsor is essential to ensure the reliability of the study. At the same time, it is important to devise ways to avoid placing excessive burdens on both parties.

1-1 Explanation of the Terms used in this Guidance

- Academia: research facilities such as universities and medical institutions
- Sponsor: a pharmaceutical company which consign a non-clinical study to Academia
- Sponsor's Representative: a person in charge of the consignment such as pharmaceutical companies
- Study Director: a researcher of the Academia responsible for a consignment study
- Study Personnel: staff and students of Academia in charge of practical work of the study
- Reliability Standard: "The Standards of Reliability of Application Data", Article 43 of the Enforcement Ordinance of the Pharmaceuticals and Medical Devices Act
- Study Records and Materials: study-related documentation (such as study protocol, raw data, final report, and electronic files) and physical items (such as test articles, specimens, and samples) associated with the study

1-2 Considerations

This guidance has been prepared based on examples of non-clinical pharmacological studies commissioned for pharmaceutical products. When applying this guidance to studies involving medical devices, regenerative medicine products, or collaborative research, the content of this guidance should be adapted and interpreted as appropriate.

2 Purpose

This guidance aims to contribute to ensuring the reliability of non-clinical pharmacodynamics and pharmacological studies conducted in Academia, which are used as supporting documents attached to New Drug Applications (hereinafter referred to as "regulatory submission documents").

3 Contracted Study Flow

The flow of contracted study is shown in Figure 1. It is for illustrative purposes only and may vary depending on Academia, Sponsor, and specific study methods.

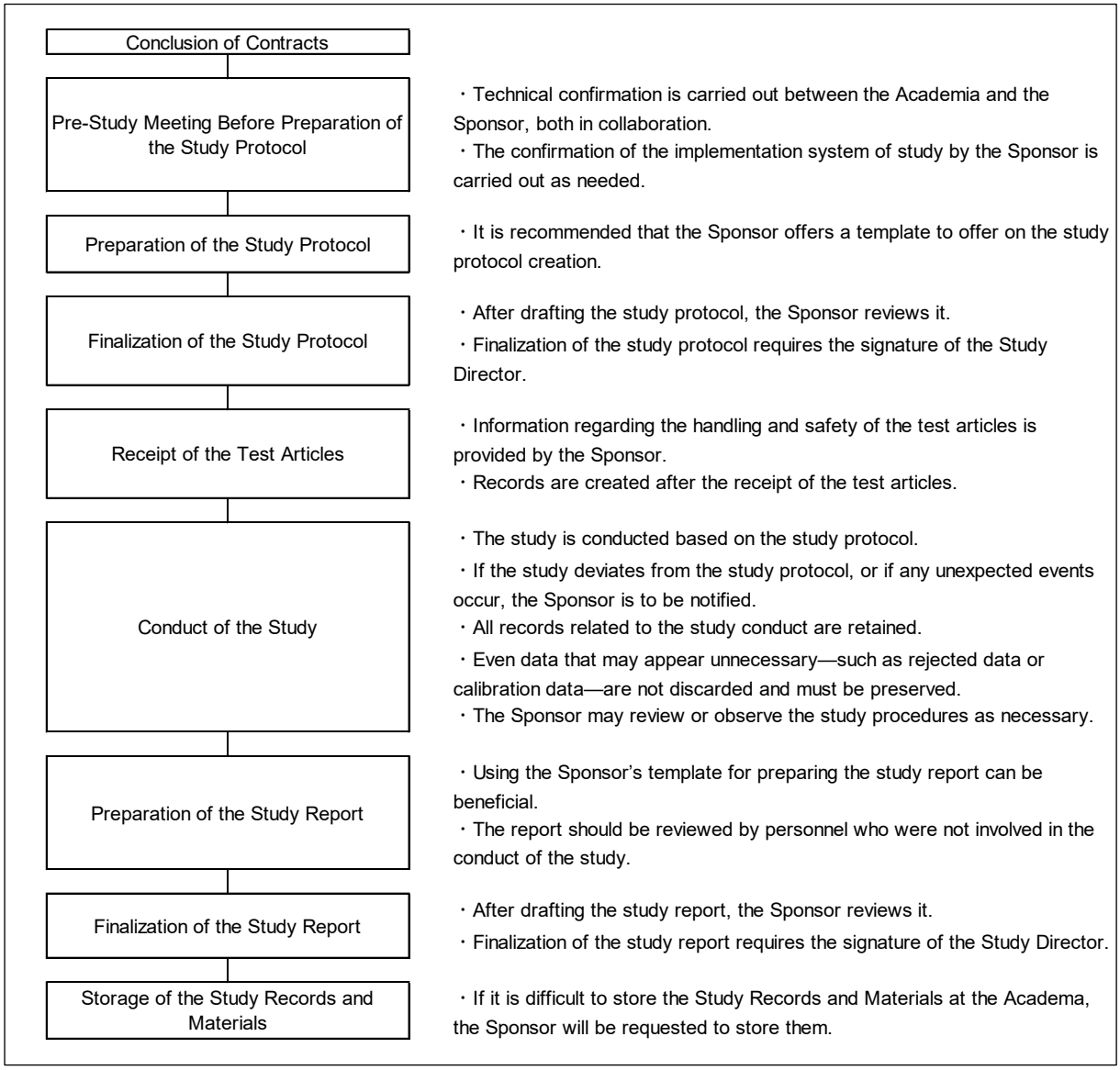

Figure 1. Example Flow of Contracted Study

4 Conclusion of Contracts

Before starting the study, it is necessary to conclude the contract. First, before concluding the contract for commissioned study, a confidentiality agreement should be concluded to prevent information leakage because confidential information will be disclosed between the Academia and the Sponsor during discussions about the study content.

Next, it is important to conclude the contract for commissioned study and other related documents to clarify the relationship (rights and obligations) between the Academia and the Sponsor.

Items to be included in the contract may vary depending on the Academia, the Sponsor and the study itself. This section lists items that are considered desirable to be included in the contract and other related documents. Items not included in the contract and other related documents should be considered for inclusion in other documents, such as study protocol, which will be described later.

Following items should be included in the contract and other related documents when accepting a study. All these items should be clearly defined and agreed upon by both the Academia and the Sponsor.

1) Information that can identify study title and content of the study
2) The Study Director and the Study Personnel
3) Provision of necessary information for the study by the Sponsor (e.g., handling of test articles)
4) Explanations and reports to third parties, such as document-based inspection
5) Methods for the Sponsor to verify the reliability of the study and related records
6) Responses to unexpected or unforeseen circumstances (hereinafter referred to as "unexpected events")
7) Review of records by the Academia
8) Storage period and location of Study Records and Materials
9) Ownership of intellectual property rights related to study content and results
10) Outsourcing of tasks related to the study
11) Prohibition of unauthorized use of test articles
12) Publication of study results
13) Compliance with laws and regulations

4-1 Key Points

1) Conclusion of the contract before initiation of the study
2) Prior consultation regarding items to be included in the contract

4-2 Supplementary Notes

1) Conclusion of the contract before initiation of the study
   - Since this is contracted study, it is necessary to conclude the contract before initiation of the study.
2) Prior consultation regarding items to be included in the contract
   - The contract should include the preparation of the study protocol and the conduct of the study in accordance with it. The study protocol will be used as part of regulatory submission documents.
   - The Sponsor should provide information on test articles and other necessary details for conducting the study. Additionally, matters related to the management, return and disposal of test articles and related substances should be included in the contract as necessary.
   - The contract should include provisions regarding communication in the event of unexpected events or deviations/changes from the study protocol.
   - The contract should include agreements regarding the publication of study results in academic conferences or journals, and cooperation with the Sponsor in responding to document-based inspection by regulatory authorities after approval application.

- If necessary, the contract should state that the Sponsor may verify the test facility, test procedures, raw data and other related records.
- The contract should state that the Academia is required to conduct self-inspections of records.
- The contract should specify in detail the handling procedures for Study Records and Materials to be stored, including matters related to their return to the Sponsor. In cases where the Study Records and Materials are stored at academic institution, the contract should also specify storage period for Study Records and Materials and handling procedures after expiration of storage period.
- Other agreements
  - Approval by the Sponsor when commissioned study is subcontracted to another facility
  - Ownership of intellectual property rights related to study content and results
  - Handling of costs and other matters in the event study is discontinued due to the Sponsor's circumstances

5 Pre-Study Meeting Before Preparation of the Study Protocol

To prepare the study protocol, it is necessary for the Academia and the Sponsor to confirm each other's methods and equipment used, verify the study methods and contents, and work on identifying and resolving issues in advance.

In addition, matters to be included in the study protocol, matters not included but requiring mutual understanding for conducting the study, and records of study conduct shall also be discussed and confirmed.

5-1 Key Points

1) Information sharing between the Academia and the Sponsor
2) Discussion and confirmation regarding study records (use of record forms prepared by the Sponsor is recommended)

5-2 Supplementary Notes

1) Information sharing between the Academia and the Sponsor
   - To prepare the study protocol, both the Academia and the Sponsor verify their respective methods and equipment and confirm that methods and equipment necessary for conducting the study are available.
2) Discussion and confirmation regarding study records
   - To ensure that results of the study conducted based on the study protocol are fully and accurately reported in the study report, the reliability of the study records is required.
   - It is important that records of study conduct (laboratory notebooks, worksheets, etc.) are promptly recorded with unalterable writing instruments* including date and time of conduct, personnel involved, and methods used. Records transcribed later, written after the fact, or recopied may be altered unintentionally through transcription errors or memory lapses, compromising reliability. Therefore, records that cannot be kept promptly are not acceptable as official records.

* : Specifically, a standard ballpoint pen is intended. Pencils or pens with erasable ink such as friction-based ink pens are considered alterable writing instruments and are not permitted.

- Records related to use and storage of test articles, preparation of reagents, and use of equipment must be agreed upon in advance with the Sponsor regarding what should be recorded. Since these records are subject to inspection for the New Drug Applications, use of templates provided by the Sponsor is recommended. If record forms prepared by the Academia are used, prior confirmation by the Sponsor is required.

6 Preparation of the Study Protocol

An ethically and scientifically appropriate study protocol is essential to ensure the quality and integrity of study results. To ensure the scientific validity of the study protocol and prevent arbitrary changes, the study protocol must be prepared before study initiation, clearly defining study outline.

6-1 Key Points

1） Confirmation before preparation of the study protocol
2） Format of the study protocol
3） Agreement between the Sponsor and the Academia regarding the study protocol
4） Changes to the study protocol
5） Precautions during preparation of the study protocol

6-2 Supplementary Notes

1） Confirmation before preparation of the study protocol
   - The Study Director must be clearly designated prior to the study. The Study Director shall have comprehensive responsibility for understanding study content, interpretation and analysis (evaluation) of results, as well as records and the study report.
   - The Study Personnel must have received training on research integrity and research ethics; education on Reliability Standard is desirable.
   - The schedule for study report preparation must be confirmed.
   - Items requiring sharing between the Sponsor and the Academia (e.g., transfer of test articles, details of experimental procedures, specific contact methods in abnormal situations, examples of unforeseen circumstances) should be discussed and documented as much as possible for mutual understanding.

2） Format of the study protocol
   - The study protocol shall be prepared as a document independent from raw data such as laboratory notebooks prior to study initiation. Use of templates provided by the Sponsor, similarly to record forms, is recommended.
   - Examples of items to be included in the study protocol
     - Study title and study number

- Study objective
- Study start date and scheduled study completion date
- Information on test articles and specimens
- Information regarding use of test systems (animals, cells, microorganisms, biological samples)
- Information regarding reagents used
- Information regarding equipment used
- Study conduct methods
- Procedures for data processing and analysis
- Criteria for evaluation (if applicable)
- Details on re-measurement implementation (if applicable)
- Signature and date of the Study Director
- Applicable guidelines (if applicable)
- Facility name and location of the Academia conducting the study
- Sponsor's name, address, and contact information
- Sponsor's Representative
- Procedures for the test article transfer
- Procedures for handling changes to the study protocol and unexpected events
- Scheduled date for submission of the study report to the Sponsor
- Matters related to storage of Study Records and Materials
- References (if applicable)

3) Agreement between the Sponsor and the Academia regarding the study protocol
   - A prepared study protocol requires agreement by both the Study Director and the Sponsor.
   - After agreement, the Study Director shall sign the study protocol and keep it properly for the defined retention period.

4) Changes to the study protocol
   - Procedures for handling study protocol changes shall be agreed upon between both parties prior to study initiation.
   - Possible differences in understanding about what constitutes a change shall be discussed and agreed upon by the Academia and the Sponsor with reference to anticipated examples.
   - When changes become necessary due to reasons of the Sponsor, the Sponsor's Representative shall consult with the Study Director and request the study protocol amendments.
   - When changes become necessary due to reasons of the Academia, the Study Director shall promptly consult with the Sponsor's Representative and obtain approval. In emergencies requiring immediate action, changes may be made at the discretion of the Study Director without prior notification, but the Sponsor shall be informed and approval obtained as soon as possible afterward.
   - When changes become necessary during the study conduct, the rationale and background for changes shall be recorded in laboratory notebooks, worksheets, or study records. Preparation of a

formal study protocol amendment document is not always required. However, confirmation by the Study Director (signature and date) is necessary.

5) Precautions during preparation of the study protocol

- Failure to perform prior amendment procedures, or delays in communicating amendments causing untimely implementation, shall be considered as non-compliance with the study protocol. In such cases, reasons and justifications for deviations shall be clearly documented in the study report.

7 Handling of Test Articles

Improper handling of test articles, control items, and reference items (Hereinafter, test article, etc.) may have a significant impact on study results. Therefore, be sure to obtain information on handling of test articles, etc. from the Sponsor. In addition, keep a record of their use from time of receipt to time of return to show that they were used properly, including that they were not used for other purposes.

7-1 Key Points

1) Sharing information on test articles, etc.
2) Receipt of test articles, etc.
3) Storage of test articles, etc. (including transportation)
4) Weighing and preparation of test articles, etc.
5) Return of test articles, etc.

7-2 Supplementary Notes

1) Sharing of information on test articles, etc.

- Be sure to receive information on test articles from the Sponsor. Specific information includes information on handling (including safety) and quality (stability, etc.).
- To prevent problems such as shortage of test article during the study, provide the Sponsor with basis for calculating amount of test articles required from the Academia.

2) Receipt of test articles, etc.

- When receiving test articles, confirm that there are no mistakes in information such as names and amounts of test articles, and batch numbers contained in shipping document. Also, confirm that there is no damage to container and that there is no deterioration due to temperature, humidity, light, etc. during transportation, and record this.

3) Storage of test articles, etc. (including transportation)

- Temperature control is important to ensure the quality of test articles. The Study Director should confirm in advance with the Sponsor how to record temperatures during transportation and storage of test articles. For temperature control during transportation and storage, confirm with the Sponsor how to record temperature so that there are no deficiencies. For recording temperature control, it is recommended to use recording paper provided by the Sponsor as well as recording paper for test operation. In addition, since the Sponsor usually lends a calibrated data logger for temperature

control, use it appropriately. If test articles are hygroscopic, store them in a desiccator where humidity can be controlled appropriately.

- For proper management, store test articles so that deterioration, mix-ups, and contamination do not occur.

4) Weighing and preparation of test articles, etc.

- It is recommended to use a record form prepared by the Sponsor (Reference Figure 2) to record weighing and preparation of test articles.
- The Study Director should receive specific information on the preparation method of the test articles from the Sponsor.

5) Return of test articles, etc.

- In principle, test articles should be returned to the Sponsor.
- In principle, the Sponsor collects preparation solution. If the Academia disposes of preparation solution, the Sponsor should provide information on specific disposal method (including information on the environmental impact).

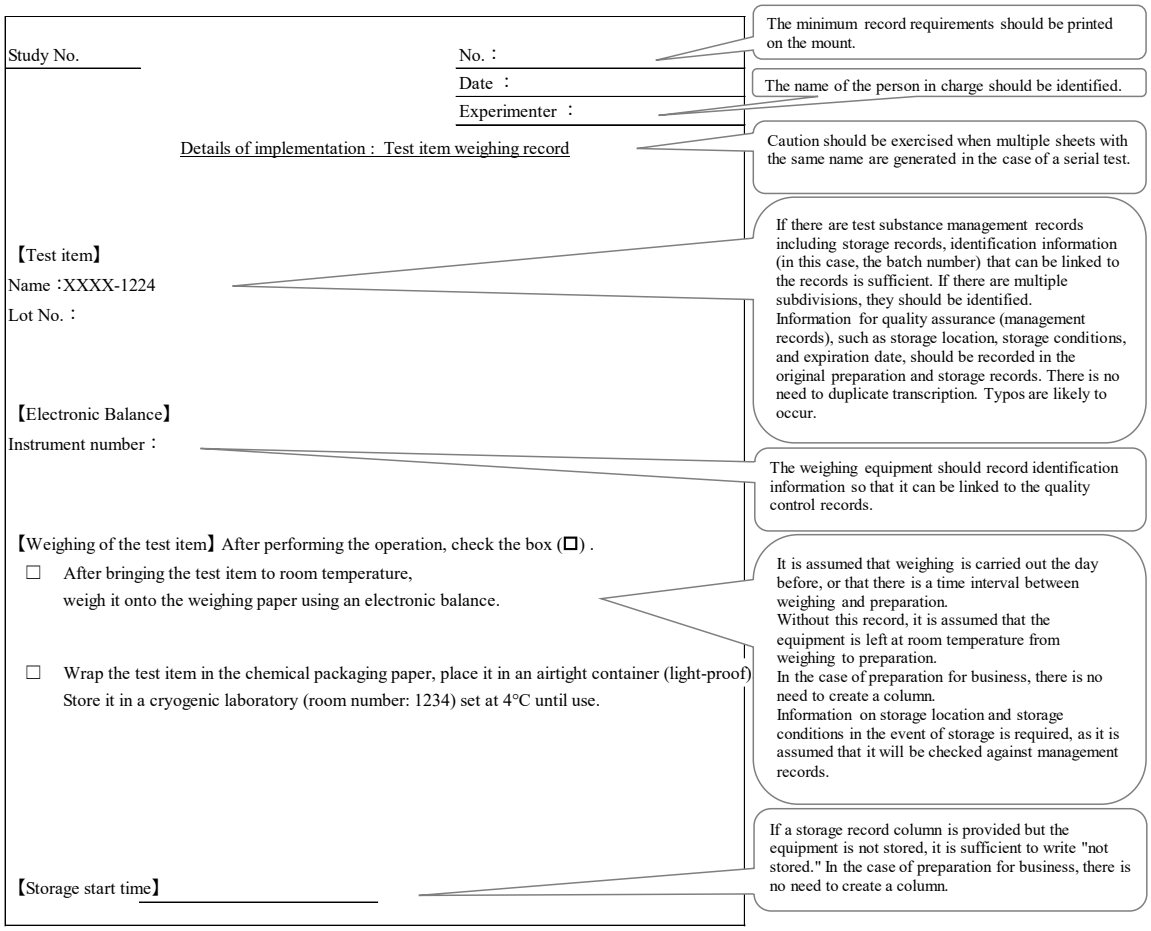

Figure 2. Test articles weighing record (example)

8 Handling of Reagents

As with test articles, quality deterioration or improper handling of reagents (including serum etc.) may affect test results. Therefore, consult with the Sponsor to determine which reagents require storage and use records.

8-1 Key points

1) Determining which reagents require storage and use records
2) Implementation of appropriate management of all reagents from acquisition to storage and use
3) Preparation of records on acquisition, storage, and use of reagents

8-2 Supplementary Information

1) Determining which reagents require storage and use records
   - The reagents for which records are to be prepared should be determined in advance in consultation with the Sponsor.
2) Implementation of appropriate management of all reagents from acquisition to storage and use
   - The reagents should be managed in an environment that maintains quality (appropriate temperature and humidity, light shielding, etc.).
   - The reagents should be used within expiration date indicated on container/package.
   - The handling of reagents without expiration date should be determined in consultation with the Sponsor.
3) Preparation of records on acquisition, storage, and use of reagents
   - As with test articles, it is recommended to use record form (Reference Figures 3 and 4) provided by the Sponsor to record storage and preparation of reagents.
   - Storage method, storage location, and expiration date and other details for reagent should be recorded on record sheet.
   - When solution is prepared, preparation details should be recorded.
   - There is no need to manage use of reagents if there is a record of use on worksheet.
   - Since quality of reagents may vary by manufacturer and product lot, be sure to record manufacturer and product lot number for the reagents that need to be recorded.

Reagent Storage and Usage Record

Reagent Name	●●●●	Manufacturer	××××	Lot No.	△△△△
Storage Location	Medication Storage Room Refrigerator No.2	Storage Conditions	Refrigerated Storage	Person in Charge	○○ ○○

Date	Abstract	Initial quantity	Usage quantity	Remaining quantity	User
20XX/3/10					
20XX/3/19					

Figure 3. Storage and use record sheets (example)

Study No.

No.：
Date ：
Experimenter ：

Details of implementation： Preparation of solution A

Name of preparation：solution A

Method of preparation Weigh the required amount of the following reagents, dissolve in Milli-Q water, and scalpel up with Milli-Q water.

●●		Lot No.	△△△△
		Catalog Number	◇◇◇◇
Molecular weight	238	Company name	××××

Amount collected
Electronic balance ABC123 (g)
2.38 ☐

Milli-Q water

Graduated cylinder
Make the total volume 100 mL. ☐

Storage Method：Refrigerate after preparation
Storage location：Medical refrigerator ### (4°C setting), room number ###
Expiration date：○○○○

First, by listing the information on the experimental materials, it will be easy to check the contents of the report and make a record that is easy to read.

In the case of :
When the materials are weighed on the previous day.
When some time is allowed for preparation after weighing.

Without this record, it is regarded as that the materials was left at room temperature from weigt to preparation. If the materials are not stored, no column is required.

Figure 4. Reagent preparation record (example)

9 Management of Test Systems (Cells, Microorganisms, Biological Samples, Animals)

From the viewpoint of ensuring the reliability of the study, the test systems must be used with animals such as cells, microorganisms, and biological samples that have appropriate characteristics and quality for the purpose of the study. When handling the test systems, care must be taken to prevent mix-ups, contamination, and deterioration.

For each test system to be used, conduct of the study in accordance with guidelines and regulations listed below.

- For cells, microorganisms, and biological samples
  - Biorisk management for handling microorganisms in microbiological tests
  - Ethical guidelines for life science and medical research involving humans
  - Cartagena Protocol on Biosafety, etc.
- In the case of animals
  - Act on the Welfare and Management of Animals
  - Basic Guidelines for the Conduct of Animal Experiments in Research Institutions, etc. (Ministry of Education, Culture, Sports, Science and Technology Notification No. 71)
  - Basic Guidelines for the Conduct of Animal Experiments, etc., by Implementing Institutions Under the Jurisdiction of the Ministry of Health, Labour and Welfare (the Ministry of Health, Labour and Welfare Guidelines for Evaluation of Scientific Research and Development No. 0220-1)
  - Standards, etc., for the Care and Storage of Laboratory Animals and the Mitigation of Pain

9-1 Key Points

1) Use of cells, microorganisms, biological samples, and other animals with appropriate characteristics and quality for test purposes
2) Prevention of mix-ups, contamination, and deterioration of cells, microorganisms, biological samples, and animals
3) Quality confirmation and records of control and use

9-2 Supplementary Information

1) Use of cells, microorganisms, biological samples, and other animals with appropriate characteristics and quality for test purposes
   - For each cell, microorganism, biological sample, and animal, it is necessary to obtain the characteristic information* necessary for conducting the study, and to be able to confirm the "Correct use of animals, including cells, microorganisms, and biological samples of appropriate quality."

     *: Information supporting the scientific validity of the test system for the test purpose (obtained from literature, books, etc.)
   - It is necessary to be able to confirm "Correct use of animals, including cells, microorganisms, and biological samples of appropriate quality."
     - Confirmation of characteristics and quality at the time of acquisition
       - ✧ For cells, microorganisms, and biological samples, it is necessary to confirm the condition at the time of arrival in addition to the assurance of characteristics and biological activity (quality) by the manufacturer.

- ✧ For animals, it is necessary to receive them from an appropriate breeder and to inspect them at the test facility. If more animals are received than the number ordered, they are not included in the study protocol and should not be used for the study.

➢ For genetically modified animals and genetically modified cells, microorganisms, and biological samples constructed in the patient's own tissue, it is necessary to collect literature information and obtain basic data in advance in addition to confirming the characteristics and quality (e.g., comparing Ki values of typical inhibitors of an enzyme with literature values to demonstrate the scientific validity of the test system).

➢ When using cells of human origin, it is necessary to obtain informed consent from the cell donor and to obtain approval from the ethics committee.

2） Prevention of mix-ups, contamination, and deterioration of cells, microorganisms, biological samples, and animals

- For cells, microorganisms, and biological samples, misidentification must be prevented through labeling and other measures. These materials must be stored appropriately in temperature-controlled freezers or refrigerators with contamination prevention measures in place. Additionally, to ensure their quality, a scientifically justified expiration date must be set, and the proper functioning of the study must be demonstrated, for example, by the use of positive controls.
- For animals, from arrival to the end of the study (euthanasia), they must be housed, dosed, and measured in an appropriate environment without error. Each individual animal must be identifiable through marking or other means, allowing for continuous verification throughout the study.

3） Quality confirmation and records of control and use

- The records must include information to confirm that the cells, microorganisms, and biological samples for which characteristics and quality can be confirmed were obtained appropriately, and that they were raised, stored, used, and disposed of correctly. Use the record forms provided by the Sponsor is recommended because these forms are subject to the reliability assessment in the approval review of new drugs.

➢ Cells, Microorganisms, and Biological Samples

- Records of acquisition and quality confirmation
  - ✧ The records to ensure characteristics and biological activity (quality) by the supplier
  - ✧ The records to confirm the condition at the time of acquisition
  - ✧ When passage records from acquisition and establishment of cell lines, etc. are not available, passage records after thawing and the data to ensure the function of cells to confirm the quality of the test system used in the study
  - ✧ In the case of biological samples, background information of the animal/patient from whom the biological sample was collected
  - ✧ Other information that should be obtained

- ✓ Information to identify the test system, such as the name, lot number, date of acquisition, and amount of acquisition
- ✓ Records to confirm information on storage methods, such as storage temperature, the container, and the need for shading

• Records of management
  - ✧ The records to confirm that there are no changes in biological activity (potency) of enzymes, etc., or changes in viability or transformation during storage
  - ✧ The records of temperature at the storage location
  - ✧ The records to ensure quality during transportation (records of temperature using a data logger, records of conditions at the time of arrival (remaining ice packs, dry ice, etc.)) if there is a risk of deterioration due to temperature conditions

➢ Experimental animals
• Records of acquisition and quality confirmation
  - ✧ The records related to delivery and receipt, such as delivery slips, shipping slips, and reception records of breeding animal care facilities, and the breeding records in the case of self-breeding
  - ✧ The records for quality confirmation, such as records of quarantine or preliminary breeding, and records of observation of general conditions during use, which can confirm that there were no problems with the animals used in the study
• Administrative record
  - ✧ The records of quarantine, acclimatization, breeding, and breeding environment, which can confirm that the animals used are appropriate for use in the study
  - ✧ Items related to the breeding environment (For example, the records on feed and water quality)
  - ✧ In the case of repeated administration, the records related to the environment in the breeding room or, if necessary, in the laboratory (e.g., temperature and humidity conditions)
• Usage record
  - ✧ The use records that confirm that the animals were used according to the study protocol in terms of income and expenditure (Reference Figure 5)
  - ✧ Administration records that confirm the appropriate administration of the test substance, etc.
  - ✧ When the same animal is used repeatedly, the records confirm in advance that there is no effect of previous treatment including administration
  - ✧ When animals such as dogs and monkeys are used in multiple studies, the records that confirm the history of use and progress of use (records must be kept so that you can reach the arrival record by tracing the usage history.)

- ✧ When animals for multiple studies are purchased in bulk, the records that confirm the movement of all purchased animals as common records for multiple studies (indicate the number of animals used for each study)
- ✧ The records of the history of all the animals used in the study (including excluded animals)
- ✧ When animals are euthanized, the records of the method, etc.
  See Guidelines for Euthanasia of Laboratory Animals, etc.

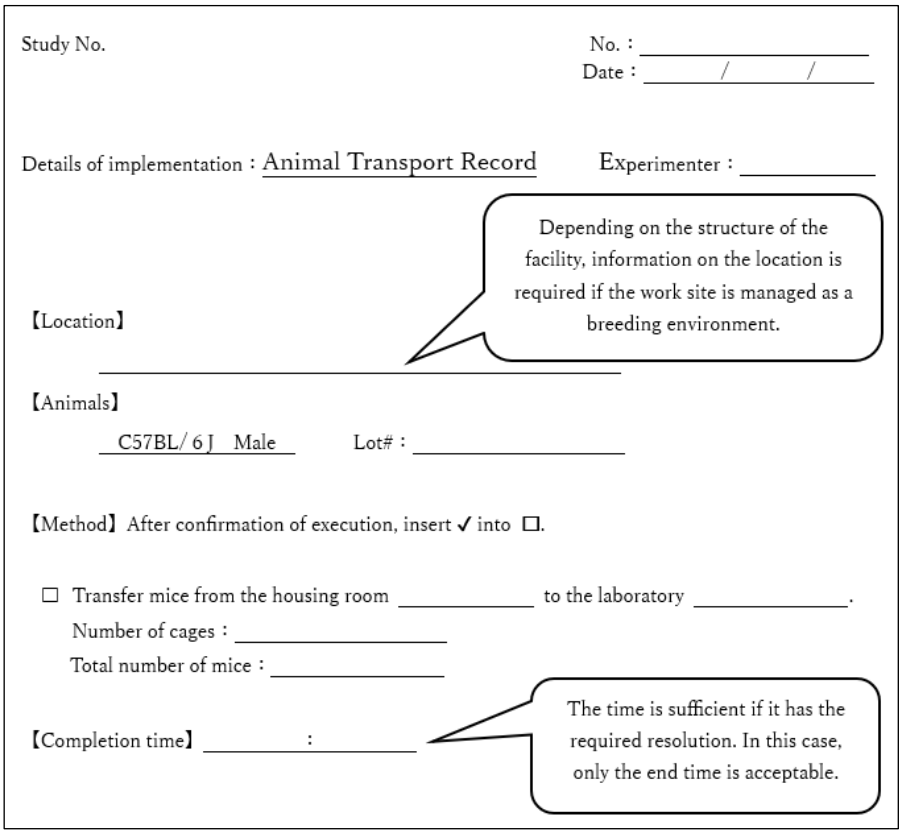

Figure 5. Example of Animal transport record format

10 Management of Equipment

If the equipment used for testing does not operate properly, the test results will be greatly affected. Therefore, it is important to check the equipment's performance and operation before use. Equipment should be used in accordance with the instruction manuals, etc.

10-1 Key Points

1) Verifying that equipment to be used operates properly
2) Preparing and storing records of equipment performance verification and operation verification before use
3) Preparing and storing records of equipment use

10-2 Supplementary Information

1) Verifying that equipment to be used operates properly
   - Verify in advance that the equipment operates properly according to the procedures specified in the instruction manuals, etc.

2) Preparing and storing records of equipment performance verification and operation verification before use
   - Verify the equipment's performance (Inspection, calibration and standardization) as follows:
     - Inspection: In-use inspection and periodic inspection. Concretely, visual inspection and measurement/operation tests with equipment are performed to detect damage or abnormality of the equipment concerned and to confirm its function.
     - Calibration: To determine the relationship between the value indicated by the equipment and the true value using standard instruments, standard samples, etc. After calibration, the equipment is adjusted as necessary.
     - Standardization: To prepare a calibration curve using a standard sample of known concentration.
   - When a repair is performed by a contractor, a record of the results and confirmation of normal operation should be kept, and the test should be restarted after the Study Personnel and the person who requested the repair confirm the record.
   - For maintenance records of inspection and repair of equipment that directly affects the test data, including balances and pipettes in particular, the method of preparing and storing specific records should be discussed with the Sponsor in advance.
   - For equipment that cannot be checked or does not need to be checked every time it is used, inspection should be performed by the Study Personnel or contractor at appropriate intervals if possible, and the records should be stored.

3) Preparing and storing records of equipment use
   - For usage records of equipment that directly affects the test data, including balances in particular, the method of preparing and storing specific records should be discussed with the Sponsor in advance.
   - When using multiple units of the same equipment, identify the specific one used. Attaching an ID number is recommended for clear differentiation.

11 Conduct of the Study

The study shall be conducted in accordance with the study protocol. Before the study is initiated, it is recommended that the study protocol and related documents be reviewed again to reconfirm the methods and contents of the study.

Furthermore, if the Study Personnel are unable to perform any part of the study as specified in the study protocol, they shall record the details and promptly communicate this to the Sponsor, and, if necessary, consult with the Sponsor regarding appropriate measures.

For study records, refer to the following section.

11-1 Key Points

1） Confirmation of the study protocol and related documents with Study Personnel
2） Procedures for handling unexpected events
3） Handling changes to study content without amending the study protocol
4） Communication with the Sponsor

11-2 Supplementary Information

1） Confirmation of the study protocol and related documents with Study Personnel

- Before initiating the study, it is important that the Study Director with Study Personnel confirm the following items:
  – the study protocol
  – the worksheets and other recording forms
  – the methods of recording using those forms
  – procedures that require special attention
  – reagents
  – the communication system to be used in the event of unexpected events.

2） Procedures for handling unexpected events

- If unexpected events occur during the study, the Sponsor should be contacted promptly, and additional measures should be discussed as necessary.
- The details of the event and the response taken must be documented. The Study Director must assess the scientific validity of the response and its impact on the study results and record this assessment.
- The following are examples of events that constitute changes to the study protocol or are considered unexpected by the Sponsor. In such cases, the procedures described above should be followed. The comments in parentheses are examples of judgments made by the Study Director. If timely consultation with the Sponsor is not possible, the reliability of the study may be affected.
  - One animal died unexpectedly during the study period (only one animal in the low-dose group, so likely not caused by the test article).
  - The plasma concentration of the test article was higher or lower than expected (similar results have occurred with other articles, so not considered problematic).
  - The average body weight of disease model animals purchased from the usual breeder was generally lower in this study (the lower weight is not expected to affect the study results).
  - After the start of the study, it was found that the control article could not be obtained (a substitute reagent is available and can be used).

- The display of the data logger for temperature measurement, which was provided by the Sponsor, indicated a temperature outside the acceptable range for the freezer (the deviation was minor, and a built-in thermometer was also available, so it was considered acceptable).

3） Handling changes to study content without amending the study protocol

- Such changes are considered deviations from the study protocol and must be documented accordingly. (Refer to Section 6, Preparation of the Study protocol, 6-2 Supplementary Information, 5)

4） Communication with the Sponsor

- Any changes to the study protocol or unexpected events, regardless of their scale, must be reported to the Sponsor. It is also necessary to prepare a written procedure in advance that specifies the items to be communicated and the method of communication, and to confirm it with the Sponsor.
- During the conduct of the study, it is important to maintain appropriate communication with the Sponsor, such as providing updates on the status of the study as needed.
- Even if prior meetings have been held, differences in background between the Sponsor and Academia may lead to discrepancies in the recognition of unexpected events. To detect such discrepancies in a timely manner, it is recommended to promptly share study results with the Sponsor.

12 Recording of the Study Data

Accurate and comprehensive records must be maintained to allow reconstruction of the study. Therefore, the Study Director shall discuss and agree with the Sponsor on the specific contents to be recorded and the methods of recording.

12-1 Key Points

1） Definition of raw data and importance of recording

2） Ensuring accuracy, completeness and comprehensiveness, and retention

3） Points to consider regarding electronic data

12-2 Supplementary Information

1） Definition of raw data and the importance of recording

- Raw data refers to observations and measurement results obtained in individual experiments (such as laboratory notebooks containing experimental results, worksheets, charts, electronic data, etc.) and records of study performance (such as date of the study, names of the Study Personnel who actually performed the study, and identification of animals or specimens), which are necessary for the reconstruction and evaluation of the study.
- All raw data shall be recorded appropriately with the name of the personnel performing and the date to ensure it remains legible and tamper-proof.

- Raw data refers to "the first instance in which the information is expressed in writing or symbols". Even a simple memo constitutes raw data and therefore must be handled carefully and not discarded.
- The original record refers to "the first instance in which the information is expressed in writing or symbols". Even a simple memo constitutes an original record and therefore cannot be discarded.
- If unexpected events occur, the Study Director shall confirm the situation, record how it was handled, and document the impact on the study.

2） Ensuring accuracy, completeness and comprehensiveness, and retention

- To accurately compile the study results in the final report and ensure the reliability of the study, all raw data must be retained. The study records shall also include data that were not adopted to demonstrate that no arbitrary selection was made.
- All raw data shall be recorded directly, promptly and can be understood by a third party in a tamper-proof manner except when entered into a computer. All data should be stored promptly to prevent loss or damage.
- If multiple Study Personnel are involved in the study and several operations may affect the study results, it is necessary to record which personnel performed each operation in a way that clearly identifies their responsibilities.
- If data corrections are required in the study records, original records must remain identifiable. To ensure the corrections can be verified, the Study Personnel shall document the reason using the 5W1H approach, along with the date of the corrections and their signature (Please refer to the following [Example of Correction Method]). In particular, when correcting dates after a significant time has passed, inconsistencies in the chronological order may arise. Therefore, consult with the Sponsor regarding the appropriate method for making such corrections and documenting the reasons.
- The linkage between the figures of study records and those of data analysis shall be clearly indicated.
- All calculations and their associated procedures conducted during data analysis shall be properly recorded. In addition, if analytical software is utilized, the formulas used for calculation must be validated, and relevant records shall be maintained.
- If the Study Personnel conducted the re-analysis or re-measurement, the fact that such re-analysis or re-measurement was performed, as well as the corresponding data, must be recorded. If there is excluding data, the reason for exclusion must be recorded. For any records that were not adopted, the reason for exclusion must be recorded, and such records must be retained appropriately.

3） Points to consider regarding electronic data

- When electronic raw data is generated from equipment related to measurement, storage, or incubation, the handling requirements shall be confirmed with the Sponsor in advance, and the handling procedures shall be agreed upon.

- If printed copies of electronic data are to be considered as raw data, the printouts shall be dated and signed promptly after printing. When the output volume is large, the printed pages may be bound (with page numbering, etc.), and the cover page shall be dated and signed.
- When re-analysis is to be conducted, confirm the relevant considerations with the Sponsor in advance.

[Example of Correction Method]

i. Incorrect entries shall be marked using strikethrough formatting. However, the original contents must remain legible.
ii. Correct entries shall be written in the blank space near the incorrect entries.
iii. Study personnel making corrections shall record the date and provide their signature.
iv. The reason for the correction shall be briefly stated.

Example：If the value '100.1' was incorrectly recorded as '101.0', the correction must be made according to the procedure described above.

101.0 100.1

[Date of correction:20xx(year)/xx(month)/xx(day)] [Signature] [Reason: Transcription error]

13 Preparation of the Study Report

The study report must accurately reflect all study results obtained against the study protocol, including results that differ from expectations.

To ensure the reliability of the study report, necessary and sufficient verification (such as review sessions and multiple reviewers) is critically important. If possible, verification by a third party (researcher not involved in the study) should also be requested.

13-1 Key Points

1） Preparation of the study report based on an ethically and scientifically appropriate study protocol
2） Accurate reflection of all obtained study results
3） Documentation of unexpected events during the study and deviations from the study protocol
4） Measures to enhance reliability of the study report
5） Request for verification by the Sponsor
6） Confirmation and signature by the Study Director
7） Procedures for correction of the study report

13-2 Supplementary Notes

1） Preparation of the study report based on an ethically and scientifically appropriate study protocol

- The study report must be prepared based on the study protocol. Since the study report is subject to reliability assessment during new drug approval review, use of templates provided by the Sponsor is recommended.

2) Accurate reflection of all obtained study results
- All obtained study results, including those differing from expectations, must be accurately reflected.
- Conclusions should be specifically described based on the study records, avoiding arbitrary conclusions.
- The study records must be accurately reflected in the study report, and consistency between the main text and tables/figures must be maintained. Thorough verification is required to ensure this consistency.

3) Documentation of unexpected events during the study and deviations from the study protocol
- If unexpected events or deviations from the study protocol are suspected to affect study reliability, their impact on study results must be described. If it is judged that study reliability is not affected, detailed documentation is unnecessary but consultation with the Sponsor is advised as needed.

4) Measures to enhance the reliability of the study report
- Verification necessary and sufficient for reliability assurance (e.g., review sessions and multiple reviewers) should be conducted, and if possible, independent third-party verification should be obtained.

5) Request for verification by the Sponsor
- Verification of the draft study report is the responsibility of the Sponsor and must be requested. When comments are received, the Study Director shall discuss and make appropriate revisions with the Sponsor.

6) Confirmation and signature by the Study Director
- The study report must be prepared or reviewed by the Study Director. The Study Director's signature and date clarify accountability and the issuance date of the report.

7) Procedures for correction of the study report
- If corrections are needed after the Study Director's signature, the Sponsor must be promptly informed.
- A correction document should be prepared after Sponsor approval (use of correction templates provided by the Sponsor is recommended).
- The correction document shall record corrected items, reasons for correction, and correction dates, and must be confirmed and signed by the Study Director. Since it is subject to reliability assessment during new drug approval, use of templates provided by the Sponsor is recommended.

【Reference】

Items to be included in the study report (examples): Items described in the study protocol should, in principle, also be included in the study report. Whether items are mandatory or not is based on the study protocol.

(1) Study title and study number
(2) Summary
(3) Study objective
(4) Study start date and study completion date (study period)

- The period includes dates such as animal acquisition and measurement operations.

(5) Information on test articles and specimens
(6) Information on test systems (cells, microorganisms, biological samples, animals)
(7) Information on reagents
(8) Information on equipment
(9) Study conduct methods
(10) Procedures for data processing and analysis
(11) Criteria for evaluation (if applicable)
(12) Details of re-measurement or similar procedures (if applicable)
(13) Study results
(14) Conclusions and discussion (as needed)
(15) Signature and date of the Study Director
(16) Names of Study Personnel

- Inclusion of personnel names other than the Study Director is not mandatory and should follow the facility's policy. It is recommended to predefine key personnel such as those who performed the main study operations.

(17) Applicable guidelines (if applicable)
(18) Facility name and location of Academia conducting the study
(19) Sponsor name, address, and contact information
(20) Sponsor's Representative
(21) Procedures regarding receipt and transfer of specimens
(22) Changes to the study protocol, unexpected events, suspected reliability-impacting events, and deviations from the study protocol (including the Study Director's judgment on deviations)
(23) Storage locations of Study Records and Materials and specimens (if applicable)
(24) References (if applicable)

14 Retention of Study Records and Materials

Studies used for approval applications must be traceable with accuracy. Therefore, all records obtained from the study, including unexpected results and rejected data, must be retained. However, due to the property of each sample (e.g., specimens), it may not be possible to prevent qualitative deterioration. In preparation for such cases, the handling of these materials should be discussed and agreed upon in advance with the Sponsor.

When archiving Study Records and Materials, it is necessary to prevent dispersion, mix-ups, loss and deterioration. Countermeasures against disasters such as fire and earthquakes should also be considered.

The responsibility for archiving Study Records and Materials used in New Drug Applications lies with the Sponsor. If it is difficult for the Academia to archive the Study Records and Materials, the Sponsor will properly archive them.

14-1 Key Points

1） Definition of Study Records and Materials to be retained and retention period
2） Proper archiving management of Study Records and Materials
3） Considerations for retaining electronic data

14-2 Supplementary Notes

1） Definition of Study Records and Materials to be retained and retention period
- All records obtained from the study, including unexpected results and rejected data, must be retained. However, the handling of samples should be discussed and agreed upon with the Sponsor.
- The retention of facility-wide records, such as equipment use records in other studies or temperature records managed centrally in animal housing facilities, should be discussed with the Sponsor.
- Study Records and Materials must be retained for the period specified in the contract and other related documents. Details regarding retention of Study Records and Materials should be clearly stated in the contract and other related documents.
- Archiving management of Study Records and Materials to prevent loss or other issues requires time and cost. Therefore, if possible, it is recommended to include in the contract that the Study Records and Materials will be returned (hand over) to the Sponsor. In such cases, the Study Records and Materials to be handed over should be determined in advance through consultation with the Sponsor.

2） Proper archiving management of Study Records and Materials
- It is necessary to establish a proper archiving management system of Study Records and Materials, including the designation of responsible personnel, storage location and procedures.
- Countermeasures must be taken to prevent dispersion, mix-ups, loss and deterioration, as well as to prepare for disasters such as fire and earthquakes.
- In some cases, the Study Director or Study Personnel may store Study Records and Materials individually. To prevent loss, records should be promptly filed, and specimens and similar items should be kept under lock and key. It is also recommended that Study Records and Materials be archived and managed at a designated archiving facility (place).

3） Considerations for storing electronic data
- If raw electronic data is available, the Sponsor should provide information on handling precautions, and both parties should confirm and agree on how the electronic data will be handled.

This concludes the guidance.