Detailed Regulations on Animal Experimentation

Daiichi-Sankyo Company, Limited

CONTENTS

Preamble

Animal experimentation plays such an important role across so-called life science research that it is no exaggeration to say that its current development would not have been possible without it. Animal experimentation is also indispensable in medicine development, and no medicine that has made a significant contribution to human health and well-being would have been developed without it. Although the efficacy and safety of a medicine candidate must ultimately be evaluated in clinical trials in human subjects, basic information on the efficacy and safety of the compound should be ascertained through animal experiments prior to initiating a clinical development program. This is as expressed in the Declaration of Helsinki as "Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experiments. The welfare of animals used for research must be respected.," and also clearly stated in the Ministerial Ordinance on Good Clinical Practice (ICH E6 Guideline) as "Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP".

On the other hand, animal experimentation inevitably causes stress, pain, and/or death to laboratory animals. Causing distress on animals meaninglessly is unethical and not permitted by the society. Therefore, when conducting an animal experiment, the life of the animals must be respected from the ethical point of view and their distress must be minimized from animal welfare's point of view, as far as the experimental objective can be achieved, while ensuring that experimental conditions are such that the results of the experiment are reproducible for reasons based on the general principles of research in natural science. Namely, anyone who engages in an animal experiment must treat the animals with thankfulness and seriousness, and also make an effort to practice the 3Rs to reduce pain or distress, i.e., Replacement (active adoption of an alternative testing method), Reduction (reduction number of animals used), and Refinement (relief of pain or distress through refinement of experimental techniques). In housing laboratory animals, an environment should be developed that allows the animals to live in a healthy and peaceful manner and to behave normally in a manner intrinsic to respective species (fulfillment of the Five Freedoms).

Animals have been integrated into the human society not only as laboratory animals but in various forms such as companion animals, farm animals, or working animals. Significant care should also be taken in the fact that humans concerned with those animals may have special feelings toward them.

In addition, it is important to note that using laboratory animals have special risks such as animal-derived allergies and bite/scratch injuries.

Animal experimentation must be conducted in an appropriate manner, taking into account these matters concerning ethics, animal welfare, and the safety of laboratory personnel, while considering all the requirements for the experiment to ensure a high scientific reproducibility.

In Japan, regulations and standards related to animal experimentation have been formulated as laws, ordinances, or guidelines, such as the Act on Welfare and Management of Animals (Act

No. 105, October 1, 1973), the Act Partially Amending the Act on Welfare and Management of Animals (Act No. 39, June 19, 2019), the Basic Guidelines for the Conduct of Animal Experiments in implementing agencies under the jurisdiction of the Ministry of Health, Labour and Welfare (June 1, 2006), the Standards relating to the Care and Keeping and Reducing Pain of Laboratory Animals (Notice No.88 of the Ministry of the Environment, April 28, 2006), the Standards relating to the Methods of Destruction of Animals (Prime Minister's Office, Notice No. 40, July 4, 1995), and the Guidelines for Proper Conduct of Animal Experiments (Science Council of Japan, June 1, 2006). International guidelines include the Guide for the Care and Use of Laboratory Animals, 8th ed. (US National Research Council, June 2011). In addition, regulations and standards related to industrial safety have been formulated as laws, ordinances, or guidelines, such as the Industrial Safety and Health Act (Act No. 57, June 8, 1972).
This document, Detailed Regulations on Animal Experimentation ("the Regulations" hereinafter), describes institutional regulations concerning animal experimentation and indicates what must be followed when animals are housed and managed or an animal experiment is designed and conducted in the Institution of the R&D Division of Daiichi-Sankyo Company, Limited, in accordance with the above laws, ordinances, and guidelines.

Article 1. Purpose

These Regulations apply to animal experiments conducted in the Institution of the R&D Division of Daiichi-Sankyo Company, Limited ("the Institution" hereinafter) or in third-party facilities under outsourcing contract. The Regulations stipulate what should be followed from ethical, scientific, and animal welfare points of view to ensure the proper conduct of those animal experiments, animal welfare, and occupational health and safety.

Article 2. Definitions

2.1 Laboratory animals: Vertebrate animals bred for the purpose of animal experiments and maintained in the Institution, or those that are maintained in a third-party facility under an outsourcing contract.

2.2 Animal experiment: An experiment that uses laboratory animals is conducted in the Institution or outsourced to a third-party facility. An animal experiment includes activities for the education or training, and animals for monitoring required for the conduct of the experiment.

2.3 Animal experiment protocol: A protocol established in advance to conduct an animal experiment.

2.4 The Institutional Official: The person who is responsible for administering the Institution.

2.5 Facility Manager: The person who supervises the management of laboratory animals maintained in the Institution and of animal facilities and related equipment of the Institution.

2.6 Laboratory Animal Manager: The person who assists the Facility Manager and

oversees the management of laboratory animals.

2.7 Attending Veterinarian: The person who is responsible for the veterinary care of the laboratory animals kept in the Institution.

2.8 Principal Investigator: The investigator for the animal experiment who supervises the activities concerning the animal experiment.

2.9 Investigator: A person who carries out the animal experiment.

2.10 Animal Care Personnel: A person who takes care of and manages laboratory animals and conducts related tasks under the Facility Manager.

Article 3. Scope

3.1 These Regulations shall apply to all animal experiments that use laboratory animals and are conducted at the Institution. Among Paragraphs in the Regulations, those concerning outsourced animal experiments shall apply to all animal experiments outsourced by the Institution.

3.2 Although the Regulations except this Article will not apply to experiments with invertebrates, which are not included in the category of laboratory animals, those animals shall also be treated humanely so that unnecessary pain or distress will not be inflicted.

Article 4. Responsibilities of the Head of Research and Development (R&D) Division

4.1 The Head of R&D Division shall, as the head of the experimentation site defined in the Basic Guidelines for the Conduct of Animal Experiments in implementing agencies under the jurisdiction of the Ministry of Health, Labour and Welfare, have final responsibility concerning the conduct of animal experiments and related activities in the Institution. The Head of R&D Division shall establish what should be followed regarding the care and management of laboratory animals and planning and conduct of animal experiments, and ensure that laboratory animals are properly taken care of and managed, and animal experiments are appropriately conducted.

4.2 The Head of R&D Division shall have a responsibility to review, revise and/or abolish these Regulations in a timely manner in response to relevant changes in laws and regulations, standards, or socially accepted ideas concerning animal experimentation or changes of the Daiichi-Sankyo's organization for conducting animal experimentation.

4.3 The Head of R&D Division shall have a responsibility to establish an Institutional Animal Care and Use Committee, as an advisory body that objectively reviews the appropriateness of all kinds of activities related to the animal care and animal experiments, in each Institution.

4.4 The Head of R&D Division shall have a responsibility to have the Principal Investigator submit an animal experiment protocol prior to the initiation of the

animal experiment in the Institution or outsourced to a third party, have the protocol deliberated by the Institutional Animal Care and Use Committee, and determine whether the experiment should be conducted or not, taking into account the results of the deliberation.

4.5 The Head of R&D Division shall have a responsibility to have the Principal Investigator report the results of an animal experiment conducted in the Institution or outsourced to a third party, and to take appropriate corrective actions, as necessary.

4.6 The Head of R&D Division shall have a responsibility to conduct an education and training program for personnel who administer or manage the Institution and personnel who use it to fully understand the spirit of animal welfare and master the knowledge and skills required for conducting their tasks.

4.7 The Head of R&D Division shall have a responsibility to carry out self-inspections regarding the maintenance and management of each Institution and the status of laboratory animals and animal experiments in the Institution, and have the Institution take a verification by an external third-party certification body.

4.8 The Head of R&D Division shall appoint a person as the Institutional Official for each Institution and have them administer their Institution to fulfill the responsibilities described in Paragraphs 3 to 7 of this Article.

4.9 The Head of R&D Division shall summarize and evaluate the activities of each Institution and disclose its results through appropriate media such as the corporate website, together with the results of verification by an external third-party certification body.

Article 5. Responsibilities of the Principal Investigator

5.1 The Principal Investigator shall submit an animal experiment protocol to the Institutional Official prior to the initiation of the animal experiment planned to be conducted in the Institution or outsourced to a third-party and have it approved by the Institutional Official. The Principal Investigator shall not conduct any unapproved animal experiment for any reason.

5.2 The Principal Investigator shall conduct the animal experiment, supervising and instructing the Investigators, according to the Animal Experiment Protocol, and with consideration for animal welfare.

5.3 The Principal Investigator shall report the results of the animal experiment to the Institutional Official.

5.4 Specific procedures to fulfill the responsibilities of the Principal Investigator defined in Paragraphs 1 to 3 of this Article shall be determined for each Institution as part of the site-specific regulations or standard operating procedures (SOPs).

Article 6. Membership of the Animal Care and Use Committee (IACUC) and Its Responsibilities

6.1 The IACUC in each Institution established on the basis of Paragraph 3 of Article 4 shall have the following members:

(1) The IACUC shall consist of one chairperson and at least three committee members.

(2) The committee members shall include at least one person with excellent insight into laboratory animals, at least one person with excellent insight into animal experiments and related matters, and at least one person with other scholarly knowledge.

(3) If necessary, the IACUC can invite a third-party member(s).

(4) Other requirements for committee members and other details such as the term of membership shall be determined for each Institution as part of the site-specific regulations.

6.2 An Animal Care and Use Committee Secretariat (IACUCS) that engages in the operation of and office work for the IACUC shall be placed within each Institution. Any staff member of the IACUCS cannot be a member of the IACUC.

6.3 The IACUC has a responsibility to submit a report after investigation and deliberation on an animal experiment in response to inquiries by the Institutional Official, and recommend or advise improvements, as necessary. What should specifically be deliberated shall be determined for each Institution as part of the site-specific regulations or SOPs.

6.4 In the deliberation mentioned in the previous Paragraph of this Article, the IACUC shall refer to the regulations and standards cited in the Preamble of the Regulations and, as necessary, other related regulations and standards. The IACUC shall evaluate the matters so that the activities in the Institution comply with them, are done with scientific rationale, and keep animal welfare and occupational health and safety.

6.5 In deliberating an animal experiment protocol, the IACUC shall fulfil, in addition to the previous Paragraph, the following requirements:

(1) To review the submitted animal experiment protocol in view of scientific rationale, animal welfare, and occupational health and safety, with respect to the following subjects, and require revision of the protocol, if necessary:

(i) Objective of the experiment

(ii) Possibility of adopting an alternative method that uses, e.g., subcultured cells, microorganisms, or chemical substances.

(iii) The species/lineage/genetic quality/microbial quality of the laboratory animals used

(iv) Number of animals used

(v) Housing environment

(vi) Avoidance of unnecessary pain or distress

(vii) Presence or absence of multiple major survival surgery on an identical animal
(viii) Restraint of laboratory animals
(ix) Method of animal management after treatment on the animals
(x) Duration of experiment
(xi) Final disposal of laboratory animals
(xii) Contents of the education and training program provided to each personnel who work for the Institution
(xiii) How to ensure the health and safety of each personnel who work for the Institution

(2) To review the extent of animals' pain or distress caused by the operations described in the submitted animal experiment protocol and classify the distress level of the experiment according to "Appendix: Classification of Animal Experiments Based on Ethical Standards" and determine whether the protocol should be approved or not.

6.6 The chairperson or a member of the IACUC shall not participate in the deliberation of the animal experiment protocol or of the report of the results of the animal experiment, if they participate in the experiment by themselves.

6.7 Specific procedures to establish an IACUC within the Institution and fulfill the responsibilities defined in Paragraphs 3 to 6 of this Article shall be determined for each Institution as part of the site-specific regulations or SOPs.

Article 7. Responsibilities of the Institutional Official

7.1 The Institutional Official is responsible for administering the Institution.

7.2 The Institutional Official shall, on the basis of Paragraph 8 of Article 4, establish an Animal Care and Use Committee in the Institution, approve animal experiment protocols, grasp the results of animal experiments, implement programs of education and training, perform self-inspections, and report these results to the Head of R&D Division at least once a year, and getting verification by an external third-party certification body as frequently as defined by the certification body.

7.3 The Institutional Official shall determine the organization of the Institution so that the Institution can be administered and managed properly, after having the appropriateness of the proposed organization deliberated by the IACUC of Article 6, which has been consulted from the Institutional Official in advance on this matter.

7.4 The Institutional Official shall appoint a person as the Facility Manager who is responsible for the management of the equipment placed and laboratory animals kept in the Institution.

7.5 The Institutional Official shall appoint persons as the Attending Veterinarian who is responsible for the veterinary care of the laboratory animals kept in the Institution.

7.6 The Institutional Official shall take measures to ensure the occupational health and safety of the personnel who administer or manage the Institution and users of the Institution, as well as measures to prevent these individuals from being affected by diseases derived from laboratory animals.

7.7 The Institutional Official shall direct the proper housing and management of laboratory animals and the proper conduct of animal experimentation in the Institution, as well as installing or establishing equipment, regulations, and SOPs necessary to maintain the living environment and ecosystem outside the facility and public health.

7.8 The Institutional Official shall establish a procedure for all unfavorable events including inappropriate treatment of animals to be promptly reported to the Institutional Official. This procedure must be established in a way that protects the informant.

7.9 The Institutional Official shall establish measures to, when an emergency such as earthquake or fire occurs, protect laboratory animals and prevent occurrence of harm to humans due to, e.g., run-away of laboratory animals and issues concerning environmental conservation.

7.10 The Institutional Official shall confirm in advance that the external institution to which the conduct of an animal experiment is outsourced conducts animal experiments at a level equivalent to or higher than the Institution from an animal welfare perspective, in accordance with the regulations and standards mentioned in Preamble of the Regulations.

7.11 Specific procedures to fulfill the responsibilities of the Institutional Official defined in this Article shall be determined for each Institution as part of the site-specific regulations or SOPs.

Article 8. Responsibilities of the Facility Manager

8.1 The Facility Manager shall supervise the management of laboratory animals as well as the management and administration of the animal facility.

8.2 The Facility Manager shall appropriately maintain the animal facility and its equipment as well as laboratory animals kept in the facility by directing and supervising the personnel who carry out the task of maintaining the Institution and the Animal Care Personnel.

8.3 Specific procedures to fulfill the responsibilities of the Facility Manager defined in Paragraph 1 of this Article shall be determined for each Institution as part of the site-specific regulations or SOPs.

Article 9. Responsibilities of the Attending Veterinarian

9.1 The Attending Veterinarian shall be responsible for the veterinary care of the laboratory animals.

9.2 The Attending Veterinarian shall ensure the well-being of the animals kept in the Institution and endeavors to minimize the pain or distress of them.

9.3 Specific procedures to fulfill the responsibilities of the Attending Veterinarian defined in Paragraph1 of this Article shall be determined for each Institution as part of the site-specific regulations or SOPs.

Article 10. Responsibilities of the Laboratory Animal Manager

10.1 The Laboratory Animal Manager shall assist the Facility Manager and be responsible for the management of the laboratory animals.

10.2 The Laboratory Animal Manager shall provide information to personnel who engage in the animal experiment and confirm the number and condition of the laboratory animals housed.

10.3 Specific procedures to fulfill the responsibilities of the Laboratory Animal Manager defined in Paragraph 1 of this Article shall be determined for each Institution as part of the site-specific regulations or SOPs.

Article 11. Responsibilities of All Personnel Who Engage in Animal Experiments

11.1 Anyone who engages in an animal experiment shall participate in the education and training program implemented by the Institutional Official to deepen the understanding of the spirit of animal welfare and the significance of animal experimentation.

11.2 Anyone who engages in an animal experiment shall carry out the task assigned to them, thoroughly understanding the physiology, biology, habits, etc. of the animal species used in the experiment.

11.3 Anyone who engages in an animal experiment shall, if laboratory animals must be sacrificed, use a method that minimizes the anxiety and distress of them from an animal welfare perspective. Animal carcasses and other related materials shall be disposed in a way that adequately addresses public health so as to prevent environmental contamination.

11.4 Anyone who engages in an animal experiment shall participate in memorial ceremonies for laboratory animals hosted by the Institutional Official as much as possible to think about the preciousness of life and renew the feeling of thankfulness to laboratory animals.

Article 12. Considerations Concerning the Safety Management of Animal Experiments in the Institution

12.1 When an animal experiment is conducted that uses physically or chemically sensitive samples, pathogens, or gene modified organisms, adequate measures shall be taken to prevent environmental contamination and to conserve the

ecosystem, as well as ensuring the safety of Investigators, Animal Care Personnel, etc., in accordance with relevant regulations and standards in addition to general precautions.

12.2 In an animal experiment involving sensitive substances such as pathogens, manuals or other relevant reference materials prepared separately shall be followed.

Article 13. Retention of Records

13.1 The IACUCS shall retain the records concerning these Regulations.

Supplementary Provisions

Article 1. Department in Charge

1.1 The Research Innovation Promotion Department shall be the primary office in charge of these Detailed Regulations.

Article 2. Type of Rule

2.1 These Regulations shall fall under Detailed Regulations.

Article 3. Effective Date

3.1 These Regulations shall come into effect as of April 1, 2007.

Ammended on April 1, 2010.
Ammended on April 1, 2012.
Ammended on August 1, 2012.
Ammended on April 1, 2013.
Ammended on April 1, 2014.
Ammended on April 1, 2015.
Ammended on April 1, 2016.
Ammended on April 1, 2017.
Ammended on April 1, 2019.
Ammended on October 1, 2019.
Ammended on April 1, 2021.
Ammended on April 1, 2022.
Ammended on April 1, 2024.

Appendix: Classification of Animal Experiments Based on Ethical Standards

Category A: Experiments not involving the use of laboratory animals (Submission of protocol to the Institutional Official for approval is not mandatory for experiments of Category A.)

Examples:

- Experiment with cultured cells
- Experiment with unicellular organisms
- Experiment with invertebrates
- Experiment with eggs that completes final disposal of them before 80% of the time to hatching

Category B: Experiments consisting of only manipulations that are thought to cause no or almost no discomfort to laboratory animals

Examples:

- Painless, noninvasive manipulation such as light retention, observation of clinical signs, and measurement of body weight
- Administration of less harmful substances to laboratory animals
- Simple manipulation such as sparse blood sampling (1-2 times) from the superficial vessel
- Food or fluid restriction for short duration (approximately 2-3 hours)
- Sacrifice by a standard method of euthanasia
- Experiment in which manipulations are performed on unconscious animals under deep anesthesia and after completion they are sacrificed before recovery of consciousness
- Experiment that is performed with the tissues and/or organs collected from animals euthanized with a standard method
- Experiment with eggs in which they are allowed to mature until or beyond 80% of the time to hatching

Category C: Experiments with manipulations that may cause minimal stress or distress (pain or distress with short duration) to laboratory animals

Examples:

- Manipulation causing mild distress such as frequent blood sampling
- Short retention causing stress to a conscious animal
- Immunization with Freund's incomplete adjuvant
- Imposition of stimulation that causes pain or distress but allows the animal to take avoidance behavior
- Experiment in which animals undergo a surgical procedure under anesthesia and recover consciousness with mild pain or distress

Category D: Experiments which include manipulations that cause inevitable severe stress or pain or distress to laboratory animals

Examples:

- Manipulation that deliberately causes severe stress in a behavioral experiment
- Manipulation or imposition of stimuli that causes severe distress such that animals cannot take any avoidance behavior

- Retention for long duration (several hours or longer)
- Manipulation that makes animals take offensive behavior, resulting in self-damage or damage on other animals of the same species
- Experiment that causes short but severe pain or distress to unanesthetized animals
- Experiment in which animals undergo a surgical procedure under anesthesia and recover consciousness with severe pain or distress
- Experiment that sacrifices mother animals and gives surrogate mothers
- Immunization with Freund's complete adjuvant

Category E (strictly prohibited): Experiments that cause maximum endurable distress for conscious animals or even greater pain or distress to unanesthetized laboratory animals

Examples:

- Surgical procedure on an unanesthetized animal that is immobilized with a muscle relaxant or paralytic drug only
- Manipulation causing severe burn or trauma to unanesthetized animals
- Sacrifice with a microwave oven or strychnine
- Experiment that kills animals with stress
- Experiment in which a substance such as an adjuvant is administered to both soles to promote occurrence of ulcer