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Regulations for the Use of Laboratory Animals at INGEBI-CONICET

I. PREMISE

The advancement of knowledge and scientific development aimed at improving the health and well-being of both humans and animals requires experimentation with live non-human vertebrate animals of a wide variety of species to test scientific hypotheses and/or conduct preclinical trials. It is the responsibility of research centers and their authorities to establish standards so that these works are conducted considering the welfare of the animals, making their appropriate care and use a scientific and ethical imperative to minimize discomfort and pain.

II. Main Background Supporting the Need for the Creation of an IACUC at INGEBI

1. Major international journals that publish scientific works involving experimental animals require authors to sign a commitment to comply with specific standards and recommendations, including: a) "Guide for the Care and Use of Laboratory Animals" sponsored by NIH USA (latest edition published by National Academy Press USA 2011) and b) "Directive 86/609/EEC on the Approximation of Laws, Regulations, and Administrative Provisions of the Member States of the European Economic Community Regarding the Protection of Animals Used for Experimental and Other Scientific Purposes."
2. The Council for International Organizations of Medical Sciences (CIOMS) adopted in 1985, as a result of extensive international and interdisciplinary consultations, the "International Guiding Principles for Biomedical Research Involving Animals," which provide a conceptual and ethical framework for subsequent regulations.
3. In Argentina, although there is not yet specific national legislation regarding the use of laboratory animals for biological and/or biomedical experimentation, Law 14346 on the Protection of Animals applies where pertinent. The Ministry of Science and Technology, through the National Agency for Scientific and Technological Promotion, requires projects involving the use of experimental animals to have protocols approved by an Institutional Animal Care and Use Committee (IACUC) belonging to the institution where the experiments will be conducted.
4. The National Administration of Medicines, Food, and Medical Technology (ANMAT) of the Ministry of Public Health of Argentina sanctioned a "Regulation for Laboratory Animal Facilities Producing Medical Specialties and/or Analysis for Third Parties" (ANMAT Provision 6344/96), which would apply to collaborative work related to entities regulated by ANMAT.
5. There are international recommendations specifically related to safety in work with animals, as described in publications such as: ILAR/NRC USA "Occupational Health and Safety in the Care and Use of Research Animals" National Academy

Press Washington D.C. 1997 and CDC/NIH USA "Biosafety in Microbiological and Biomedical Laboratories" 4th Ed. US Government Printing Office Washington D.C. 1999.

Based on the points raised in I and II, the INGEBI executive council establishes the following regulations to regulate the preparation of experimental protocols with laboratory animals through an IACUC.

III. SCOPE OF APPLICATION

These regulations will apply to all work conducted with live vertebrate animals within the scope of INGEBI. This includes work conducted not only for scientific research but also for teaching, production, and/or testing of therapeutic, prophylactic substances, or diagnosis of infections, intoxications, or physiological or pathological states involving the use of live vertebrate animals.

IV. GENERAL RULES

1. All laboratory animals introduced or kept at INGEBI must be obtained from legal sources, which must be declared following the procedures established by the IACUC to ensure compliance with relevant ethical and sanitary aspects.
2. Animals may only be introduced and/or kept in authorized premises, which must be properly identified. Exceptionally, laboratory animals may be kept outside these premises for no more than 12 hours when circumstances require, provided they are used with protocols authorized by the IACUC.
3. Animal facilities must comply with the minimum micro and macro environmental conditions determined by the IACUC of INGEBI.
4. All personnel involved in the care and use of laboratory animals must demonstrate that they have received specific training for this purpose. The minimum programs for each category are defined in ANNEX I, based on the recommendations of FELASA.
5. Procedures to be performed with laboratory animals must be previously approved by the IACUC to ensure compliance with ethical and safety aspects.
6. The International Ethical Principles Guiding Biomedical Research Involving Animals established by CIOMS are adopted (https://cioms.ch/publications/product/international-guiding-principles-for-biomedical-research-involving-animals-2/) , and their adapted Spanish version is incorporated as ANNEX II of these regulations to serve as the basis for the ethical evaluation of procedures.
7. Regulations established in the following documents are adopted: "Guide for the Care and Use of Laboratory Animals" 8th Edition Natl. Acad. Press; AVMA Guidelines for the Euthanasia of Animals 2020, Resolution D 1047 Appendix II 2005 CONICET Argentina. Ethical reference framework for biomedical investigations with specific ethical principles for investigations with laboratory, farm, and nature animals. ((https://evaluacion.conicet.gov.ar/wp-content/uploads/sites/4/REGLAMENTO-DE-COMITE-DE-ETICA.pdf).

8. In cases involving the use of pathogenic, toxic, carcinogenic, mutagenic, or radioactive substances, as well as substances whose dangers have not yet been determined, appropriate safety containment elements must be available according to the case, and it must be verified that the involved personnel have received specific training to ensure the safety of people, other animals, and the environment. The disposal of animal carcasses and other related waste will be carried out according to the directives issued by the INGEBI biosafety committee.

V. CONSTITUTION OF THE IACUC

1. Compliance with general and particular norms will be supervised by an Institutional Animal Care and Use Committee (IACUC), which will be appointed by the INGEBI Executive Council. The IACUC will consist of three scientific representatives from animal users (researchers and/or technicians). These individuals must have experience in research and/or other uses of laboratory animals mentioned in item III (SCOPE OF APPLICATION). The IACUC will also include an external (non-INGEBI) veterinarian with experience in the care and use of laboratory animals and a non-scientific member.

VI. RESPONSIBILITIES OF THE IACUC

The IACUC will be responsible for:

1. Ensuring compliance with these regulations and suggesting any necessary modifications to INGEBI.
2. Proposing the adoption of principles, policies, programs, and standards aimed at guaranteeing the safe and ethical use of Laboratory Animals.
3. Setting INGEBI's standards regarding Procedures and Conditions for Facilities deemed suitable for Animal Care and Use; authorizing the operation of Animal Facilities within the scope of its jurisdiction, and inspecting the activities of Authorized Animal Facilities at least semi-annually to verify compliance with the programs and standards established by INGEBI.
4. Representing the interests of USERS and the general community concerning the Care and Use of Laboratory Animals.
5. Evaluating the protocols of works involving animals in terms of compliance with ethical criteria and safety standards. To this end, it will develop a standardized protocol to be submitted by the project managers to the IACUC for discussion and approval.
6. Ensuring that all projects involving the use of animals conducted at INGEBI have a protocol approved by the IACUC. Assigning a corresponding number for subsequent follow-up once each investigator's protocol is reviewed and approved.
7. Reviewing the protocols annually and/or when changes are proposed. Reviewing, approving, disapproving, or requiring changes to ongoing or future protocols.
8. Promoting the education and training of users and personnel in charge of the animals, ensuring they have the minimum necessary knowledge and training to perform the specified procedures on the species to be used.

9. Establishing procedures to ensure no unnecessary pain or suffering is caused, that anesthetics or analgesics are appropriately used when applicable, that proper pre-, intra-, and post-operative care is provided, and that experiments where pain or suffering are integral to the protocols undergo a particular analysis to guarantee no viable alternatives exist and that they have adequate scientific justification.
10. Reviewing the Institute's program for the care and humane use of vertebrate laboratory animals semi-annually.
11. Inspecting the Institute's animal facilities semi-annually (e.g., breeding and experimental facilities, cage washing routines, surgical procedures).
12. Ensuring the monitoring of animals by veterinarians, animal care technicians, and IACUC staff.
13. Ensuring that experimental protocols provide written guarantees that the proposed activities do not duplicate previous experiments.
14. Monitoring the use of approved protocols following a post-approval program (PAP) designed to ensure compliance with regulations by researchers, technicians, and participants. PAP visits will be notified to the Principal Investigator and scheduled two weeks in advance. During these visits, improvements may be proposed, and relevant documents filed.
15. Conducting PAP visits semi-annually to each group, proposing improvements, and filing documents related to the post-approval program.
16. Reporting the results of PAP visits to the INGEBI Executive Council.
17. Reporting to the INGEBI Executive Council any potential violations of these regulations by laboratory animal users.

VII. AUTHORITY OF THE IACUC

On behalf of INGEBI, the IACUC will have the ultimate authority to:

1. Halt any procedure if it is considered that unnecessary suffering is being caused to the animals.
2. Prevent any use of animals not explicitly stated in the approved animal use protocol.
3. Sanction the person responsible for violations, potentially banning them from conducting work with animals within the scope of INGEBI's influence for a determined period.
4. Order the immediate euthanasia of an animal in pain or suffering that cannot be alleviated or that has not been explicitly approved in the protocol for scientifically justified reasons.
5. Revoke the authorization for the operation of animal facilities that do not meet the established conditions and norms.

VIII. OPERATION OF THE IACUC

The IACUC will be chaired by a scientist with experience in the Care and Use of Laboratory Animals, who will coordinate its operation. The committee will meet as often as necessary to study protocols and address complaints (at least once per quarter). The IACUC may consult external experts on items generating doubts or for which there is no experience

among its members and will have administrative support for all tasks to expedite processes and avoid delays between the submission of protocols or their modifications and the issuance of the respective opinion.

ANNEX I

EDUCATION AND TRAINING OF PERSONNEL WORKING WITH LABORATORY ANIMALS

Anyone using laboratory animals at INGEBI must complete the Laboratory Animal Handling course offered at the Faculty of Exact and Natural Sciences, University of Buenos Aires.

CATEGORIZATION

Four categories of personnel requiring appropriate education and training are defined:

Category A: Personnel who care for the animals
Category B: Personnel who perform Procedures on the animals
Category C: Personnel responsible for directing or designing Procedures
Category D: Specialists in Laboratory Animal Science and Technology

The following guidelines should be interpreted as the necessary foundation for the topics to be included, to the extent required by the work to be performed, in the education and training programs to acquire the minimum level required by INGEBI for personnel working with Laboratory Animals.

GUIDELINES FOR CATEGORY A

Training of personnel who care for the animals

1. Basic instruction in the ethical, legal, and regulatory aspects related to the care of Laboratory Animals.
2. Handling and General Care of animals;
    - Environment, equipment, cages, and accessories used in animal facilities; description, usage, and maintenance.
    - Handling and restraint of animals.
    - Basic knowledge of humane methods of euthanasia for relevant species.
    - Elements of general physiology and behavior of animal species used for experimental purposes.
    - General care and, where appropriate, basic knowledge of animal reproduction.
    - Environmental control in animal rooms.
3. Recognition of health and disease;
    - Hygiene and disease control.
4. Recognition of signs of pain, suffering, and distress.
5. Local practices related to safety, administration, transportation, and receipt of animals and supplies, and disposal of animals.

6. Specific training, if necessary, for any task associated with assisting in procedures.

GUIDELINES FOR CATEGORY B

Training of personnel who perform procedures on laboratory animals

1. Basic appropriate knowledge of animal care and local practices related to safety, administration, transportation, receipt of animals and supplies, and animal disposal.
2. Instruction in the ethical, legal, and regulatory aspects of laboratory animal use.
3. Handling of animals and basic principles of general care;
    - Biological characteristics, particularly physiology and main behavioral characteristics, of the species, strains, and colonies of animals relevant to the work to be performed.
    - Handling and restraint of animals.
    - Humane methods of euthanasia for relevant species.
4. Recognition of health and disease;
    - Practical aspects of health and disease monitoring.
5. Recognition of signs of pain, suffering, and distress.
6. Relevant education and training to perform procedures at the appropriate level for the work to be done;
    - Appreciation of the elements of experimental design, including refinement, reduction, and replacement.
    - Relevance of housing systems and local environmental conditions for procedures.
    - Anatomy of animals used for experimental purposes.
    - Anesthesia, analgesia, and appropriate application of terminal procedures to minimize animal suffering.
    - Relevant surgical techniques and procedures.

The training of personnel in category B must have a significant practical component, usually conducted under the supervision of someone with substantial experience in these areas. Personnel in category B should also receive instruction on the implications of the animals' microbiological status.

GUIDELINES FOR CATEGORY C

Training of personnel responsible for directing or designing procedures

Professionals responsible for the design or direction of experiments involving animals can be considered competent upon completing the following two requirements:

- Completion of a full University Course, or equivalent, in a discipline such as Animal Biology, Medicine, Veterinary Medicine, or other Biological, Biomedical, or related disciplines.
- Attendance at a Basic Course in Laboratory Animal Science designed to develop an appropriate level of responsibility for the use of animals according to high scientific standards. The duration of the course will vary depending on the training methods

used and the participants' experience but, as a guide, a program of approximately 80 hours is considered satisfactory for a person without relevant experience in animal procedures. This total can be achieved through a coherent modular course or by accumulating appropriate instruction, studies, and experience that collectively provide the required breadth and depth of knowledge.

This Basic Course should include the following main topics: a. Ethical aspects and legislation. b. Biology and general care of laboratory animals. c. Microbiology and diseases. d. Safety in animal facilities and animal use. e. Design of animal experiments. f. Anesthesia, analgesia, and experimental procedures. g. Alternatives to animal use. h. Analysis of relevant scientific literature. Specialized additional training should also be considered.

GUIDELINES FOR CATEGORY D

Specialists in Laboratory Animal Science

These individuals, in addition to having an appropriate university degree, may require additional knowledge and experience similar to the items listed in the program for Category C personnel. It may be necessary to extend knowledge to laboratory procedures and animal species with which the individual is not normally familiar.

These individuals may require more specialized knowledge and experience than other laboratory personnel in areas of their responsibilities, such as microbiology of relevant species, quality control, health monitoring, pathology, prevention and treatment of diseases, ethical and legislative aspects, humane euthanasia techniques, and post-procedure nursing care. In general, this knowledge is acquired in postgraduate courses.

ANNEX II

INTERNATIONAL ETHICAL PRINCIPLES GUIDING BIOMEDICAL RESEARCH WITH ANIMALS

I. The advancement of biological knowledge and the development of better means for the protection of health and welfare, both human and animal, require experimentation on living, intact animals of a wide variety of species.

II. Whenever appropriate, methods such as mathematical models, computer simulations, and in vitro biological systems should be used.

III. Animal experimentation should only be conducted after evaluating its importance for human or animal health and for the advancement of biological knowledge.

IV. Animals selected for experimentation should be of an appropriate species and quality, and the minimum number required to obtain scientifically valid results should be used.

V. Researchers and other personnel should always treat animals as sentient beings and consider the proper care and use of animals and the avoidance or minimization of discomfort and pain as an ethical imperative.

VI. Researchers should assume that procedures causing pain in humans will also cause pain in other vertebrate species, even though much remains unknown about the perception of pain in animals.

VII. Any procedure that may cause more than momentary or minimal pain or distress in animals should be performed with appropriate sedation, analgesia, or anesthesia, in accordance with accepted veterinary practice. No surgical or painful procedures should be performed on unanesthetized animals paralyzed by chemical agents.

VIII. When deviation from the provisions in Article VII is required, the decision should not be made solely by the researcher directly involved but by a properly constituted review body, in accordance with Articles IV, V, and VI. Such exceptions should not be made solely for demonstration or teaching purposes.

IX. At the end of the experiment, or when appropriate during it, animals that may suffer chronic or severe pain, discomfort, or disability that cannot be alleviated should be painlessly euthanized.

X. Animals maintained for biomedical purposes should be kept under the best possible living conditions. Normally, animal care should be supervised by veterinarians experienced in Laboratory Animal Science. In any case, veterinary care should be available when needed.

XI. The director of the institute or laboratory where animals are used is responsible for ensuring that researchers and other personnel are appropriately qualified or experienced to perform procedures on animals. Adequate training opportunities should be provided through courses and training sessions.

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