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TABLE OF CONTENT

GENERAL PRINCIPLES REGARDING ETHICAL EVALUATION OF PROJECTS INVOLVING LABORATORY ANIMALS IN SCIENTIFIC RESEARCH

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Abstract

A large part of global biomedical research is still relying on animal models. In Europe, the use of animals is strictly regulated. The 86/609/EU Directive was updated in 2010 (2010/63/EU Directive) in order to harmonize the regulatory frameworks across European Union and to protect the animal welfare better. This Directive started to be transposed into Romanian legislation in 2014 and all the welfare standards have been fully implemented in 2015. Authorization of the projects using animals in scientific purposes is now mandatory for all institutions working on animal models. The centerpiece of the authorization file is the ethical evaluation, which is performed by a commission established by the user institution. Assessment should be done according to some of ethical principles to ensure the awareness use of animals if otherwise not possible. These principles include the justification of project goals for the use of animals, harm/benefit analysis, staff competence, and details of animal welfare. Only evaluating projects using animals and respecting the principles of ethics we can provide a good science and respect for life.

Key words: laboratory animals, project authorization, ethical evaluation, harm/benefit analysis.

Introduction

It is well known that there are multiple debates whether animals should be or should not be used in scientific research. Probably, sometime will pass until a clear "no" or "yes" could be stated regarding this issue. Some refer to them as nonhuman animals, laboratory animals, experimental animals or simply, animals. How they are called is less important, the most important side in this issue is the fact that they are "beings". Animals as beings, must act the same as Woody Allen does when he speaks about death "I'm not afraid of death; I just don't want to be there when it happens." Moreover, human beings always try to improve the condition of life searching for wellbeing and prosperity. It is likely that animals would choose the same as humans when speaking about life and wellbeing. Accepting this means: no experiments on animals, no breeding and killing animals for food, clothes or medicine, no use

of animals for hard labours, no selective breeding for any reason other than the benefit of the animal, no hunting and no zoos or use of animals for entertainment (Animal rights, 2009). For these reasons, when using animals in research, care should be taken into account in two major steps: one is planning or designing the experiments and other is the assessment of the project involving laboratory animals in scientific research. Apart from specific legislation there is plenty of information to be used in this domain such as: articles and guidelines for ethical conduct in the care and use of animals in research and models of ethical reviews in animal experimentation. As time passed, as more important became the ethical evaluation of studies which use animals. Many countries have regulations which state that animal experiments must be assessed by ethics committees. Recently, Romania has become one of them. Due to current legislation, the use of laboratory animals in scientific research can't be done until obtaining favourable endorsement issued by the competent authority. The most important component of the documents to be included in the file in order to receive the endorsement is the ethical assessment result of the project that should be done by an independent ethics commission. Our aim is to set up a blueprint based on the major principles that should be taken into account when establishing experimental designs involving laboratory animals. Researchers should be aware that depending on their intentions, pain and suffering could be generated in animals. This is to be avoided and due to this, they should consider an ethical and moral thinking from the early beginning of the idea.

Legislation

Even though animal testing is being done for a long time, the legal regulation in the field appeared approximately 35 years ago, on the one hand due to the pressure of public opinion and nongovernmental organizations which were fighting and are still fighting to ban animal experimentation, and the pressure of scientific society to create a single framework for the use of laboratory animals, on the other hand.

The aim of regulations was from the beginning, to put under the control of a government, the breeding and use of laboratory animals in order to ensure the welfare of this category of animals. Thus, in 1983, the Council of Europe elaborated and adopted "The European Convention for the protection of animals used for experimental and other scientific purposes", a document which will be the base for all legislation further elaborated in the European Union in this area and adopted by all Member States.

Only three years away, the EU Council adopted Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes. Because we are talking about a directive and that it undergoes a process of harmonization in each Member State, since its adoption, disparities between Member States have increased. Some Member States have adopted national measures for implementing and guaranteeing a high level of protection of animals used for scientific purposes, while others have only applied the minimum requirements of the Directive.

In time, it was concluded that the rules should be more detailed and so in 2010 the European Parliament along with the Council of the EU adopted Directive 2010/63/EU on the protection of animals used for scientific purposes (European Parliament, 2010), with a content about five times larger than the first one and more restrictive than that being more explicit in what is allowed or not to do in this area.

Beginning in 2000, during accession negotiations, the adoption process of normative acts continued, based on the European Convention for the protection of animals used for experimental and other scientific purposes, Romanian legislation now completely reflecting the European legislation.

Thus, the Directive 2010/63/EU was transposed into domestic law by Law 43/2014 (Romanian Parliament, 2014) which 75% of it is a mere translation of the Directive where are

mainly provided the conditions of housing and feeding of animals used in procedures, while for the remaining 25% must be drawn an additional legislation on the approval of establishments, authorization procedures, establishment of a bank of tissues and organs, projects authorization through simplified administrative procedure and others (Gonciarov & Coman, 2015).

As secondary legislation so far has been developed a single act, namely the Order of the President of the National Sanitary Veterinary and Food Safety (ANSVSA) No. 97/2015 (2015) approving the "sanitary veterinary procedures for authorization of user, breeder and supplying unit of animals used for scientific purposes, and for approving the sanitary veterinary authorization of procedures of the veterinary projects involving the use of animal in procedures ".

The latter rule is mainly based on ethical and moral principles, which the authors have proposed to discuss in this work, since in the first place is the ethical evaluation of projects imposed by the Directive, but also the setting up of ethics committees imposed both by the European Directive and the Law 206/2004 on "Good conduct in scientific research, technological development and innovation," committees that will be responsible for evaluating projects involving the use of animals in procedures.

According to Law 206/2004, units and institutions that are part of the national research and development and leading research and development projects, as well as units providing optimization of the results, are responsible for compliance with rules and ethical values in research and development. Therefore in these institutions should be set up ethics commissions that must work besides of scientific councils, where appropriate, in addition to administrative councils. Membership of committees of ethics must be proposed by the scientific councils or by the boards of directors and approved by the head of the institution. Also in the Law 206/2004 are laid down the rules of conduct in research and development, which are taken over and detailed in the code of ethics and professional deontology of research and development, adopted by Law no. 319/2003 regarding the status of personal involved in research and development.

Referring to the second key issue covered by the Order 97/2015, namely authorization of the projects, according to this order, the projects involving the use of animals in procedures are carried out only with prior authorization from the competent authority, in our case the Directorates Sanitary Veterinary and Food Safety from Romanian Counties and Bucharest. Authorisation of the projects is carried out only after receiving the application for veterinary authorization project, accompanied by a favourable opinion from the Ethics Commission established in the specialized academic centres or user establishments as appropriate. Another novelty of this order is that projects will be carried out in establishments veterinary authorized as user.

If Law 43/2014 provides that the ethical evaluation of projects will be carried out by the competent authority, which is ANSVSA, Order 97/2015 stipulates that the ethical evaluation should take place at specialized university centres or at the level of user. This change of attitude occurred after the competent authority has realized that it doesn’t have the necessary structures or the time needed to create structures capable of ethically evaluate projects using animals for scientific purposes. This approach to institutional assessment and authorization regionally exists only in Greece and Spain (Silva, Lassen, Sandøe, & Olsson, 2015). This authorization has more weaknesses than strong points, because beyond the expertise of the ethics committee at the level of user and knowledge in detail of the conditions for conducting projects, there may be conflicts of interest and pressure from units taking into account that there may be financial interests for the conduct of projects.

Principles for Ethical Evaluation

The ethical principles that will be presented below are part of any ethical evaluation of projects using animals for scientific purposes in procedures. The legislation sets criteria for project evaluation, criteria which are duplicated also in authorization, but only administrative.

1) The project must be justified in terms of scientific or educational value or required by law;

Projects that involve animals for scientific purposes cannot be made unless there is a strong justification that these can only be performed on live animals. If possible, use of live animals in experiments must be avoided. The justification in scientific terms must be clearly explained and the use of animals must be integrated in scientific context. Basic research was responsible for the majority of discoveries in biomedical and knowledge consolidation and it can be justified only by the potential long-term benefits. The assumptions made must be realistic and scientifically justified and possible conversion of basic research into applied research must be scientifically documented. Project justification from educational point of view must consider why the training can be done only on live animals, the type of training, the course type, the skills and knowledge gained by students, and whether these skills will be useful in their future work. If the use of animals is required by law and legal regulations, then those normative acts must be nominated. Since European Union legislation transcends national legislation for these regulations should be checked if there is no alternative, and national legislation is not yet brought to the European level. Legal regulations usually require the use of animals for safety testing, diagnostic or production. Production must contain justification for service contracts or supply products, market requirements, alternatives and the possible waiving on them.

The scientific justification of a research on animals must prove that there are no alternatives to research on animals and there are well-founded arguments that support the idea that there is a high probability to obtain a benefit by its execution.

2) Project goals must justify the use of animals;

Project goals have to be only those included in Article 4 of Law 43/2014 respectively: basic research; translational or applied research; protection of natural environment in the interests of the health or welfare of human beings or animals; research aimed at preservation of the species; higher education or training for the acquisition, maintenance or improvement of vocational skills; forensic investigations.

Translational or applied research must be aimed at the following:

a) The avoidance, prevention, diagnosis or treatment of diseases in humans, animals or plants;

b) The assessment, detection, regulation or modification of physiological conditions in humans, plants or animals;

c) Animal welfare and improving production conditions for animal breeding for agricultural purposes.

The project goal must state clearly the scientific aspects that will be included in the project. It is not allowed to conduct experiments on animals in research projects which aim other than those mentioned above.

3) Competence of personnel involved in carrying out the project;

Project leader has to prove competence of the team that will implement the project, i.e. the team members have the necessary skills and certification to perform the procedures, that in the research team exists a biostatistician who will determine the design of statistical experiment so as to apply the 3R's principles (replacement, reduction, refinement) (Festing & Altman, 2002).

Specification on staff competence is directly related to the quality of procedures performed in laboratory animals. When the personnel involved into performing procedures is competent, the chance of success is greatest. It avoids a failure (compromising experiment with or without generating unnecessary suffering to animals). Experience is proved by the involvement of the team members in previous research, their scientific publications in the field in question and the existence of certificates attesting their training in the field.

4) Ensuring humane endpoints;

The humane endpoints are the points of the experimentation that cannot pass any further. These points should be used in conjunction with human scientific objectives and the goal of the project, but they must be established in time before installation the state of suffering. In the past it was unusual that euthanasia to be chosen as a humane endpoint (Heuvel et al., 1990).

Rarely death of the animals occurs as a consequence of the direct effects of the procedures, in most cases is due to indirect effects such as dehydration and starvation caused mainly by the inability of the animals to drink or eat (Morton, 1999).

In such situations the experimentation cannot continue. The initial definition and implementation of the humane endpoints requires expertise in this field since before the beginning of the experiment the researchers should anticipate and decide its endpoints. When we cannot predict the course of the experiment it is recommended a pilot study to be conducted.

5) Killing methods chosen;

The use of some inappropriate methods for killing an animal can cause significant pain, stress and suffering, to the animal. Killing methods must be appropriate to the animal species and age. The method must be described and must be done by an experimented professional.

6) The existence of a retrospective evaluation system of the project;

Although Section 38 of the Act (Romanian Parliament, 2014) explains clearly in what terms the retrospective assessment can be done, this assessment should be made on all projects because it would determine whether the expected benefits have been achieved, if the harm were higher / lower than those potential early anticipated, how the entire project was managed.

This analysis takes effect for future projects as the results and way of conducted the project can inform and may be used in future scientific, welfare and ethical analysis.

When the retrospective assessment is made, the results publication is analysed as well. Whether they are in compliance with expectations or not, their publication leads indirectly, but certainly, to globally reducing the number of animal experiments by avoiding the increase of their number.

7) Harm-benefit analysis of the project;

To assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations and could ultimately be a benefit for human beings, animals or the environment ;

Harm - benefit analysis is difficult, it cannot be done automatically and many details must be considered. The analysis can sometimes be subjective but many factors that will make it objective must be taken into account. Harm caused to animals through their use relates to stress, pain, suffering and death.

Before starting this analysis must be determine whether the project complied with the requirements of the 3Rs:

Replacement - the project cannot be done only on live animals, it must be explained if the researchers had considered alternative solutions and whether alternative solutions are being applied. There is the possibility of the existence of alternative methods cannot be used at which submitted the project, but also alternative methods that do not provide the results expected by the customer. All this must be scientifically justified.

Reduction – the use of a minimum number of animals proved by statistical methods, sharing of animals with other laboratory / institute. Special attention should be given in case of too few animals, a number that cannot provide relevant research or incorrect results, which will lead to repetition of the studies.

Refinement - choice of species, strains of animals, the use of analgesia and anaesthesia, other ways of reducing the suffering of animals, the degree of suffering expected in animals, housing conditions, microclimate conditions, the application of the methods of the project (administration of substances, surgical methods, etc.). In this aspect, according to the law (Romanian Parliament, 2014) consulting can be requested and obtained from bodies or persons designated for this purpose.

The harm analysis should be done exactly to determine the nature and extent of the harm. The researcher must set the severity of procedures, both for each procedure and for the whole project. The harm determination must consider the cultural traditions, conservatism of the researchers accustomed to working with certain models, the request waivers for other methods of killing than those established by law, the use of species endangered, nonhuman primates, animals captured from wild, straying animals and / or animals that have been bred for use in procedures, conducting studies outside of approved establishments, the reuse of animals in procedures and their continue use to request waivers from standards of care and accommodation. Harm analysis have to highlight whether procedures have been done once before and elsewhere, and their duplication is justified or not.

The benefit analysis has to show if the project will bring new knowledge and in how much time, who will benefit from the project: people, animals or the environment, how they will benefit, if the benefits are direct or indirect, which will be the impact of the expected benefit.

Benefits must be always related to the project purposes: research, education, diagnosis, testing, etc. Potential benefits must also be established as in immediately, medium or long term. The impact should not be neglected if benefits are limited or it is a wider range of beneficiaries. Benefit must be considered as potential and it is good to take into account a possible failure.

Analysis harm - benefit is unique; it is made for each project. Not being an easy thing to accomplish, for this analysis is important to request the input from experts outside the institution, and to search the literature and international databases (Maisack, 2015).

Ethical evaluation of the projects that use animals for scientific purposes ensure both public opinion and scientific community that an animal sacrifice on the altar of science will not be in vain.

Conclusions

1. Authorisation of projects using animals for scientific purposes by the competent authority became a legal requirement.
2. The central point of the authorization dossier is the result of the ethical evaluation.
3. Ethical evaluation of a research project must necessarily go through at least the principles mentioned above, as well as not mentioned any other principle that can contribute to assessing the effects of any behavioral and physiological changes.

4. The final outcome of ethical evaluation has to be favourable only when there compliance to all mentioned principles.

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