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ЭТИЧЕСКИЕ И ПРАВОВЫЕ АСПЕКТЫ ПРОВЕДЕНИЯ ЭКСПЕРИМЕНТАЛЬНЫХ БИОМЕДИЦИНСКИХ ИССЛЕДОВАНИЙ *IN VIVO*

Часть II

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История опытов на животных начинается со времён анатома А. Везалия (XVII в.), когда эксперименты на животных (вивисекции, от лат. *vivus* – живой и *sectio* – рассекание, дословно – «резать по живому») проводились без обезболивания и отличались чрезвычайной жестокостью. В настоящее время использование лабораторных животных разительно отличается от первых опытов и регламентируется определенными нормативными актами. ***Целью*** второй части нашей работы является анализ правовых аспектов использования животных в экспериментах *in vivo*, в т.ч. оказания им адекватного анестезиологического пособия. Рассматриваются нормативные акты, регламентирующие принципы работы с лабораторными животными на различных этапах эксперимента: условия содержания и ухода за животными, включения в эксперимент, ведение эксперимента, выведение животных из эксперимента и определение судьбы животного после эксперимента. Обсуждается международная и отечественная нормативная база по данному вопросу, в частности такие документы как Европейская Конвенция о защите позвоночных животных, используемых для экспериментов или в иных научных целях (18 марта 1986 г., Страсбург), Директива 2010/63/EU Европейского Парламента и Совета Европейского союза (22 сентября 2010 г.) по охране животных, используемых в научных целях и пр. ***Заключение.*** В настоящее время существует достаточное количество нормативных актов, регламентирующих проведение экспериментальных исследований *in vivo*. Однако, большинство из них требует значительной доработки, с учетом последних нововведений в медицинской науке и технике. Актуальным остается и вопрос о контроле за исполнением данных нормативных актов, которые в большинстве своем носят рекомендательный характер.

Ключевые слова: *этика; эксперимент; лабораторные животные; биомедицинские исследования; обезболивание; анестезиологическое пособие; эвтаназия.*

ETHICAL AND LEGAL ASPECTS OF *IN VIVO* EXPERIMENTAL BIOMEDICAL RESEARCH OF THE CONDUCT

Part II

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History of experiments on animals began since the time of the anatomist Andreas Vesalius (XVII century) when experiments on animals (vivisection, from Latin *vivus*, meaning «alive»

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and *sectio*, meaning «cutting», literally «cutting the living tissue») were conducted without anesthesia and were extremely cruel. Nowadays use of laboratory animals considerably differs from that in the time of the first experiments and is regulated by certain legal enactments. ***The aim*** of the second part of our work is analysis of legal aspects of using animals in *in vivo* experiments, in particular, provision of them with adequate anesthesiological support. Normative acts regulating principles of work with laboratory animals in different stages of an experiment are considered: animal care, inclusion into experiment, implementation of experiment, withdrawal of animals from the experiment and determination of animals' fate after the experiment. International and Russian regulatory framework on this issue, in particular, such documents as European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986 March 18, Strasburg), Directive 2010/63/EU on Protection of Animals Used for Scientific Purposes, etc., are considered. ***Conclusion.*** At present there exists a sufficient amount of normative enactments regulating implementation of *in vivo* experimental research. However, most of them require further finalization taking into account recent innovations in medical science and technology. The problem of control of execution of the normative enactments which are in most cases advisory rather than mandatory, remains actual.

Keywords: *ethics; experiment; laboratory animals; biomedical research; vivisection; in vivo; anesthesia; euthanasia.*

At present the most important principle in the ethical and legal aspect of *in vivo* experimental practice is the principle of three «R» (William Russell, 1959) based on humane conduction of experiments on animals. *Replacement* – use of alternative materials and methods such as tissue cultures (skin, endothelium, etc,) and of microorganisms, replacement of vertebrate animals with invertebrate ones, use of computer and mathematical methods of modeling, exchange of information between scientific schools to exclude unreasonable doubling. *Reduction* – a decrease in the amount of animals used in experiment, but so that their number remains sufficient for evidentiality. *Refinement* – principle of improvement of an experiment according to which an experimenter minimizes pain, discomfort and inconveniences inflicted on experimental animals, here, it is not a question of protection of an animal against an experiment, but protection of it directly in the course of research [1].

Aim of work – to consider legal aspects of using animals in *in vivo* experiments on the basis of the data published in the open literature, and to analyze mention of species of animals and of normative-legal enactments (directed to protection and procedure of *in vivo* experiments) in experimental thesis works on specialty 14.01.17 (Surgery) carried out in the Russian Federation in recent 5 years.

In XX century a necessity arose in establishment of international medical organizations, since that form of joining efforts was considered to be most effective in struggling diseases especially of epidemic ones that threatened development of economics, trade being a condition for development of science, for expansion of contacts, exchange of information and implementation of joint scientific research. The result of this agreement was creation of international governmental and non-governmental organizations for development, realization and coordination of collective measures, for cooperation of coun-

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tries in the field of medical science and healthcare. One of these organizations is CIOMS (*Council for International Organizations of Medical Sciences*) that in 1985 established eleven basic principles of working with animals based on «three R» concept. It follows from these principles that an essential condition for development of medico-biological knowledge and of more perfect means of health protection and for assurance of well-being of humans and animals is an experiment on intact animals (laboratory animals not subjected to any experimental factors) of different species. An important method is use of mathematical models or of computer modeling and also creation of biological systems *in vitro*. Besides, experiments on animals should be conducted only after a thorough consideration of its reasonability, that is, of their significance for health of humans or animals themselves and for progress of biological knowledge [2,3].

The first document that regulated treatment of animals used or intended to be used in any experiment or in any other scientific procedure, was European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (Strasburg, 1986 March 18). The documents consists of 37 Articles (where the basic terms used in the Convention, the aims of using animals are stated, procedures of taking care of animals are described, sources of animals ((special nurseries)), institutions-users of animals are indicated), and of two Annexes containing description of the requirements to management of animals (Annex A), and to acquisition of statistical information (Annex B). Annex A underwent last amendments in 2006 and served the basis of intergovernmental GOST standards on management and care of animals for countries-members of the CIS. In particular, GOST standard 33215-2014 «Guide for the Care and Use of Laboratory Animals. Rules of Fitting of Facilities and of Organization of Procedures», GOST 33218-2014 «Guide for the Care and Use of Laboratory animals. Rules of Care and Management of Laboratory Rodents and Rabbits», GOST 33218-2014 «Guide for the Care and Management of Laboratory Animals. Rules of Care and Management of Nonhuman Primates», and some others. The above documents were elaborated by a non-commercial partnership Association of Specialists for Work with Laboratory Animals (*Rus-LASA*) and are applicable in the territory of the Russian Federation. Ethical rules and norms are described in the convention in general declarative form [4,5].

Turning to history, it should be noted that in the USSR there also existed documents regulating experiments on animals, one of them was Order of Healthcare Ministry of the USSR №755 of 1977 August 12 «On Measures for Further Improvement of Organizational Forms of Work with Use of Experimental Animals». In this document a detailed description of rules of management of laboratory animals, conditions of keeping animals in a vivarium (from Latin «*vivus*» – alive) were stated. A vivarium is a building or a special facility in a medico-biological institution, research institute, laboratory, intended for keeping laboratory animals and used in experimental work or in the academic activity. Vivaria should provide normal conditions for experimental animals, that is, make existence of animals before, during and after experiments maximally comfortable (taking into account their physiological peculiarities and demands). For example, the dimensions of cages should permit free movement of an animal. Depending of the species of an animal, the following dimen-

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sions of cages are recommended: for mice (10-20 animals) – 20×30×15 cm, for rats (10-15 animals) – 33×45×20 cm, for guinea-pigs (5-10 animals) – 48×45×20 cm, for rabbits (1-2 depending on age and breed) – 48×45×30 cm. Dogs are kept in kennels with dimensions not less than 2×2×2 m [6].

The most important conditions for keeping animals in vivarium are: availability of ventilated, illuminated, heated rooms, provision of an animal with drinking water and with food according to their physiological demands (non-tilt drinking cups with fresh water and special feeders); regular cleaning of the room. Feeding of animals should correspond to the established norms (by weight, by products assortment and quality). The rations should be diverse and of full value (containing all the required nutrients: proteins, fats, carbohydrates, dietary fibers, nitrogen-free extractive substances, mineral substances and vitamins).The rations of laboratory animals should include complete proteins containing essential amino acids (mostly proteins of animal origin present in milk, meat, fish, egg powder, blood flour, fish flour, meat and bone meal). Thus, laboratory rodents are usually fed on plant food (hay, roots, grain, press cake) with addition of the above mentioned products of the animal origin. The source of mineral substances is kitchen salt, precipitated and powdered chalk, bone flour or bones (for cats and dogs), and also 0.02-0.04% calcium chloride or mineral water. Rabbits, guinea pigs, white rats and white mice can be fed on grain of the wheat, barley, oats and maize in the form of mixtures. For dogs, cats and rats boiled animal meat may be used [7,8]. In vivaria a possibility for rendering veterinarian care is provided including days off and feast days, animals are daily examined by a veterinarian according to a plan of veterinary interventions.

At present the basic document concerning rules of working with laboratory animals is Directive 2010/63/EU of the European Parliament and of the Council on Protection of Animals Used for Scientific Purposes of 2010 September 22. This Directive replaced the outdated document – Directive 86/609/EEC [9,10]. The modern document consists of 66 Articles and 8 Annexes where the aspect of ethical norms alone contains a detailed description and strict regulation of the requirements to a procedure of ethical expertise of the conducted research work, to methods of euthanasia, to special education of personnel, and also classification of procedures according to the level of supposed pain and sufferings inflicted on the animal in this procedure.

This document is mandatory for execution by scientists of all countries of the European Union, however, it has no force of Law in the territory of the Russian Federation. Nevertheless, the influence of European normative acts on the work of Russian researchers is realized through European, some American and the leading Russian scientific journals that require researchers to observe the rules stated in the Directive 2010/63/EU. In view of the fact that Russian scientific workers performing scientific research are obliged to publish the obtained results in a peer-reviewed journal, the requirements of the above mentioned Directive, in fact, become obligatory for them as well [11,12].

A document in the Russian Federation that partly concerns ethical aspects of relation to laboratory animals, is Rules of Good Laboratory Practice adopted in 2003 (approved by Order of Ministry of Health of Russia №267 of 2003 June 19 and reapproved by Order of Ministry of Health, Labor and Social Development of Russia №708n of 2010 August 23). The document

set out the requirements to organization, planning and implementation of preclinical study of medical drugs for application in medicine, to presentation of results and to control of the quality of research in the territory of the Russian Federation [13].

Here, the Rules contained Article 48 which said that the plan of preclinical study should include «legal and ethical norms of use of animals', and also Article 58 stating that in case of performing an experimental study with use of animals, the report of the results of preclinical study should include information about observance of legal and ethical norms of management of animals. With this, the term «ethical norms» was not determined anywhere, and no references were given to any additional materials.

At present the document in effect in the territory of the Russian Federation is Rules of Good Laboratory Practice approved by Order of Ministry of Health of Russia №199n of 2016 April 1 «On Approval of Rules of Good Laboratory Practice» (further: Rules) [12,13]. The given Rules state the requirements that regulate the quality of preclinical studies of drugs for medical application, but any mention of ethical norms in this document is absent [14].

In Article 17 of the Rules it is stated that a necessary condition for experimental study is a vivarium that meets sanitary-epidemiological requirements, with reference to Sanitary-Epidemiological rules SP (SR) 2.2.1.3218-14 «Sanitary-Epidemiological Requirements to Organization, Fitting and Management of Experimental-Biological Clinics (Vivaria)» approved by a decree of Chief State Sanitary Doctor of the Russian Federation №51 of 2014 August 29. These rules contain the requirements to management and care of laboratory animals under normal conditions [15].

In result of content-analysis of 50 thesis works under 14.01.17 code (Surgery) devoted to experimental studies (search depth – 5 years), that were in the open access, the following data were obtained (Table 1).

Table 1

Documents Used as Legal Framework in Conduction of in vivo Experiments

Animal Species / Document	Rats	Mice	Guinea Pigs	Rabbits	Dogs
Declaration on Humane Treatment of Experimental Animals of Helsinki (1975)	2	1	0	1	0
European Convention for Protection of Vertebrate Animals (Strasburg, 1986)	16	4	2	2	2
Order on Ministry of Health of the USSR №755 of 1977 August 12 «On Measures for Further Improvement of Organizational Forms of Work with Use of Experimental Animals»	4	1	1	2	0
Order of Ministry of Health of Russia №199n of 2016 April 1 «On Approval of Rules of Good Laboratory Practice»	8	2	2	0	0

It is important to note that in experiments on animals researchers primarily rely on the European Convention for the Protection of Vertebrate Animals (Strasburg, 1986) – 60% of the total amount of analyzed works. Authors of only 24% works refer to Order of Ministry of Health of Russia №199n of 2016 April 1 «On Approval of Rules of Good Laboratory Practice» in our opinion, it can be attributed to relative

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«freshness» of this normative enactment and to unawareness of researchers of it. Mention of archaic documents containing obsolete data, also confirms suggestion about a weak legal background of experimenters.

According to the above mentioned Order of Ministry of Health of Russia, vivaria for keeping laboratory animals are placed in separate buildings or separate facilities of the organization with observation of sanitary-epidemiological requirements to sanitary protection zones. A modern vivarium contains separate rooms for keeping experimental animals, quarantine, isolation ward, operation room, manipulation room, rooms for euthanasia, for washing and disinfection of instruments. Boxes for laboratory animals are provided with special equipment for disinfection and reduction of microbial contamination of air [16,17]. In planning of vivarium the principle of division of the areas to «clean» and «dirty» should be observed, and conditions should be provided that exclude countercurrent or intersecting flows of the equipment, inventory, vivarium personnel, and of laboratory animals with different degrees of epidemiological danger. Conventional animals delivered to vivarium, are kept before experiment in a special quarantine unit (mice, rats, hamsters, guinea-pigs – 5-15 days; rabbits, cats, dogs, mini-pigs – 20-30 days) isolated from other rooms and equipped with autonomous air supply system.

Requirements to quarantine units are standard. The aims of quarantine are: registration of probable manifestations of infectious diseases in animals, of clinical manifestations of latent processes after stress situation, e.g., after transportation, etc.; in case of initiation of an infectious disease – diagnostic examination of an animal, assurance of safety of the personnel, of the main stock of animals and of the environment. Animals suspected of an infectious disease are subjected to comprehensive laboratory examination. In case of confirmation of an infectious disease by laboratory tests, the animals of the given batch are eliminated. The corpses are treated with disinfectants and burnt. In case of detection of an infectious disease the head of the quarantine units informs the supplier and regional veterinarian service about it in written form [18,19].

Work of guarding, distribution, animal breeding services in constituent entities of the RF is under control of bioethical commission (Commission for Control of Management and Care of Laboratory Animals). It is an independent agency with the staff having scientific/medical education, whose liabilities include protection of rights, safety and well-being of objects of research that are laboratory animals. This is implemented by consideration and approval of a protocol of preclinical study, of acceptability of researchers, instruments, and also of methods and materials supposed to be used in the experiment. The main practical (expert) work is, as a rule, realized at the regional level [20].

Experts of bioethical commission pay special attention to anesthesia and anesthesiological support to which animals will be subjected in a planned *in vivo* experiment. Therefore, one of important conditions of an experiment on animals is use of effective modern means of anesthesia. Animals, unlike humans, do not possess the second signaling system and cannot describe the quality of pain. Moreover, there exists a significant difference between humans and animals in the ethological aspect. If a human demonstratively conveys the presence of pain, for an animal external demonstration of pain, that is, of their temporary helplessness, is often non-beneficial. Animals do not often indicate physical pain by vocalization, however, such behavior of animals should not misinform an experimenter as to the level of their well-being on exposure to damaging factors. To evaluate the extent of pain

in the laboratory conditions, different tests are used. Thus, in rats this test consists in evaluation of the time period during which they are tolerant to exposure of the tail to heating. The same test is used with pigs to evaluate effectiveness of anesthetic drugs. There also exist other more extremal kinds of testing the pain level. For example, indexing of arthritic pain or burning feeling after subcutaneous introduction of a certain dose of formalin [21,22].

Methods of analgesia (Table 2) intended for maximal possible elimination of long-term damages, pain, suffering or anxiety, should be used in every invasive procedure along its entire length. Interventions that are not referred to short-term or minimal, should be performed with use of proper sedative, analgesic or narcotic means in compliance with the modern norms accepted in veterinarian practice [23,24].

Table 2

***Medical Drugs Used for Anesthesiological Support in Experimental Animals (according to A.A. Bunatyan, V.M. Mizikov, 2011* [25])**

Medical Drug	Dose, Introduction Method							
	Mice	Rats	Hamsters	Guinea Pigs	Cats	Rabbits	Pigs	Calf, Sheep
Atropin, mg/kg	0.2-0.3; s/c	—	0.10-0.25; s/c	0.10-0.25; s/c	0.3; s/c	0.6-1.0; s/c	0.3-2.0; s/c	0.5-0.7; s/c
Morphine, mg/kg	0.2; s/c	1.0; s/c	—	—	0.1; s/c	2.0; s/c	0.5; s/c	—
Trimeperidin, mg/kg	—	—	—	—	0.3; s/c	—	—	—
Fentanyl, μg/kg	0.625, i/p	0.125; i/p	0.4; i/p	—	—	—	—	—
Droperidol, mg/kg	30.2; i/p	12.5; i/p	20.0; i/p	—	—	0.125; i/m	0.05-0.15; i/v	—
Chlorpromazine, mg/kg	—	—	—	—	2.0; i/m	0.025; i/v	—	0.5-5.0; i/m
Diazepam, mg/kg	—	—	—	—	0.015-0.060; i/v	12.5; i/m	2.0-4.0; i/m	—
Pentobarbital, mg/kg	4.0; i/m	0.26; 20.0-30.0; i/v	6.0-10.0; i/p	100.0-120.0; i/p	30.0-40.0; i/v	—	—	20.0-25.0; i/v
Thiopental sodium, mg/kg	—	—	30.0-50.0; i/v	60.0-80.0; i/v	15.0-20.0; i/v; i/p	—	30.0-40.0; i/m	—
Sodium oxybate, mg/kg	—	—	—	—	—	30.0-50.0; i/v	15.0-20.0; i/v	—
Propanidid, mg/kg	—	—	—	—	25.0; i/v	30.0-50.0; i/v	100.0-150.0; i/v	8.0-10.0; i/m
Ketamine, mg/kg	5.0; i/v	0.3-5.0; i/v	5.0; i/v	2.0-5.0; i/v	—	5.0; i/v	—	2.0-3.0; i/v
Rocuronium bromide, mg/kg	23.0; i/p	—	—	—	—	—	8.0-10.0; i/m	—
Altesin, mg/kg	—	140.0-400.0; i/v	—	—	—	—	2.0-3.0; i/v	—
Suxametoinum iodide, mg/kg	0.1; i/v	0.1; i/v	0.1; i/v	0.1; i/v	0.1; i/v	1.0; i/v	1.0-2.0; i/v	1.0; i/v
Tubocurarine chloride, mg/kg	—	0,5; i/v	—	—	—	—	7.5-15.0; i/v	—
Tiletamine, zolazepam, mg/kg	0,18mg/ 100 g; i/m	4 mg/100 g i/m	3 mg/100 g i/m	2.0g/100 g i/m	15.0 i/v	20.0-25.0 i/m	0.025 i/m	—

Note: i/v – intravenously; i/m – intramuscularly; i/p – intraperitoneally; s/c – subcutaneously, pr. – premedication; an. – anesthesia

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Table 3

Modern Methods of Euthanasia of Laboratory Animals (according to Directive 2010/63/EU of the European Parliament and of the Council on Protection of Animals Used for Scientific Purposes of 2010 September 22 [9])

Method / Animal	Fish	Amphibia	Reptiles	Birds	Rodents	Rabbits	Cats, Dogs, Polecats, Foxes	Large Mammals	Nonhuman Primates
Overdose with anesthetic drug	1	1	1	1	1	1	1	1	1
Air gun	+	+	2	+	+	-	+	-	+
Carbon dioxide	+	+	+	-	3	+	+	+	+
Displacement of cervical vertebrae	+	+	+	4	5	6	+	+	+
Concussion of the brain/blow on the head	-	-	-	7	8	9	10	+	+
Decapitation	+	+	+	11	12	+	+	+	+
Electric discharge	13	13	-	13	-	13	13	13	+
Inert gases (Ar, N_2)	+	+	+	-	-	+	+	14	+
Shooting off with bullets from appropriate guns, other weapons and ammunition	+	+	15	+	+	+	16	15	+

Notes: «+» – the method is used without additional instructions; 1 – if necessary, with preliminary intake of sedatives; 2 – used only for large reptiles; 3 – used only in case of gradual filling of the chamber with carbon dioxide; not used for fetuses and newborn rodents; 4 – used only for birds with weight under 1 kg; birds with weight more than 250 g should be preliminarily given a sedative drug; 5 – used only for rodents with the weight under 1 kg; rodent with the weight more than 150 g should preliminarily receive a sedative drug; 6 – used only for rabbits with the weight under 1 kg; rabbits with the weight more than 150 g should be preliminarily given a sedative drug; 7 – used only for birds with the weight under 5 kg; 8 – used only for rodents with the weight under 1 kg; 9 – used only for rabbits with the weight under 5 kg; 10 – used only for newborns; 11 – used only for birds with the weight under 250 g; 12 – used only in case if use of other methods is impossible; 13 – requires special equipment; 14 – used only for pigs; 15 – used only in field conditions by experienced shooters; 16 – used only in field conditions by experienced shooters if use of other methods is impossible

In surgical interventions in experiments on animals the following groups of analgesics are used: no inhalation analgesics (pentobarbital, thiopental sodium, phenobarbital, allobarbital, ketamine); inhalation analgesics (isoflurane, diethyl ether, cyclopropane, methoxyflurane, halothane). A researcher should be very careful in choice of a method and

means of narcotization and of premedication of laboratory animals (Table 2) [25]. Nowadays for premedication, as a rule, a combination of medical drugs is used analogous to that used in clinical practice in surgical interventions on humans: M-cholinergic antagonists (atropine), antihistamine drug (diphenhydramine), neuroleptic (chlorpromazine), anxiolytic (diazepame). Insufficient anesthesiological support (for example, use of only myorelaxants, such as diplazin dichloride, bis-dimethyl succinate bis-dimethyl sulphate, etc.), induces a great resistance in an animal which does not permit to reduce pain sensitivity and to perform the planned manipulations in full volume, and increases share of risk that may result in failure of the experiment and even in death of an animal [26].

In modern experimental anesthesiology Zoletil® is widely used which contains tiletamine hydrochloride and zolazepam hydrochloride as active substances. Zolazepam induces anxiolytical and sedative effects, relaxation of striated muscles and enhances analgesic effect of the general anesthetic tiletamine.

According to the above stated ethical norms, in the postoperative period after the experiment the animal should receive professional care and, if necessary, adequate anesthesia.

Upon completion of any procedure a decision is taken about preservation of animal's life or scarification of it by a humane method. The animal is sacrificed if there is area son to suggest that it will constantly feel pain and anxiety. If upon completion of the procedure the animal is decided to be kept alive, it must receive the required care and should be under observation of a veterinarian or of some other competent person [27].

The animal that remained mutilated or non-viable (in result of an experiment or another procedure) should be sacrificed in due time with observation of all humanity requirements. Euthanasia (from Greek *εὖ* – good and *θάνᾰτος* – death) is a deliberate interruption of life with the aim of stoppage of suffering [28]. On the one hand, with the help of euthanasia an animal is released from sufferings, besides, it permits to reduce financial expenses on supporting life of an ill animal. On the other hand, euthanasia contradicts religious convictions and moral principles of the society; besides, in many countries it is not possible to control correctness of implementation of this procedure [29].

At present, feasibility and humanity of euthanasia continue to remain the subject of dispute. Euthanasia is performed by a sufficiently wide range of different methods (Table 3). Besides medicinal methods, it is possible to use carbon monoxide and dioxide, decapitation, electric shock, cervical dislocation, air embolism, etc. In recommendations of international zooprotective organizations (World Federation for the Protection of Animals, WFPA, International Society for the Protection of Animals, ISPA, World Society for the Protection of Animals, WSPA, Laboratory Animals Specialists Association, Rus-LASA) it is stated that the most humane method of scarification is overdose of narcosis. For this, a lethal dose of the anesthetic drug is introduced, that is three timed the normal dose required for effective dropping-off to narcotic sleep [9]. Unacceptability of the method of euthanasia is determined by insufficient safety of the personnel and of the environment, and also by infringement of ethical norms in relation to laboratory animals.

In withdrawal of animals from the experiment, a record about death is obligatorily made stating the a ascertaining factors. The corpse of an animal can be eliminated only after death has been verified by a person responsible for work with animals or by an experimenter himself [1].

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Conclusion

So, each research work that suggests conduction of an experiment on laboratory animals should be carried out in compliance with the national and international normative-legal acts, in particular, with the requirements of humane handling of animals used in an experiment, such as Directives of the European Parliament and of the Council on Protection of Animals Used for Scientific Purposes, and also «local» regulating documents [Order of Ministry of Health of Russia of 2016 April 01 №199n «On Approval of Rules of Good Laboratory Practice» (registered in Ministry of Justice of Russia №43232 of 2016 August 15)]. However, despite abundant normative system [9,14,15,29], the issues concerning ethics and legal regulation of experiments on animals remain open [30] which may be due to advisory character of the normative acts.

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