Medical Research involving Animals in Russia – an Overview

A Report for TRUST working towards Equitable North South Research Partnerships

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Executive Summary

Ethical issues associated with medical research involving animals (MRIA) must be addressed in regulation and policy, as well as implementation of best practice. This report summarises current regulations, policies and practices associated with ethical issues and MRIA in Russia. It is concluded that animal research in Russia is based on the universal humanitarian standards for MRIA, and is internationally recognized in terms of good practice.

Historical Overview

Medical research involving animals (MRIA) has brought great benefits to humanity. The outcome of this research has been of international societal value, promoting human health and saving human lives through prevention and treatment of illnesses. At the same time, historically there has been increasing concern about animal welfare linked to animals used in research. The result has been the international development and implementation of good ethical practice standards in MRIA.

This report reviews ethical consideration of MRIA in Russia, to enable comparison with international practices. The iconic image of good practice regarding animals used in experimentation in Russia is the monument to “Pavlov’s dog”, located in the Saint-Petersburg Institute of Experimental Medicine, on the initiative of Ivan P. Pavlov himself, who won the Nobel Prize for Medicine in 1904.

Despite Pavlov’s interest in the ethical treatment of research animals, the issue of replacement with alternative methods was not, at this time addressed. An important question arises today as to whether we should assess the consequences of continuing with MRIA, or use non-animal alternatives. As part of this, there is a requirement to understand from an ethical perspective the suffering of animals, the moral need to protect them from harm, and to define their rights in experimental contexts.

A fundamental scientific issue within biomedical research is to improve our understanding of animals’ lives. The seminal research into animal behaviourism, which was initiated by Pavlov, has been and continues to be one of the justifications for using animals in research. It also provided the basis for the study of ethology, which is a multidisciplinary research area combining experimental, philosophical, ethical and technical elements related to the study of animal behaviour. The Russian contribution to Physiology and Ethology includes animal research. I provide some examples below.

- V.A. Wagner (1849-1934) – formulated ideas about the evolutionary origins of instincts and the importance of the comparative study of behaviour for the development of problems of phylogeny as a whole, and anticipated a number of provisions of ethology (V.A.Wagner, 1913).
- V.M. Bekhterev (1857–1928) - claimed that the source of knowledge about the behaviour and work of the brain of humans and animals are objective observation and experiment, and not a subjective analysis of behaviour (V.M. Bekhterev, 1924)

- The representations of L.A. Orbeli (1882-1958) received brilliant confirmation in modern studies of the ability to generalize and use symbols in higher vertebrates (L.A. Orbeli, 1949)
- P.K. Anokhin (1898–1974) – developed the theory of functional systems and the concept of systemogenesis, i.e. on the regularities in the development of functional systems (P.K. Anokhin, 1949). The same principle is the cornerstone of cybernetics.

Russian Contribution to Research

In a significant number of research activities, observations of animals in natural conditions have been combined with observations in enclosures, which has made it possible to specify many details of behaviour unavailable in observations made only in nature, including those related to the organization of communities and communication in a number of species. Examples are the fundamental research into the higher nervous activity of anthropoid apes (see Firsov, 1977, 1993 and documentary films “Monkey Island”, 1974 and “Boy, Lel, Chingiz and others”, 1974) as well as the significant work of V.M Smirin (1991) and V.P. Poshivalov (1978), who were not only talented scientists, but were also skilful artists who created unique drawings and paintings illustrating animal behaviour.

This was an important contribution in the field of MRIA, which established good practice for the treatment of experimental animals based on pharmaco-ethology research, and ethological atlases of species-specific behaviour of laboratory rodents and primates, as conducted by Poshivalov. An ethological atlas includes the registration and comprehensive analysis of a large number of specific animal behaviours, together with a system for their classification (for an example see Fig 1):

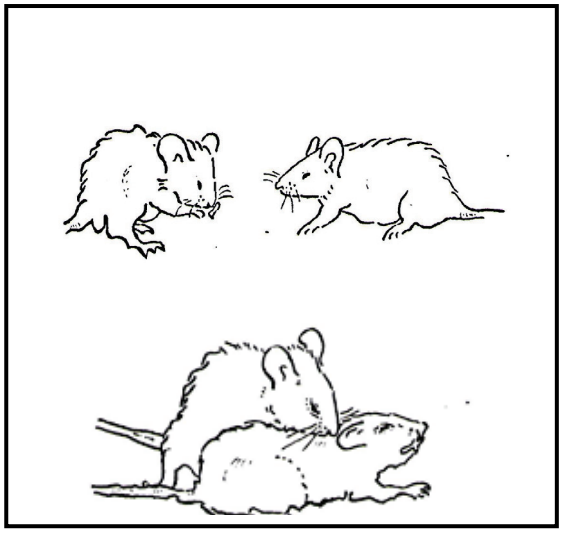

Figure 1. – from V.P. Poshivalov “Ethologic atlas for pharmacological research on experimental rodents”. – M.: Deposited in VINITI. – 1978. – P.3164-3178”.

In addition, Poshivalov created the «Etograf», which became a prototype for the modern electronic observation device “Noldus” for studying the behaviour of animals.[2]

Thus Russia has had a long scientific tradition of developing theories and tools for using animals in research, which has led to modern regulations and policies regarding Russian MRIA.

[2] http://www.noldus.com/

Legislation, Regulation and Policy relating to scientific procedures on Animals in Russia

International Background

There were no common regulations regarding the welfare of experimental animals until the end of the 20th century in Europe. The exception was the "Universities Federation for Animal Welfare" published in the UK (1942). The great influence on developing regulations and policies in relation to MRIA was the publication of "The Principles of Humane Experimental Technique", (Russel and Burch, 1959), where 3 basic principles, "Refinement, Reduction, Replacement", (the "3Rs") were formulated.

Subsequently, the Council for International Organizations of Medical Sciences has issued "International Guiding Principles for Biomedical Research Involving Animals" (CIOMS, 1985 (most recent edition 2012)). This publication has provided the 11 main ethical principles associated with MRIA, and has been credited with stimulating the development of national and international regulation in the field.

In 1986 the first European Directive 86/609 was established, where limited requirements regarding the welfare of experimental animals were presented; this document was subsequently upgraded and the main normative act regulating research involving animals in Europe is EU Directive 2010/63/EC. Important information in relation to safety in MRIA is also required by Good Laboratory Practice (GLP). These are covered by Directives 2004/09/EC and 2004/10/EC of the European Union.

National background

The first document which relates to the humane use of animals in research in Russia was the Order of the Minister of Health Care of USSR №755 (12.08.1977). It was developed on the basis of the principles of the Declaration of Helsinki (1964), and the "Sanitary Rules" № 1045-73, (06.04.73). The Order included requirements for a vivarium for experimental animals, and described the rules for prevention of pain for animals (app. 3) and the obligations for narcosis (app. 4). In Russia the legislative field on this subject was developed in harmonization with international standards, including the European standards described above. Implementation of European Directive 2004/10/EC in Russia is laid down in the following documents:

1. Federal Law (FZ) "On technical regulation", No. 184-27.12.2002. This was implemented on 02.12.2009. The law replicated the "Principles of Good Laboratory Practice", published by OECD (1998)
2. The main legislative instrument is the Law "On Circulation of Medicines" N 61-FZ, 12.04.2010. According to article 11, the requirements for GLP were approved (last update 29.12.2016)

3. Order of the Ministry of Health and Social Development No. 708n “On the approval of laboratory practice rules” (23.08.2010)[3]
4. Order of Government RF 17.12.2013 N 1172 “On acceptance and evaluation of the compliance of experimental laboratory (centres) to the Principles of GLP” (last updated15.12.2016 by Statement of Government of RF , N 1363[4]
5. GOST (State Industry Standard) 31886-2012 "Principles of Good Laboratory Practice (GLP)” Application of the GLP principles to short term studies.
6. The quality of research, including ethical treatment in the context of MRIA, depends not only on the existing regulation, but also on the ability of experimental centres to follow the rules and guidelines provided. Different GOSTs cover the different aspects of the management system of GLP quality[5]. These include the following:
    - GOST 31879-2012, 01.01.2013 provides guidelines for procedures monitoring compliance with GLP
    - GOST 31880-2012, 01.01.2013 provides guidelines for inspection and audit
    - GOST 31884-2012, 01.01.2013 provides guidelines for ensuring compliance for suppliers of animals with the principles of GLP
    - GOST 31890-2012, 01.01.2013 relates to the application of the principles of GLP to the organisation and management of multicentre trials on animals
    - GOST 31891-2012, 01.01.2013 relates to the application of the principles of GLP to in vitro research
    - GOST 31891-2012, 01.01.2013 relates to the organization and control of the archives in compliance with the principles of GLP and documentation
    - GOST 33044-2014 provides guidelines on the acceptability of the results of scientific research
    - GOST 33044-2014, GOST 33215-2014, GOST 33216-2014, GOST 33217-2014, GOST 33218-2014, GOST 33219- 2014, Standard Rules 2.2.1.3218-14 [8], and (as mentioned above) Directive 2010/63/EU and the Order of Government RF 17.12.2013 N 1172 (last update 15.12.2016), “On acceptance and evaluation of the compliance of experimental laboratory (centres) with the Principles of GLP”. These relate to carrying out experiments, data storage, sampling, quality of forages and other materials, through to rooms for research personnel. They highlight important factors which need to be considered if high-quality research is to be conducted involving animals. In addition to maintaining appropriate conditions in relation to air exchange, light and temperature conditions, the regulations cover the quantity of animals to be housed per unit area, in order to provide optimal zoo-social conditions. Daily supervision in relation to individual and group

[3] http://www.fondmrt.ru/en/services/pharma/clinical-studies
[4] http://www.pravo.gov.ru
[5] http: //www.pharmjournal.ru

behaviour of animals kept in contained conditions is necessary (as described in the work of V.P. Poshivalov, noted above). The relevant regulations are:

- GOST P50258-92, which stipulates requirements for forage. GOST 51232-98 does the same for water
- GOST 2552017 № 2 provides the Guidelines for test-systems for targets of pharmacological activity in vitro, in silico, ex vivo and in vivo. GOST P 57146-2016 covers these issues in relation to carcinogenicity, and GOST P 57130-2016 in relation to genotoxicity
- GOST P ISO 5725-1-2002 provides guidelines for the validation of methods and measurements, and is equivalent to the International Organization for Standardization (ISO) requirements
- GOST 33044-2014 details the responsibility for administration of Experimental Centres, establishing the Standard Operating Practices and Reporting in accordance with GOST 7.32-2001, GOST P 7.0.5-2008 and GOST P 7.0.12-2011
- GOST P ISO 9001-2015 and GOST 31883-2012 detail the mechanisms for feedback to sponsors

Practical achievements, Transparency and Cooperation

Legislation regarding MRIA in Russia has been developed in harmonization with international standards, as noted above. It is important to emphasize the extent to which the responsible authorities in Russia collaborate with international partners. The administrative body (Roszdravnadzor) has been designated by the Russian Government (30th June 2004, N 323), as the Russian GLP Monitoring Authority. Collaboration between Roszdravnadzor and the European Directorate for the Quality of Medicines and HealthCare (EDQM) was initiated in 2006. Since 2010, Russia has been an Associated Member of the Official Medicines Control Laboratories (OMCL). In April, 2009, the Memorandum between Roszdravnadzor and Pharmacopeia USA (USP) was signed, for exchanging information, and common training and common inspection was agreed.

At the present time, one of the main tools for developing cooperation in regulations has been focused on the establishment of common legislation in the frame of the Euro-Asia Economical Union (EAEU). Great progress was made regarding the development of cooperation in the area of MRIA on 3 November 2016; see N81 “Approval of the Rules of Good Laboratory Practice in the Euro-Asia Economic Union in the Sphere of Circulation of Medicines”[6].

The future holds good prospects for the harmonisation of Russian regulations with the EU and the EAEU; this is based on common understanding and trust. This will promote the application of the 3Rs principles: the restriction of impacts on animals (limits on pain, restriction on the reuse of animals);

[6] http: // www.consultant.ru, 18.11.2017

toughening requirements for use of primates, and increased societal transparency in relation to MRIA.

In order to realise these recommendations in actual research practices in Russia, it is important to gradually reduce the number of animal experiments and replace these with alternative methods. It is important that discussion relevant to reduction is published and regularly updated in important scientific journals in Russia. Recent examples are the article, "Optimization of pre-clinical trials: on the way to humane experimental techniques" (V.A. Volskaya, 2016), and the publication of "Recommendations for the health monitoring of mouse, rat, hamster, guinea pig and rabbit colonies in breeding and experimental units, Recommendations of the European Laboratory Animal Science Associations", in a Russian journal in 2014[7] (FELASA).

As mentioned above, there are rapidly developing techniques regarding alternatives to animal testing. These are being developed by representatives of the research and academic communities, as well as the pharmaceutical industry and biotechnology companies. The implementation of replacement could be exemplified by the use of the biological principles that are employed in the culture of Chlamydia trachomatis in cell monolayers (McCoy cell cultures) in many research and academic centres in Russia (St.Petersburg Pasteur Institute, laboratory for the identification of pathogens, (V. A. Isakov, L. B. Kulyashova, L. A. Berezina and others, 2010).

The other urgent area for applying humane experimental techniques is related to the ethics of space life. Kasatkina T.V. and Kaplansky F.S. (2000) present an historical sketch on the ethics of the use of animals in life sciences experiments. It is emphasized that these experiments must be performed with observance of ethical principles, and utilise as few animals as possible to obtain statistically significant data.[8]

A serious problem is that the validation procedure to confirm the equivalence of methodologies which can act as alternatives to animal testing is complex and can take up to several years (E.A. Volskaya, 2016). Therefore, it is important to have relevant regulations, good training specialists, available administrative systems and research centre inspections aimed at improving the situation in the field of MRIA in Russia.

It is also important to note the mechanism of independent evaluation in relation to the protection of animals in research by Research Ethics Committees (RECs). Ethics committees have been established in all scientific academic centres in Russia where animals are being used in research. For example, in relation to MRIA, such a committee was established in Saint-Petersburg State University, by the Order of University Rector, (N 7387, 09.12.2014). The REC is guided by both international and national regulations including: GOST P 53434-2009 – Principles of GLP; CIOMS "International Guiding Principles for Biomedical Research Involving Animals"; the "European Convention for the Protection

[7] http: //www. pharmjournal.ru
[8] http://pravo-zoozahita.ru/etika-eksperimentalnyx-issledovanij-na-zhivotnyx-v-kosmicheskoj-biologii-i-medicine

of Vertebrate Animals used for Experimental and other Scientific Purposes"; and the "Guide for the care and use of laboratory animals".

Transparency of Russian activities in research involving animals in general needs to be actioned through wide and open publication and discussion in the media. Exemplar websites include:

- http://www.pharmjournal.ru
- http://acto-russia.org/
- http://www.minzdravsoc.ru/find
- www.grls.rosminzdrav.ru
- http://www.roszdravnadzor.ru/
- http://www.consultant.ru/
- www.pravo.gov.ru
- www.pharmjournal.ru

Conclusion and Perspectives

The focus of this report has been on ethical treatment of animals in research in Russia. The historical background to the current regulatory and policy situation in Russia has been provided, together with a general overview of current regulations regarding animal research, and how they are policed, and connected with international regulations). Different examples of MRIA were considered in the scope of international cooperation in this field.

Particularly important for Russia from a legislative perspective, is the need to approve and action the Law "About protection of Animals against ill treatment (cruelty)", which was adopted by Russian Parliament (State Duma), on the 01.12.1999. This Law addressed the need to protect /or reduce the suffering of animals when used in scientific experiments, biological testing, educational processes and also when receiving biological preparations. However in the 1999 law, there were not many provisions linked to the fundamental international documents regulating experimentation on animals. In addition, in Russia, there was at that time no system of registration and licensing of scientific projects, specialists, or centres using animals. Now, as presented above, all of these defects have been addressed and eliminated, so this Law can play a significant role in the recognition of the Russian legislation system for using animals in research.

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