

Nonclinical studies in the Russian Federation

Problems, regulatory norms, and harmonisation with international standards

Anna Buryakina and Natalie Merkulova
OCT Rus (OCT Group), Saint-Petersburg,
Russia

Correspondence to:

Anna Buryakina
OCT Rus
5 Kovensky lane
6-7 floor
Saint-Petersburg, Russia, 191014
+7 (812) 449 86 34
aburyakina@oct-clinicaltrials.com

Abstract

Drug product developers and sponsors face a number of problems when organising a nonclinical study in Russia, especially, the diverse range of standards and few certified animal breeding centres, complicating adaptation of the available experimental data to domestic legislation. In this article, we discuss the main regulatory documents in Russia, their compliance with international standards (Good Laboratory Practice), the structure of the responsible authorities, and problems with implementing the regulatory documents. Finally, we discuss the current regulatory trends in Russian nonclinical studies.

Laws regulating nonclinical trials in the Russian Federation

Federal Law No. 61-FZ

In the Russian Federation, Federal Law no. 61-FZ dated April 12, 2010,¹ is the principal document regulating the circulation of medicines. Paragraph 11 of this law defines the scope of nonclinical studies and requirements for performing them, including methods for assessing the quality, efficacy, and safety of a drug product. In addition, it stipulates the right to involve scientific and research institutions and relevant higher education organisations. It also requires that the study follows the approved plan and protocol so that the study results can be submitted to an authorised federal authority to



register the drug product. According to this law, nonclinical studies must follow the rules of laboratory practice approved by a relevant federal authority.

Implementation of Good Laboratory Practice (GLP)

Decision nos. 2603-r, 2067-r, and 1172

In Decision no. 2603-r dated December 28, 2012,² the Russian government approved implementation of the Organisation for Economic Co-operation and Development (OECD) GLP guidelines for test facilities (laboratories) conducting nonclinical studies. This was followed by Decision no. 2067-r dated November 8, 2013,³ which specified the list of documents governing compliance of test facilities with the GLP principles. These documents are identical to the OECD's GLP and have been adopted in the Russian Federation as the national standards. In addition, Decision no. 1172 dated December 17, 2013,⁴ specified the procedure for assessing test facility compliance with GLP principles.

Inspection, certification, and maintenance of the register of GLP-certified test facilities are handled by the Federal Service for Accreditation of the Ministry of Economic Development. As of August 1, 2017, this service had certified 10 test facilities, two of which were also accredited by the Slovak National Accreditation System.

Decree no. 965

Bringing the performance of nonclinical studies of medicines in compliance with the GLP rules is one of the tasks of the National Strategy for Development of the Pharmaceutical Industry (Pharma2020), which was established by the Ministry

of Industry and Trade of the Russian Federation in Decree no. 965 dated October 23, 2009.⁵ The main goal of this programme was to create a modern system for developing and manufacturing medicines in the Russian Federation.

"Guidelines for the Testing of Chemicals" from the Federal Agency for Technical Regulation and Metrology

Following announcement of this programme and in response to Decision no. 2603-r and Decision no. 2067-r, in 2013-2014, the Federal Agency for Technical Regulation and Metrology developed an additional series of documents governing nonclinical studies. The new documents, "Guidelines for the Testing of Chemicals",⁶ cover methods for assessing how a chemical affects the human body and, to a large extent, replicate the OECD Test Guidelines that are applicable to drug products. Currently, the Russian Federation has standards identical to Test Guidelines 402, 403, 406-408, 410-415, 421, 423, 424, 431, 452, 453, 471, 476, 477, and 487, which are available at <http://docs.cntd.ru>.

Standards for nonclinical studies based on International Conference on Harmonisation (ICH) documents

In the 2000s, the Ministry of Health of the Russian Federation issued some decrees on implementing GLP principles for nonclinical studies of medicines, and in 2015-2016, the Russian government introduced a series of the national standards entitled "Medicines for Human Use". Most of these standards are translated ICH documents (Table 1).

Decree no. 199

Currently, the only valid document regulating nonclinical studies is Decree no. 199 "On Approval of the Principles of Good Laboratory Practice" dated April 1, 2016.⁷ This document contains general provisions correlating with the key national standards, GOST 33044-2014 "Principles of Good Laboratory Practice" and GOST R 53434-2009 "Principles of Good Laboratory Practice",⁸ which are identical to the OECD's GLP. Decree no. 199 states that the GLP principles are applicable for all studies related to developing medicines, whereas Federal Law no. 61-FZ does not require a full compliance with these rules



Table 1. National standards in the Russian Federation regulating nonclinical studies and their ICH equivalents

Document	ICH equivalent
GOST 56700-2015 Medicinal Products for Human Use. Safety Pharmacology studies for human pharmaceuticals ^a	Similar to ICH S7A:2001 “Safety Pharmacology studies for human pharmaceuticals”
GOST 57147-2016 Medicinal Products for Human Use. Nonclinical evaluation for anticancer pharmaceuticals	Similar to ICH S9:2009 “Nonclinical evaluation for anticancer pharmaceuticals”
GOST 57146-2016 Medicinal Products for Human Use. Studying for carcinogenicity of pharmaceuticals and excipients	Contains main regulatory provisions of ICH S1A:1995 “Guideline on need for carcinogenicity of pharmaceuticals”; ICH S1B:1997 “Testing for carcinogenicity of pharmaceuticals”; ICH S1C(R2):2008 “Dose selection for carcinogenicity studies of pharmaceuticals”
GOST 57130-2016 Medicinal Products for Human Use. Genotoxicity testing and data interpretation ^b	Similar to ICH S2:2011 “Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use”
GOST 56702-2015 Medicinal Products for Human Use. Nonclinical toxicology and pharmacokinetic studies of safety	Contains requirements of ICH S3A:1994; ICH S3B:1994; ICH S3A “Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies”; Section 5: ICH S3B: “Guidance for repeated dose tissue distribution studies”
GOST 56699-2015 Medicinal Products for Human Use. Preclinical safety evaluation of biotechnology-derived pharmaceuticals. General recommendations	Similar to ICH S6 (R1):2011 “Preclinical safety evaluation of biotechnology-derived pharmaceuticals”
GOST 56701-2015 Medicinal Products for Human Use. Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals	Similar to ICH M3(R2):2009 “Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals”
GOST 57129-2016 Medicinal Products for Human Use. Part 1. Stability testing of new drug substances and products. General recommendations	Similar to ICH Q1A:2003 “ICH Topic Q1A (R2) Stability Testing of New Drug Substances and Products. Part 1. Stability testing of new drug substances and products”

^a Title changed to correspond to those adopted in the “Medicinal Products for Human Use” standards.

^b Applicable only for chemically synthesised medicines, not valid for biological products

when screening and evaluating the active substance. In other words, paragraph 11 of the Federal Law no. 61-FZ conforms with international practice, which is to not regulate pilot medical and biological studies conducted during research and development.

The need to adhere to the quality standards at the initial R&D phases is clear, but the legal framework in the Russian Federation does not include principles similar to the quality standards for biomedical studies. Despite this, safety is a key aspect of GLP; they require assessing the public and ecologic safety of chemical substances, including medicines. Applying GLP principles to the development of medicines, as

required by the Ministry of Health, may lead to the loss of sources, prolongation of studies, repression of progress and block of new approaches, etc.

“Guidelines for Preclinical Trials of Medicinal Products”

Since 2000, the Scientific Centre for the Expert Evaluation of Drug Products for Human Use, which is part of the Ministry of Health, has provided expert review of planned clinical trials, related documents, and registration dossiers. The Centre produces compilations of their recommendations on nonclinical studies of medicinal products. Their latest document,

“Guidelines for Preclinical Trials of Medicinal Products”, which comprises two volumes, was released in 2012.^{9,10} The first volume contains, in addition to a list of known and well-proven tests, recommendations on evaluating the safety of prospective drug products.⁹ According to these recommendations, the safety of the original drug product, its mechanism of action, and acute and sub-chronic toxicity should be demonstrated using two animal models, one of which is non-rodent. In addition, the recommendations require providing data on immunotoxicity, reproductive toxicity, embryotoxicity, mutagenicity, cancerogenic activity, cumulative properties, sensitising activity, pharmacokinetics, and metabolic effects.

The second volume of “Guidelines for Preclinical Trials of Medicinal Products”¹⁰ defines the scope of obligatory safety evaluation studies for bio- and nano-technological drug products, combined drug products, galenic formulations, paediatric drug products, and generics. According to these Guidelines, to comply with GLP requirements, nonclinical studies must be performed for both the active pharmaceutical substance and its finished dosage form. Even though the Centre’s compilations do not have regulatory status in Russia, local drug developers consider them mandatory.

Federal Law no. 429-FZ

On July 1, 2015, amendments to Federal Law no. 61-FZ, defined by Federal Law no. 429-FZ,¹¹ came into force. Law no. 429-FZ takes into account the need for federal approval of rules for proper pharmaceutical practices, including GLP. The amendments do not directly affect nonclinical studies, but it introduced new terms (e.g. orphan drugs, biological preparations, and bioanalogues) and their definitions. This led to implementation of new approaches and methods for nonclinical research. The new law also introduced scientific consulting procedures for issues related to nonclinical and clinical research, assessing drug quality, evaluating efficacy and safety, and registering medications.

Barriers to implementing the guidelines

In summary, for nonclinical studies of drug products, the investigators and the study teams must follow:

- GLP rules,
- the set of documents approved as national standards and compliant with the OECD, the ICH, and Decree No 199N, and
- Guidelines for Preclinical Trials of Medicinal Products.

Several problems have created barriers to implementing all these guidelines, including inconsistencies in toxicity study designs, inconsistencies in terminology, and an insufficient supply of good-quality animals.

Inconsistencies in toxicity study designs

A number of problems arise in applying recommendations because of inconsistencies between the standards set forth in “Guidelines for the Testing of Chemicals”⁵ and tests traditionally used by Russian investigators and

experts. For instance, in Russia, acute and single-dose toxicity studies are not seen as different. As a rule, acute toxicity experiments allow the lethal dose to be determined exactly or at least to be approximated, but the OECD methods do not always require a 50% lethal dose to be determined. According to the “Guidelines for Preclinical Trials of Medicinal Products”,^{9,10} which is strictly followed by experts of the Ministry of Health, the 50% lethal dose (LD50) should be determined by the Litchfield and Wilcoxon method,¹² and cumulative properties of the drug product should be determined as suggested by Lim et al,¹³ which depends on the LD50. The guidelines also state that for studies in large animals, even if the LD50 has not been determined, describing only the toxic effects is allowed and that small animal studies should not be continued at higher doses if death has not occurred at 2000 mg/kg. In other words, determine the LD50 is not always necessary according to the OECD.

ICH M3R2, adopted as the national standard in the Russian Federation (Table 1) recommends performing an extended single-dose toxicity study. In addition to evaluating acute toxicity, such studies determine clinical, chemical, haematological, haemostatic, toxic, kinetic, and other parameters. They provide a wider overview than the common approach and results that are compatible with those obtained by repeat-dose studies. In the most cases, single-dose toxicity can be evaluated in escalation-dose or in short-dose experiments. To predict short-term safety in people, toxicity is evaluated according to ICH S7A and S7B, which are identical to the national standard in Russia (Table 1). However, investigators usually choose to comply with the “Guidelines for Preclinical Trials of Medicinal Products”,^{9,10} as recommended by the Ministry of Health, which do not use the term “pharmacological safety”, and investigators rarely perform the types of study described in the ICH guidelines, evaluate the maximum tolerated dose in a repeat-dose experiment, or perform individual safety experiments. At the same time, the more recent “Guidance on Expert Assessment of Medicinal Products”¹⁴ states that the safety of a drug product must be evaluated before the first-in-human studies.

Despite barriers to implementing the guidelines, the Russian Federation is gradually beginning to understand that without common standards, new treatments will not become available.

Terminology inconsistencies

Inconsistencies in terminology has been an important barrier to introducing GLP principles in the Russian Federation. For example, the Decree no. 199n⁷ and the Federal Law no. 61-FZ¹ use the term “preclinical studies”, whereas GOST 33647-2015 uses the more

correct term “nonclinical studies”.¹⁵ The term “preclinical studies” assumes that all respective studies are completed before the first administration of a drug in human, whereas most of them are conducted at the same time as the clinical trials.

A standard for terminology, GOST 33647-2015,¹⁵ has been developed and includes terms consistent with the GLP definitions for nonclinical safety studies of chemicals, provided in both Russian and English.

Insufficient supply of good-quality animals for nonclinical studies

Another barrier to implementing GLP principles in Russia is the lack of a sufficient supply of animals. Only the “Pushchino” animal breeding centre of the Institute of Bioorganic Chemistry of the Russian Academy of Sciences has an international veterinary certificate, and until recently, animal breeding centres at research institutes were the only sources of laboratory animals. In addition, due to a lack of funding, breeding facilities have been poorly maintained or abandoned. Although GLP studies cannot be performed without SPF animals, they are bred at only two centres in Russia. Furthermore, the range of animals is limited because no centres breed cats or dogs, only one breeds primates, and only a few breed ferrets, gerbils, and mini pigs.

Going forward

Despite barriers to implementing the guidelines, the Russian Federation is gradually beginning to understand that without common standards, new treatments will not become available. Members of the Eurasian Economic Union, which includes Russia, Belarus, Kazakhstan, Armenia, and Kyrgyzstan, have compiled common regulatory requirements and have therefore developed legal regulations for the circulation of medicines. The Union has created a unified system for drug registration, is discussing issues related to

inspections and mutual recognition of preclinical (nonclinical) and other research, and has translated and adopted nearly all appropriate European pharmaceutical practice guidelines. GLP principles have been developed taking into account the approaches adopted by the European Union, OECD, and ICH.

Conflicts of interest and disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

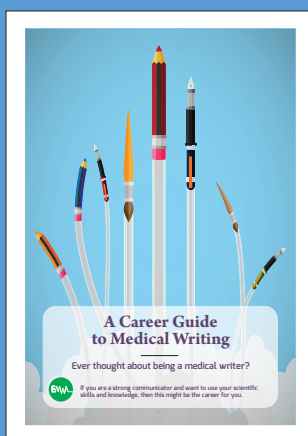
References

1. Russian Federation Federal Law no. 61-FZ "On Circulation of Medicines" dated April 12, 2010. Available from: https://www.unodc.org/res/cld/document/rus/federal-law-on-circulation-of-medicines_.html/Russian_Federation_Federal_Law_On_Circulation_of_Medicines_61-FZvEN.pdf.
2. Decree no. 2603-r dated December 28, 2012 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/document/902392511>.
3. Decision no. 2067-r dated November 8, 2013 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/document/499056249>.
4. Decision no. 1172 dated December 17, 2013 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/document/499065307>.
5. Decree of the Ministry of Industry and Trade of the Russian Federation no. 965 dated October 23, 2009 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/document/902186334>.
6. "Guidelines for the Testing of Chemicals", 2014 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/search/intellectual/q/Методы+испытания+по+воздействию+химической+продукции+на+организм+человека/r/1>.
7. Decree no. 199 n "On approval of the principles of Good Laboratory Practice" dated April 1, 2016 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/document/420350679>.
8. National standard of the Russian Federation GOST R 53434-2009 "The principles of Good Laboratory Practice" dated April 1, 2016 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/document/1200075972>.
9. Mironov AN, editor. Guidelines for Preclinical Trials of Medicinal Products. Part 1. Moscow: Grif i K; 2012.
10. Mironov AN, editor. Guidelines for Preclinical Trials of Medicinal Products. Part 2. Moscow: Grif i K; 2012.
11. Federal Law "On amendment of the Federal Law 'On Circulation of Medicines'" no. 429-FZ dated December 22, 2014 [cited October 13, 2017]. Available from: <http://pravo.gov.ru/proxy/ips/?docbody=&firstDoc=1&lastDoc=1&nd=102364596>.
12. Litchfield JT, Wilcoxon F. A simplified method of evaluating dose-effect experiments, *J Pharmacol Exp Ther*. 1949;96(2):99–113.
13. Lim RK, Rink KG, Glass HG Soaje-Echague E. A method for the evaluation of cumulation and tolerance by the determination of acute and subchronic median effective doses. *Arch Intern Pharmacodyn*. 1961;130:336–53.
14. Guidance on expert assessment of the medicinal products. V. 1-4; 2013-2014. Available from: <http://fptl.ru/biblioteka/razrabotka-i-ekspertiza-lekarstv.html>.
15. GOST 33647-2015 "Principles of good laboratory practice (GLP). Terms and definitions", 2015 [cited October 13, 2017]. Available from: <http://docs.cntd.ru/document/1200129061>.

Author information

Anna Buryakina, PhD, is an Associate Professor in Clinical Pharmacology and a preclinical project manager at OCT Rus (OCT Group), a full-service contract research organisation operating in Russia, Ukraine, Belarus, Latvia, Lithuania, and Estonia. Her responsibilities include expert review, writing, and advising on toxicology, pharmacology, and clinical pharmacology. Before joining OCT Rus, she worked for many years as an educator and researcher in general and clinical pharmacology.

Natalie Merkulova is a medical writer at OCT Rus. Her responsibilities include regulatory writing and editing. Before joining OCT Rus, she worked for several years in medical translation, nonclinical and clinical toxicology, and molecular biology.



EMWA's Medical Writing Career Guide

Included in the guide:

- What is medical writing
- The different types of medical writing
- The skills and qualifications needed to be a medical writer
- Where medical writers work and what they do
- How to get started
- How much to expect to get paid
- Career prospects for medical writers

Download at: <https://www.emwa.org/resources/useful-reading/a-career-guide-to-medical-writing/>