Nonclinical studies in the Russian Federation

Problems, regulatory norms, and harmonisation with international standards

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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.

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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-р, 2067-р, and 1172**

In Decision no. 2603-р dated December 28, 2012, 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-р dated November 8, 2013, 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, 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. 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


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. 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", 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.
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, carcinogenic activity, cumulative properties, sensitising activity, pharmacokinetics, and metabolic effects.

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

<table>
<thead>
<tr>
<th>Document</th>
<th>ICH equivalent</th>
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<tbody>
<tr>
<td>GOST 57147-2016 Medicinal Products for Human Use. Nonclinical evaluation for anticancer pharmaceuticals</td>
<td>Similar to ICH S9:2009 “Nonclinical evaluation for anticancer pharmaceuticals”</td>
</tr>
<tr>
<td>GOST 57130-2016 Medicinal Products for Human Use. Genotoxicity testing and data interpretationb</td>
<td>Similar to ICH S2:2011 “Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use”</td>
</tr>
<tr>
<td>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</td>
<td>Similar to ICH M3(R2):2009 “Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals”</td>
</tr>
</tbody>
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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
The second volume of “Guidelines for Preclinical Trials of Medicinal Products”10 defines the scope of obligatory safety evaluation studies for biomedical 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 have been an important barrier to introducing GLP principles in the Russian Federation. For example, the Decree no. 199n7 and the Federal Law no. 61-FZ3 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 guide-lines, 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


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