

Russian legal alert



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New law – old problem: New Russian Drug Law and non-interventional post-authorization studies – are they still possible?

I. SUMMARY

The new law “On the Circulation of Medicinal Products” (the “Law”) only regulates phase IV clinical trials but not non-interventional post-authorization studies (“NPA Studies”). Yet, the need for NPA Studies remains. The routine use of a drug under every day conditions must be properly monitored. The lack of their regulation in the Law is regrettable. To differentiate post-authorization trials under the Law from NPA Studies, international standards such as the Directive 2001/20/EC, the Volume 9A of the Rules Governing Medicinal Products in the European Union as well as industry codices such as the FSA Code and LIF Code should be used.

Russian authorities such as the RF Ministry of Health and Social Development and Roszdravnadzor might consider NPA Studies not only as circumvention of the Law but also an inducement to prescribe a particular medicinal product. In order to best avoid any of their concerns, the requirements of international standards and recommendations such as the IFPMA Code, EFPIA Code and AIPM Code as well as others should be complied with in Russia.



II. INTRODUCTION

The development of a pharmaceutical drug is a time-consuming, difficult and costly process. The bulk of the research and development expenses are caused by clinical trials. Only if the data generated by such trials justify approval by the regulatory authorities may the drug in question be sold to the market. As a result, such data are thoroughly reviewed both by the pharmaceutical company submitting its application for the marketing authorization and the competent regulatory authority. Yet the relatively small number of patients enrolled in the three pre-approval clinical studies may not reveal rarer side effects or adverse events. Certain statistical effects do not manifest themselves in the controlled study environment with said restricted number of subjects. Usually this is the case with chronic or repeated exposure to the drug, varying medical histories of the patients, incorrect drug administration in the daily routine of the patients, unknown drug interactions etc. They may not be detected until the drug is made accessible to the general public. Therefore, it is crucial to closely monitor the drug in market conditions to best assure the safety of the patients.

This is not only done by collecting spontaneous notifications of healthcare professionals or patients about adverse events but also by conducting post-marketing studies. Their objective is to detect, categorise and analyse the expected and unanticipated effects of marketed drugs. Such studies may either be requested by regulatory authorities or be conducted voluntarily by the sponsoring pharmaceutical company which markets the drug in question. Various types of studies may be distinguished, such as interventional and non-interventional post-authorisation studies. The distinction is not always easy and will be explained below in Section IV.

Now, for the first time the Russian legislature has adopted regulations regarding post-authorisation studies. This is done in a new law:

III. SITUATION IN RUSSIA

I. NEW LAW AND POST-AUTHORIZATION TRIALS The Law has passed its third and last reading in the Duma; it has been adopted and will enter into force on 1st of September 2010. It replaces the current law "On Drugs". The new Law contains a variety of changes and detailed regulations. This includes a limit of sales prices, a procedure for registration of drugs and more specific provisions about clinical trials. For the first time, post-authorization trials (*пострегистрационное клиническое исследование*) are expressly defined: in para. 44 of Article 4 of the Law it is stated that

"post-authorization clinical trials of medicinal products for medical use are clinical trials of such medicinal products for medical use which are placed on the market after receipt of a marketing authorization; such trials are conducted by the manufacturer of the medicinal product and serve the purpose of gaining additional safety and efficacy data, of broadening the indication of administration as well as of identifying adverse reactions to the medicinal product by patients."

According to Article 38 para. 1 of the Law, clinical trials as well as said post-authorization trials are to be conducted in compliance with Good Clinical Practice ("GCP"). The requirements of clinical trials mentioned in Article 38 expressly apply to post-authorization trials. This includes, inter alia, the necessity to provide an investigator's brochure, a study protocol, adequate insurance etc.



2. NON-INTERVENTIONAL POST-AUTHORIZATION STUDIES The Russian Association of Clinical Trials Organizations ("ACTO") had tried to incorporate regulations about NPA Studies. In the course of the legislative procedure ACTO suggested a definition of such NPA Studies to be included in the Law. The definition was almost literally identical to Article 2 (c) of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001: in this Directive a so-called 'non-interventional trial' is

"a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data."

The purpose of these NPA Studies has great overlap with the studies defined in para. 44 of Article 4 of the Law. They also serve the purpose of gaining additional safety and efficacy data as well as of identifying adverse reactions. Because of this, ACTO had tried to incorporate those NPA Studies into the Law to create some legislative framework and guidance as to their admissibility and scope. Hence, in the commentary to the legislative procedure ACTO stated in line with international practice that NPA Studies do not require the same strict regulatory parameters as formal clinical trials; neither do they need any official approval (except the positive opinion of the ethics committee in case of data protection issues), nor any insurance coverage. The goal of ACTO was to exclude NPA Studies from the regulatory requirements of clinical trials for the purposes of clarity. The main argument was that these studies are merely observational



and do not interfere with the usual routine of the administration of the drug by the patient under everyday conditions; they merely collect data generated without intervention. Furthermore, another difference is that the sponsor does not provide the study drug. Finally, NPA Studies are not conducted in line with GCP. The typical design and the characteristics of such NPA Studies are set forth below in Section IV.

3. IMPACT OF THE LAW ON NPA STUDIES Despite the efforts of ACTO, neither a definition nor any other mention of the NPA Studies has been adopted in the Law. As a result, NPA Studies are not regulated by the new Law. As in the past, this field of studies continues to lack a solid regulatory framework. Thus, no guidance is given by the Russian legislature. Therefore, this raises certain issues:

a) Are NPA Studies still allowed after the Law enters into force, or do they need to comply with the requirements of the Law? If so, any design of NPA Studies would have to amount to a full blown clinical trial according to Article 38 of the Law, with GCP compliance, insurance coverage, investigator's brochure and the like. Yet, by the nature of such studies, this would neither be feasible nor correspond to current international practice. As they are conducted to observe the every day administration, they are not conducted in line with GCP and the necessity of additional insurance would make them more difficult. To prohibit NPA Studies would be fatal: the need for such studies remains, namely to have a tool to receive information about the routine use of a drug under everyday conditions. As stated above, rare side effects, adverse events and potential interactions with other drugs or food products can and need to be determined on a high

number of patients. This also applies to the necessity to gain better knowledge about the efficacy and safety of the drug after market entry. This need to know extends finally to information about certain population groups such as pregnant women who are unlikely to subject themselves to trials. Finally, a pharmaceutical entrepreneur has to monitor his product on the market for safety reasons¹.

b) Where is the borderline between the non-regulated NPA Studies and the regulated phase IV clinical trials and who determines this? As the Law failed to provide a definition, international standards might help to determine the delineation line, see Section IV below.

c) If NPA Studies are still admissible, will they henceforth not be more carefully scrutinized and perceived with mistrust and scepticism on the part of Russian authorities? In fact, such dynamics might occur. Authorities such as the RF Ministry of Health and Social Development and the Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor), the Federal Antimonopoly Service or even law enforcement authorities might distrust any such NPA Studies as an unregulated "marketing tool". They might consider them not only as circumvention of the Law but also a simple sales trick to increase the interaction with physicians and an inducement to prescribe a particular medicinal product. This might even lead to criminal investigations of suspected bribery of healthcare professionals participating in such studies and receiving respective remuneration. To reduce such risk, NPA Studies should comply with international standards as set forth in Section V. below.

¹ This follows from the various provisions, such as from Articles 41, 45 of the current law "On Drugs" and articles 64 and 69 of the Law.

d) And finally, what are the requirements to properly conduct NPA Studies in Russia? International principles and practices set forth certain industry standards which should be applied also in Russia, see also Section V.

IV. DIFFERENTIATION BETWEEN THE POST-AUTHORIZATION STUDIES

Widely recognised international standards help filling the gap to clearly differentiate phase IV clinical trials as defined under the Law from NPA Studies which are not mentioned in the Law in Russia:

1. The aforementioned Article 2 (c) of the Directive 2001/20/EC emphasizes that a study is an NPA Study where the medicinal product is prescribed in the usual manner and the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice.

2. Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use – refers in its Article 7.1 to the aforementioned Directive 2001/20/EC. It specifies furthermore that interviews, questionnaires and blood samples may be considered as normal clinical practice. It also states that if the aforesaid definition of NPA Studies is not met, the study should be considered as interventional and be treated as a formal clinical trial. It is recommended that studies exploring new indications, new routes of administration or new combinations, after a product has been authorised, should be considered as interventional and therefore as formal clinical trials.

3. The Code of Conduct on the Collaboration with Healthcare Professionals of the German “Voluntary Self-regulation for the Pharmaceutical Industry” (“FSA Code”) explains in its Section 19 (1) the following:

“Non-interventional studies, to which drug monitoring projects also belong, are prospective studies with the purpose of gaining new insights from the treatment of patients on the application of pharmaceuticals in accordance with the instructions laid down in the marketing authorisation (e.g. harmlessness or efficacy of pharmaceuticals). The principle of non-intervention applies to all therapeutic and diagnostic measures. The inclusion and treatment, including the diagnosis and supervision, do not therefore follow a previously laid down study plan, but solely the physician’s medical practice. The decision to include a patient in a non-interventional study has to be clearly separated from the decision on the prescription of a medicinal product.”

4. The Swedish Association of the Pharmaceutical Industry (“LIF”) has its “Ethical rules for the pharmaceutical industry in Sweden” (the “LIF Code”) which gives further guidance and states in its CHAPTER IV, Section 4.3:

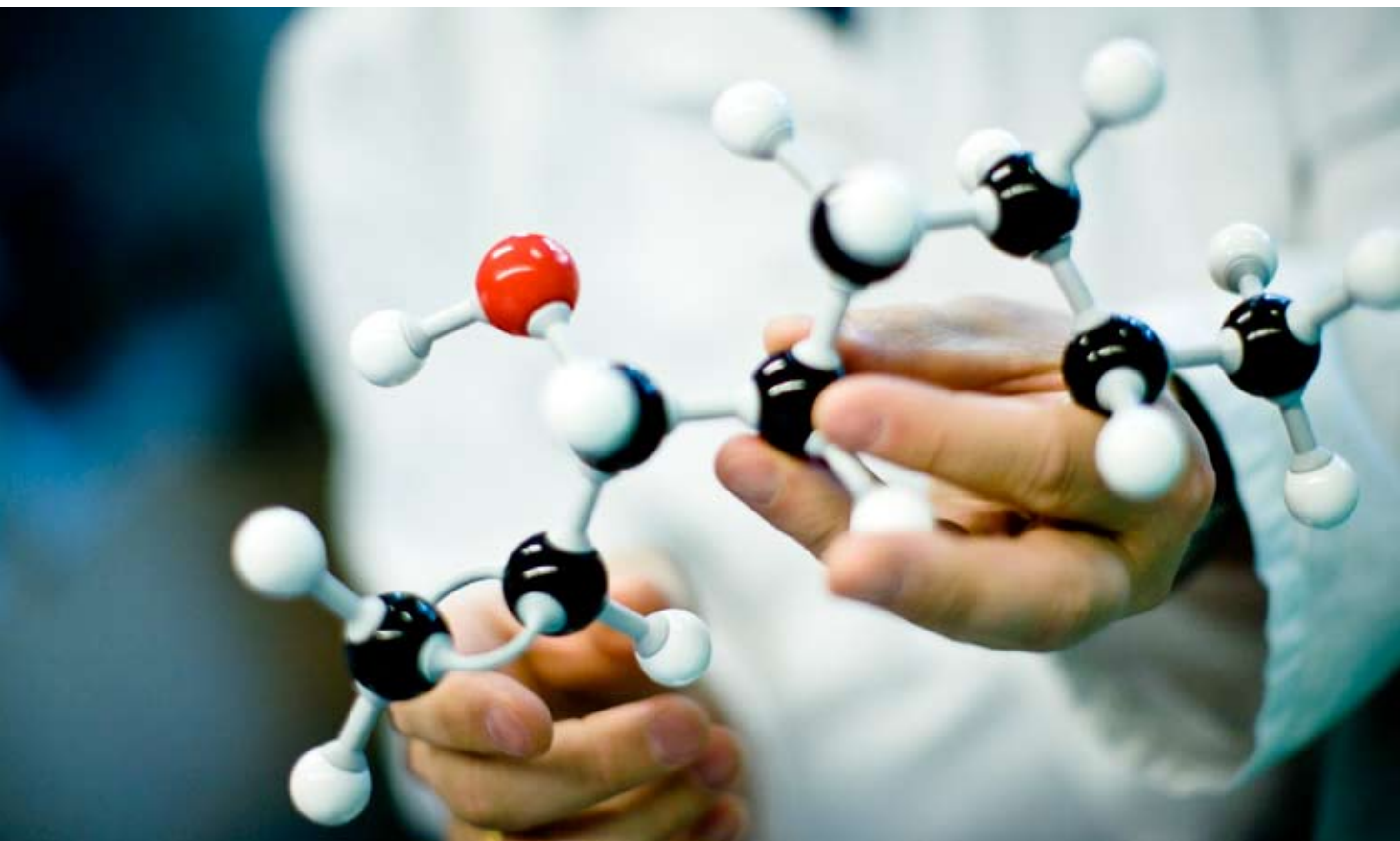
“The design of the study determines whether it is a clinical trial or a non-interventional study. A clinical trial generally studies a selected group of patients (patients chosen on the basis of various exclusion and inclusion criteria) in a controlled manner. Patients are normally randomised to one or more treatments. These studies are always prospective and often take quite a long time to perform. A non-interventional study includes patients on the basis of one or more selection criteria, e.g. by diagnosis or treatment received. Data is then collected retrospectively or prospectively using forms, or obtained from existing databases or medical records. In a cross-sectional study, information is obtained about the situation at a particular point in time. No study-related intervention is made.”



These international regulations will help to find answers in the Russian practice how to differentiate the newly regulated phase IV clinical trials from NPA Studies. Nonetheless, the latter have caused intensive disputes in Western countries. It has been criticized that the design of these NPA Studies was not sufficiently elaborated methodically, protocols were missing or of poor quality, results were not published and the primary objective of the pharmaceutical companies was merely to gain better access to healthcare professionals to induce them to prescribe their drugs.

This criticism might be aggregated in Russia and cause major problems for two reasons:

- a) The Law does specifically define post-authorization trials and - despite the efforts of ACTO - remains silent on NPA Studies. Russian authorities might come to the conclusion that the latter might not be admissible or be allowed only in exceptional cases to avoid a circumvention of the Law.
- b) Secondly, Russian anti-bribery law is vague and does not give clear guidance as to the extent to which interaction with healthcare professionals is allowed. Sections 290 and 291 of the Russian Criminal Code penalize officials for receiving bribes (which include monetary and other benefits), and correspondingly any person for granting the aforementioned benefits to such officials for any action or inaction in favour of such person, or for any promotion of such action or inaction or for general patronage. Such action or inaction can even be lawful and within the competence



of the official. A similar provision is contained in Section 204 regarding representatives of profitmaking private/commercial organizations who perform management functions.

A literal interpretation of these provisions might result in healthcare professionals who receive a monetary benefit from a pharmaceutical company, such as the remuneration for conducting NPA Studies, being seen as participants in dubious marketing and promotion practices of the drug. Again, this point must be viewed in the context of the criticism of such studies in Western countries, where the remuneration of healthcare professionals is said to be an inducement for prescribing more drugs in favour of the paying pharmaceutical company.

To best avoid any such risk and stifle said criticism, NPA Studies should comply with international standards as set forth in the next Section V:

V. RECOMMENDATION

The following standards are not an act of Russian legislation, but they can be understood as best industry standard. They provide for regulations and restrictions which are by far more detailed than Russian law. Even if the respective healthcare company is not a member of the following industry associations, it might be advisable to comply with the provisions of their codes, as they reflect common industry standards and best state-of-the-art practice. The latter might play a key role for maintaining the reputation in the market and vis-à-vis authorities.

I. RECOMMENDATIONS OF THE EFPIA CODE The European Federation of Pharmaceutical Industries and Associations (“EFPIA”) has adopted the EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals (the “EFPIA Code”). In its Article 15.01. the definition of the Directive 2001/20/EC of NPA Studies is repeated. Section 15.02. gives detailed recommendations which are summarized as follows:

- a) The NPA Study is conducted with a scientific purpose;
- b) There is a written NPA Study plan (protocol) and there are written contracts between healthcare professionals and/or the institutes at which the NPA Study will take place, on the one hand, and the company sponsoring the NPA Study, on the other hand, which specify the nature of the services to be provided and, subject to clause c) immediately below, the basis for payment of those services;
- c) Any remuneration provided is reasonable and reflects the fair market value of the work performed;
- d) Where ethics committees are constituted to review such NPA Studies, the NPA Study protocol should be submitted to the ethics committee for review;
- e) Laws, rules and regulation on personal data privacy (including the collection and use of personal data) must be respected;
- f) The NPA Study must not constitute an inducement to recommend, prescribe, purchase, supply, sell or administer a particular medicinal product;
- g) The NPA Study protocol must be approved by the company’s scientific service and the conduct of the NPA Study must be supervised by the company’s scientific service;

- h) The company should send a summary report of the NPA Study to all healthcare professionals that participated in the NPA Study and should make the summary report available to industry self-regulatory bodies and/or committees upon their request. If the NPA Study shows results that are important for the assessment of benefit-risk, the summary report should be immediately forwarded to the relevant competent authority; and
 - i) medical sales representatives may only be involved in an administrative capacity. Such involvement must be under the supervision of the company's scientific service which should also ensure that the representatives are adequately trained. Such involvement must not be linked to the promotion of any medicinal product.
- c) the total number of patients and the number of patients per investigator,
 - d) data collection, namely how data is to be collected, patient information, questionnaires, etc.,
 - e) data processing and collation, and
 - f) adverse event reporting.

2. FSA CODE The German "Voluntary Self-regulation for the Pharmaceutical Industry" gives in Section 19.2 of its FSA Code detailed instructions as to the organisation and scope of NPA Studies. They are similar to the recommendations of the EFPIA Code.

It might be worth mentioning that the FSA Code stresses that the performance of the NPA Study may not be misused to influence therapy-, prescription or procurement decisions. Furthermore, a prior written informed patient consent is recommended. In addition, within 21 days of starting to recruit patients, information on the planned NPA Study must be entered in a publicly accessible register (to contain at least the title of the NPA Study, its aims, the name of the study leader, the planned number of study centres and the number of cases involved). Finally, the summary of the NPA Study results is to be made public at the latest 12 months after finalisation (e.g. via the Internet). If the results of the NPA Study are of importance for the use-risk analysis, the summary is also to be sent to the competent regulatory authority.

- 3. LIF CODE** Articles 46 to 53 of the LIF Code set forth strict requirements for NPA Studies. In great parts, they overlap with the aforementioned recommendations, in some parts they are even stricter than the EFPIA Code or the FSA Code. Thus, for example Article 48 of the LIF Code specifies the study plan/protocol which has to contain information about:
- a) the background, namely the motivation for performing the NPA Study,
 - b) the aim, namely the description of what is to be studied (the scientific purpose),

4. AIPM The Russian Association of International Pharmaceutical Manufacturers ("AIPM") states in Section 2.1.3. of its AIPM Code of Marketing Practices ("AIPM Code") that promotion may not be disguised. As a result, NPA Studies must not be disguised promotion and must be conducted with a primarily scientific purpose and should not be conducted for purposes of stimulating the writing of prescriptions of the pharmaceutical products by healthcare professionals.

5. IFPIA The International Federation of Pharmaceutical Manufacturers & Associations ("IFPMA") stipulates in Section 2.5 of its IFPMA Code of Pharmaceutical Marketing Practices ("IFPMA Code") the same as Section 2.1.3 of the AIPM Code, namely that post-marketing surveillance and experience programmes and post-authorization studies must not be disguised promotion and must be conducted with a primarily scientific purpose.

VI. RESULT

The new Law only regulates phase IV clinical trials but not NPA Studies. Yet, the need for NPA Studies remains. The market and the routine use of a drug under every day conditions must be properly monitored. Better knowledge about efficacy and safety of the drug and potential interactions with other drugs or food products after market entry make NPA Studies indispensable. The lack of their regulation in the Law is regrettable. To differentiate post-authorization trials under the Law from NPA Studies, international standards such as the Directive 2001/20/EC, the Volume 9A of the Rules Governing Medicinal Products in the European Union as well as industry codes such as the FSA Code and LIF Code should be used.

In order to best avoid any concern of Russian authorities, the requirements of international standards and recommendations such as the IFPMA Code, EFPIA Code and AIPM Code as well as others should be complied with.

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