Three Myths About Clinical Trials in Russia

PEER REVIEWED

With its population of 145 million and total pharmaceutical sales of almost 29 billion dollars in 2013, Russia today is among the world's ten largest pharmaceutical markets. According to IMS Health, of the major emerging markets, strong growth is expected to continue in Russia, where pharmaceutical sales are expected to more than double in by 2016, growing to $179 per capita. Together with other BRIC countries, which account for nearly two-thirds of the world's population total, estimated 2016 sales in these so-called pharmerging markets will amount to 267 billion dollars, or about 25 % of the global pharmaceutical sales.

Nevertheless, their untapped potential is more promising in the drug development area, especially in clinical trials. Sponsors can instantly improve the cost-effectiveness and shorten time to market for innovative drugs, addressing the top challenges of today's drug R&D process. According to A.T. Kearney's Country Attractiveness Index for clinical trials, BRIC countries are on the top of the heap, closely following the United States, who had the highest score of 6.88. Russia, with its 5.55 score, is ranked third. The report once again opens the widely-known secret of lower costs and faster patient recruitment ("10 times faster than in the United States"), which allows completing studies "up to six to seven months sooner."

The question is, why do international drug developers not rush to take advantage of what we refer to as the Russian Troika Promise of Speed, Cost and Quality? They truly don't, because the number of international clinical trials in Russia grew at a CAGR of only 3.17 per cent from 2005 to 2013, while worldwide CAGR is 5.73 per cent. There are some frequently cited stereotypes that deter sponsors from starting clinical trials in Russia and leveraging the advantages of the region. Let's explore those stereotypes and whether they have merit.

1.Russia has Weak IP Protection

Many people believe that Russia has poor protection for intellectual property and is a source of piracy and poor IP security. This is simply not true. Russia is a member of all key international IP treaties and conventions (oldest to newest):

- The Paris Convention for the Protection of Industrial Property 1883;
- The Berne Convention for the Protection of Literary and Artistic Works 1886;
- The Madrid Agreement on the International Registration of Marks 1891;
- The Universal Copyright Convention 1952;
- The Nice Agreement Concerning the International Classification of Goods and Services for the Purposes of the Registration of Marks 1957;
- The Convention Establishing the World Intellectual Property Organization 1967;
- The Patent Co-operation Treaty 1970;
- The Madrid Protocol 1989;
- The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) 1994;
- WIPO Copyright Treaty 1996;
- The Singapore Treaty on the Law of Trademarks 2006.

Legally, IP protection in Russia is based upon the Russian Civil Code (hereinafter The Code) introduced in 2008. Part Four of The Code is comprised of 326 articles and is fully dedicated to the protection of various intellectual results, including inventions, know-how, trademarks etc. In addition to the Code there is a significant group of orders and administrative regulations (Russian, "reglaments") issued by the Russian Agency for Patents and Trademarks (Rospatent) that regulates various IP protection aspects in greater details The major improvements were stimulated by the accession of Russia to the World Trade Organization (WTO) in 2012 comprising:

- Codification and general reform of the Russian IP protection law to comply with WTO standards (2008-2012);
- Obligation for all companies, innovators and other market players to act in good will (2013);
- Special IP protection court established in 2013;
- New "anti-piracy" law to protect copyright and internet rights introduced in 2013;
- Further improvements of the confidentiality and personal data law to conform to European legal standards (2012-2013).

And finally, data exclusivity provisions were incorporated into Article 18(6) of the Federal Law on Circulation of Medicines, saying that "it is forbidden to obtain, disclose or use for commercial purposes or for state registration of medicines the information about the results of preclinical studies of medicines and clinical studies of medicines, which has been provided by the applicant for the state registration of medicines without the applicant's consent for 6 years from the date of state registration of the medicine."

Another factor behind these dramatic improvements was Skolkovo - akin to the US Silicon Valley, the innovative project initiated in 2009 by the Russian former President and today's Prime Minister Dmitry Medvedev, a big fan of modern gadgets and innovation. He is still supervising the projects and doing his best to create favourable conditions to attract foreign investors and stimulate innovations in Russia, so IP protection, as a key factor, will keep improving. According to the Ernst & Young analysis conducted in the beginning of 2014, "Russia is now at the forefront of innovation protection."

2. Russian Regulatory System does Not Meet International Standards

An in-depth analysis of the Russian clinical trial regulatory system was undertaken by the European Commission during 2001 through 2012. A survey of the relevant regulatory and legislative documents was made and three co-inspections were conducted. The findings were summarised in the 66-page analytical report *Cooperation in the field of clinical trials* (The Report) issued in September 2012. It concludes that "in general, it can be stated that for the conduct and supervision of clinical trials in the EU and the Russian Federation equivalence of the respective regulatory/legislative framework provisions is given."

However, a number of differences exist, which have been identified and classified in four major categories. Some rules are less strict than in the European Union whilst others are more so. For example:

- Study sites need to be accredited by the Russian Ministry of Health;
- Principal investigators must have at least five years' experience.

The Report explains the Russian regulatory system in great detail, including legislation, the list and structure of bodies, procedures and timelines.

Interestingly enough, the usual criticisms of the Russian clinical trial regulatory system are twofold: on the one hand, it is too slow, and on the other it is too fast. They say it is too slow to approve clinical trials, and too fast to change, so it is hard to follow. Let's examine both of these criticisms.

According to the ACTO (Russian Association of Clinical Trial Organizations), the industry average clinical trial approval time was 87 days in 2013, 25 % faster than in 2012, which is quite impressive progress. According to Synergy analytics, based on 44 submissions in 2013, the average approval time is even faster - 77 days in total, which is very close to the European 60-day approval time established by 2001/20/EC Directive. It's also worth mentioning that the fastest approval was received in 32 days.

Even though The Report confirms the general alignment of the Russian GCP regulatory system to international standards, a number of recommendations were made. These recommendations have been vectored into legislative changes, which are moving in the right direction towards full harmonisation with international practice. To track these changes you need qualified local experts, since all new documents are immediately published on the official website of the Russian MoH in Russian only. Frequency is not a problem; flexibility is the key.

According to The Report, "many stakeholders share a common positive view of the changes triggered by the implementation of the new On Circulation of Medicines Law: clinical trial application, the registration process etc. are now more transparent and fast."

3. Russian Sites Produce Suspicious and Poor-quality Data

According to the FDA, 51 FDA inspections were conducted in Russia since 2008, almost the same number as in Germany where the number of studies is almost five times higher than in Russia, and the results are self-explanatory (see Figure 1).

There is also an increase of GCP inspections in third countries (those outside the European Union) conducted by the European Medical Agency since the implementation of the GCP inspection policy in 2006, with a significant increase in routine inspections. Countries with the highest number of requested inspections are the US (21.57 per cent) followed by India (4.48 per cent), Canada (4.48 per cent) and Russia (3.08 per cent).

In addition to international inspections, a vast number of inspections are conducted by Roszdravnadzor (RZN), the

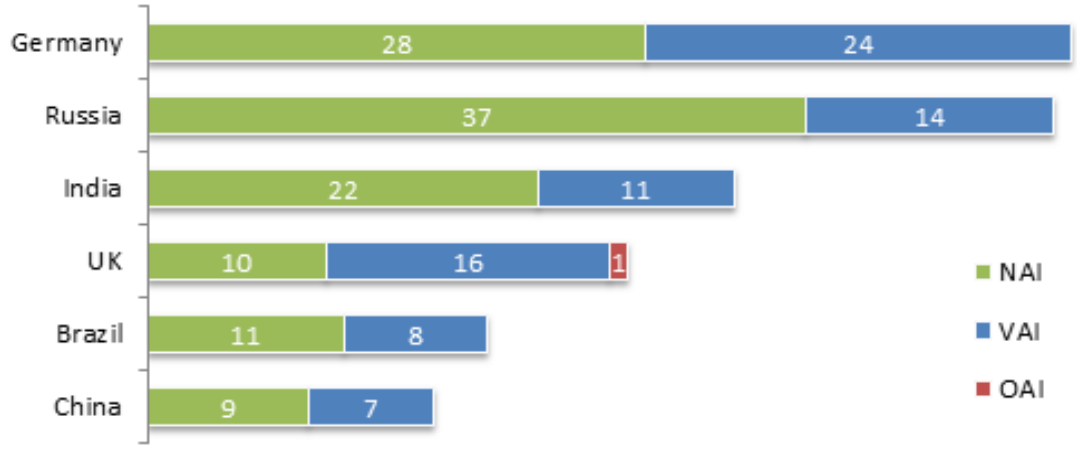

Figure 1. FDA findings in BRIC and EU countries.

body responsible for clinical trial control and drug safety. 113 inspections of Russian sites were conducted by RZN in 2013, and 70 per cent of them ended in a No Action Indicated (NAI) result. It is worth mentioning that RZN inspectors were trained by the FDA, within the scope of a Statement of Intent on Collaboration between the FDA and RZN, signed in 2010.

According to the report prepared by the FDA Division of Scientific Investigations in 2009, there were "no specific concerns specific to clinical trial data generated in Russia." Mistakes and errors have no nationality, they are all human. High quality depends on individual investigator training, experience and attitude. It is also worth noting that the initial reason for study site accreditation and 5-year PI experience was to assure the highest quality data.

Today's Russian clinical trial market is worth 880 million dollars and will continue to grow under any circumstances. The only question is, at what rate? Even if the perception of Russia remains as is, the total number of studies will continue to grow at the current rate of 4.65 per cent per year to 2020, reaching a total number of 1086 new studies over a total of 790 in 2013. The main contribution will be made by big pharma sponsors and a growth in local and bioequivalence studies stimulated by Russia's Pharma 2020 programme. Once the myths about the Russian clinical trial market are dispelled, the number of international clinical trials will grow at a CAGR of 11.4 per cent, the total number of studies will almost double by 2020, and the total clinical trial market in Russia will hit the value of 1.6 billion dollars.

There is a Russian saying: "It's better to see once than hear a hundred times." The closest English analog is: "A picture paints a thousand words." The common misconceptions about clinical research in Russia have no basis in fact. Russia is an attractive region for clinical trials and that will only grow in the future. Despite any hype, Russian investigators keep their promises. The Troika Promise of Speed, Cost and Quality is being proved every day through the successful completion of trials in the region - 53 of 114 new drugs registered by the FDA in 2013 were tested in Russian sites

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