Russian Troika: Speed, Cost, Quality

The world's leading pharmaceutical companies discovered Russia in the beginning of 1990s, and Russia's clinical trials industry has been enjoying significant growth since then. This is especially true for the last ten years during which period the number of studies conducted in Russia by foreign sponsors has nearly tripled - a healthy sign for an emerging clinical trials market.

Russia's success is driven by three factors which are crucial for each and every clinical trial: high patient recruitment rate, reasonable study costs and good data quality. This is the Russian Troika - Speed, Cost and Quality.

The last is by no means the least. The data obtained from Russian sites is accepted by the US Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA). As an example, six of nineteen drugs approved by FDA in 2007 were developed using the data coming from Russian sites. The high quality of Russian investigators is also confirmed by FDA inspections, with the lowest deficiency rate among emerging markets including India, China and Latin America.

Another factor behind the rapid growth is that pharmaceutical manufacturers have recently begun regarding Russia as a potential market for their new drugs. According to the data provided by DSM Group, in 2007 the total sales in the Russian pharmaceutical market stood at 14.3 billion US Dollars , an increase of 16% over 2006.

"Another factor behind the rapid growth is that pharmaceutical manufacturers have recently begun regarding Russia as a potential market for their new drugs"

The investment power of Big Pharma has created a well-developed study infrastructure in Russia during the past 15 years, and established a favourable environment for the "second wave" of sponsors to step into the door. This will be cost-sensitive middle and small-size biotechnological and pharmaceutical companies, whose venture capital makes great demands for return on investment. Since these innovative companies rarely have their own full-size clinical research function, they are highly dependant upon the local clinical trials infrastructure and outsourcing facilities.

There are about 55 international and local contract research organisations (CRO) currently operating in Russia. With its vast population and almost untapped market potential, the country's clinical trials industry is increasingly attracting the interest of global players. This has been highlighted in particular by two recent acquisitions. At the beginning of this year, two Russian CROs were acquired by big multinational companies - in February PPD bought Smolensk-based Innopharm, and in April i3 announced the purchase of Moscow-based Lege Artis.

Regulatory: documents, bodies, process

Clinical trials in Russia are regulated by two major documents: the Federal Law on Medicines of 1998 and the National Standard on Good Clinical Practice introduced in 2005, which is in fact a comprehensive and exact translation of ICH GCP.

All clinical trials are approved by the Federal Service on Surveillance in Healthcare and Social Development of Russian Federation (alias RosZdravNadzor, or RZN) which is the main regulatory authority for clinical trials in Russia. RZN was established in 2004 and is also responsible for maintaining a database of sites all studies commenced in Russia, investigational product import and biological material export licensing, and conducting quality inspections of the Russian sites.

Before a study is approved by RZN, in addition to the positive opinion from NEC, it has to successfully pass the examination of the Scientific Center of Expertise of Medicines and Medical Devices (alias FGU) – the federal state institution operating under the RZN umbrella. According to the agreement between an applicant and FGU, the examination is made within 35 days and costs about 3,600 Euros.

The current NEC was established in August 2007, and consists of 37 members appointed by RZN. According to the NEC standard operating procedures (SOP) the review meetings are held on a bi-weekly basis, and the decisions are made by majority opinion. Detailed information about NEC functioning, including SOPs, meeting time-table, submission dossier contents, contacts, etc. is presented on the RZN Website . According to NEC policy the decision is made within 30 days from the date of the study documents submission.

The submission dossier is more or less the same for all three bodies (NEC, FGU and RZN) and comprises the following basic documents: study protocol, investigator's brochure (IB), informed consent form (ICF), case report form (CRF), list of study sites, insurance, principal investigators' CVs, and patient documents, if applicable. While all documents have to be submitted in Russian, the officials can refer to the original language of a particular document in case of uncertainty. The documents are submitted in either electronic or paper format. If the submission is done by a CRO, the Power of Attorney should be enclosed.

After positive opinions are obtained from NEC and FGU, documents are submitted to the RZN for the formal study approval. According to the Russian Ministry of Health and Social Development (MoH) Order, this process should not exceed 15 days. Then, if necessary, the study drug import license and biological samples export license can be received from RZN.

Even though FGU and NEC can be approached in parallel, the approval time in Russia still remains disagreeably long, and it is one of the primary factors impeding the booming growth of the Russian clinical trial market. According to the latest survey conducted by the Russian Association of Clinical Trials Organizations (ACTO) in 2008, the whole

approval process from the initial document submission to receiving the import license takes 106 days on average.

There is a Russian proverb: "Slow to harness, but fast to ride". That's especially true for the Russian clinical trials industry…

Patient Recruitment

According to the Federal State Statistic Service (FSSS) Russia's population stood at 142.2 million in 200 . 73% live in urban areas, while the remaining 27% live in rural areas.

The population is highly concentrated around big industrial cities. For example, while Russia's average population density is 8.7 inhabitants per square kilometre, in the Moscow region this figure stands at 320 per kmÇ. Table 1 shows the distribution of Russia's population and cities by Federal Region.

Russia's healthcare system is highly urbanised too. According to the FSSS, as at the end of 2006, there were 7,500 hospitals in Russia. The vast majority of them are located in the cities, and this is especially true for large regional hospitals located in the capitals of Federal Districts and cities with populations above 500,000. Such a high concentration of both hospitals and potential subjects in big cities gives certain advantages. These large medical centres specialise in multiple therapeutic areas, have access to a huge number of potential study subjects, and usually maintain a patient database making possible the speedy pre-selection of subjects.

Besides hospitals, there are about 18,800 outpatient clinics in Russia, with the total screening capacity of 3.6 million patients per shift. The combination of researchers' close ties with each other and their personal knowledge of the subjects' contingent produces patient recruitment rates that are three to five times higher than in Western Europe and the USA.

Traditionally, the general Russian public consider the medical doctor to be a highly competent and prestigious profession. For that reason, the investigator-subject relationships are usually built on trust and mutual understanding. Patients rarely refuse to participate in a study, and consciously and voluntarily sign up for additional procedures to help the doctor fight the disease. Such a close rapport between a subject and an investigator also helps to reduce the study drop-out rate. Another major advantage that Russia enjoys, especially for the long term studies, is a low migration rate of population. Subject drop-outs due to moving are very rare in Russia.

Another advantage of Russia as a clinical trials market is the significant number of treatment-naïve patients. According to the Russian MoH data, as of 2006, there were 109 million treatment-naïve patients in Russia .

According to the Pharmaprojects' 2008 annual review , the top therapeutic areas in pharmaceutical R&D are cancer, diabetes, cardiovascular diseases and asthma. Table 2 shows the number of treatment-naïve patients in Russia, as well as the total number of patients in the most popular therapeutic areas of drug development.

According to the RZN data, as of April 2008 there are 877 hospitals entitled to conduct clinical trials in Russia. About sixty new sites are accredited by RZN every year. The top ten Russian cities by the number of sites are shown in Table 3.

Traditionally, it is considered that capital sites (located in Moscow and Saint-Petersburg) combine all key study benefits – involving opinion leaders, providing patient recruitment, saving monitoring costs including travel, and ensuring high data quality.

However, as the number of studies grows, the number of concurrent trials conducted at a single site grows even faster. At present, the number of parallel studies in the same nosology can number up to ten (!). As a result, all three of Troika's "horses" become lame. Firstly, the patient recruitment rate falls. Secondly, the data quality decreases, because investigators are sometimes physically unable to pay adequate attention to every trial conducted at the site. Finally, investigators need to be additionally motivated financially to get the first two back on track.

Unfortunately, most CROs, as well as sponsors, prefer to keep to the beaten tracks rather than develop new sites in the Russian regions.

The progressive local CROs realise that regional sites are usually better recruiters, and that the bright future of the Russian clinical trials industry lies in the regions, so they utilise the regional potential intensively. In addition to better enrolment, the use of regional cities with a relatively large number of sites (see Table 3) lowers overhead and monitoring visit-related expenses. The average monitoring costs can be cut even further – by up to 40% – by visiting more than one site per trip. The local CROs have the largest geographic span over Russia.

Investigative sites in the regions of Russia have all the necessary means for conducting clinical trials, including adequate rooms for drug storage, proper equipment that is able to maintain special storage conditions, computers with high-speed Internet access that support Voice Over Internet Protocol (VOIP) etc. Many study centres are equipped with the latest high-tech equipment acquired during previous studies.

The high quality of the Russian study sites is confirmed by the 39 FDA inspections conducted since 1995. About two-thirds of the inspections were conducted in the regional sites. No shortcomings were found in 20 (51%) of the cases (NAI - No Action Indicated), 18 (46%) inspections ended with VAI (VAI - Voluntary Action Indicated), and only one case produced the OAI – Official Action Indicated (see Figure1). For comparison, the results of the FDA inspection in the US are 19%, 75%, and 6% , respectively.

Clinical Research Professionals

According to local experts, the total number of clinical research professionals in Russia is somewhere between 2,500 and 4,000. Ninety percent of the monitors in Russia are medical doctors (MD), some of them have scientific degrees (PhD), and many have some research experience. Usually, CROs and pharmaceutical companies hire personnel whose English language skills are at least at the solid upper-intermediate level.

If a newcomer has no clinical trial experience, he or she is required to take a mandatory basic GCP course. An employer can offer its own training, or suggest a public course. The number of public training programmes is on the rise, and their quality is constantly improving. The choices vary from basic one-day seminars to full-prep CRA five-day programmes. After the initial training, personnel professional improvement is continued according to the company's SOPs. Lately, Russian CROs have begun implementing the Western experience of conducting computer-based and online web training courses for their employees with regular testing and certification. In addition to GCP and CRA training, many companies conduct regular in-house English language courses.

During the past three years, the companies have developed their own local Project Managers who are able to manage multi-centre projects in several continents at once. These are true professionals with several years' experience in different areas of clinical research who are able to conduct a study from A to Z, and are equally competent in study budgeting, Gantt chart preparation, and in writing newsletters in several languages.

Most of the Russian investigators are GCP-trained, can fluently read and write professional literature in English, possess solid business writing skills, and have at least intermediate English speaking and listening skills. It is important that besides income, the motivation for their participation in clinical research is also scientifically driven. Many sponsors note that an interesting piece of research with some scientific "kick" often has a strong positive correlation with a higher recruitment rate and better data quality.

Intellectual Property

It is considered as common knowledge that intellectual property (IP) protection in Russia is weak. However, this is not exactly true. The history of modern IP protection began at approximately the same time that the first clinical trials came to Russia, i.e. in the early 1990s. The regulatory framework comprised a whole group of federal laws: Patent Law, Trademark Law, Copyright Law, Integral Chip Topology Protection Law and Software and Database Copyright Protection Law. All of them adhered to free-market principles and reflected the worldwide tendencies described in, among others, WHO's Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement.

The above laws were recently replaced, and since January 2008, IP in Russia has been regulated by two legal documents: the Federal Law on Trade Secrets of 2004 and Part IV of the Civil Code completely devoted to IP protection.

The only weak point of the current legal field which is important for the pharmaceutical industry (beyond the clinical trials area) is the absence of regulation of data exclusivity. The resolution of this issue is one of the conditions under which Russia can join the World Trade Organization (WTO), and a number of alternative bills fixing the problem are under active consideration.

Although intellectual property in Russia is pretty much covered legally, there is a general lack of application of the laws in everyday life. This relates not only to the copyright violators, but to the IP owners as well. As an example, according to the Federal Law on Trade Secrets, confidential documents must be clearly marked with the stamp "Trade Secret" in Russian and bear the IP owner's name, otherwise it is not regarded as IP, since, from the legal point of view, and it means that the IP owner did not undertake the necessary actions to protect the IP. It is worth mentioning that very few foreign sponsors have complied with this requirement since the law was introduced in 2004.

Conclusion

According to SynRG Orange Paper, RZN has approved 1,374 new studies since its foundation in 2004. This number brings Russia to the top of the heap in initiating new clinical trials among the E7 countries. Nevertheless, in comparison with the well-established markets of Western Europe and North America, the potential of the Russian clinical trials industry has only been realised at slightly more than five per cent. Russian Troika still welcomes new riders… ■

The author would like to thank Svetlana Zavidova, ACTO Executive Director, for her advice and input during the preparation of this article.

References

1. *DSM Group Analytics. http://www.dsm.ru/en/analytics/*
2. *National Ethics Committee http://www.roszdravnadzor.ru/etika/et/norm*
3. *Association of Clinical Trials Organizations http://acto-russia.org/en/*
4. *Federal State Statistics Service http://www.gks.ru/free_doc/2007/b07_12/05-01.htm*
5. *Pharmaprojects' 2008 annual review http://www.pharmaprojects.com/therapy_analysis/annual-review-0508.htm*
6. *FDA. Investigational Human Drugs: Clinical Investigator Inspection List. http://www.fda.gov/cder/regulatory/investigators/*
7. *SynRG Orange Paper http://www.synrg-pharm.com/en/article31.htm*

Igor Stefanov is Director for Business Development for Synergy Research Group (SynRG™), a Russian CRO with offices in Moscow, St.Petersburg, Novosibirsk, Perm, Yekaterinburg and Almaty (Kazakhstan). Prior to joining SynRG in January 2007, Igor was Managing Director for Smartlock, the Russian biometric company and was recognized as Entrepreneur of the Month by the Russian edition of Forbes magazine in May 2005. With MBA in Economics and strong local expertise Stefanov has been providing business consulting services to large multi-national companies including Pfizer, J&J, GlaxoSmithKline, F.Hoffmann-La Roche and others in Russia since 1993.

Table 1. Population and city distribution in Russia by Federal Region

Federal Region	Population, million	% Total	Density, per kmÇ	No. of cities
Central	37.1	26.1	54.5	296
Privolzhsky	31.9	22.4	31.5	101
Southern	21.7	15.3	47.8	56
Siberian	17.4	12.2	4.1	97
North-Western	14.4	10.1	42.0	146
Ural	12.5	8.8	25.2	41
Far East	7.2	5.1	1.2	13

Source: FSSS

Table 2. Treatment-naïve patients in Russia

Therapeutic area	No. of patients, thousand	
	Total	Treatment-naïve
Oncology	5,121.3	1,417.7
Cardiovascular diseases	6,810.9	684.5
Diabetes	2,684.2	249.5
Asthma	1,266.3	119.4

Source: MoH

Table 3. Top ten Russian cities by the number of sites

No	City	Population, thousand	No. of sites
1	Moscow	10,101.5	196
2	Saint-Petersburg	4,669.4	127
3	Novosibirsk	1,425.6	35
4	Kazan	1,105.3	25
5	Nizhny Novgorod	1,311.2	24
6	Yaroslavl	613.2	21
7	Ekaterinburg	1,293.0	20
8	Rostov-on-Don	1,070.2	16
9	Perm	1,000.1	15
10	Saratov	873.5	14

Source: FSSS, RZN

Figure 1. FDA inspections in Russia