Federal Factors

Image: © tashatuvango – Fotolia.com

Russia has built its clinical trial industry from scratch over the last 20 years, although it is open to question whether the market growth of recent years can be sustained. Research quality continues to catch the eye of sponsors, but regulatory moves in the country have arguably been as much a hindrance as a help

Maria Bomer at Bomer Pharma Consultancy

Over the last decade, the number of clinical trials conducted in Russia has grown steadily by more than 50%. The total number of trial approvals climbed from about 500 in 2004, to 791 in 2013, with the high point being 2012, when 915 approvals were issued (1).

Yet, for a country with a population of around 140 million, the limit may be far from being reached. According to Igor Kagramanyan, Deputy Minister of Healthcare, currently only 10% to 15% of the country's potential for conducting clinical trials is being realised (2).

The statistical data indicate that, in terms of the sheer number of annually issued approvals for trials, Russia is not that far behind its European counterparts. For comparison purposes, in the EU, which has a total population of more than 508 million, some 4,400 clinical trials are applied for each year (3).

At the same time, the country's trial market has been hit by a slowdown since 2013, and approvals have dropped sharply, which some attribute in part to new regulation. In addition, the total number of applications for trials in the EU has dropped by 25% from 2007 to 2011 (4). Russia is also having to contend with increasing competitiveness from other emerging countries. So is further growth in Russia really achievable?

In considering this, one has to remember that some 20 years ago, Russia's clinical trial industry was virtually non-existent; its whole infrastructure – including the regulatory framework – had to be established from scratch. From the recent initiatives

of the government directed towards boosting investment for the healthcare and pharmaceutical sectors, it is clear that Russia is committed to improving its clinical trial climate and making conscious efforts to become an attractive destination for innovative drug development.

The generally acknowledged advantages of conducting clinical trials in Russia are:

- The costs involved: the average cost per patient can be up to 1.5 times lower than in Western countries (5)
- An easy to reach population which tends to reside in major urban areas, plus the presence of large, centralised health institutions
- A relatively high number of treatment-naïve patients
- Committed relationships between patients and well-qualified physicians

These benefits are not only directly cost-efficient; through facilitating the enrolment process and diminishing the drop-out, they offer more time and, therefore, cost-saving benefits.

Language and Quality

When some people consider Russia, they perceive the language barrier and the quality of conducted trials as potential problem areas – but how legitimate are these concerns?

While the older generation of Russian medical doctors are less likely to speak English, the young doctors – especially those located in major urban centres – tend to be more proficient. This trend is only expected to increase in the years to come. Furthermore, the growing army of local and global CROs operating in the country appear to successfully address issues around both language and quality.

The post-capture data correction rate is comparable or lower than that in the Western world – this further indicates the high level of efficiency and quality (6). Data from Good Clinical Practice inspections does not identify any significant issues. In fact, it demonstrates that the quality of conducted research is in no way inferior – and is often superior – to the West (7).

In addition, the presence of good clinical and quality standards in Russian medical institutions helps ensure trials are conducted effectively. Anthony N DeMaria, Editor-in-Chief of the *Journal of the American College of Cardiology*, has dismissed what some see as concerns around quality. Following a personal visit to the Moscow City Center of Interventional Cardioangiology, he commented: "The implications of my Russian experience were particularly impressive for clinical research. Given the standard of care, one could be confident that medical practice would not invalidate the extrapolation of the results to the rest of the world. Patients in these centers are managed in a standard fashion according to existing guidelines by knowledgeable and skilled physicians using up-to-date pharmaceuticals, supplies and equipment" (8).

Federal Law

Clinical trial regulations in Russia, however, may not stand up to scrutiny. The federal law, 'On circulation of medicines', came into effect in April 2010 as a major regulatory step designed in part to help transform the country into an attractive place for clinical R&D. But, while the introduction of the new law was a tangible effort to establish improved practices – for example, limiting the timeframe for reviewing application documents and safeguarding the interest of patients – the growth in trial approvals up to 2012 quickly turned into the slowdown of 2013.

Many analysts attribute this stagnation to the shortcomings in the federal law. The Association of Clinical Trial Organisations said: "As a result of the reforms, the Russian market for clinical trials has significantly turned towards copy medicines" (9).

While the intention of the regulation was to enhance the growth of international trials, the actual number of approvals issued in Russia in 2013 fell sharply to 2006 levels – a decrease of 9.5%. The data from the first half of 2014 does not look optimistic either, showing a drop of nearly 15% in the number of international multi-centre trial approvals, compared to the same period in 2013 (10).

Import Provisions

Certain provisions of the federal law proved to be more of a hindrance than a help, and have had to be revised. For example, there was an obvious omission in the legislation regarding the import of already registered medicinal products for trials. The lack of regulation here resulted in the situation where, from October 2010, the country's Ministry of Healthcare and Social Development refused to issue related import permits.

Furthermore, the Ministry of Industry and Trade turned away those sponsors that did not hold a pharmaceutical licence to the registered study drug. It took eight months – and many unnecessary trial delays and cancellations – before new amendments were made to the law that finally addressed this problem, allowing the Ministry of Healthcare and Social Development to deal with import of both unregistered and registered medicinal products for clinical trials.

Local Registration Studies

Article 38(1) of the federal law explicitly prohibits the conduct of Phase 1 trials for establishing the safety and/or tolerance on healthy volunteers in a situation where investigational medicinal product is manufactured outside the Russian Federation. Another highly controversial regulation (Articles 14, 18, 21 and 27) requires the conduct of so-called local registration studies on the territory of the Russian Federation prior to the registration procedure, unless Russia has originally been included among the participating countries of the respective international multi-centre trial.

This requirement to repeat safety and efficacy trials is widely criticised within Russia itself, mostly from an ethical standpoint, and subsequently for its inconsistency with the principles of the Declaration of Helsinki, which sets out ethical principles for medical research involving human subjects.

The fact that the Russian population is genetically no different from that of other European countries makes it difficult to justify the exposure of patients to unnecessary risks during the conduct of confirmatory trials that have already been successfully carried out elsewhere. The same can be said for the lack or delay in drug availability for those patients who stand to benefit from them.

In March 2012, the Federal Antimonopoly Service of the Russian Federation came forward with proposed amendments to the federal law, 'On circulation of medicines'. Among others, it called for the requirement to conduct local registration studies to be made redundant by way of recognising the results of international clinical trials (11).

Long-Awaited Changes

Some steps have already been taken. New amendments to the federal law, published by the Ministry of Health, were approved in November 2014 by the Russian Parliament. The changes introduce new terminology for innovative and biogeneric drugs. Most importantly, the law now defines the status of orphan drugs and allows for their accelerated registration procedure.

The first three generic drugs of an original medicine which has not been previously registered in the Russian Federation as generic – with the exception of biogenerics – as well as drugs that are intended exclusively for paediatric practice, are also eligible to benefit from accelerated registration (12). Referring to orphan drugs, Elena Maksimkina, the Director of the Department for the Provision of Medical Products, commented: "These products will benefit from significant preferential treatment, which means the requirement to conduct local clinical trials for this category of drugs will be dropped" (13).

There are also plans to legalise, by the end of 2015, a fast-track registration procedure for immune-biologic agents and vaccines developed for the treatment of infectious diseases caused by newly emerged microorganisms (14).

However, many critics remain sceptical and frustrated in a situation where long-awaited changes like these come too slowly. Svetlana Zavidova from the Federal Antimonopoly Service of the Russian Federation was disappointed with the insufficient response from the Ministry of Health, pointing out that even though the recent amendments make an exception for orphan medicines, for the rest of the drug candidates this requirement still remains in force. "No doubt, sooner or later the regulatory authorities will revise this requirement. The question is, how long will it take and how many patients will have to suffer the consequences of this delay?" (15).

Policy Direction

Russia has many natural advantages to further explore its clinical trial potential; it is for the country's legislator to address those issues which might impede its full utilisation. Deliberate policy directed towards international harmonisation of trial regulations, easing the administrative burden, introducing more transparency in study data, and accelerating the registration process for drugs addressing conditions with unmet medical needs are all expected to become beneficial for sponsors and patients alike.

Furthermore, in view of the new EU Clinical Trial Regulation – due to come into effect in 2016 with the aim of addressing the very issues mentioned above – it would be to Russia's advantage to timely align its regulations with wider global trends. This would help share the gain from introducing and promoting measures to enhance clinical trial development.

References

1. Visit: www.grls.rosminzdrav.ru and www.roszdravnadzor.ru
2. Visit: www.rosminzdrav.ru/news/2013/12/19/1676-intervyu-zamestitelya-ministra-igorya-kagramanyana-rossiyskoy-gazete
3. Visit: http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf
4. Visit: http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf
5. Medidata PICAS database. Visit: www.samedanltd.com/magazine/13/issue/201/article/3577
6. Medidata Insights database. Visit: www.samedanltd.com/magazine/13/issue/201/article/3577
7. Visit: www.fda.gov
8. Visit: http://content.onlinejacc.org/article.aspx?articleid=1478373&resultclick=1
9. Visit: http://acto-russia.org/files/ACTO_Newsletter_8.pdf
10. Visit: http://acto-russia.org/files/ACTO_Newsletter_9.pdf
11. Visit: http://fas.gov.ru/legislative-acts/legislative-acts_50891.html
12. Visit: www.rosminzdrav.ru/news/2014/12/23/2183-vneseny-izmeneniya-v-federalnyy-zakon-ob-obraschenii-lekarstvennyh-sredstv12
13. Visit: www.rosminzdrav.ru/news/2014/02/27/1740-rukovoditeli-departamentov-minzdrava-rossii-prinyali-uchastie-v-kruglom-stole-posvyaschennom-probleme-orfannyh-zabolevaniy
14. Visit: www.rosminzdrav.ru/news/2014/05/16/1835-veronika-skvortsova-prinyala-uchastie-v-zasedanii-prezidiuma-soveta-pri-prezidente-rossiyskoy-federatsii-po-modernizatsii-ekonomiki-i-innovatsionnomu-razvitiyu-rossii
15. Visit: http://fas.gov.ru/fas-in-press/fas-in-press_38143.html

About the author

Maria Bomer is a Pharmaceutical Industry Physician. After practicing general medicine for several years, she joined the biopharma industry and now has more than 10 years of pharmaceutical development experience. Maria currently works as an Independent Consultant at Bomer Pharma Consultancy in the Netherlands, providing services with a focus on pharmacovigilance and clinical research. She holds an MD degree from Vladivostok State Medical University, Russia.

Email: info@bomerconsult.nl