Drug Registration in Russia and the New Law

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On 13 April 2010, after much controversy and critique, the Russian government enacted a far-reaching piece of new legislation to regulate the pharmaceutical industry. This new law went into effect on 1 September 2010, and although its exact implications cannot be known with certainty, it is clear that the regulatory landscape in Russia will be fundamentally changed.

This article examines the previous process for drug registration in Russia, as well as the various requirements for conducting clinical trials in the country as they stand today. It then considers in greater detail the new law, in particular some key differences from the former regulatory system.

Although the regulatory framework for the pharmaceutical market in Russia is presently in a state of transition, insights gleaned from the current situation and the changes that result from the new legislation should assist foreign drug manufacturers contemplating a foray into the Russian market in the future.

Registration of Pharmaceuticals

Russia requires a Certificate of Product Registration before a pharmaceutical product can be manufactured, imported or sold in the country. Moreover, medical devices and drugs require a Sanitary Epidemiological Conclusion Certificate as well, unlike most products that require one or the other. The state agency that issues the Certificate of Product Registration is the Federal Service on Supervision in the Sphere of Public Health Services and Social Development (Roszdravnadzor).

Registering a pharmaceutical product in Russia has involved a review of its quality, efficacy and safety by the National Center of Pharmaceutical Products Expertise (FGU), which is comprised of a number of different sections and institutes and is the only center authorized to provide independent expertise to Roszdravnadzor. Any pharmaceutical company registering a drug in Russia must submit the registration dossier directly to the National Center, and the regulatory specialist must communicate with its experts on a weekly basis.

After this independent review is provided to Roszdravnadzor, the agency issues the registration certificate and the drug is entered into a database of registered products. If the review is not satisfactory, registration is denied and the drug will not be entered into the database of registered pharmaceutical products. Since 2008, certificates have been issued for an unlimited period (previously they were issued for only five years). Russian customs officials verify the Certificate of Product Registration at the Russian border, and trade inspectors check it at the time the product is put on retail shelves.

It is worth noting that while the procedure itself is the same for both Russian and foreign applicants, the registration costs and documentation are different. Moreover, foreign manufacturers must be certified in Good Manufacturing Practice (GMP). It is not mandatory that the product be registered in the country of origin or elsewhere; it is entirely acceptable to have only Russian registration.

The dossier submitted to Russian regulatory authorities has six components: administrative documents, description of pharmaceutical properties, data about manufacturing of the pharmaceutical product, data about quality control of the finished pharmaceutical product, data about preclinical pharmacological and toxicological studies of the pharmaceutical product, and data about clinical studies of the pharmaceutical product.

Since all of the data required for Russian registration are included in an EU filing and the structures of the two registration files are comparable, if the applicant already has an EU registration file, a separate document for the Russian filing is not needed. However, the dossier for Russia must be translated into Russian.

The Russian registration certificate indicates participants along the entire spectrum of the manufacturing process, namely the marketing authorization (registration certificate) holder; the manufacturer of the finished pharmaceutical product; the entity responsible for primary packaging; the entity responsible for secondary packaging; and the batch release site. Each of these activities can be undertaken by different companies, and for any one of these activities, more than one company can be indicated. However, the contract agreements between participants along the various manufacturing stages must be submitted as part of the registration.
The applicant can be either the registration certificate holder or its representative in Russia; a physical person; or a Russian juridical company (a third party). While the applicant is not required to open a company in Russia in order to register its product there, the right to represent the interests of the registration certificate holder must be legalized with a properly executed power of attorney. Having done so, a pharmaceutical company can register its product prior to starting any business activity in Russia.\textsuperscript{12}

Other documents required for product registration in Russia include the Certificate of Pharmaceutical Product, the GMP Certificate and the Manufacturing License. However, if these documents were issued by a state that is a member of the Hague Convention, it is sufficient that the documents be authenticated by an apostille; otherwise, the Russian Embassy must legalize the documents.\textsuperscript{13}

The framework for the registration process can be loosely divided into three stages. During the first stage, an applicant compiles all of the needed documentation for its dossier, translates the documents into Russian and submits the file to FGU. During the second stage, arguably the most lengthy and complex in the entire process, the file is assigned to the appropriate experts at the Institute of Products Quality Control and the Institute of Preclinical and Clinical Expertise for review of quality, efficacy and safety. Finally, the third stage includes the completion of this review and the submission of the final dossier to Roszdravnadzor for issuance of the Certificate of Product Registration.\textsuperscript{14}

Although both innovative pharmaceuticals and generic products are required to pass all three stages in the registration process, generic products may be exempt from certain registration procedures while new drugs must pass through each one. One example is the need for clinical trials to be performed in Russia. While this is mandatory for new pharmaceuticals, only bioequivalence studies are required for generics, and such studies need not be conducted in Russia.\textsuperscript{15}

The duration of the registration process varies, depending upon the regulatory specialist’s organization and efficiency. The need to conduct additional clinical studies or implement quality controls, or the delay involved when additional clinical data are requested by the state authorities, will also increase the timeline of the registration. However, as a general rule, the applicant can expect Stage I to take approximately two months, Stage II to take 12 months and Stage III to take about four months, for a total of about 18 months for the issuing of the
The cost associated with registering a pharmaceutical product in Russia is actually comprised of two separate payments: one official payment to the state authorities (Roszdravnadzor) and another to the regulatory expert. Together, the payments can total approximately $49,000 (US). Of this sum, approximately $24,000–$36,000 can be accounted for by the official payments to FGU. This cost is associated with the examination of the dossier and the laboratory expertise; the latter cost will vary according to the number of dosages evaluated and the analytical methods. Not until the invoice for examination of the dossier is paid in full can the laboratory quality testing be undertaken, which is an integral part of the regulation process.\textsuperscript{17}

As discussed above, the second stage of the registration procedure includes the verification of quality, safety and efficacy. The product must pass laboratory controls based on an approved normative document, which in Russia is based on the manufacturer’s finished product specifications and Russian, US and EU pharmacopeias.\textsuperscript{18} One challenge presented by the laboratory control process is the importation of samples and standards. Special permission to import these items is required from Roszdravnadzor; this can take anywhere from one to two months, prolonging the time it takes to register the product. Because a full analysis of the pharmaceutical product as well as the first three batches imported into Russia for sale on the market is done at the time of registration, the product will be held by Russian customs during laboratory control and the time needed to import the necessary samples and standards (a total of six months).\textsuperscript{19}

Even after the registration process is complete and the applicant has received a Certificate of Product Registration, the applicant will still need to provide additional documents for the final dossier, which will be submitted to FGU for review. The review process may take several months, during which time the applicant will need to provide any additional information requested by FGU.

\textbf{Figure 1: Drug Registration Process in Russia}
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of Product Registration, state approval may be needed for any changes to these documents. Certain postregistration variations, such as changing the manufacturer’s name or packaging design do not require additional quality, efficacy or safety expertise. However, if the variation is more significant, such as changing the manufacturing site, the quality or quantity composition of the product or the instructions for administering the product, quality, efficacy or safety expertise will be required. The minor variations can take two to three months to receive approval from the state regulatory authority, whereas the latter types of changes can take anywhere from six months to a year to be approved.20

**Clinical Trials**

Since 2005, when Russia adopted the National Standard, its regulatory framework for conducting clinical trials has been fully compliant with international standards because the National Standard is actually an adaptation of the ICH Harmonized Tripartite Guideline for GCP E6.21 As of January 2010, clinical trial supervision authorities have inspected 153 clinical trials for compliance with regulatory requirements and 10,012 medical institutions in Russia have been authorized to perform clinical trials.22 In order to obtain such authorization, a clinical site must prepare a submission package consisting of an application, a presentation of its facilities and a statement of its intentions with respect to the actual conduct of the clinical trials. The level of expertise that the clinical site’s staff exhibits is an important consideration in the approval of the site.23

In 2004, Russia became a member of the World Health Organization International Drug Monitoring Program and three years later, Roszdravnadzor created the Federal Center for Monitoring of Drug Safety. Russia’s pharmacovigilance framework is further reinforced by regional monitoring centers; the 51 centers established since August 2009 in each of the administrative districts in Russia act as the backbone of pharmacovigilance efforts.24

The decision to conduct clinical trials in a given country is affected by a number of considerations, chief among them the timeline for setting up the clinical trial. In Russia, this process has two stages: first the study documents must receive approval from the National Ethics Committee (NEC) and the Russian Research Center for Expertise of Medical Products; the Ministry of Health will then issue a final approval. A separate set of procedures must be followed when acquiring import and export licenses for the clinical trial materials.25

While no legally established timelines currently exist (the effect of the new drug legislation discussed below may change this), on average, clinical trial approval in Russia takes 90 calendar days. Of course, in many cases delays may arise due to inaccuracies in the submitted documents, various administrative obstacles, etc.26

Last year, NEC received approximately 3,000 applications, up by about 10% from the year

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**Figure 2. Distribution of Clinical Trial Applications 2009**

- **Phase I**: 8%
- **Phase II**: 27%
- **Phase III**: 42%
- **Phase IV**: 9%
- **Biosimilars**: 15%
before (see Figure 2). Across the various phases, most of the clinical trials were in oncology, cardiology, neurology, endocrinology and psychiatry. Although more applications were submitted in 2009 than in 2008, the number of clinical trials approved declined by 6%, with 577 approvals in 2009 versus 615 in 2008. One likely cause was the overall global financial crisis.

Nearly two-thirds of the clinical trials in Russia in 2009 were conducted by multinational corporations (62%), while domestic clinical trials accounted for 23%. Bioequivalence trials represented the remaining 15%. Of the multinationals conducting trials, the largest group was US pharmaceutical companies, (22%) followed by companies from Germany (9%), Switzerland (7%) and the UK (6%).

### New Legislation

Earlier this year, the Russian government passed new legislation controlling the pharmaceutical market in Russia. The new law, replacing the previous Federal Law on Medicines of 1998, came into effect on 1 September 2010, and resulted in several fundamental changes to the existing regulatory regime. When the new law was first introduced in 2009, it was met with much criticism and fervent debate within the Russian government and the pharmaceutical industry. Nevertheless, after significant redrafting, the subsequent version was approved and signed into law on 13 April 2010.

Although initially the new legislation was heavily criticized, arguably the new regulatory system that it mandates will be a substantial step forward from the previous framework, which was encumbered by lengthy procedures and a lack of accountability for undue delays by regulators. The new law introduces set timelines for every step in the regulatory process and thereby creates a timeframe for registering new drugs of no more than 210 days.

The new law also abolished the two-part registration fee and replaced it with a single fee paid to federal authorities. The maximum payment is fixed at 300,000 rubles (~$10,200). If results from an international clinical trial conducted outside the registration process are used, the overall fee is 425,000 rubles (~$14,500). Under the new legislation, the applicant no longer has to deal directly with the expert organizations; the state authorities are tasked with interacting with the bodies performing expert examinations.

### Clinical Trials

One of the most noteworthy changes in the new legislation is the integration of the registration process with the conduct of clinical trials. By intertwining the two, it would seem that the new law allows for only a single clinical trial within the registration process. In other words, the applicant cannot apply for approval to undertake a Phase IV clinical trial once the first clinical trial has been successfully completed for the same indication.
The new law introduces the requirement for conducting clinical trials of new drugs in Russia before they can be registered. However, a clinical trial undertaken internationally is permissible as long as Russian patients are among the participants. Moreover, the new law provides that clinical trials undertaken outside Russia will be accepted based upon mutuality if so accorded in international agreements to which Russia is a party. However, currently there are no such agreements.

Clinical trials are further regulated in the new legislation in a number of different ways. For example, another measure in the new law addresses Phase 1 clinical trials: such trials, which test the safety of the drug in healthy volunteers, cannot be conducted in Russia if the pharmaceutical was manufactured abroad.

The previous regulatory structure scrutinized agreements between the organization approved to conduct the clinical trial (the sponsor) and the duly accredited healthcare institution, namely FGU. While such agreements need to include the overall cost for the clinical trial program, and in particular the cost for investigators, they no longer need to contain provisions addressing insurance. However, the new legislation does mandate life and health insurance for patients in the clinical trial and sets a minimum level for life insurance to cover each patient.

Under the new legislation, clinical trials conducted in Russia will now be obligated to use principal investigators with a medical specialization related to the clinical area of the trial, and at least five years of clinical trial experience.

Miscellaneous Issues
A number of miscellaneous crucial issues are dealt with in the new legislation. The new law takes into account measures regulating the registration of generic drugs in Russia, for instance by permitting their registration based upon bioequivalence studies, although this is not allowed for immunological medicines, insulin and new registered medicines.

While the Certificate of Registration for newly registered pharmaceuticals will continue to be of indefinite duration, the new law now requires that state registration be confirmed five years after the initial date of registration.

Other new provisions are rules governing pharmaceutical sales by wholesalers directly to healthcare institutions, new pharmacovigilance rules, labeling rules, rules regulating the state pharmacopoeia, and other timely and important matters related to the pharmaceutical industry in Russia.

Impact of the New Legislation
Because the new law has only recently gone into effect, it is premature to judge whether, or to what extent, it will be advantageous to foreign pharmaceutical manufacturers. For instance, drug manufacturers have already expressed dissatisfaction with the absence of amendments to address limiting access to clinical trial data by generic drug producers. As a consequence, these manufacturers are ready to sell their version virtually the moment a drug goes off patent.

Another gaping hole in the new legislation concerns orphan drugs, pharmaceutical products used in the treatment of rare diseases. These drugs are extremely expensive in Russia, and since the new law makes no mention of orphan drugs, the close to five million Russians afflicted with a rare disease are unlikely to be able to receive treatment. Amid public outcry from the media and nonprofit organizations, the Russian government has indicated its intention to address these concerns with a special regulation on orphan drugs. Presumably, this measure will be written by the end of 2010, though its parameters at this point remain ambiguous.

In accordance with the Russian government’s stated intentions of promoting the local pharmaceutical industry in Russia, certain protective measures have been pushed through. For example, neither pharmaceuticals intended for export nor drugs that have been on sale in the Russian market for more than 20 years need to go through the registration process. However, beginning in 2014, all local drug manufacturers...
will have to comply with GMP requirements as part of an overall quality system in Russia.43

Conclusion

According to some estimates, Russia is poised to be among the top five global pharmaceutical markets in terms of value in the next five years.44 Coupled with the evolution of the Russian regulatory framework for pharmaceutical products, this and other market trends suggest that Russia will soon become a powerhouse destination for pharmaceutical manufacturers and contract research organizations.

The current procedure for registration of pharmaceutical products in Russia may appear daunting to the inexperienced. While the process is arguably not particularly more complex than in other developing geographies, certainly a pharmaceutical company should approach registration of a product in Russia with careful deliberation and attention to detail. Table 1 outlines a summary of the registration process.

Today, Russia stands at the threshold of becoming a major force in the global pharmaceutical market. The exact contours of its future are as yet undefined; challenges and opportunities exist in equal measure. The Russia of today is not the Russia of yesterday, and tomorrow’s Russia will take yet a different face again. As the country continues its evolution, so too will its pharmaceutical industry.

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