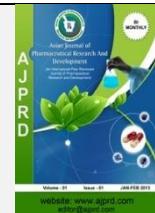


Available online on 15.04.2020 at <http://ajprd.com>

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

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Review Article

Regulatory Pathway for Registration of Biosimilars in Russia

Raj Shekhar^{1*}, Namrata Hallur², P Muralidharan³, SB Puranik⁴Assistant Drugs Controller (India), CDSCO, Sub Zone, Bangalore, Government of India, 2nd Floor, Palace Road, Bangalore, India

ABSTRACT

Biological products or biopharmaceuticals are medicinal products derived from living organism systems and manufactured by using modern biotechnology that differ widely from the conventional synthetic drugs. According to some estimates, Russia is poised to be among the top five global pharmaceutical Markets in terms of value in the next couple of years. Due to the impetus shown by the government regarding 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.

Russian law allows the registration of biological drugs defined as medicinal products containing a biological active substance. A biological active substance is a substance that is produced by or extracted from a biological source and requires physical, chemical and biological testing, characterization of its quality, along with its production process and control. It does not define a biosimilar, nor it provides a regulatory framework for the biosimilar approval; this implies that a full clinical developmental program, similar to the innovator biological product, must be completed even for a biosimilar. An applicant must submit a registration dossier to the Ministry of Health (MoH), the regulatory body for drugs evaluation, with its affiliation Federal State Budgetary Institution - Scientific Centre for Expert Evaluation of Medicinal Products (FSBI-SCEMP). The complete dossier in Russian must be submitted to the MoH, and should include administrative documents, description of pharmaceutical properties and data about the manufacturing process, quality control, preclinical studies (pharmacological and toxicological) and clinical studies regarding the biological drug. Russia follows the European Guidelines for biosimilars for data requirements for the registration of a biological drug. Today, Russia stands on the verge of becoming a major force in the global pharmaceutical market. The exact contours of its future are as yet undefined; challenges and opportunities co-exist in equal measure. The Russia of today is not the Russia of yesteryears, and tomorrow's Russia will take yet a different face again.

The objective of this manuscript is to explore the Regulatory pathway for registration of Biosimilars in Russia.

Keywords: Biosimilar; Biologics; Roszdravnadzor; Russia

ARTICLE INFO: Received 13 Jan 2020; Review Completed 11 March 2020; Accepted 28 March 2020; Available online 15 April. 2020



Cite this article as:

Shekhar R, Hallur N, P Muralidharan, SB Puranik, Regulatory Pathway for Registration of Biosimilars in Russia, Asian Journal of Pharmaceutical Research and Development. 2020; 8(2):79-87. DOI: <http://dx.doi.org/10.22270/ajprd.v8i2.673>

*Address for Correspondence:

Sh. Raj shekhar Assistant Drugs Controller (India) O/o Assistant Drugs Controller. CDSCO, Sub Zone, Bangalore, Government of India, 2nd Floor, Palace Road, Bangalore India

INTRODUCTION

The Russian pharmaceutical market is unpredictable and complex. Throughout 2017, there were many articles that praised the prospects of pharma in Russia. Strong growth potential" and predictions of the Russian pharma market being worth to touch \$38 billion by 2021. The Russian pharmaceutical bear was awakening.

A brief history on Russian pharmaceutical market

Over the past two decades, it has been noted that Russia's pharma market was outside the ambit of the world's 10 largest pharma markets, but this may change in near future. It is projected to be worth \$36.61 billion by 2021 according to reports. This represents an annual compound growth of

13%, which should push it firmly placed within the top 10 largest markets in the globe. Russia's domestic market is predominately made of generics, which contributes to around 70% of its pharmaceutical makeup. There were two main markets. The commercial market and the state government procurement market. The commercial market accounts for a whopping 85% of overall volume. Russia has historically been an importer of drugs, predominantly European made drugs. But this trend is changing and other emerging market players are entering into Russian market.

Circa 2013, it has been known that the collapse of the Russian Ruble, resulting in currency devaluation, economic slowdown, and a significant decrease in purchasing power among the general population and a

flood of sanctions from foreign governments has also astounded the economy, which comprised a reduction in pharmaceutical drug imports to Russia.

Naturally, this would raise uncertainty over the stability of the country's pharmaceutical market. But, there has been a silver thin line. The above factors have made the government to push through legislative action to substitute pharmaceutical imports and give the region's pharma market more self-sufficiency.

Recent regulations

It has been observed that amongst regulatory rules and legislation that were activated or announced in 2017 one of the chief programmes was the Federal Drug Reimbursement Programme which provides its citizens free access to over 350 pharmaceutical products.

In addition, revamped rules for the storage and transportation of medicine ensured that third party contractors were under more scrutiny to keep warehouses up to global standards.

The Russian Ministry of Trade has also issued a state program to improve domestic healthcare in Russia in general. Currently, the domestic share of Russia's pharmaceutical products manufactured is 27%. The government aims to increase its domestic share to 50% by 2020.

From 29 November 2019, medicines for human use will no longer be put on the market based on declarations of compliance and certification. More complex quality control requirements will be introduced. Pharmaceutical companies will have to submit documents on the quality of each batch of medicines to the Russian pharmaceutical regulator (Roszdravnadzor), conduct tests of the first three batches produced or imported and periodically submit test reports of batches of any medicine put into circulation.

Also, since 28 November 2018, pharmaceutical companies have to notify the authorized bodies of any planned termination or suspension of the production or importation of medicines for the coming year. This has led to the revitalization of the industry and an overall positive effect of domestic drug production. In 2017, Russia passed the National Plan for Development and Competition. As part of the plan, the Russian Government may allow the creation of an invention without the consent of the patent holder. The plan states that it will only pertain to matters of national defense and security and the protection of human life. However, the potential for misuse has been a source of concern for many American pharmaceutical companies.

Pricing legislation and imports

Pharmaceutical products in Russia are placed on a priority list to determine costs of selling drugs. The government negotiates prices with manufacturers, so they are inexpensive for even the lowest earners; whereas, the drug manufacturers want to protect their interests to make their balance sheet in profit. This has led to backing out of many manufacturers from the pharmaceutical market. This scenario is enraged by the fact that newer manufacturers rely on selling a certain amount of product at a set price. The government may lower the price and the manufacturer will be inclined to stop shipping the drug to Russia. Currently, this system has made it difficult for many important drugs to be created locally.

Russian pharma market prognosis in 2019

The projected years ahead are to be seen more optimistic and pharmaceutical companies can look out few areas to keep an eye on entering the Russia market.

In August of 2017, the Russian government demonstrated its position on private companies with the merger of the manufacture, Marathon Group, and the state run Rostec. No doubt, this is just beginning in Russia's commitment to create a self-sufficient pharma market and the future relationship between public and private interests.

Medicine labelling is now mandatory, enabling drugs to be accurately tracked throughout the entire chain, further bringing the Russian industry in line with its western counterparts.

Generally, Russia has gone to great lengths to reduce the prevalence of counterfeit drugs, culminating in the Law on Amendments to the Law on Circulation of Medicines - which was passed late in 2017. In addition to labelling, the law required that all hospitals, manufacturers, distributors and all other stake holders have to enter medicine information into the state system.

A new draft law was implemented late last year for the tracking and tracing of medicines, ensuring that legal drugs reach the shelves.

Biotechnology market:

One area of interest that pharmaceutical companies will look towards is Russia's increasing prioritisation of biotechnology sector, with a dedicated programme that is set to receive 31\$ billion in financing through to 2020. Also, working towards developing biosimilars guidelines.

Further, an additional 10 factories for the manufacturing of biosimilars is set to be completed by 2020, it shows the high priority status of pharmaceuticals among Russian decision makers, success of these initiatives is largely shaped by its domestic and foreign policymakers.

Russian counter sanctions will apply to pharmaceuticals that can be replaced with local products. However, in consideration of the quality gap and the frequency of drug shortages, Russia's ability to rapidly replace imported drugs without hurting its own citizens will be difficult.

The collaboration between the Russian government, regulators, and private manufacturers in the market will likely change over the coming years, and the ability for the Russian market to self-regulate is already looking like a steep challenge.

Drug shortages and logistical issues are a common occurrence in Russia, with many patients suddenly finding that the drug they rely on has suddenly vanished from the shelves. Other issues such as misleading advertisement, rampant price changes, and Low R&D expenditure will surely have to be dealt with the stakeholders. The pharmaceutical industry is constantly changing, a thriving pharmaceutical industry requires innovation, plenty of financial support, and the right government legislation to tie it all together. While the Russian government continuously evolving that they are building a modern and competitive pharmaceutical market,

The Ministry of Industry and Trade has developed the "Pharma 2030 Strategy," which will be a continuation of the existing "Pharma 2020 Strategy." Over the next few years, strong growth can be expected in every segment of

Russian market, the market for generic drugs/biosimilars will continue its growth due to incentives from the Russian government, as well as population's preference for

affordable medicines, highlights the need to improve the population's confidence in Russian made medicines through "educational work"^{1, 2, 3, 4}.



Figure 1: Russia Map

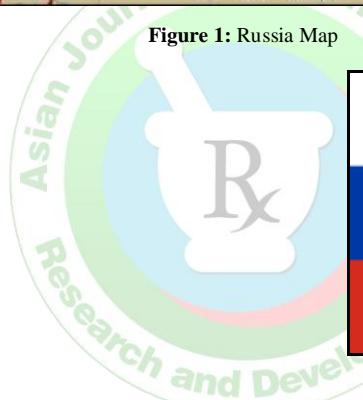


Figure 2: Flag Tricolor and Emblem

Before, explaining on Russia market, it is critical to discuss about sociodemographic aspects. Russia is a land of superlatives. By far the world's largest country, it covers nearly twice the territory of Canada, the second largest. It extends across the whole of northern Asia and the eastern third of Europe, spanning 11 time zones and incorporating a great range of environments and landforms, from deserts to semiarid steppes to deep forests and Arctic tundra. Russia contains Europe's longest river, the Volga, and its largest lake, Ladoga. Russia also is home to the world's deepest lake, Baikal, and the country recorded the world's lowest temperature outside the North and South poles. The inhabitants of Russia are quite diverse. Most are ethnic Russians, but there also are more than 120 other ethnic groups present, speaking many languages and following disparate religious and cultural traditions. Most of the Russian population is concentrated in the European portion of the country, especially in the fertile region surrounding Moscow, the capital. Moscow and St. Petersburg (formerly Leningrad) are the two most important cultural and financial centers in Russia and are among the most picturesque cities in the world^{5, 6}.

| | |
|----------------------------|--|
| Official Name | Rossiyskaya Federatsiya (Russian Federation) |
| Languages Spoken | Russian |
| Is Landlocked | No |
| Latitude/Longitude | 61.5240° N, 105.3188° E |
| Currencies Used | Ruble (RUB) |
| Demonym | Russian |
| Capital | Moscow |
| Top cities of South Africa | Saint-Petersburg, Novosibirsk, Nizhny Novgorod, Ekaterinburg, Samara, Omsk, Chelyabinsk, Kazan, Perm, Ufa, Rostov-on-Don and Volgograd |

Federal Service For Surveillance In Healthcare (Roszdravnadzor) was established by the President of the Russian Federation in Decree on March 9, 2004 № 314 "On the System and Structure of the Federal Executive Bodies" and is a federal executive body responsible for control and supervision of the Healthcare system.

Roszdravnadzor is subordinate to the Ministry of Health of the Russian Federation and guided by the Russian Federation Constitution, federal constitutional laws, federal laws, Acts of the President of the Russian Federation and State Government, international agreements, Acts of the Ministry of Health of the Russian Federation and the

Table: 1 The Key details pertaining to Russia are tabulated below;

Regulation stated in Decree dated June 30, 2004 № 323 "On the Federal Service for Surveillance in Healthcare".

The Federal Service for Surveillance in Healthcare operates directly or through its regional offices in cooperation with other federal agencies, state executive bodies, local authorities, public associations and other institutions.

The structure of the Federal Service for Surveillance in Healthcare currently includes the central head office (9 departments), 80 regional offices in constituent entities of the Russian Federation, 1 interregional office and 3 federal state budget institutions.

Roszdravnadzor exercises the following powers:

1. State control and supervision of :

- Medical devices circulation;
- Quality and safety of medical practice by carrying out inspections and audits;
- Circulation of medicines
- pricing for medicines included in the list of vital and essential medicines;
- Execution of the Russian Federation regional healthcare modernization programs and measures to modernize public healthcare institutions and state institutions implementing healthcare information systems deployment and upgrade in the Russian Federation constituent entities;
- Reliability of primary statistics presented by medical institutions and individual medical entrepreneurs.

2. Control and supervision of State government bodies of the Russian Federation constituent entity regarding annual payments to persons awarded the "Honorable Donor of Russia" title. Roszdravnadzor is in charge of identifying violations and initiation of the prosecution of local officials responsible for failure to exercise the delegated authority.

3. The Federal Service for Surveillance in Healthcare performs the following:

- Monitoring of the list of vital and essential medicines and their prices;
- Monitoring of medical devices safety, registering side effects and adverse reactions, as well as facts and circumstances, related to the circulation of registered medical devices that might be posing threat to life and health of people.

4. Licensing of certain types of practices within the competence of the Service.

5. The Federal Service for Surveillance in Healthcare issues:

- Permits for transit of superpotent substances which are not precursors of narcotic drugs and psychotropic substances through the territory of the Russian Federation;
- Permits for import of medical devices into the Russian Federation for the purposes of state registration;
- Certificate for import (export) of narcotic drugs, psychotropic substances and their precursors;

FZ dated 12 April 2010 (hereinafter – the "Law"). The key amendments include the following:

Certificates of a specialist to persons with foreign medical or pharmaceutical education.

6. The Federal Service for Surveillance in Healthcare performs state registration of medical devices.
7. The Federal Service for Surveillance in Healthcare maintains the state registry of medical devices and institutions manufacturing medical devices;
8. Service publishes the information about the decisions made based on results of medicines safety monitoring;
9. The Federal Service for Surveillance in Healthcare performs inspections of Healthcare institutions;
10. The Federal Service for Surveillance in Healthcare has reception hours, provides timely and complete processing of citizens appeals;
11. The Federal Service for Surveillance in Healthcare performs other functions subject to the Regulation on Roszdravnadzor, as well as functions stipulated by federal laws, regulatory acts of the President of the Russian Federation or the Government of the Russian Federation.

In Russia, Research and Commercialization of Biotech product and Similar Biologics Governed as per theFederal rules details are mentioned in below table:

There are two key regulators of pharmaceuticals in Russia: the Ministry of Health and the healthcare products and surveillance agency, Roszdravnadzor. The MoH is a federal executive body in charge of working out state policy, as well as legal regulations in healthcare. The Roszdravnadzor is a MoH subordinate agency, responsible for control and supervision in healthcare, including GCP inspections and pharmacovigilance.

The MoH is the principal regulator for drug MAAs and clinical trials. It grants MAAs for drugs, issues clinical trial authorizations, grants import/export licenses for the purposes of MA and clinical trials, approves accreditation of clinical sites, maintains corresponding registers and operates a register of principal investigators. The MoH organizes the regulatory assessments of registration dossiers and clinical trial documents through its expert bodies: the Ethics Council and the Scientific Center for Expertise of Medicinal Products (SCEMP). A positive MoH decision is based on both positive EC and SCEMP expert conclusions⁷.

In 2010 the Ministry of Health of the Russian Federation issued Federal Law #61. The law changed the registration process for drugs, introducing the requirement for a local clinical or bioequivalence study for every submitted drug – a costly new step for international drug firms. There is just one exception to this requirement; if a molecule has been marketed for more than 20 years in Russia then this obligation can be avoided⁸.

Changing and new Rules:

The Federal Law "On amendment of the Federal Law "On circulation of pharmaceuticals" No. 429-FZ (hereinafter – the "Law No. 429-FZ") was signed on 22 December 2014. This legal act introduces significant amendments into the Federal Law "On circulation of pharmaceuticals" No. 61-

- Introduction of new definitions, as well as adjusting of existing definitions, including, *inter alia*, introduction of such definitions with respect to pharmaceuticals as

- orphan pharmaceutical, biologic pharmaceutical, biosimilar, interchangeable pharmaceutical, introducing a definition of a holder or owner of a registration certificate (Marketing Authorization Holder);
- Separation of clinical trials from the state registration of pharmaceuticals along with adjustment of the mentioned procedures;
 - Establishing new grounds for cancellation of pharmaceutical's state registration;
 - Establishment of a possibility to provide scientific consultations upon request from a participant of pharmaceuticals turnover;
 - Introduction of requirements on development and enactment of good practices rules;
 - Establishment of procedure for determination of pharmaceuticals interchangeability;
 - Imposition of responsibility and liability on a holder or owner of a registration certificate (Marketing Authorization Holder);
 - amendment of rules for the state registration of maximum selling prices for pharmaceuticals included into the List of essential and vitally important medicines (hereinafter – "EDL pharmaceuticals");
 - Establishment of potential possibility for pretrial closing of websites containing information on distant retail of pharmaceuticals.

Apart from separate provisions the amendments to the Law was into force from 01 July 2015⁹.

Clinical Trials in Russia¹⁰

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. 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.

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 effort.

The decision to conduct clinical trials in a given country is affected by a number of considerations; important factor is the timeline for the clinical trial set-up and initiation⁷

To obtain a permission for the clinical study, it is necessary to prepare a complete Registration dossier in a paper and electronic form (on the portal <http://grls.rosminzdrav.ru>), complete an application on state registration of pharmaceutical product, pay a state duty (75000, 00 rubles) and submit a paper Registration dossier to the Ministry of Health of the Russian Federation, the Department of state regulation of medicinal product circulation (Moscow City, Rakhmanovsky lane, 3). A local clinical trial in Russia is mandatory for obtaining an MA for domestic and foreign drugs. Foreign manufacturers can get waived off to conduct a confirmatory local registration clinical trial if Russia is part of IMCT referred below as a local clinical trial – by involving Russian investigative sites in international multicenter clinical trials (IMCTs) of their drugs in the course of their R&D process.

The Ministry of Health of the Russian Federation checks if the submitted dossier contains all necessary documents and then sends the registration dossier for two parallel evaluations: ethical evaluation (performed by an Ethics Committee) and evaluation of documents for the purpose of granting a clinical study permission (performed by the FSBI SCEMP of the Ministry of Health of the Russian Federation). In case of positive results of the both evaluations, the Ministry of Health of the Russian Federation makes a decision to grant a permission to conduct the clinical study. This decision appears in the applicant's personal account on the portal <http://grls.rosminzdrav.ru>. After this decision appears, it is necessary to prepare the second package of clinical study documents, to complete an application on the portal and submit paper versions of the documents to the Ministry of Health of the Russian Federation which then issues a permission to conduct the clinical study of the pharmaceutical product in the Russian Federation. All approved clinical studies are included in the Register of permitted clinical studies and available on the portal <http://grls.rosminzdrav.ru>¹¹.

The MoH issues an IMCT authorization in 45 business days upon receipt of positive conclusions from the Ethics Council and SCEMP. State tax for expert review and IMCT approval is about 2,350 Euros. All submitted documents should be in Russian or translated into Russian. The list of documents required for local clinical trials and IMCTs authorization varies.

| | |
|--|--|
| Regulatory Agencies | Federal Service for Surveillance in Healthcare (ROSZDRAVNADZOR Ministry of Health Ministry of Trade and Industry |
| License Approving Authorities | Head of the Federal Service for Surveillance in Healthcare |
| Pharmaceutical Laws and Regulations/ Guidelines | Federal Law #61 Law No. 429-FZ" In accordance with paragraph 5.1.4.1 of the Resolution of the Government of the Russian Federation dated June 30, 2004 № 323 |

Table 2: Comparison of Documents required for local clinical trial and IMCT authorization

| S.No | Local Clinical Trial | IMCT |
|------|--|---|
| 1 | Cover letter, comprising information on expected time frame of clinical trial | Cover letter, comprising information on expected time frame of clinical trial |
| 2 | Application Form | Application Form |
| 3 | Power of Attorney that specifies contract research organization's activities on behalf of sponsor in Russia | Power of Attorney that specifies contract research organization's activities on behalf of sponsor in Russia |
| 4 | Document evidencing payment of state tax | Document evidencing payment of state tax |
| 5 | Review of results of non-clinical and previously conducted clinical trials | Review of results of non-clinical and previously conducted clinical trials |
| 6 | Protocol | Protocol |
| 7 | Investigator's brochure on a study drug | Investigator's brochure on a study drug |
| 8 | Informed Consent Form | Informed Consent Form |
| 9 | List of Russian clinical site to be involved in clinical trial | List of Russian clinical site to be involved in clinical trial |
| 10 | List of Principal Investigators CV | List of Principal Investigators CV |
| 11 | Compulsory insurance agreement | Compulsory insurance agreement |
| 12 | Information on payments and compensations to healthy volunteers or patients (if any) | - |
| 13 | Information on a study drug composition | |
| 14 | Quality certificate (Certificate of analysis) of a study drug and its placebo (if needed) | Quality certificate (Certificate of analysis) of a study drug and its placebo (if needed) |
| 15 | Document confirming study drug registration (MA) status outside Russia | - |
| 16 | Study drug manufacturer good manufacturing practice (GMP) certificate, issued by competent authorities | - |
| 17 | Study drug manufacturing process flow chart and its description | - |
| 18 | Study drug specification and analytical procedures (so called Study drug normative document, a kind of chemistry, manufacturing and control (CMC)) | |
| 19 | Quality certificate (Certificate of analysis) of active pharmaceutical ingredient (API) | - |
| 20 | API manufacturer GMP certificate, issued by competent authorities | - |
| 21 | API specification and analytical procedures (so called API normative document, a kind of CMC) | - |
| 22 | Instruction for medical use of study drug (equivalent to SmPC + patient's leaflet) | - |
| 23 | Study drug primary and secondary packages mock-ups | - |

Bureaucratic challenges at the MoH or inadequately prepared submission packages by the applicant can sometimes delay the approval of a local clinical trial or IMCT by up to three or four months. Direct contact between applicants and regulators is prohibited as this is regarded as a potentially corruptive activity. There is also no scientific advice procedure available under the legislation. Applicants can submit additional data to

support their concept if requested to do so by the Ethics Council and SCEMP, but they can only submit this data via the MoH. In case of such a request, an applicant has to provide the MoH with an answer and additional data within 90 business days.

After the clinical trial has been approved, it takes an additional two to three weeks to receive the study drug import license and the biological samples export license. Both export and import licenses are free of charge and valid for the entire study duration.

Clinical trials must be conducted at medical institutions accredited by the MoH; the MoH register comprises 1,052 clinical sites. Most clinical sites are located in central, northwestern, Siberian and Volga federal regions. As per law, a principal investigator is a person who has at least five years' experience in conducting clinical trials and a medical specialty corresponding with the profile of the clinical trial. Insurance for all study participants is compulsory. The insurance rate is set by law and depends on the clinical trial phase. Insurance costs approximately 120 Euros per subject in case of BE/Phase I studies and about 18 Euros per subject in case of Phase III studies. Insurance policies must be issued only by Russian insurance companies. While no legally established timelines currently exist (the effect of the new drug legislation discussed below may change this), on an average, clinical trial approval in **Russia takes 90 Calendar days**.

The length of the clinical trial period depends on the study type, duration of treatment, etc. Typically, the clinical trial period lasts at least six months although on average, it is approximately 10-18 months. During the clinical study period, the registration procedure is suspended.

The list of documents required for local clinical trial authorization will be similar to the documents required for IMCT authorization (see Table 2). The procedures for authorizing local clinical trials and IMCTs will include scientific and ethical review, and the duration for both types of studies will be 40 business days. Sponsors should include the results of local clinical trials in their drug registration dossier.

Registration of Biosimilars products in Russia¹¹

The submission of documents and timelines for Biosimilars is the same as for the registration of a biological product (which is considered to be a "pharmaceutical product")¹¹.

To enter into Russian market all pharmaceutical products must be registered with the MoH. Registration is a procedure of expertise of the pharmaceutical product quality, efficacy and safety by State Regulatory Authority. After such expertise review they will grant Registration Certificate and the product is introduced in the database of registered products in Russian Federation. From 2008 onwards, Registration Certificate validity is unlimited. But before this date Registration Certificates were issued only for 5 years validity. A big number of already registered products must pass re-registration. Registration Certificate is the same document which would be considered as a Marketing Authorization. In Russia there are 2 strictly divided categories:

1. Pharmaceutical products (one category) and food supplements and
2. Cosmetics (another category).

Pharmaceutical products (medicines and medical products), Medical devices, food supplements and Cosmetics. The registration requirement of above categories differs in their review processes. Pharmaceutical products pass more detailed and strict examination; need more documentation and additional expertise compared to the cosmetics. Occasionally, problems arise because of the distinction

between medicines or medical devices and food products (including biological food additives) and cosmetics. In the event of a dispute it should be borne in mind that all these products have different regulatory regimes, and it is necessary that they be governed by the criteria stipulated in the related legislation.

Documents requirements for Registration:

Registration file (or dossier) must contain the following the documents which is to be submitted to State Regulatory Authority for registration. Russian registration dossier file consists of 6 parts:

1. Administrative documents
2. Description of pharmaceutical properties
3. Data about manufacturing of pharmaceutical product
4. Data about quality control of the finished pharmaceutical product
5. Data about PRE-CLINICAL pharmacological and toxicological studies of pharmaceutical product
6. Data about CLINICAL studies of pharmaceutical product

Russian registration file must be presented to State Regulatory Authorities in Russian language.

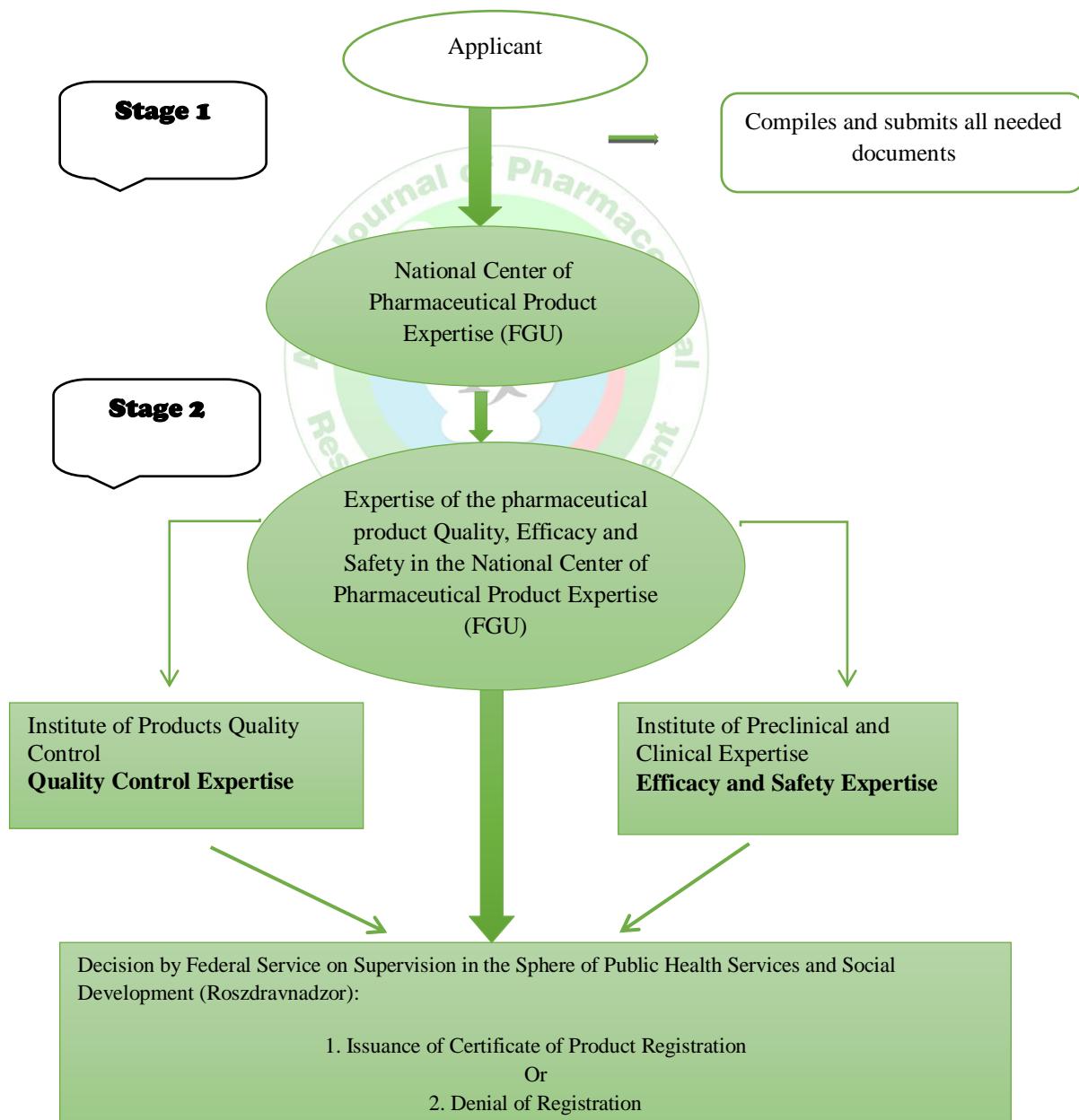


Figure 4: Steps involved in the registration process

The fees 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.

The most difficult and longest is the II stage. Registration dossier after submission and payment of necessary fees is directed to appointed experts from Institute of Products Quality Control and Institute of Preclinical and Clinical Expertise.

In the Institute of Products Quality Control, verification of Finished Product Specifications called in Russian Normative Document is performed.

In the Institute of Preclinical and Clinical Expertise, the instruction for administration is checked. In case if necessity of preclinical or clinical tests the product is directed to specialized Research Institute.

Original and generic products pass the same stages of registration. Original products must pass through all registration procedures while the generic products are exempted from some of them. For original products clinical trials are must. Whereas for generic products; only the bioequivalence studies are to be conducted. The preclinical and clinical studies performed in foreign countries are also accepted.

Laboratory Control of pharmaceutical products during registration and post-registration Control at the stage of import for selling (essential moments, possible difficulties).

There are 2 types of Variations:

| TYPE | CLASSIFICATION | EXAMPLE |
|-------------------|--|---|
| Variation type I | Don't need Quality, Efficacy or Safety expertise | Change of the Manufacturer's name; Change of Marketing Authorization holder; Change of package design |
| Variation type II | Need Quality, Efficacy or Safety expertise | Change of manufacturing site; change of quality or quantity composition; change of instruction for administration |

Terms of variation approval:

| Type | Terms |
|-------------------|-------------|
| Variation type I | 2-3 Months |
| Variation type II | 6-12 Months |

Summary of Drug Registration Process in Russia

| | |
|--|--|
| Translation Y/N | Yes |
| Overall regulatory agency | Federal Service on Supervision in the Sphere of Public Health Services and Social Development (Roszdravnadzor). |
| Dossier contents | Administrative documents, description of the pharmaceutical properties, data about manufacturing of the pharmaceutical product, data about quality control of the finished pharmaceutical product, data about pre-clinical pharmacological and toxicological studies of the pharmaceutical product, and data about the clinical studies of the pharmaceutical product. |
| Additional information | If the applicant already has a European registration file, a separate document preparation for the Russian filing isn't needed (but the dossier must be submitted in Russian). |
| Documents required to be legalized | Power of attorney, Certificate of Pharmaceutical Product, GMP Certificate, and Manufacturing License (note: if these documents were issued by Hague Convention Member State, they need only be apostilled). |
| Approval time | ~18 months total for Certificate of Registration to be issued. |
| Import license | Yes, special license from Roszdravnadzor to import samples/standards for laboratory control process. Takes one to two months (in addition to approval time above). |
| Changes to Certificate of Registration | Allowed, but approval for certain types of variations can take two to three months. |
| Cost | ~\$49,000 (US) total (note: this includes official payment and payment to the regulatory expertise organization). |

CONCLUSION

According to some estimates, Russia is poised to be among the top five global pharmaceutical Markets in terms of value in the next couple of years. Due to the impetus shown by the government regarding 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.

Russian law allows the registration of biological drugs defined as medicinal products containing a biological active substance. A biological active substance is a substance that is produced by or extracted from a biological source and requires physical, chemical and biological testing, characterization of its quality, along with its production process and control. It does not define a biosimilar, nor it provides a regulatory framework for the biosimilar approval; this implies that a full clinical developmental program, similar to the innovator biological product, must be completed even for a biosimilar. An applicant must submit a registration dossier to the Ministry of Health (MoH), the regulatory body for drugs evaluation, with its affiliation Federal State Budgetary Institution - Scientific Centre for Expert Evaluation of Medicinal Products (FSBI-SCEMP). The complete dossier in Russian must be submitted to the MoH, and should include administrative documents, description of pharmaceutical properties and data about the manufacturing process, quality control, preclinical studies (pharmacological and toxicological) and clinical studies regarding the biological drug. Russia follows the European Guidelines for biosimilars for data requirements for the registration of a biological drug.

Russia has an enormous market for biological drugs, including biosimilars. In fact, many biosimilars have been granted authorization even though they don't have any particular guidelines about similar biological products. These products include EPO, interferons, monoclonal

antibodies, insulin, somatropins, G-CSF, heparins, plasma coagulation factors, r-coagulation factors. The biosimilar authorized in Russian market was Biocad's Acellbia, a non-originator of rituximab, in April 2014.

Today, Russia stands on the verge of becoming a major force in the global pharmaceutical market. The exact contours of its future are as yet undefined; challenges and opportunities co-exist in equal measure. The Russia of today is not the Russia of yesteryears, and tomorrow's Russia will take yet a different face again. As the country is focused towards evolution, spending on R&D, manufacturing domestically as part of the "Pharma 2030 Strategy," rolled out by The Ministry of Trade and Industry.

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