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REGULATORY REQUIREMENTS FOR GENERIC AND NEW DRUG REGISTRATION IN RUSSIA

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ABSTRACT

The purpose of the study was to generic drug registration process in Russia. It can be concluded that the world pharmaceutical economy, the fastest growing and largest emerging markets economies of Brazil, Russia, India, China and South Africa (BRICS) countries are showing positive growth and increasing direct foreign investment by creating significant opportunities for pharmaceutical companies to expand into these markets. They would be the largest entity on the global stage. The drawback in Russia are the regulations are in their local languages and the documents required for registration of drugs should translate into their local languages. It takes time to understand the rules and regulations and for registration. To rectify the differences of the guidelines, we need to go for harmonization. So that we can expect a common guideline worldwide. It will take time to harmonize the guidelines. But once harmonized the guidelines, emerging countries like Russia will get benefit. With ICH formation, the industry foresees harmonization of regulations, so that we can do filing easily. In the interest of industry, we are opinion that all regulations are harmonized and unified regulations are emerged.

KEYWORDS: Regulatory Requirements, Registration Process, Russia, Generic Products.

1. INTRODUCTION

Russia is a country in northern Eurasia. It is a federal semi-presidential republic, comprising 83 federal subjects. At 17,075,400 square kilometres (6,592,800 sq. miles), Russia is the largest country in the world, covering more than one eighth of the Earth's inhabited land area.

Russia is also the ninth most populous nation with 143 million people as of 2012. Extending across the whole of northern Asia and most of Eastern Europe, Russia spans nine time zones and incorporates a wide range of environments and landforms. Russia has the world's largest reserves of mineral and energy resources and is the largest producer of oil and natural gasglobally. Russia has the world's largest forest reserves and its lakes contain approximately one-quarter of the world's fresh water.

Role Of Russia In Global Pharmaceutical Market

With the Global expenditure on medicines estimated to rise from $956 billion in 2011 to nearly $1.2 trillion by 2016, Russia is playing significant role in the Global Pharmaceutical Market. According the recent survey conducted by IMS Health; Russia along with other Emerging Markets like Brazil, India, China etc., account to about 13% of the sales in the world.

Russian Pharmaceutical Market

The pharmaceutical industry in Russia has seen considerable expansion in the past several years, with double-digit growth rates. In view of recent developments, market researchers anticipate that the upward trend will continue at an even greater pace. As mentioned earlier, the size of the market was USD 8.6 billion in 2010, and the compound annual growth rate for the past four years was 14.2 percent. By comparison, the pharmaceutical markets in France and Germany had compound annual growth rates of only 1.8 percent and 3.4 percent from 2006 to 2010. While it is true that the size of those markets is larger than that of the Russian pharmaceuticals sector (USD 36 billion and USD 37.9 billion respectively), Russian pharmaceuticals manufacturers are making steady efforts to catch up with their European counterparts.

Pharmaceuticals in the “other therapeutic” treatment category represented the best-performing subsector with nearly USD 4 billion in sales. Alimentary and metabolism pharmaceuticals constituted the second-highest market segment, where revenues reached USD 1.5 billion in 2010. Thus, the “alimentary and metabolism” category accounted for 17.8 percent of the overall market size.

While the Russian pharmaceutical market is forecast to grow at a compound annual growth rate of 20.9 percent in the next five years, the French and the German markets are estimated to grow at compound annual growth rates of 0.7 percent and 1.8 percent respectively over the

same timeframe. Thus, when the Russian market reaches the value of USD 22.1 billion in 2016, the market of France will have the value of USD 37.7 billion, and the market of Germany USD 44.5 billion. In 2010 alone, the Russian pharmaceutical market expanded by 17 percent. Today, Russia accounts for 4.4 percent of the European pharmaceutical market. By comparison, Germany's share of the European market is 17.8 percent.

Highlights of the Russian Pharma Market

- Total value is 15 billion USD
- In Russian Pharma Market, 80% share is of imported products and 20% is locally manufactured, in which less than 1% are innovative products.
- 15280 Pharmaceutical products are registered out of which 13850 are finished products.
- 26% growth observed in local currency in 2008.
- 70% of the market is of OTC product and 30% is of prescription products.
- Market mainly dominated by foreign companies like Novartis, J&J, Novo Nordisk, Roche, Sanofi-Aventis, Nicomed and generic companies like Gedeon Richter and Lek.

2. DRUG REGULATORY AUTHORITIES IN RUSSIA

➢ **Ministry of Health and Social Development (MOH)**

- Draws up state policy and regulation in healthcare, circulation of medicines for human use, social development and protection of consumer rights.
- Adopts general pharmacopeial articles, and publishes state pharmacopoeia.
- Registers medicinal preparations for human use.
- Issues permits for the conduct of clinical trials.
- Issues permits for importing specific unregistered medicines for clinical trials and their expert examination for state registration.
- Registers maximum manufacturer prices of EDL medicinal preparations.
- Certifies qualified persons for the manufacture of medicines.

➢ **Federal Service for Surveillance in Healthcare and Social Development (*Roszdrvanadzor* or Federal Service)**

- Exercises control over pre-clinical trials of medicines and clinical trials of medicinal preparations, quality, manufacturing of medicines, production of medicinal preparations, storage, transportation, importation to Russia, advertising, sale, and destruction of medicines and application of medicinal preparations.

- Exercises control over the application of prices of EDL medicinal preparations.
- Conducts monitoring of the assortment and prices of EDL medicinal preparations.
- Conducts monitoring of the safety of medicinal preparations that are circulated in Russia.
- Grants licences for pharmaceutical activities.
- Keeps a register of licences granted.

➢ **Ministry of Industry and Trade (MIT)**

- Plays an important role in the procedure of declaration of conformity of medicinal preparations.

3. REGISTRATION IN RUSSIA

Conception

- To enter into Russian market all pharmaceutical products must be registered.
- Registration is a procedure of expertise of the pharmaceutical product quality, efficacy and safety by State Regulatory Authority. After such expertise it is issued Registration Certificate and the product is introduced in the database of registered products in Russian Federation. From 2008 Registration Certificate is unlimited. But before this date Registration Certificates were issued only for 5 years. A big number of already registered products must pass re-registration. Registration Certificate is the same document as Marketing Authorization.
- In Russia there are 2 strictly divided categories: pharmaceutical products (one category) and food supplements and cosmetics (another category). The product must be associated with one from these categories. It is absent such category as “curative cosmetics”. The registration expertise of these 2 categories differs very much. Pharmaceutical products pass more detailed and strict examination; need more documentation and additional expertise.
- **State Registration of** Pharmaceuticals
- As a general rule, pharmaceuticals may be produced, imported, sold, and used in the Russian Federation only if they are registered with the state authority exercising control over the quality of pharmaceuticals. Presently, these functions are vested in the Federal Health Service.
- Registered **pharmaceuticals** shall be entered into the State Register of **Pharmaceuticals**. Domestic and foreign **pharmaceuticals** enjoy the same treatment **for** the purposes of registration.

Registration file (or dossier) represents the documents submitted to State Regulatory

Authority for registration. Russian registration file consists from 6 parts:

- Administrative documents
- Description of pharmaceutical properties
- Data about manufacturing of pharmaceutical product
- Data about quality control of the finished pharmaceutical product
- Data about PRE-CLINICAL pharmacological and toxicological studies of pharmaceutical product
- Data about CLINICAL studies of pharmaceutical product

The following miscellaneous documents and information shall be filed with the Federal Health Service to register pharmaceuticals:

- Application for state registration of a pharmaceutical;
- Document evidencing payment of state registration fee;
- Legal address of the manufacturer of the pharmaceutical;
- Name of the pharmaceutical including International Non-proprietary Name (INN), any scientific name in Latin, and principal synonyms;
- Original name of the pharmaceutical if it is registered as a trademark;
- List of ingredients specifying their quantity,
- Instructions for use of the pharmaceutical made in compliance with the Pharmaceutical Law requirements;
- Quality certificate for the pharmaceutical;
- Manufacturing data for the pharmaceutical and pharmacopoeia;
- Methods for quality control;
- Results of pre-clinical trials;
- Results of pharmacological and toxicological testing of the pharmaceutical;
- Results of clinical trials;
- Samples of the pharmaceutical for its quality examination;
- Proposals on price; and
- Documents confirming the registration of the pharmaceutical if it has been registered outside Russia.

The above documents shall be filed **in** the Russian language or be supplied with a certified Russian translation.

4. DOSSIER STRUCTURE

This is an example of a Dossier from the Internet

Documents needed for the State Marketing Authorisation:

Application for the Marketing Authorisation

BI Administrative Documents

V.I.1 Content of documents and data showing the number of pages and copies.

V.I.2 Application Letter for Marketing Authorisation of a medicine or for making changes in registration documents.

V.I.3 Documents confirming the authority to apply for state registration (power of attorney to submit documents and data for state registration (making changes), a letter about absence of unfair use of intellectual property).

V.I.4 Receipt on the implementation of fees for the State Marketing Authorisation of medical products.

V.I.5 Original of the payment order confirming payment of the State Dues for state registration of a medication.

V.I.6 Application Form to Roszdravndzor for registration of a medication or for making changes

V.I.7 Names of medicinal product, including international non-proprietary name, scientific name in Latin, basic synonyms.

V.I.8 Original name of the medication if it is registered as a trademark in accordance with the law of the Russian Federation on trademarks, service marks and names of places of origin of goods (trademark certificate).

V.I.9 List of components included in the medication, their quantities, description of the medication.

V.I.10 Package leaflet of a medicinal product designed in accordance with the requirements of the Federal Law on Drugs.

V.I.11 Certificate of quality of medicinal product (a certified copy with the translation, signed by an authorized person on behalf of the applicant).

V.I.12 Proposal for the price of a medicinal product.

V.I.13 Documents certifying the Marketing Authorisation of a medicinal product if it is registered outside Russia.

B.II Description of the pharmaceutical properties

V.II.14 Components of the medicinal product.

V.II.15 Active substance(s) (certificate of the manufacturer).

V.II.16 Auxiliary substances (certificate of the manufacturer).

V.II.17 Pharmaceutical form (contents of main efficacious substances; allowed deviations, physical, chemical and biological properties); justification of the production method and packaging (primary and secondary); microbiological properties.

B. III Data on the manufacture of medicinal product

V.III.18 Legal address of the manufacturer of the medicinal product (confirmation of the country of manufacture).

V.III.19 Location(s) of manufacture (confirmation of compliance with the rules of production organization).

V.III.20 Material balance.

V.III.21 Summary overview of the manufacturing process and production control methods.

V.III.22 Control over production stages and intermediary products.

V.III.23 Validation and/or the description of the manufacturing process.

V.IV. 24 Original article of the Pharmacopoeia or Specification and a draft of the Normative Document.

V.IV. 25 Methods of quality control of medicinal product specifications, analytical procedures, validation of analytical procedures; charges analysis, potential impurity characterization of impurity, justification of specifications.

V.IV.26 Standards substances and reference substances (for the standard substance - documentation from the manufacturer, for the reference substance - a copy of the manufacturer's certificate with a certified Russian translation).

V.IV.27 Samples of the medication for expert evaluation of its quality (confirmation of readiness for quality expert evaluation).

V.IV.28 Primary and secondary packaging (confirmation of permission to use in the country of manufacture).

V.IV.29 Primary and secondary packaging labeling mock-ups.

V.IV.30 Results of stability tests in the declared primary packaging.

B.IV The data for quality control of the drug

B. V Information on the results of pre-clinical, pharmacological and toxicological studies for the medicinal product

V.V.31 Introductory summary of the pre-clinical studies.

V.V.32 Reports of performed studies.

V.V.33 Pharmacology, the results of studies confirming the pharmacological strength of medication.

V.V.34 Pharmacokinetics, the results of studies confirming absorption, distribution, metabolism, excretion or interaction with other drugs.

V.V.35 Toxicology, general toxicity, specific toxicity.

V.V.36 List of the scientific literature used.

V.VI Information on results of clinical studies

V.VI.37 Consolidated analysis of the results of efficacy and safety studies. Consolidated and separate test results; comparative analysis of results of separate studies; tested populations; comparison of efficacy results received in different studies; comparison of results received from separate patient groups; analysis of recommended dosage test results.

V.VI.38 Consolidated analysis of the safety studies. Methods for evaluation of safety, the nature and frequency of undesirable events, clinically significant changes in laboratory performance, interaction with other medicinal products.

V.VI.39 List of the scientific literature.

5. NORMATIVE DOCUMENT

Normative Document (ND) needs for "Scientific center for medicines expertise of Rozdravnadzor" (FSI SC MER) based on the quality of the Dossier. ND. The Normative Document is comparable with short form of CTD in the EU countries. Usually, the approved ND is scanned and placed in the database of the Authority. Different experts for control andcertification of the products could use the Normative Document (ND), which refers to drug products in Russia covering information about:

- Trade name;
- Pharmaceutical form and strength;
- Active substance /INN;
- Manufacturer of drug product;
- Country;

• Pharmacological group;
• Specification;
• Description and composition of the drug product;
• Analytical procedures;
• Validation of analytical procedures;
• Batch analysis;
• Characterization of impurities;
• Reference standards or materials;
• Primary and secondary packaging description;
• Stability.

Approval Certificate

The Approval Certificate consists of three pages.

The first page

• Name of the applicant, country;
• The Approval Certificate number. This must not be changed during the State Marketing Authorisation and Renewal period;
• Issue date;
• Trade name;
• Active ingredients, INN, strength;
• Pharmaceutical form;
• Expiry date.

The second page

• Trade name;
• Active ingredient;
• Pharmaceutical form;
• Composition;
• Name and address of the manufacturers responsible for bulk, packaging, batch release, and other involved manufacturers;
• Copy of package leaflet as attachment;
• Copy of ND as attachment.

The third page

• Storage conditions;

• Primary and secondary packaging description.

The number of the Approval Certificate consists of a code for product type: medicinal product or device, and 6 figures, coding the Order of State Marketing Authorisation number and the year of issue.

The Approval Certificate grants the Federal Service authority for control and supervision in the field of healthcare and social development, and this Certificate is signed by the head of the Federal Service.

5. PROCEDURE FOR AUTHORIZATION

State Regulatory Authority is called Federal Service on Supervision in Sphere of Public Health Services and Social Development (Roszdravnadzor). Roszdravnadzor takes the decision to register the product and issues Registration Certificate. The expertise of all pharmaceutical products quality, efficacy and safety is done by National Center of Pharmaceutical Products Expertise (FGU). Only this National Center is authorized to execute independent expertise especially for Roszdravnadzor. According to new Medicines Act which is under approval additional Centers will be authorized to make registration expertise of pharmaceutical products.

National Center of Pharmaceutical Products Expertise consists from different Sections and Institutes. The biggest and the most important part of the registration procedure pass in the mentioned Center. Applicants for products registration submit registration documents directly to National Center. The registration procedure is organized in the way that regulatory affairs specials must communicate with experts every week. It is fixed the schedule of visiting days. Terms of registration depend a lot from the correctly organized work of the regulatory affairs specialist. The registration procedure is the same for Russian and Foreigner manufacturers. Differences appear in cost and documents. Also the important fact is that foreigner manufacturer must have GMP-certificate. The product is not necessary to be registered in the country of origin or another country. It is admitted to apply for registration products which will be authorized only in Russian Federation. State Regulatory Authorities are situated only in Moscow. There are absent divisions in other regions on Russian Federation. European registration file consists from 5 modules. The structure of Russian and European registration files is very similar. If manufacturer has European registration file it is not necessary to

prepare separated docs for Russia. All data required for Russian dossier are available in European file. Russian registration file must be presented to State Regulatory Authorities in Russian.

6. SUMMARY

Table 1. 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).
Key government body responsible for quality, safety and efficacy review	National Center of Pharmaceutical Products Expertise (FGU).
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).

7. CONCLUSION

The purpose of the study was to generic drug registration process in Russia. It can be concluded that the world pharmaceutical economy, the fastest growing and largest emerging markets economies of Brazil, Russia, India, China and South Africa (BRICS) countries are showing positive growth and increasing direct foreign investment by creating significant

opportunities for pharmaceutical companies to expand into these markets. They would be the largest entity on the global stage. The drawback in Russia are the regulations are in their local languages and the documents required for registration of drugs should translate into their local languages. It takes time to understand the rules and regulations and for registration. To rectify the differences of the guidelines, we need to go for harmonization. So that we can expect a common guideline worldwide. It will take time to harmonize the guidelines. But once harmonized the guidelines, emerging countries like Russia will get benefit. With ICH formation, the industry foresees harmonization of regulations, so that we can do filing easily. In the interest of industry, we are opinion that all regulations are harmonized and unified regulations are emerged.

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