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Generic Drug Approval in Russia

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ABSTRACT

Generic drugs at present are commanding a lion's share in the market and the affordability of the generics facilitates many peoples from all rungs of society to have access to quality medicines. The generics are considered as growth driving factors as they attempt to reduce the cost by wider procurement. The Russian government also eyeing for market entry of major generic manufacturers and blockbusters as they reduce the overall procurement of medicines and facilitate growth. At present, the generic account for 20% of the market share and are expected to conquer the market by 2016. Domestic production is accounted for 20% whereas foreign production is 80% in the region of Russia. Russia is positioned at the inception of becoming a major force in the global pharmaceutical market, particularly in the generic sector. In the years to come, Russia would be serving as a platform, particularly for foreign investors, and facilitate them to tread on success.

INTRODUCTION:

Basics information about Generics and their sales in the region selected:

Providing a complete picture of the registration procedure applicable to generic drugs in the country selected and the understanding of basic information in turn would help in the dissertation work.

Current situation of Generics in the country selected[1-6]:

To support the work, the main frame of the thesis is also based upon the situation of generics in the Russian country and emphasizes the sales and growth of the generics drugs in the country The current situation of the propagation of the generics helps in understanding the market potential.

The regulatory body governing the basic health care and pharmaceuticals & Registration procedure[7-12]:

The regulatory bodies in the country are at the helm of the affairs about the affairs of drug registration approval, denial and any other further works carried out by the such organization. The correct understanding of the functioning of the regulatory body helps in providing a vivid picture to the applicant and helps in reducing a lot of time and money. Hence to provide a vivid picture the functioning of a regulatory body is covered.

Timelines involved:

The timelines involved vary from one country to another country, and in the same country, the timelines vary based on the type of the product and the class of the product. Therefore, to get a better picture of the time taken to approve a drug the timelines are studied and presented.

Generic Drug is defined as a drug product that is equivalent to the brand product in the following:

- Dosage form
- Strength.
- Route of Administration

- Quality
- Performance characteristics
- Intended use[11].

Brand vs. Generic;

Table no 1: Comparison between Branded Drug and Generic Drug Requirements

Brand	**Generic**
Labeling	Labeling
Pharmacological and Toxicological studies	Pharmacological and Toxicological studies
Chemistry	Chemistry
Manufacturing	Manufacturing
Controls	Controls
Microbiology	Microbiology
Inspection	Inspection
Testing	Testing
Animal Studies	**Bioequivalence studies**
Clinical Studies	
Bioavailability	

Generic Drug Registration:

- Drug registration is defined as the procedure of review of pharmaceutical product quality, safety, and efficacy by the State Regulatory Authority.
- In Russia, for a product to be marketed and sold the product must be registered first. After the registration, the product is entitled to a registration certificate from the Roszdravnadzor and the product is introduced in the database of registered products in Russian Federation.

In Russia, there are 2 strictly divided categories[13-16]

1. **Pharmaceutical products.**

2. **Food supplements and cosmetics**

For a product to be registered it must be associated with any of these categories. The registration review for the above products differs to a greater extent from one another and the different regulatory pathway is applicable. Pharmaceutical products require much documentation, and much expert review when compared to food supplements and cosmetics, which require less expert review.

Applications for Drug Registration are forwarded to the "National Center of Pharmaceutical Products expertise" (FGU) for review.

The registration procedure is organized in such a way that there exists a flow of communication between regulatory affairs personnel and experts reviewing the application for the dossier.

Registration procedure for foreign applicants:

The registration procedure is the same for foreign manufacturers and local manufacturers. Differences appear only in the cost and documents. The most important pre-requisite for a foreign manufacturer is that he should be having a valid GMP certificate for the product to be registered.

The product is not necessarily to be registered in the country of origin or another country.

Applicant Credentials:

1. Marketing authorization holder or its representation in Russia

2. Physical person.

3. Russian Juridical Company (Third Party).

- If any firm is representing the interest of the ***Marketing Authorization Holder***, the representation must be legalized by a ***Power Of Attorney.***

Documents to be legalized:

1. Certificate of Analysis.
2. GMP- Certificate.
3. Manufacturing license.
4. CoP (Certificate of Pharmaceutical Product).

If the documents are state official documents issued by a state member of the Hauge Convention, such documents must be apostilled. If not the documents should be endorsed by the Russian Embassy.

For *Generic Drug Products* there is no need to carry out time-consuming and pocket-burning, clinical trials. Only *Bioequivalence studies* should be carried out and they need not be carried out in *Russia*. Whereas for *New Drugs* there is a need to carry out clinical trials and the clinical trials must be conducted in Russia only, particularly in the *Russian Population*.

During the registration process, all the products must pass laboratory control as per the approved ***Normative Document***.

Normative document:

- The submission of a document according to which the quality of a drug will be controlled is required for the registration of a drug product or a drug substance.
- This document is a regulatory document (normative document) for products and substances manufactured abroad and in Russia.
- The documents are similar both in purposes and in contents.

The normative document consists of:

- specification, where quality parameters of a drug, evaluation of every parameter, and limits are determined;
- description of composition (active ingredient and excipients) and appearance of the product;

- description of identification, mean weight, pH, disintegration, dissolution, content uniformity methods; microbiological quality, assay, and impurities methods;

- description of the container closure system, labeling, storage conditions, and shelf life.

Import of the samples to carry out laboratory control tests:

To import samples in Russia it is important and the standards for laboratory control it is necessary to receive special import permission from Roszdravnadzor. The time duration to import these samples is 1-2 months depending on the satisfaction of the customs dept., and specifications.

The full analysis of the pharmaceutical product is done during the stage of registration and it is done on the first three batches imported into the Russian market for selling. The time taken to carry out laboratory control tests is 4 months and additional two months are required to import necessary standards. The laboratory control tests can be done only when sufficient standards are available in the laboratory.

License to carry out the pharmaceutical activity in Russia

To obtain a license for pharmaceutical activity license applicant sends or submits to the Federal Service on Surveillance in Healthcare and Social Development the following documents (in Roszdravnadzor control subjects of the Russian Federation):

An application for a license to pharmaceutical activities, which shall include:

➢ Full and (if applicable) the abbreviated name, including the company name and legal form of a legal entity, its location, the address of the place of the pharmaceutical activities, which the applicant intends to carry out the state registration number of the record to establish a company and the data of the document confirming the entry of data on a legal entity in the state register of legal entities for a legal entity.

➢ The name and (if applicable) first name of an individual entrepreneur,

- his place of residence,

- the address of the place of the pharmaceutical activities, which the applicant intends to carry out,

- the data document proving his identity,

- the main state registration number of the record of the state registration of an individual entrepreneur

- Data document confirming the fact of information about an individual businessman in the state register of individual entrepreneurs - for a sole proprietor.

➢ A taxpayer identification number and document data about the production of the license applicant for tax registration.

➢ Licensed activity that the license applicant intends to carry out.

➢ Copies of the constituent documents - for a legal entity.

➢ A document confirming payment of the state fee for consideration by the licensing body of the application for a license.

➢ copies of documents confirming the right of ownership or other legitimate reason to use the premises and equipment for pharmaceutical activities.

➢ copies issued in the established order of the sanitary-epidemiological certificate of conformity to sanitary facilities;

➢ copies of the higher or secondary pharmaceutical education, the work experience in the relevant specialty, and specialist certificates (degrees, certificates, etc.).

➢ All documents for the licensing of pharmaceutical activity are served in Russian or have a certified translation into Russian.

Registration documents required:

Registration documents consist of a set of documents that contain the complete data set of information about drugs that aid in the approval process of Drug registration.

The registration dossier consists of 6 parts which are as follows:

1. **Administrative documents.**
2. **Description of pharmaceutical properties (Drug Substance).**
3. **Data about the manufacturing of the pharmaceutical product.**
4. **Data about quality control of the finished product.**

5. Data about preclinical pharmacological and toxicological studies of a pharmaceutical product.

6. Data about clinical studies of a pharmaceutical product.

Administrative documents:

The official document(s) confirming the right to produce the drug, the presence of the necessary manufacturing environment, and its accordance with the local or international standards as well as the marketing information (the Manufacturer's national market or the market of any other country). The documents must be issued by correspondent authorized agencies and attested following legislation prescriptions (notarized and legalized (if necessary) [17].

These official documents can be the following documents:

- CPP (certificate of pharmaceuticals product) prepared following WHO's recommendations or Registration Certificate;
- Free Sale Certificate and GMP;
- Production license (for local Russian Manufacturers) and Registration Certificate;
- Other equivalent documents.

The mentioned above documents have to contain information about all organizations involved in the drug production process at all its stages (patent medicine production, packing, output quality control, and other intermediate production stages).

Legally attested documents (agreements, etc.), containing information about all participants of the drug production process;

Power of attorney for the activity dealing with the drug quality, efficiency and safety experts' examinations conducted, issued to the person representing the Applicant.

Table no 2: Administrative Documents

Sl. No	Administrative documents
1.	Power of Attorney issued by the Registration certificate Holder of the product in Russia to the company which will represent the interests in the questions of registration *(legalized by Russian Embassy or apostilled)* *(draft is provided upon request)*
2.	Original payment order of state tax payment in Russian rubles
3.	Patent for registered brand name *(in case of existence)*
4.	Summary of Product Characteristics (SPC) or instruction for administration for specialists
5.	Certificate of Pharmaceutical Product *(legalized by the Russian Embassy or apostilled)*
6.	Copies of Registration Certificates (Marketing Authorizations) from other countries in case the product is registered in other countries (*in case of existence*)
7.	Colored mock-ups of primary and secondary packaging (with Pantone codes)

Table no 3: Data about API (active pharmaceutical ingredient) used for manufacturing of the finished pharmaceutical products.

Sl. No	Data about API
1.	***GMP-certificate of API-manufacturer*** (legalized by the Russian Embassy or apostilled) – in the document obligatory must be mentioned the following information: • INN or chemical name of API, • Name • Address of API manufacturer
2.	***Certificate of analysis of API*** issued by API manufacturer (for recent batch valid at least 6 months) Original or a copy with signature and stamp of the finished product manufacturer's authorized person).

3.	Certificate of analysis of API issued by the manufacturer of the finished product (for the same batch as CoA provided in point 9) Original or a copy with signature and stamp of the finished product manufacturer's authorized person).
4.	Certificate of suitability for API issued by EDQM (in case of existence).
5.	• Nomenclature (INN or chemical IUPAC name), • Classification, • Structural formula, • Molecular formula, • Molecular weight, • General physicochemical • Microbiological properties of API, • impurities of API and their description.
6.	Specification and analytical methods for quality control of API (+ Monograph from EP, USP, BP) or Russian Normative Document (ND) for API registered in the Russian Federation, Registration Certificate of API.
7.	Data about validation of analytical procedures of API: summary (it is not required in case API has a monograph in EP, USP, BP, or Russian Ph.)
8.	Stability data for API for 3 batches: • Justification of the shelf-life, • Storage conditions, • Type of stability study *(could be provided as a table, report, or short review)*
9.	API manufacturing process scheme: Should be provided as a flow chart with reflection on the consequence of all manufacturing stages (and steps) and their obligatory enumeration. Details to be present in the scheme: • Raw material used • Intermediate products and • Product yield.
10.	Description of the API manufacturing process:

	Described consecutively by stages (and steps) following the scheme provided on p.16. Also, intermediate control should be provided.
11.	Material balance: • Batch size (including product yield); • Quantity of starting material used for manufacturing of one API batch and/or all chemical reactions (main and auxiliary) on every stage with a molecular weight of substances; • Explanation of the principle of API batch number generation.

Table no 4: Data about the manufacturing of the finished pharmaceutical product

Sl. No	**Date to be present.**
1.	Name and address (juridical and production site) of the finished product manufacturer at all stages: • Finished product, • Primary packaging, • Secondary packaging, • Batch release
2.	***GMP-certificate*** Good Manufacturing Practice of the finished product manufacturer legalized by the Russian Embassy or apostilled. *For a foreign manufacturer/ applicant the presence of a GMP certificate from the country of origin is a must and should*
3.	Manufacturing License of the finished product manufacturer *(Legalized by Russian Embassy or apostilled).*
4.	***Finished product manufacturing process scheme:*** Should be provided as a flow chart with the reflection on the consequence of all manufacturing stages (and steps) and there • Obligatory enumeration. • Intermediate control at every stage should be shown.
5.	***Description of the finished product manufacturing process with intermediate control:*** It has to be described consecutively by stages (and

	steps) following the previous step.
6.	***Material balance:*** • Quantity of active and auxiliary substances used for manufacturing one batch of the finished product; • One batch size expressed in the quantity of finished product packs received; • Explanation of the principle of the finished product batch number generation.
7.	Finished product manufacturing process validation
8.	***Pharmaceutical development:*** • Formulation development; • Manufacturing process development

Table No 5: Data about quality control of finished pharmaceutical Products.

Sl. No	**Documents**
1.	***The full composition of the finished product per one dosage unit:*** • Including the composition of the capsule shell, • Coat of tablet, printing ink used for printing of text on the capsule shell, etc
2.	Release and shelf-life specification and analytical procedures for quality control of the finished pharmaceutical product.
3.	Validation of analytical procedures with information about the number of batches (quantity of samples) used for validation
4.	Certificate of analysis for 3 batches of the finished product (for recent batches valid at least 6 months) (original or a copy with signature and stamp of the finished product manufacturer's authorized person).
5.	Certificate of analysis of excipients (for recent batch valid at least 6 months) (original or a copy with signature and stamp of the finished product manufacturer's authorized person).

6.	Certificate of analysis of reference standards used for quality control of the finished product (original or a copy with signature and stamp of the finished product manufacturer's authorized person)
7.	Characterization of impurities of a finished pharmaceutical product.
8.	Description of container closure system (primary and secondary packaging)
9.	Justification of container closure system selection.
10.	Certificate of analysis of primary and secondary packaging. • A layout or schematic drawing of the package could be provided in case of necessity.
11.	***Packing of the product for the Russian market:*** • Quantity of the product in primary packaging and secondary packaging (for ex. X tablets in Alu/PVC/PVDC blister; XX blisters in carton)
12.	***Stability data:*** • Stability data tables for 3 batches under normal (and/or accelerated) conditions for the whole shelf-life, performed on all quality tests included in the specification for the finished product. • stability summary with a conclusion about received stability data for all types of primary packaging.
13.	Information about storage conditions and shelf-life of the finished product

Table no 6: Data about Non-Clinical Pharmacological and toxicological studies of finished Pharmaceutical Products.

Sl. No	**Documents**
1.	Report about results of the own preclinical study which contains description, results, and statistical analysis of the results (copy with signature and stamp of the authorized person): • Non-clinical Pharmacology – major pharmacodynamics studies; • Non-clinical Pharmacokinetics – major pharmacokinetics studies; absorption; distribution; metabolism; excretion; drug interaction; • Non-clinical Toxicology – single-dose toxicity (acute), repeat-dose toxicity (subchronic and chronic), genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other

	studies; • General conclusions of the study; • Literature references.
2.	**Literature overview of preclinical data:** • Non-clinical Pharmacology – results of studies that confirm the pharmacological activity of pharmaceutical products; • Non-clinical Pharmacokinetics – absorption; distribution; metabolism; excretion; pharmacokinetic Drug Interaction; • Non-clinical Toxicology – single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other studies.

Data about studies:

- Reports of bioequivalence conducted outside the Russian Federation (BE study reports.
- **Literature clinical efficacy and safety overview.**

Documents necessary for receiving official permission for clinical trial beginning in Russian Federation (applicable for New Drugs):

- Draft of the protocol for a clinical trial in the Russian Federation
- Researcher brochure
- The information leaflet for the patient
- Information about payments and compensations for patients-participants in the clinical trial
- Data about researchers' experience as a specialist and their experience in clinical trial conduction
- Copies of the contracts for life and health insurance of the patients

Timelines for registration:

The timelines for registration of drug product varies by type of the product and based on its application and differs from that of Medical Devices. The duration of the registration process varies, depending upon the regulatory specialist's organization and efficacy.

The need to conduct additional studies or implement quality control systems or sometimes the need for additional information delays the application approval process[18].

Table no 7: Timelines for registration of Drugs

Stages	***Time Required***
Stage 1	2 Months
Stage II	12 Months
Stage III	4 Months
Total Time for Registration	18 months

Table no 8: Registration fees

Name of procedure	***Cost in Dollars***	***Cost in Euros***
Examination of Documents	22,000-30,000	16,000-25,000
Laboratory quality expertise	2,000-6000	1,400-4000
Total	24-36,000	17,400-29,000

The applicant has to pay the whole sum of money at the beginning of the registration process. The registration review process will not begin unless the applicant pays the raised invoice for the fees.

The cost of laboratory quality review depends upon the number of dosages and the analytical method adopted by the expert review board to analyze the given sample of drug.

Language Requirements:

The language accepted for the submission of the dossier file must be the Russian language. Any other document/ supporting documents if any present, which accompany the dossier must also be in the Russian language. For documents present in a language other than

Russian language, translation into the Russian language is a must and should be done taking the help of expert language translators. The meaning of the contents should not change after the translation of the documents.

Post Registration variations:

Once after reviewing of the dossier is by the regulatory authorities in Russia, the out of the review would be either approval or denial of the registration certificate. Along with the registration certificate, the applicant gets the following documents:

1. Normative documents
2. Instruction for administration.
3. Colored design of the packaging.

All the above documents are signed by the representative of ***Roszdravnadzor.***

There are two types of variation post-approval. They are as follows:

- Variation type I
- Variation type II.

Table no 9: Types of Variations

Type	Review	Examples
Variation type I	Does not require review by quality, safety, and efficacy expert	Change in the name of the manufacturer, change of marketing authorization holder, change in the package design
Variation type II	Requires review by quality, efficacy, and safety expert	Change in the manufacturing site. Change in quality or quantity composition Change of instruction for administration

Table 10: Approval Times

Type of variation	Time Required
Variation type I	2-3 Months.
Variation type II	6-12 Months.

Format of the dossier file:

The format and structure of the Russian and European dossier are very much similar in nature and contents. Applicant need not prepare a Russian dossier file if he has a European dossier file, as a European dossier file is accepted in Russia. The only mandate requirement for the acceptance of the European dossier file is the language of the European dossier file must be translated into the Russian language for review purposes.

Registration certificate:

Registration certificate encompasses the entire participants along the spectrum of the manufacturing process, namely the marketing authorization holder**,** the manufacturer of the finished pharmaceutical product, the company responsible for primary packaging, the entity responsible for secondary packaging, and the batch release site.

Agreements between the companies and contract manufacturers should also be mentioned and submitted at the time of submission[19,20].

Summary of the work:

The pharmaceutical growth in this sector is promising, with many companies aiming to set up their facilities in this region. Today the affordability of medicines limits people from the base class's accessibility to quality medicines and they are deprived of quality medicines. Generic drugs help people from coming over this gap and grant access to them quality medicines that can be of immense help. Generics in this region conquer about 20% of the pharmaceutical market and by the year 2016 they are expected to conquer a 50% share of the pharmaceutical market in this region this serves as a bottom line for the pharmaceutical growth in this sector and this, in turn, is the main contributing factor for choosing the market. The number of generic drug approvals in this region has raised considerably and has gained momentum. Russian Federation is marked by continuous economic growth and the evidence of the growth

is reflected in the market's GDP (Gross Domestic Product). The work also covers the miscellaneous issues such as drug trafficking, etc. that are a matter of concern from manufacturers' as well as the government's point of view. The present work covers the timelines associated with the approval of the drug and vividly gives a picture of the working of the Roszdravnadzor and clearly explains the scenario of the pharmaceutical market in the Russian Federation.

The flow of the Registration process in Russia

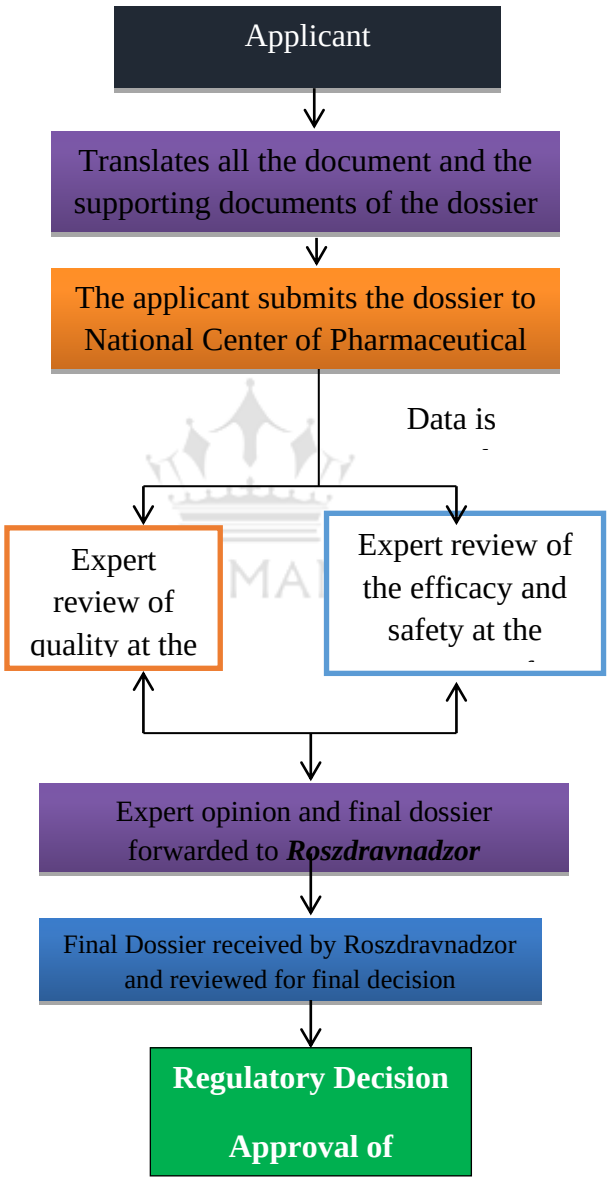

Figure no 1: Flow of Drug Registration process in Russia.

CONCLUSION:

The choice of the market always remains a point of concern for the manufacturer as the fate of the organization depends on the adaptability of the product in that market which results in profit.

The present study helps in the following way:

- **Assess** the market value by using the market's present scenario and forecast.
- **Monitor** the progress of the market by checking the latest developments.
- **Understand** the growth-promoting factors and drivers of the market and select the best factor from the lot.
- **Evaluate** the environment for the generic drugs taking into consideration the acceptability and affordability of medicines.
- **Restructuring** the business strategies to suit the market.

Russia is expected to be among the top five global markets in terms of the value in next five years. Though the process of registration is intimidating, the process does not appear to be so complex when compared to other developing countries and would surely attract foreign manufacturers.

Today one can see Russia at the edge of being the pharmaceutical hub in the years to come. Russia today would certainly take a different face which one can never imagine. As the nation goes stronger and stronger the Pharmaceutical industry in this region also follows the same pattern and may outstrip the other regulated markets in the years to come.

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