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Regulations of Biologics and Biosimilars in Russia

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Abstract

Here 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 MAs and clinical trials. It grants MAs 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 conclusions.

Key words: ***pharmaceuticals in Russia, Biologics and Biosimilars***

Introduction:

The development of an innovative molecule is a cumbersome process for any innovator, besides stringent regulations. The problems of biosimilar products are actively debated in India. A critical evaluation is needed for more efficient, cost effective widespread availability of biosimilars. It is well known that biologic products are very complex molecules and factors such as the robustness of the manufacturing process, structural similarity to the parent molecule, level of understanding of the mechanism of action, quality of pharmacodynamics assays utilized, demonstrated comparability in pharmacokinetics and immunogenicity, quantitative and qualitative clinical data, and the innovator's experience with the parent product all these need to be considered critically before initiating of marketing approval for biosimilars. Experts and clinicians require comprehensive information on biosimilars and biopharmaceuticals in general, to make knowledgeable treatment decisions. In addition, pharmacovigilance will be essential to track down any safety and efficacy problems that may arise from the use of biosimilars. Further, the regulations for the approval of biosimilar products should be the responsibility of a single authorized body and should be globally acceptable. Although biosimilars have begun to enter the global market, the biosimilar manufacturers' long-term capability to manufacture a consistent product still remains to be proven.

Biosimilars are a boon not only for biopharmaceutical companies but also for the patients, who can now have access to the otherwise unaffordable biologic drugs. Also for the government to reduce the health burden of citizens. As more and more biosimilars enter into the market, it has become necessary to harmonize the regulatory standards for biosimilars. The emerging bio-pharmaceutical markets have confidently grown and are on an accelerated growth path. The main challenge revolves around the nature and extent of these pharma markets potential. Current scenario, BRICS has rigorous and country specific regulatory requirements for approval of a new drug/biosimilars. Pharma companies in these markets with the right intent, actions and investments will take over the global pharmaceutical industry in the future.

It is imperative to harmonize the regulatory pathways of biosimilars in these countries by the respective governments in order to enable early access of these life-saving medicines to the needy patients.

Regulations

The MoH is the principal regulator for drug MAs and clinical trials. It grants MAs 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 conclusions.[4]

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 avoided.[5]

What's new and changing?

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

- 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 shall enter into force on 01 July 2015.

Clinical Trial in Russia

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 initiation[7]

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).

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.

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

Sl. 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	Power of Attorney that specifies contract

	organization's activities on behalf of sponsor in Russia	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)	-
21	Instruction for medical use of study drug (equivalent to SmPC + patient's leaflet)	-
22	Study drug primary and secondary packages mock-ups	-

Table1: Comparison of Documents required for local clinical trial and IMCT authorization

Bureaucratic red tape 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 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.

Legislative changes ahead

Draft amendments to the law "On Circulation of Drugs" were passed by Russia's principal legislative body, the State Duma, in September and November 2014, and it is highly likely that these amendments will come into force in 2015

As per the amended law, a local clinical trial will still be mandatory, but a scientific advice procedure, which could facilitate MA of foreign drugs in terms of optimal local clinical trial design selection, will be introduced. Scientific advice will be provided on a fee basis by a state higher medical educational institution subordinate to the MoH. All the information concerning a scientific advice procedure will be placed on the official website of the MoH.

The list of documents required for local clinical trial authorization will be similar to the documents required for IMCT authorization (see Table 1). 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 Russia

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”).[8]

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).

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 review process. Pharmaceutical products pass more detailed and strict examination; need more documentation and additional expertise compare to the cosmetics.

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.

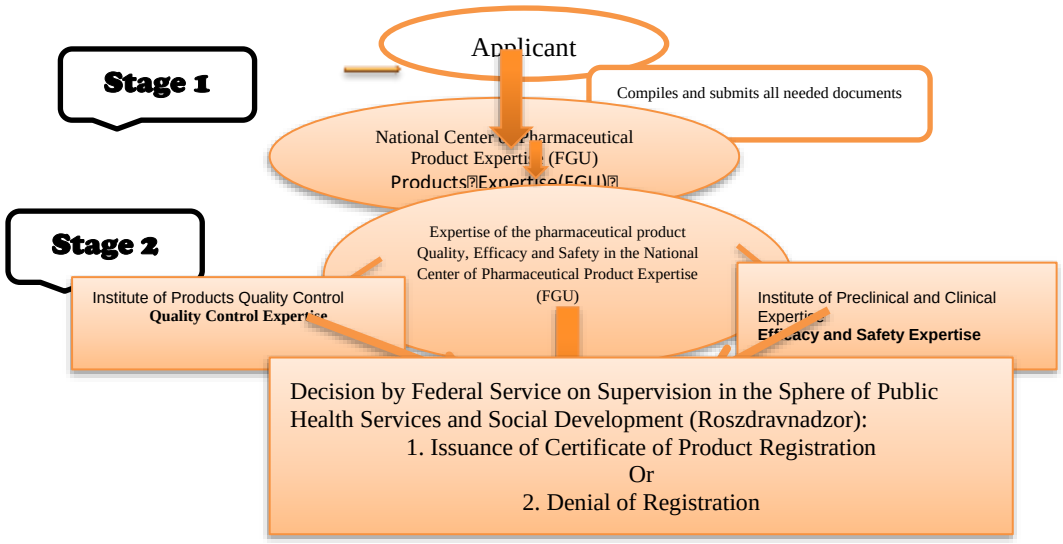


Fig 1: Steps involved in the registration process

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.

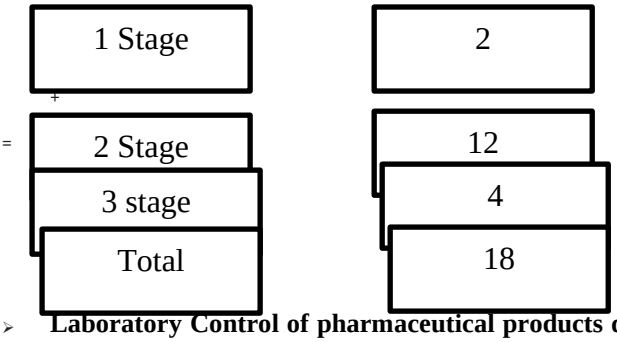
The most difficult and longest is the II stage. Registration dossier after submission and payment of necessaries fees is directed to appointed experts from Institute of Products Quality Control and Institute of Preclinical and Clinical Expertise.

In the Institute of Products Quality Control it is done the verification of Finished Product Specification called in Russian Normative Document and also is performed the laboratory control.

In the Institute of Preclinical and Clinical Expertise it is checked the Instruction for administration. 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 example for original product must conducted clinical trials in Russia. For generic products can be conducted only bioequivalence studies and not only in Russia. Preclinical and clinical studies performed in foreigner countries are accepted.

Terms of registration process:



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

During registration process all products must pass laboratory control according to approved Normative Document. Possible difficulties are: necessary of introduction in finished product specification of additional tests, importing of standards and samples.

Normative Document in Russia is compiled according to manufacturer's finished product specification, European/British Pharmacopoeia, United States Pharmacopoeia and Russian Pharmacopoeia.

To import the samples and standards for laboratory control it is necessary to receive special Import permission from Roszdravnadzor. It takes 1-2 months and prolonged the time of registration.

The full analysis of the pharmaceutical product is done on the stage of registration and on the first 3 batched imported into Russian market for selling. The time of laboratory control is 4 months, plus 2 months to import necessary standards. It is necessary to take in consideration that within this time (6 months) the product will be holed at the custom.

- **Post-Registration Variations – types, documents, terms.**

The result of registration process is obtaining of Registration Certificate. Along with it are given – Normative Document, Instruction for administration and Colored design of packaging. All these documents are signed by representative of the License Authorization (Registration Certificate) Holder and approved by Roszdravnadzor. Any changes introduced in these documents must be approved by State Regulatory Authority as Variation.

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:

The understanding of in depth and detailed regulatory requirements for registration of biosimilars in each of these markets should be known to establish appropriate regulatory strategy for advancing of the commercial launch.

Finally, there needs to be a reaffirmation and fine balance between the tenacities of gaining market access of pharmaceuticals is to protect the public health and facilitate healthy growth of pharmaceutical manufacturers. Pharmaceutical product approval process should be seen as a critical step in ensuring access to safe and effective drugs, hence approvals of biopharmaceuticals of different categories will continue to be dealt with on a case-by-case basis.

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