Russia

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Due to recent developments in Russia, many new pharmaceutical regulatory standards and procedures for registration have been developed; however, Russia has a rich historical background in this field. Regulation of drug control and approval have always been a very serious matter. As early as 1763, a special medical college that specialized in pharmaceuticals was founded. Shortly thereafter, several pharmacopoeias were published. The first was a military pharmacopoeia (1765), a Navy pharmacopoeia (1783), and a civilian pharmacopoeia in 1788, all of which were published in Latin. The current Russian pharmacopoeias are, however, based and numbered after the pharmacopoeia of 1868, which was published in Russian. In 1918, the Soviet government passed a decree on nationalization of pharmacies, and in 1925 published "The Guidelines on Registration of New Pharmaceuticals".

As fields of science and technology rapidly advanced, new developments in the field of pharmacology, as well as the growth of the pharmaceutical sector worldwide and in the USSR, called for state regulations on drug manufacturing, control, and registration. In 1962 the State Drug and Medical Device Inspection was founded. Its operations were reflected in the Russian legislation.

After the fall of the USSR the system of drug registration changed considerably. Although it has not yet been finalized, the revision of many aspects of drug control is still ongoing. For example, while this article was being written, a new law on narcotics and psychotropic agents came into effect, which will lead to new registration schemes for specific drug groups. Even more changes will be underway with the final adoption of the Law on Medicines. The draft of this law has been a work in progress for 3 years and is awaiting final approval by the Russian Duma. The purpose of this chapter is to describe and outline current drug registration procedures in Russia.
COUNTRY DESCRIPTION

Russia, formerly the largest republic of the USSR, occupies a territory of more than 17 million square kilometers and has a population of about 148 million, which consists of 130 nationalities and ethnic groups. The European part of the country is the most densely populated.

The economic situation in Russia is going through turbulent times due to administrative disintegration, broken links with other ex-republics and hectic federal-regional interactions. This has seriously influenced the healthcare system. The budget allocated for the healthcare sector amounts to 3 to 4 percent of the gross national product (GNP), which is considerably less than in other developed countries. Even after taking into consideration the 3 to 4 percent allocation, the Russian Ministry of Health (MOH) is underbudgeted on an average of 30 to 40 percent per annum. As a result, deterioration in the quality of medical care has been observed. This is happening simultaneously with disturbing demographic indices: increased number of premature deaths, lowered birth rate, higher incidence of chronic and infectious diseases, and so on. One of the principal reasons for such troubling statistics is a decline in the availability of drug products to the public.

As a result of the sharp transition to a market economy, the legal system for drug control and supply is no longer applicable today. There has been demand for new regulatory acts such as the Law on Medicines which will fill a much needed void since no uniform state policy exists either for drug supply to consumers, or for control over the drug development industry. Once the new law is in place, standard operating procedures may be developed.

In 1996, the volume of applications submitted declined. This was mainly due to the reduction of foreign products’ applications. This can be explained by more stringent requirements to submission dossiers and requirements related to clinical trials, adoption of new bioequivalency requirements, as well as the depth and saturation of the market. Between 1995 and 1996 the number of Russian products submitted for registration increased with a considerable improvement in the quality of dossiers of promising new, original and generic products.

REGULATORY AUTHORITIES IN RUSSIA

The MOH is responsible for drug regulatory issues in Russia. This includes the following responsibilities:

- Registration and control of pharmaceutical products, medical equipment and devices;
- Approval of state reference specifications for pharmaceuticals;
- Certification and control of the quality of medicinal products; and
- Certificates of manufacturers and distributors of drugs and medical equipment.

All of the aforementioned responsibilities are carried out by the Ministry's State Control Department (SCD), its expert committees and research institutes. The MOH (Ministry of Health Dec. 1997) regulates the SCD's operations.

**The SCD for Control of Pharmaceuticals and Medical Equipment**

The following bodies report to the SCD: the State Pharmacological Committee (SPLC), the Committee on New Medical Equipment, the State Pharmacopoeia Committee (SPPC), the State Institute of Preclinical and Clinical Drug Evaluation (SIPCDE), the State Research Institute of Drug Standards and Control (SRIDCSC) and the Bureau of Drug Registration (DRB) (See Figure 2).

**Figure 2. Structure of russian regulatory authorities.**
The SCD organizes and coordinates the work of these bodies, as well as affiliated analytical laboratories and drug quality control centers, the central laboratory for state control and evaluation of blood products, and the all-Russian Research Institute of Medical Equipment (only in relation to certification, safety and quality control of medical equipment).

In its work the SCD pursues the following objectives:

- State control of pharmaceuticals, diagnostic devices, (medical biological products such as vaccines), medical equipment, etc.
- Control of manufacturing facilities, pharmacies and hospitals, regardless of their legal structure and affiliation.
- Control of drug manufacturing, sales and use.
- Registration of pharmaceuticals, diagnostic equipment, biologics and medical devices.
- Approval of regulatory documents for pharmaceuticals, diagnostic equipment, biologics and medical devices.
- Publication of the State Drug Register and the State Pharmacopoeia.

In addition to the preceding, the SCD drafts regulatory acts, prepares instructional manuals and information booklets regarding drug regulatory issues, expertise, registration and state quality control of pharmaceuticals, diagnostic equipment, biologics and medical devices.

The MOH is responsible for appointing the head of the SCD. The head of the SCD has two deputies, one of whom is responsible for drug approval (the SPLC, SPPC, SIPCDE) with the second responsible for the agency's controlling functions (post-registration quality control). The SCD interacts with other countries' drug authorities: the Food and Drug Administration (FDA) in the United States, the Drug Control Agency in France, the European Medicines Evaluation Agency (EMEA) and so on.

**The Bureau of Registration for Pharmaceuticals, Medical Equipment and Devices (DRB)**

The DRB consists of two major departments: the drug approval division and the immunobiological product registration division (with a total of 15 employees). The major functions of the DRB include registration and reregistration of domestic and foreign drugs and bulk substances, the annual publication of the State Register containing marketed drugs and biologics and medical equipment and devices. The functions of the DRB as shown here are more procedural and technical in nature than the functions of the expert review divisions.

A fee is charged for registration of a pharmaceutical product. The following fees are established according to Order No. 250 of 20 August 1997 of the MOH: Registration of one drug form or one brand names costs US $12,000 (regardless of...
whether the product is original or generic) plus an additional US $1,200 for each additional drug form. Renewal of a drug's registration costs 50 percent of the initial registration fee, that is, US $6,000. Reregistration due to a change of name of the manufacturer or name of the product costs US $1,200. Fees have also been established for the registration of combination (US $3,000) and single-active-ingredient homeopathic products (US $200). The drug registration certificate is valid for 5 years.

**The State Pharmacological Committee (SPLC)**

The SPLC is the major expert authority that oversees the approval of clinical trials and reviews new drug products for regulatory approval.

The SPLC consists of well known and competent scientists who are the leading specialists in the sphere of experimental and clinical medicine. The SPLC consists of a presidium of 13 board members and 47 regular members. The SPLC also has an affiliated bureau of 17 people from the presidium and SPLC members. The SPLC presidium is authorized to resolve the most important issues of drug safety and efficacy review, as well as to develop and perfect the procedures for drug review, clinical trials and registration. The SPLC bureau deals with the registration of generic and proprietary pharmaceuticals, vitamins, homeopathic products and products of vegetable and animal origin.

The MOH approves the SPLC board and members. It operates by the Regulations of the SPLC (operations) and membership (Health Minister Order No. 189, May 1996)) and the instructions of the MOH on drug review, clinical trials, domestic (Ministry of Health May 1996) and foreign (Ministry of Health July 1997) drug registration.

The SPLC executes the following functions with regard to drug approval:

- Expert review of the drug's potency, toxicity and safety;
- Approval of efficacy and bioequivalence clinical studies;
- Review of efficacy and bioequivalence data in order to recommend the products for approval;
- Monitor and recommend the indications of marketed products;
- Review and approval of the instructions for drug's medical use and package inserts;
- Revision of the drug formulary in order to eliminate obsolete, ineffective and unsafe products from the State Drug Register; and
- Preparation and publication of the SPLC information materials.

The SPLC has specialized expert commissions in the fields of obstetrics and gynecology, anesthesiology, intensive care and blood transfusion; antibacterial and antiviral products; gastroenterology, dermatology and venereology, immunology,
nomenclature instructions, cardiology, clinical pharmacology and ethical aspects of clinical trials, neurology, psychiatry and narcology; ophthalmology, pediatrics; products of vegetal, animal and homeopathic nature, pulmonology and ear, nose and throat (ENT) diseases, rheumatology, toxicology, urology, endocrinology. These commissions are headed by chairmen (usually SPLC members), deputy chairmen, secretaries of the commissions (the SIPCDE's employees) and commission members.

These commissions review dossiers filed for original products, new product combinations, altered indications and new doses for marketed products.

The SPLC works in contact with many organizations participating in the review and approval of clinical trials and drug products, but mainly with the SIPCDE. In order to carry out its tasks the SPLC may utilize employees of other healthcare departments, establish provisional expert commissions and task forces. Thus a provisional task force consisting of members of the SPLC and SIPCDE has drafted the regulations on bioequivalence evaluation, which later were adopted by the SPLC as standard operating procedures.

The SPLC's resolutions are nonbinding and must be approved by the SCD.

**The State Institute of Preclinical and Clinical Drug Evaluation (SIPCDE)**

The SIPCDE is an expert research body of the MOH whose responsibility is to control all stages of preclinical and clinical review, provide material and work for the SPLC, interact with the SPPC, plan and coordinate research projects, as well as to perform pharmaceutical reviews of generic products.

The SIPCDE's major functions include the following:

- Initial review of all domestic and foreign drug applications;
- Set-up, control and review of efficacy and bioequivalence trials;
- Drafting expert reports based on the data from preclinical and clinical trial of new drug products;
- Drafting (or redrafting) of the instructions for nonclinical and clinical trials, product medicinal use and various pharmacotherapeutical drug groups;
- Drafting of orders of the MOH on drug approval or elimination of obsolete and ineffective drugs from the Drug Register;
- Continual collection and study of optimal methods of evaluation of potency, safety and tolerance levels of drug products;
- Monitor adequacy, sensitivity and ability to reproduce the methods presented in regulatory filings by applicants, testing of product samples, etc.

At the moment the SIPCDE employs 90 people of whom 70 are research fellows (physicians, pharmacists, biologists or chemists). The SIPCDE's organizational chart is presented in Figure 3.
The SIPCDE has several specialized departments that review submitted dossiers (for drug products used in cardiology, immunology, etc.) who work closely with the corresponding commissions of the SPLC. Normally the heads of the SIPCDE's departments are secretaries of the SPLC's specialized commissions.

The pharmaceutical evaluation department (or laboratory), which is part of the SIPCDE, plays a substantial role in the drug review process. Its functions include: review of regulatory documentation and the quality of sample drug products, control and evaluation of drugs recommended by the SPLC for efficacy and bioequivalence studies (done in collaboration with the SIPCDE), random evaluation and quality control of foreign and domestic products samples if requested by the SPLC; development of physical and chemical analysis methods; evaluation of drug concentrations in body fluids during bioequivalence studies. The SIPCDE laboratory does quality control of product samples prior to registration.

The SIPCDE's operations are regulated by the instructions of the MOH (Ministry of Health May 1996; July 1997).
**The State Pharmacopoeia Committee**

The State Pharmacopoeia Committee (SPPC) is the other important committee, also part of the SCA. The SPPC consists of a presidium, specialized expert commissions and a secretariat. The SPPC’s presidium consists of the chairman, two deputy chairmen, the secretary of the committee, presidium members (chairmen of expert commissions) and 3 representatives of other organizations: the SCD, PSC and Biologics Research Center.

The MOH approves the membership of the SPPC. The SPPC has the following commissions that deal with the following areas: phyto-products, antibiotics, hormonal and enzyme products, blood products and blood substitutes, radiopharmaceutical products, homeopathic products, recombinant products, immunobiological products and a commission for the review of domestic pharmaceuticals (created in view of the new edition of the Russian *Pharmacopoeia*).

The responsibilities of the SPPC as described in the provisions for SPPC functioning (Health Minister Order No. 200, 1992) are as follows:

- Update the State *Pharmacopoeia*, review of provisional pharmacopoeia monograph, as well as pharmacopoeia manuscripts for new drugs and drug vegetal products recommended for use by the SPLC.
- Review draft changes and amendments to pharmacopoeia monograph, prepare lists of domestic and foreign product shelf lives, prophylactic and diagnostic product approved in Russia;
- Review of foreign normative documents provided in the drug application dossiers.

The specialized expert commissions consist of a chairman, a secretary of the commission and members (who are employees of the SRIDSC laboratory). The membership is approved by the SPPC.

The expert commissions review the product’s specifications in order to determine whether they meet the quality requirements for medicinal, prophylactic and diagnostic products. They then submit a recommendation regarding the product dossier to the SPPC’s review.

In its work, the SPPC uses 5 pharmacopoeias: Russian, United States, British, German and European Union (EU), as well as the corresponding Guidelines (Ministry of Health May 1996; July 1997). The SPPC may invite representatives of other bodies to review the applications. The SPPC collaborates with a number of local and foreign organizations of the same profile. The SPPC’s recommendations are nonbinding and must be approved by the SCD.

**The State Research Institute of Drug Standards and Control**

The SRIDSC is responsible for control, certification and standardization of domestic and foreign products, as well as certification, storage and use of the corresponding standard, reference and calibration of drug samples. The SPPC and SRIDSC have organizational structures parallel to the SPLC and the SIPCDE.
The SRIDSC employs 150 people and has 13 structural departments of which 8 are leading laboratories with standard operating procedures for drug control. The other 3 laboratories are auxiliary biochemistry, microbiology and pharmacology laboratories responsible for quality control of individual parameters such as sterility, microbiological purity, determination of toxicity, pyrogenicity, biological and enzymatic activity, etc. The laboratory of drug scientific standardization is the SPPC's operational organ. Employees of this laboratory are secretaries of specialized commissions.

The SRIDSC performs state product control of the following types: preliminary, post-registration, random and arbitration. Preliminary control is performed on novel and newly approved drug products. Post-registration and random checks are for products under large scale manufacturing. The timing of these checks is specified by the SCD. Arbitration is used if there is a dispute between the customer and the supplier with respect to a drug's quality. The SRIDSC (unlike the SIPCDE) performs post-registration quality control on drug products.

Other Bodies Participating in Product Review and Registration

Organizations and establishments which structurally belong to the SCD have been described in the previous section. However, other bodies may also take part in the product review procedure. As per MOH order No. 114 of 14 April 1997, the Federal Center for Drug Adverse Events Evaluation (FCDAEE) was founded. Such an entity became necessary when the Russian market was overwhelmed with products of high biological activity, which may lead to a higher risk of side effects and iatrogenic complications.

The FCDAEE reports to two bodies, the SCD and the Agency of Public Health Control. The duties of the FCDAEE include: analysis and systemization of data on domestic and foreign drug side effects and preparation and submission to the MOH of information on drug side effects for further remedial actions, such as change to the instructions for the drug's use or its elimination. The center also works to familiarize the medical and pharmaceutical communities, as well as the public with drug safety issues, by preparing instructions and recommendations regarding prevention as well as drug-related complications.

Another organization not structurally affiliated with the SCD but necessary for product review is the Permanent Committee of Narcotics Control (PCNC), which has for many years been directed by Professor Edward Babayan.

International conventions, rules and guidelines regulate the functioning of the PCNC. The PCNC is engaged in publication of registers of narcotics, highly potent and psychotropic products. On the basis of its product review the PCNC offers to the SPLC its recommendation regarding the approval of narcotic or psychotropic products (both mono- and combination products). It also recommends a prescription status (over-the-counter (OTC), prescription and special prescription for narcotics). It is worth mentioning, however, that after the Law on Narcotics and Psychotropic Agents has been adopted the scope of the center's activities may change.
REQUIREMENTS AND PROCEDURES

As the requirements and procedures are outlined, it is necessary to note that Russia is probably the only country in the world where the requirements for review, clinical trials and registration are different for domestic and foreign drugs. It would be worth noting, however, that the registration procedures for domestic and foreign drugs have recently become more similar. There are additional preliminary and final requirements for domestic drugs. For domestic drugs, a sample pharmaceutical evaluation is required and is carried out at the laboratory of the SIPCDE. The drug filing will only be reviewed by the SPLC if the outcome is positive.

For foreign drugs, the sample pharmaceutical evaluation is performed only if the SPLC requires efficacy or bioequivalence studies. In some cases the Pharmacological Committee may go for a random evaluation of drug samples.

At the final stage of the registration procedure there is another differentiation in requirements for domestic drugs. The Russian MOH issues a special order authorizing approval for domestic drugs. The order normally contains the product’s description specifying its efficacy data, indications, storage conditions, OTC or prescription and the owner/company. For foreign products, the Registration Bureau issues a registration certificate. The most important difference is that domestic drugs are registered free of charge while there is a registration fee for foreign companies.

The following outlines the procedure for foreign drug registration, which was described in the Instructions for Review, Clinical Trials and Registration of Foreign Drugs and Bulk Substances, approved by the Russian MOH on 10 July 1997. It is a legal requirement in Russia that no drug can be used for medical purposes until it has been registered as required by the Russian MOH.

Documents Necessary for Drug Registration

A foreign company that wishes to register its product (drug or drug substance) in Russia should submit a cover letter to the SPLC (See Appendix 1), an application form (See Appendix 2), the drug dossier and samples of the product. The list of documents required for original (excluding international multicenter projects), generic and proprietary products is given in Appendices 3 and 4. Certain parts of the drug dossier must be translated into Russian.

If a drug is submitted for registration in Russia by a distributor or company, an original or notarized copy of a letter from the manufacturer authorizing the distributor or company to register the product in the Russian Federation, and sample labels containing the names of the manufacturer and distributor are additional requirements.

Drug Registration Procedure

After the drug application has been received by the SCD, it submits the application to the SIPCDE, the SPLC, the SPPC and, whenever necessary, to other bodies for their expert review.
The SIPCDE reviews the dossier and issues a recommendation; the application is then forwarded to:

- The SPLC Commission on Instructions and Nomenclature.
- Specialized SPLC commissions for efficacy and bioequivalence studies.
- The SIPCDE laboratory for pertinent review.
- The SPLC bureau for generic and proprietary homeopathic products and products of vegetal and natural origin.
- The SPLC for original products, for international multicenter clinical trials, drug name change, new indications and new combinations of already approved products.

Should the submitted data be insufficient, the applicant is issued a request for more information.

A commission usually reviews the dossier for as long as 30 days. Whenever the dossier needs to be reviewed by more than one commission, the time of review automatically increases (though usually no more than 30 days for each commission).

The SPLC Commission on Instructions and Nomenclature reviews the text of the instructions for the drug's use, physician information and package insert (patient information). In case it is necessary to have expert opinions from other specialized commissions, the term of the review may increase by an additional 30 days.

The instructions also require bioequivalence clinical trials for:

- new pharmacological products;
- products manufactured under license and not registered in Russia by the license holder; and
- generic products with no efficacy or bioequivalence data.

No clinical trials are required for:

- products which have been used in medical practice for more than 3 years with clinical data available proving their efficacy and safety;
- generics with efficacy or bioequivalence data; and
- products manufactured under license and registered in Russia by the license holder.
After the SIPCDE and SPLC commissions have reviewed the filing, a resolution is drawn up which is then reviewed at an SPLC Presidium meeting (the SPLC meets twice a month). As a result, the SPLC may decide to:

- request additional information on the product;
- perform a pharmaceutical evaluation;
- carry out efficacy or bioequivalence studies;
- recommend the product for registration.

The total term of the regulatory review is 6 months.

The review procedure is somewhat less complicated at the SPPC than at the SPLC. The review time is 3 months which is performed in conjunction with the SPLC. Three months after the application has been filed (this does not include the time spent by the applicant responding to the SPPC’s queries), the SPPC offers its recommendations regarding the drug registration to the MOH.

The SPPC specialized committee passes its preliminary resolution which is then edited and signed by the chief secretary of the committee. The committee then reviews the final document to decide whether or not it should be submitted to the Presidium and whether or not the product should be approved.

Should the committee decide that the quality control procedures require validation, the product samples undergo quality control at the SRIDSC or at the SIPCDE laboratories and then the SPPC Presidium passes its final decision regarding the product.

The SPLC’s and SPPC’s recommendations (along with the instructions on the product’s use) are forwarded to the SCD for approval.

The SCD then decides whether or not to approve the product. Once the Registration Bureau has received the registration application (Appendix 5), it issues an official registration certificate to the applicant. The SCD has the authority to suspend the product’s registration if the applicant does not respond to the queries of the expert committees within 90 days.

**Clinical Trials**

There are a number of Western publications, as well as materials from various conferences (Droujinine 1996; Loran et al. 1996; Sinackevich 1997), that address clinical trials in Russia. It is important to mention the appearance of the new “Instructions...” as well as adopting the International Conference on Harmonization Good Clinical Practice (ICH GCP) as the major guidelines for conducting clinical trials by the Russian MOH (12 August 1997).
From the regulatory point of view, 3 types of clinical trials can be distinguished in Russia:

- Clinical trials required by the SPLC if necessary for product registration in Russia.
- International multicenter clinical trials requiring approval of the SPLC.
- Post-registration clinical trials, which also require the approval of the SPLC.

Before 1990, clinical trials conducted in Russia were characterized by a number of peculiarities. Many trials had no protocol and were carried out following the recommendations of the MOH. No ethics committees existed. There was no communication between the sponsor and the investigator, and the latter had no idea about the monitoring or audits, as if no such things existed. Moreover, the clinical data (study reports) would go directly to the Pharmacological Committee without being circulated to the sponsor.

The situation has changed dramatically in recent years. All trials are now to be conducted in accordance with an approved protocol by a designated SIPCDE commission. All trials should undergo monitoring and some auditing.

Recently the number of multicenter clinical trials conducted in Russia by foreign pharmaceutical companies has considerably increased. In 1993 to 1994 most studies conducted in Russia were single- or two-sited at best, nowadays the number and complexity of multisite clinical trials is growing exponentially.

More information about multicenter trials in Russia can be found in certain publications in the referenced publications (Rudakov; Shakhov 1997).

The multicenter trial approval procedure is described herein. First, the pharmaceutical sponsor submits to the SIPCDE all relevant documentation in accordance with the “Instruction . . .” (See Appendix 6), which requires a different set of documentation in comparison to product registration dossiers. The documentation is reviewed by the SIPCDE’s specialized department and the Clinical Trials Department, as well as by specialized SPLC commissions, after which they are forwarded for the SPLC’s scientific and ethics review. The SPLC then issues a resolution which is issued to the applicant and the SCA. The procedure takes 3 months maximum (in case extra information is needed for approval) and normally lasts 1 month.

The procedure for the review an approval of post-marketing studies is the same as for international multicenter studies.

**Bioequivalence Studies**

The need for standard operating procedures regarding the bioequivalence studies arose when the SPLC started receiving numerous applications for generic product registration from little known companies with no established reputation in the domestic and international pharmaceutical market. Usually these products were produced for domestic consumption only.
The “Regulations . . .” were written by the SIPCDE with the input from local specialists in the field (Ministry of Health April 1996). These procedures are not quite the same as the analogous guidelines in Europe and the United States. The “Regulations . . .” explain the terminology, specify the requirements for the applicant/companies, set-up, procedures for conducting and reporting clinical trials, bioequivalence criteria, and the like. These guidelines were developed by taking into consideration local knowledge and experience, available facilities and restrictions for bioequivalence studies conducted in Russia. According to the “Regulations . . .” the minimum number of subjects for a bioequivalence study (both healthy volunteers and patients) should be no less than 12. The ethical principles for conducting such studies are the same as for other clinical investigations.

The procedure for bioequivalence clinical studies is described herein. The SPLC informs the applicant of its decisions regarding the necessity of the study. The SIPCDE provides the sponsor with a list of clinics and laboratories able to perform quality bioequivalence research. The study protocol is then developed by the chosen laboratory and approved by the SPLC Clinical Pharmacology Commission. Later the data reported from the study are forwarded to the SIPCDE where SPLC specialists review them at the Clinical Trials Department. A preliminary resolution is then issued by the SPLC.

Ethics Committees

Ethics committee approval is essential for conducting clinical trials in Russia as part of larger international projects. At present, almost all of the large clinics and research centers have established their local ethics committees. These medical establishments have enough experience and qualifications to conduct clinical research by international protocols. Since the number of clinical trials conducted in Russia to the ICH GCP standards grows every year, the number of newly established ethics committees increases accordingly. Their functioning is still far from perfect, however. The major problem with the ethics committees is a lack of standard operating procedures regulating their operations as well as insufficient experience in reviewing clinical trials. The membership of ethics committees is not always in perfect conformity with the GCP requirements. In some cases, ethics committees have poor record keeping. However, it is obvious that establishing ethics committees has become a major step in terms of standardization of clinical research in Russia. The National Ethics Committee has been established recently which, along with other duties, assumes an arbitrary function.

OTC Products

In the former USSR, self-medication was discouraged. In the past 3 years, a great deal of attention has been given to self-medication and OTC drugs. The MOH, which instructed the SPLC to design guidelines for OTC drug registration and classification, has also addressed this topic.
The SIPCDE has drafted the OTC classification criteria as well as the requirements for OTC product submissions, as well as criteria for products that are reclassified as OTC (See Appendix 8).

The registration procedure for OTC products is the same as for other pharmaceuticals. The decision on whether or not a drug can be considered OTC is made on the basis of a recommendation from the SPLC and final approval by the SCD.

The MOH has approved a list of OTC products (Health Minister Order No. 79, 1997) which is to be updated and published every 6 months. The list covers 514 OTC products and is divided into 2 parts: the first part covers multicomponent products (by the active substance); the second deals with combination products. The format and the breadth of the list will improve in future publications.

**Package Inserts and Labeling**

After the fall of the USSR, when various foreign drugs flooded the Russian market, little attention was paid to the contents of package inserts accompanying new drugs.

With domestic drugs, the situation has always been controlled and monitored. After the drug has been approved by the SPLC, the SIPCDE prepared an order allowing the drug for medicinal use, which is then issued by the MOH. This order basically contains instructions for the drug's use.

For foreign products, especially OTCs, the situation proved to be less clear. A random study of foreign drugs on the Russian market conducted by the SIPCDE in early 1995 yielded the following results:

- Often no information on the drug's use was inserted into the drug package.
- 50 percent of the products reviewed had package inserts in the language of the manufacturing country that were not translated into Russian.
- 30 to 35 percent of the package inserts contained inaccurate and misleading information.

With these examples of misconduct, the SIPCDE, together with the Commission on Instructions and Nomenclature, issued the regulations for package inserts for foreign pharmaceutical products. Since 1997, the SPLC has also been reviewing and approving the drug package inserts as part of the drug registration procedure.

**Product Registration Renewal**

The product registration certificate needs to be renewed if it has expired, or in case of a change of a drug's name, company's name or drug's form. In the former USSR, the registration certificate was valid for 10 years but in 1991 this term was reduced to 5 years.
To renew the registration certificate the applicant must submit documents (as described in Appendix 2) and specify the reasons for renewal to the SCD. The SCD then forwards the documents (1 copy) to the SIPCDE, the SPLC and the SPPC. Within 90 days the committees reach a decision as to the expedience of the proposed changes or reregistration which is then forwarded to the SCD and Registration Bureau.

**Registration of Bulk Substances**

For economic reasons, more and more Russian pharmaceuticals are being manufactured with the use of foreign substances. In accordance with the “Instruction...” (Ministry of Health July 1997) these substances need to be registered in Russia. The SPPC is responsible for registration and reregistration of bulk substances. The procedure is somewhat simpler as compared with that for drug registration and consists of submitting an application and other pertinent materials (See Appendix 9). The SPPC’s decision then goes to the SCD for approval.

**International Cooperation**

International agreements with the MOH have a certain impact on the foreign drug registration procedure. One of the first such agreements was the Memorandum of Understanding signed by the Russian MOH and the FDA in the United States in February 1994 (Memorandum of Understanding 1994). According to this Memorandum pharmaceutical products manufactured in the United States and approved by the FDA receive a 3-month faster clearance through the Russian registration procedure. Also, American companies have the right to submit only summary product data.

In practice, however, the outcome was quite unexpected. In 1994, the year the Memorandum was implemented, the SCD received only 55 American dossiers, which is almost 50 percent less than the previous year’s total of 103 dossiers. At the same time, the drug development strategy of the largest American pharmaceutical companies (MSD, BMS, Eli Lilly, Upjohn, Pfizer, etc.) in Russia has not changed dramatically. Moreover, it is at that time that these companies turned to larger multicenter projects as well as postmarketing research in Russia.

On the other hand, smaller American companies and distributors have become more active since 1995. The SCD received 129 American product applications in 1995. For some of these, approval was denied due to incomplete dossiers. Additionally, some of the products have been found to be obsolete or of questionable efficacy. In February 1996, the Memorandum between the MOH and the FDA was considerably revised and updated. The updated version describes the procedure of drug registration in much greater detail.

Russia has signed similar agreements with France and Canada. A draft agreement between Russia and the EC (EMEA) is now being considered.
Information on Registered Pharmaceutical Products

The State Register of Pharmaceuticals is an official publication by the Russian MOH. It consists of 2 major parts. The first part contains domestic pharmaceutical and immunobiological products, diagnostic, disinfectants, insecticide and other substances. The name, pharmacological group, dose form and reference to the approval order are given.

The second part deals with foreign drugs, prophylactic and diagnostic products. Brand name (with international name in brackets), pharmacological group, dose form, manufacturer and country and reference to the drug registration certificate is listed. The Register is published annually and is available on CD. A new Register supplemented with instructions for use is to be published in the near future.

Information on pharmaceuticals available on the Russian market that is more or less complete can be found in the commercially published “Vidal” reference books and The Register of Pharmaceutical Products in Russia (both annual editions) and New Pharmaceuticals, edited by M. D. Mashkovsky.

The federal Law on Advertising, adopted in 1995, is generally comparable to European legislation devoted to advertising. However, only Article 16.2 is devoted to advertising pharmaceuticals. It contains the following stipulations:

- Only registered pharmaceutical products may be advertised.
- Prescription drugs may be advertised only in technical publications aimed at physicians and pharmacists.

Obviously these stipulations are insufficient; there is a need for more profound legislation regarding drug advertising.

FUTURE TRENDS

In the past, the procedure for pharmaceutical product registration has changed considerably and is now approaching a level as that seen in Western countries. However, a number of serious problems still exist that are waiting to be resolved relating to poor availability of drugs to the public as well as certain deficiencies in the Russian regulatory structure. The next major step would be to create from scratch certain regulatory acts and laws, such as the Law on Narcotics and Psychotropic Agents, the Law on Licensing, and most importantly, the Law on Pharmaceuticals.

The draft of the Law on Pharmaceuticals provides for the establishment of a separate federal review body, which would be independent from the MOH. This artificially creates a situation where pharmaceutical-related activities are isolated from the sphere of healthcare, which obviously requires considerable funds and human resources. Other countries with similar departmental structures have seen negative results of such an approach. Moreover, the law liberalizes current strict regulations on human clinical studies, thus allowing unregistered and unlicensed drug usage in Russia.
An alternative approach now under discussion is the establishment of a Federal Drug Control Agency affiliated with the MOH. All federal committees and other bodies participating in drug registration and control will then report to the Federal Agency, which will not require either staff expansions or additional funding. Funding such an agency would also unite committees and institutions engaged in drug registration regulating their roles and functions.

Another urgent issue is implementing GMP in local manufacturing, which will resolve the problem of the poor quality of domestic drugs, depress the import of foreign products and help improve the pharmaceutical economy. The MOH has recently addressed the issue of GMP and in 1997 an advisory board affiliated with the SCD and responsible for GMP audits of local manufacturers was established (Health Minister Order No. 255, 1997). Western joint ventures to manufacture in Russian played an important role in the decision to improve local GMP requirements. Some foreign companies are performing various stages of drug manufacturing in Russia.

Lastly, implementing GCP in all clinical trials, as well as certification of clinical centers used in clinical research, is essential. Regarding a new state pharmacopoeia, it is important to revise the existing drug nomenclature in order to rule out ineffective, obsolete and unsafe products, as well as products of insufficient quality. In summary, it should be said that the Russian regulatory system is constantly improving towards meeting international standards and requirements.

REFERENCES


Health Minister Order No. 189. 1996. Approval of the Structure of the State Pharmacological Committee.


Health Minister Order No. 250. 1997. Revised Payment for Registration of Foreign Pharmaceuticals, Medical Equipment and Items of Medical Use.


Minister of Health. 1996. Instructions for Examination, Clinical Trials and Registration of Domestic Pharmaceuticals (substances).

Minister of Health. 1997. Regulations on the Department of State Control of Pharmaceuticals and Medical Equipment.


Statement of Revised Annex to the Memorandum of Understanding between the FDA, Department of Health and Human Services and the MOH and Medical Industry and the State Committee for Sanitary and Epidemiological Surveillance of the Russian Federation Concerning Cooperation and Information Exchange on Drugs and Biological Products Facilitating Importation. February 1996.
CHAPTER APPENDIX 1

Letter of Intent

With the present letter the company informs of its intention to register in The Russian Federation the pharmaceutical product (substance), produced by the company. The given pharmaceutical (substance) is in dosage form

The above pharmaceutical product (substance) is registered as

(registration number and the institution which has issued the registration).

This letter contains the following attachments:

• application for registration the pharmaceutical product (substance)
• certificate of registration in the country of original or other countries
• indications and instructions for usage of the pharmaceutical product
• documentation including the results of preclinical and clinical studies of the pharmaceutical product
• methods for analysis and release specification used in quality control the pharmaceutical product
• samples of the pharmaceutical product (substance) in the proposed packing form
• Signature and Corporate Seal

1Notice: This letter should accompany each pharmaceutical product (substance).
CHAPTER APPENDIX 2

Application for Registration/Reregistration of the Pharmaceutical in the Russian Federation

1. Company-Applicant, country
2. Company-Manufacture, country
3. Patent-Holder Company
4. Company-manufacture of active substance, country
5. Name of the pharmaceutical product
6. International nonproprietary name (INN)
7. Main synonyms of the pharmaceutical
8. Composition of the pharmaceutical product
9. If any changes have occurred since the time of the original registration, indicate changes*
10. Dosage form
11. Dosage of the pharmaceutical product
12. Route of administration (oral, injectable etc.)
13. Main indications
14. Period of storage and conditions
15. Standard packing form

________________________________________________________
Date and Signature of the Applicant                      Corporate Seal

*Notice: No. 9 is filled in case of reregistration of the pharmaceutical product.
CHAPTER APPENDIX 3

List of Documents for the Registration of New Pharmaceuticals in the Russian Federation

1. A collection of general information concerning the pharmaceutical made up of short summaries of each of the following points*.
2. Indications and instructions for the pharmaceutical product*.
3. Certificate of registration for the pharmaceutical product from manufacturer and other countries (notarised copy).
4. GMP certificate for the pharmaceutical product (notarised copy).
5. Methods for analysis and release specification used in quality control the pharmaceutical product*.
6. Pharmacological report (specifications) supporting all indications for usage as stated in instructions.
7. Toxicological report (acute, subacute, subchronic, chronic toxicity, accumulation).
8. Specific toxicity report (mutagenic, carcinogenic, immunotoxic, citotoxic, embryotoxic, teratogenic effects, effects on postnatal development and reproductive functions).
9. Data on clinical trials or expert report.
10. Data on pharmacokinetics of the pharmaceutical product (experimental and clinical data).
11. Clinical data on the use of the pharmaceutical product after its registration (include a copy of publications concerning only the pharmaceutical product produced by the manufacturer).
12. General data about side effects of the pharmaceutical product in comparison with the other pharmaceutical products for the same indications.
13. Samples of the pharmaceutical product in the proposed packing form.

*In original and in Russian languages here.
CHAPTER APPENDIX 4

List of Documentation for Registration of Generic and Licensed Pharmaceuticals in the Russian Federation

1. Certificate of registration in the country of the manufacturer and in other countries (notarised copy).
2. Indications and instructions for the pharmaceutical product*.
3. Methods for analysis and release specification used in quality control*.
4. GMP certificate for the pharmaceutical product for (notarised copy).
5. A copy of the Russian certificate of registration the pharmaceutical product for the licence-holder.
6. A letter issued from the licence-holder concerning production of the pharmaceutical product under licence.
7. Data on bioequivalency of the pharmaceutical product according to the rules and requirements adopted by The MOH of Russia.
8. Clinical data.
9. Samples of the pharmaceutical the proposed packing form.

Note: Documents according to p. 6 are presented for licensed products; documents according to p. 7 are presented for generics and also for licensed pharmaceutical products which are not registered in Russia by Licence-Holder.

*In original and in Russian languages here.
CHAPTER APPENDIX 5

List of Documents Required for the Bureau of Registration for Registration/Reregistration of Pharmaceuticals (New, Generic, Licensed)

1. Letter of intent.
2. Application for registration/reregistration of the pharmaceutical product.
3. Registration certificate of the pharmaceutical product in the country of manufacture (notarized copy)*.
4. Certificates of registration in other countries*.
5. Samples of the pharmaceutical product in the proposed packing form.

*In original and in Russian languages here.
CHAPTER APPENDIX 6

List of Documents Required for Permission on Clinical Trials

1. Letter of Intent
2. Protocol of Clinical Trial
3. Case Report Form
4. Investigator’s Brochure
5. Informed Consent
CHAPTER APPENDIX 7

List of Documents Required for Registration Medicine as a Nonprescription Drug (OTC).

1. Application for the registration of medicine as a nonprescription drug (OTC).
2. Certificate of registration of the pharmaceutical product in country of the manufacturer and in other countries (notarised copy).
3. GMP certificate (notarised copy).
4. Data about the registration the pharmaceutical product as OTC in the country of the manufacturer and in other countries.
5. Summary report concerning safety and efficacy of nonprescription pharmaceutical product*.
6. Sample of the labelling information on OTC drug and/or information about standard packing form*.
7. Methods for analysis and release specification used in quality control of the pharmaceutical product*.
8. Sample of the pharmaceutical product in proposed dosage form.

*In original and in Russian languages here.
CHAPTER APPENDIX 8

List of Documents Required for the Reclassification Drugs from Prescription to OTC Status

1. Application for reclassification drugs from prescription to OTC status.
2. Data on the registration the medicine as OTC in the country of manufacture and/or other countries.
3. All the documents for the pharmaceutical product concerning its safety and efficacy*.
4. Sample of the label information on OTC drug and/or information on a packing form*.
5. Sample of the pharmaceutical product in the proposed dosage form.

*In original and in Russian languages here.
CHAPTER APPENDIX 9

List of Documentation Required for Registration/Reregistration of the Substance in the Russian Federation

1. Certificate of analysis for the substance from the manufacture.
2. Free sale certificate for the substance in the country of the manufacture and in other countries (notarized copy).
3. GMP certificate of production (notarized copy).
4. Methods of analysis and release specification of in quality control of the substance*.
5. Samples of the substance for three analysis.

*In original and in Russian languages here.