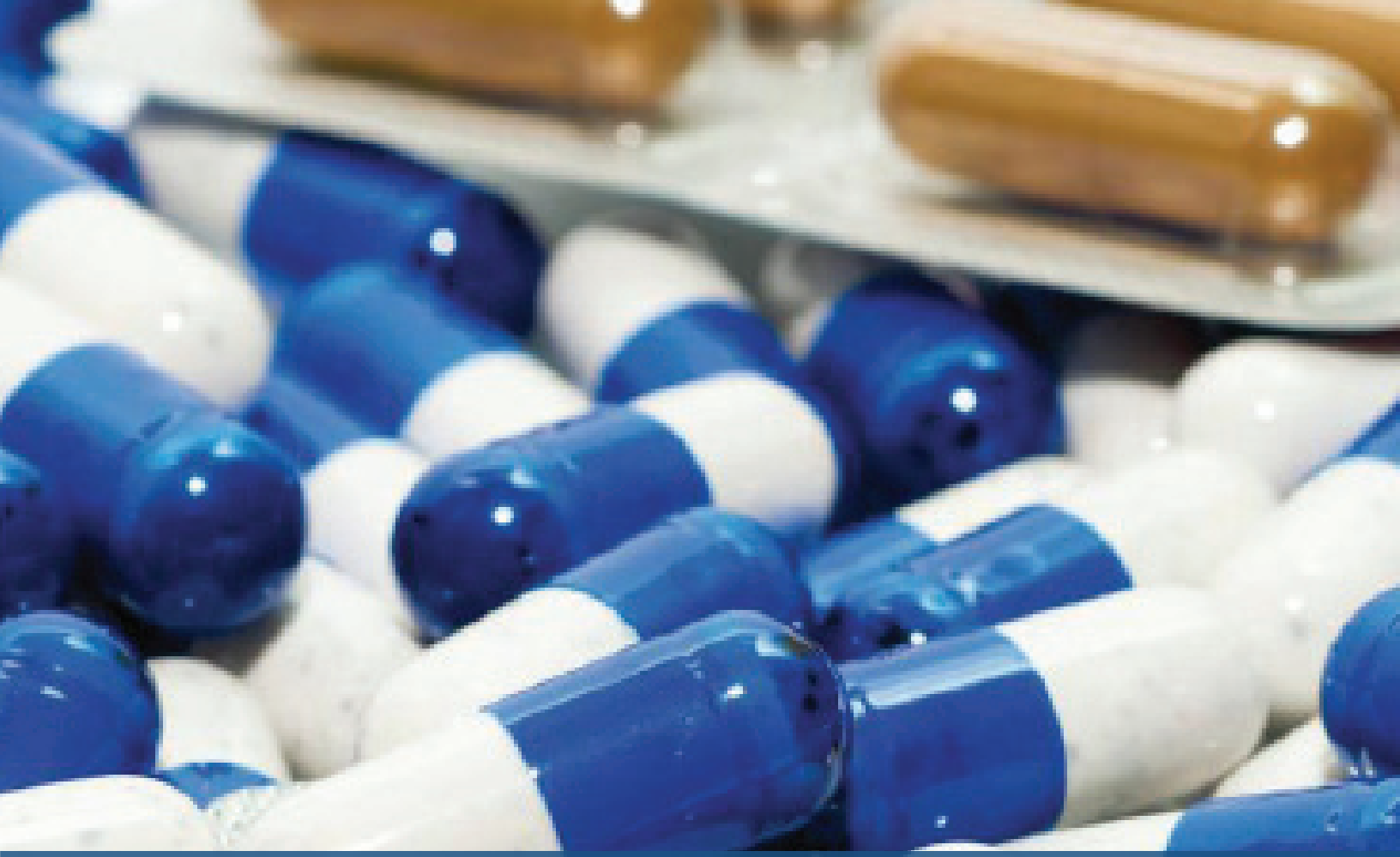

GUIDE TO PHARMACEUTICAL SECTOR

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Hardly any area of the law has such a direct connection to human health as pharmaceutical law. This fact requires fulfillment of detailed and strict conditions which have to be satisfied before a certain medicine or medical device is allowed for human use. Nevertheless, the area of pharmaceutical law extends beyond these issues. Equally important part of this area are the rules governing issuance of medicines prescription, distribution, advertising, and corruption, the purpose of which is to prevent doctors from giving priority to interests other than improvement of patient health. It is of special importance for pharmaceutical companies to obtain timely, precise, correct and high quality legal advice with respect to various legal issues in pharmaceutical industry. A new Law on pharmacy activities has been drafted in January of 2017 and is currently undergoing the procedure of adoption; this new law is also intended to define more strictly the work of pharmacies and distribution of medicines.

I Introduction

Pharmacy is the activity thoroughly regulated, with precisely defined rules for each stage a medicine or a medical device shall pass through, before it can be prescribed and distributed to patients. On the other hand, considering quantities of medicines prescribed every day, in addition to amount of money turned over in pharmaceutical industry, countries specify clear rules for purpose of making sure that doctors are not illegally influenced when rendering a decision which medicines or medical device to prescribe. Finally considering the impact of medicines/medical devices on human health, the authorities set high safety standards for pharmaceutical companies. All these rules are specified in large number of acts and subordinate acts governing requirements to be satisfied before a medicine is released on the market, granting licenses, patenting, trials, insurance, safety, efficiency and marketing. In order to avoid violation of these regulations, pharmaceutical companies need timely, reliable and high quality legal advice.

II Medicines and Medical Devices Agency

Medicines and Medical Devices Agency of Serbia (hereinafter referred to as: the Agency) has the task of regulating and controlling the Serbian pharmaceutical market. Its competence is not limited only to issuance of the licenses and placing medicines on the list, but the Agency also issues licenses for clinical trials of medicines and medical devices; monitors adverse reactions to medicines; approves advertising and exercises quality control of medicines and medical devices; it also engages in other tasks and assignments specified by the law. One of its main duties is to ensure that the pharmaceutical market is safe and accessible to everyone.

III Clinical trials of medicines

In order for a medicine to be given a license to be marketed, it must undergo pharmaceutical, pharmacological and toxicological tests in order for its safety and efficiency to be established. Before a medicine is registered and placed on the market, thorough preparatory and research work has to be done. A medicine is tested in compliance with good production practice guidelines, good laboratory practice and good clinical practice. Clinical trials programs follow set of strict rules, set to ensure that the trials procedure is adhered to and establishes positive balance between risks and benefits relating to therapeutical application of a medicine in a specific clinical practice.

The Agency receives applications from sponsor, being the carrier of a license for clinical trials, for carrying out of the clinical trials. The applications are assessed by the Ethics Board which shall render the Decision on conducting the clinical trials.

With all of the requirements met, the Agency shall issue the license on clinical trial of a certain medicine. When a license for clinical trial of a medicine and/ or medical device is granted, it is of fundamental importance that the safety and privacy of patients involved in the trial is secured. In favor of is the fact that every patient must be insured in case patient's health has been damaged during the course of clinical trial.

Also, a detailed control is conducted during the course of clinical trial for the purpose of both minimizing negative effects on patients and ensuring objectivity of the trial results.

IV Medicine marketing license

The process of registration and granting of license for a medicine is defined in the Law on Medicinal products and Medical Devices and other subordinated acts, enacted in compliance with appropriate procedural rules applicable in the EU countries. There is an alarming increase of medicinal products detected in the Union which are falsified with respect to their identity, history or source. Those products usually contain sub-standard or falsified ingredients, or no ingredients or ingredients, including active substances, in wrong dosage, posing an threat to public health. This triggers the necessity for the domestic legislative bodies to harmonize the rules and prevent falsified medicinal products from reaching the domestic market.

The marketing procedure for a medicine is a long process requiring submission of detailed documentation for the purpose of preventing medicines that do not satisfy strict quality, efficiency and safety criteria from reaching the Serbian market. A medicine shall be registered only if its quality, efficiency and safety have been demonstrated, which also includes striking positive balance between the risks and benefits of a medicine at the moment of its registration.

The Agency shall decide whether to grant a medicine marketing license. As a rule, a medicine is placed on the market on the basis of having been granted a license. The exception are the medicines for which no license is granted, such as medicines made in pharmacies, medicines intended for testing during a research and other types of medicines explicitly specified by the law as eligible for being placed on Serbian market without a license.

The applicant for the medicine license may be a local medicine producer, foreign producer representative having a business seat in Serbia, representative of a legal entity which is a medicine license holder in the EU countries. Also, the applicant may be a legal entity with headquarters in the Republic of Serbia, to which a local producer has assigned its medicine license. The application for the medicine marketing license shall be submitted to the Agency along with documentation specified by the law, with the Agency being entitled to request additional documentation (the term for providing additional documentation is 30 days). The documentation required for obtaining the license is made up of data relating to characteristics of the medicine; data on pharmaceutical – chemical – biological tests; pharmacological – toxicological tests and data relating to medicine clinical trials.

The license can be obtained through the either full or abbreviated procedure depending on the documentation that is required for submission. The type of procedure itself is conditioned by a type of medicine for which the license is being issued. The application for placing a medicine on the market with full documentation shall contain all data specified by the law and other data of importance for obtaining the license which might be requested by the Agency.

The application shall also be accompanied by samples of the medicine. The application with abbreviated documentation shall be submitted for generic, generically hybrid and biologically similar medicines.

The Agency shall, no later than 210 days following the receipt of a full application, render its resolution on granting the license with 5 years validity, or a resolution on rejection of the application, subject to the Agency Commission's opinion and assessment of documentation in terms of quality, safety and efficiency of the medicine. The license shall be renewed following expiry of the license validity term, and is subject to the Agency's re-assessment.

It is also prescribed that the Agency may grant a permanent license, provided it has established that a medicine for which the license has been granted is safe, subject to the data related to collection, discovery, assessment, understanding and prevention of adhered reactions to the medicine during the five year period from the date of granting or renewal of the license.

The validity of the license shall terminate:

1. by expiry of the validity term (if not extended) or
2. upon request of the license holder.

Also, the license shall terminate if the Agency establishes that
3. a medicine is detrimental under normal conditions of use;
4. a medicine lacks therapeutical efficiency; (
5. a medicine does not yield required therapeutical results;
6. qualitative and quantitative medicine composition does not match the declared composition of the medicine;
7. a medicine license has been granted on the ground of insufficient and incorrect data, or if the data has not been amended in compliance with the law and (viii) the license holder no longer satisfies requirements specified by the law.

The Agency may, against the previous agreement with the applicant, grant a conditional license for the medicine, requesting from an applicant to meet some specific obligations, which shall be verified by the Agency once in 12 months as of the date of granting of the conditional license.

The Agency shall reject the license application if it has established that:

1. the risk-benefit balance is not favorable under the normal circumstances of use;
2. a medicine lacks therapeutical effect or therapeutical effect has not been sufficiently proven by the applicant;
3. the composition of a medicine, in terms of quality and quantity is not in compliance with the data contained in attached documentation, or
4. the documentation is not in compliance with regulatory requirements.

V Marketing license for foreign medicines and medical devices

The license may also be obtained under special conditions, provided a medicine has the granted license subject to the centralized system of procedures applicable in the EU countries. In the Republic of Serbia, the license shall be granted in the expedited procedure when a medicine has the license in compliance with the centralized system of European Medical Evaluation Agency.

In that case the Agency shall, no later than 150 days following receipt of the full application, render the resolution on granting the license or rejecting the application, subject to the opinion on and assessment of the documentation in terms of quality, safety and efficiency of the medicine.

When the application is filed for obtaining the license with well-known application of an active substance, the applicant is not obliged to provide data on pre-clinical and clinical trials, but might, instead of its own data, submit data published in a professional publication.

Since Serbia is not an EU member, at this stage of development of the pharmaceutical regulatory system, granting of the centralized license or the marketing license on the ground of bilateral recognition is still not possible.

VI Medicine market and safety monitoring

On the pharmaceutical market there are medicines issued under prescription and paid from the mandatory insurance funds, and also medicines which are not on the prescription list of the free of charge medicines.

When a medicine is placed on the free of charge list, the criteria that are specified in the Rulebook on conditions, criteria, method and procedure for placing of a medicine on the List, amendments of the List and also the criteria for taking a medicine off the List shall all be observed.

The general criteria, which the medicines that are placed on the List are subject to are as follows:

1. its pharmacological and therapeutical justifiability;
2. pharmacological and economical justifiability of a medicine; and
3. financial funds provided in the Financial Plan of the Republic Fund for Health Insurance (RFZO).

The special criteria include:

1. the special agreements (the Agreements executed between RFZO and a producer or the marketing license holder); and
2. medicines having priority in placement on the List.

The priority in placement of medicines on the List is applied when RFZO financial funds intended for medicines are insufficient for placing all medicines, which have satisfied the general criteria on the List.

The priority in placement of a medicine on the List shall be established by the Central Commission for Medicines on the basis of following criteria:

1. the List of Medicines does not contain any medicine from the same pharmacological and therapeutical group;
2. public and health significance of a medicine;
3. ethical aspect.

In terms of monitoring of safety of medicines, it should be pointed out that following the registration, a medicine is placed on the market and begins to be utilized in daily clinical practice on large number of patients, under the rules which are not as strict as during the clinical trials period. Following placement on the market, the complete safety profile of a medicine is not known yet, meaning that information is still insufficient or is not available at all, relating to rare undesired reactions to a medicine; reactions after a long exposure to medicine; interactions; potential errors; abuse and incorrect use and application of a medicine on specific categories of patients. For these reasons and the difference between the clinical trials under strict rules and daily, routine practice, the awareness of the safety profile of a medicine is limited and shall be expanded. That is why monitoring safety of all medicines on the market, as well as gathering, discovering, assessing, understanding and preventing of undesired reactions to a medicine is of prime importance.

VII Advertising and labeling of medicines and medical devices

Labeling of medicines

The regulations define in detail the method of labeling of medicines in order to ensure the most reliable possible information to its beneficiaries. The exterior packaging of a medicine shall be in Serbian, in both Cyrillic and Latin alphabet, containing brief characteristics. The data printed on both exterior and interior packaging shall be legible, understandable and indelible.

The exterior packaging of a medicine shall contain at least the following data: name of the medicine and the international unregistered name of the active substance, if any, or generic or chemical name; active substances – in quality and quantity per dosage unit, pharmaceutical form, intensity and packing; the list of auxiliary substances having a confirmed effect; and for the medicines in the form of injections, medicine for local application and medicines for the eyes, it is obligatory to specify all auxiliary substances; manner of application; warning that a drug shall be held beyond reach of children and other necessary warnings; expiry date; special measures for disposal and destruction of a medicine; name and address of the medicine license holder; license number, batch number and EAN – code; the manner of use for medicines sold without prescription; anatomy – therapy – chemical classification (ATC); and for veterinary medicines ATC-vet and other data in compliance with the regulations. The name of the medicine shall also be written in Braille alphabet.

The interior packaging of a medicine placed on the market shall contain at least the following data: medicine name and the international unregistered name of the active substance, if any, or generic or chemical name; intensity and pharmaceutical form; name of the license holder; expiry term (month/year); batch number and other data in compliance with the regulations.

Advertising of medicines and medical devices

Advertising of medicines shall be deemed to include all measures aimed at promotion, prescription, issuance, sale or use of medicines and medical devices. Information provided through advertising must be true, whereby the advertising itself must be conducted in such manner that it does not mislead the general public or members of the professional public. Additionally, advertising of medicines and medical devices also aims to assist its application by presenting properties of a product truthfully, fully and without exaggeration, in a manner and under conditions defined by the law.

There are several avenues for advertising of medicines: through the public media including the Internet; advertising in public places; and visits by sales agents to persons entitled to prescribe or sell medicines.

In that sense, it is prohibited to advertise the professional and medical procedures, methods of health protection including methods and procedures of traditional and alternative medicine in the public media, subject to the laws governing health protection.

Also, the results on application of the professional and medical procedures and methods of health protection shall be presented only at professional and scientific gatherings and published in professional and scientific magazines and publications, in compliance with the laws governing health protection.

The advertising shall be objective and the public must not be misled. The list of medicines which may be advertised shall be prepared by the Agency. Any form of advertising of medicines and medical devices shall receive prior approval by the Agency.

It should be noted that there is a difference between advertising of medicines to the general public and to the professional public. The general public implies the citizens of the Republic of Serbia, while the professional public includes medical and veterinary personnel prescribing medicines and medical devices, graduated pharmacists and other professionals in field of production, wholesale and retail sale of the abovementioned, as well as professionals employed within organization of the mandatory health insurance.

The difference is made for the sake of establishing more stringent requirements for advertising medicines and medical devices to the general public than to the professional public. So, the following medicines shall not be advertised to the general public: medicines issued under prescription; medicines that are issued at the expense of health insurance; medicines containing opiates or psychotropic substances; medicines for tuberculosis; infective diseases, diabetes and other metabolic diseases; medicines used for treating of sexually transmitted diseases and chronic insomnia. Advertising of medicines or medical devices to the general public shall not be exclusively or primarily directed towards children. In addition, it is not permitted to show children taking medicines or using of medical devices without adult presence and supervision. Also, advertising to the general public shall not include names of pharmacies, private practices, specialized shops or legal entities dealing with wholesale trade of medicines, including location where a medicine or medical device may be purchased. For the purpose of data protection it is not allowed, when advertising to the general public, to gather and present personal data on medical condition of a specific person, diagnosis, therapy procedures applied during a treatment, or a medicine/medical device used in medical treatment of a certain person or a group of persons.

Special rules apply to advertising of a medicine to the professional public. The advertising materials intended for the professional public shall be marked with the term "Only for professional public" and shall also be approved by the Agency. Advertising of medicines without license is prohibited both to general and professional public.

Promotion of a medicine to the professional public shall include principal data on a medicine as contained in the license. This includes the data corresponding to brief characteristics of a medicine, as well as data on the medicine selling regime. The data shall be correct, updated, confidential and sufficiently complete, so that the recipient may be able, on such basis, to form an opinion on therapeutic value of a certain medicine. The data shall also contain the date when a medicine was made or when it was last tested.

Such promotion of medicines to the professional public shall be made by professional associates of an advertiser, who have graduated from medical, dentistry, pharmaceutical or veterinary medicine faculty. These persons shall be specially educated in the field of clinical and pharmacological characteristics of medicines they promote, and an advertiser shall be obliged to ensure continuous education of professional associates promoting them, verifying their knowledge in order to ensure full, precise and correct information on a promoted medicine.

For the purpose of providing information to the professional public on characteristics of medicines or medical devices being introduced to the market, it is permitted to present them with one sample of a medicine or medical device, with the special note on packaging: "Sample free of charge, not for sale"

VIII Corruption in pharmacy

In the world of pharmacy, there has been a growing criticism of lobbying attempts and impact on doctors by way of promotional gifts and through delegation of doctors to attend various specializations and seminars. The question arises as to the limits of acceptable gifts and activities crossing beyond the promotion and education threshold into the sphere of illegality.

The laws and the subordinate acts explicitly define which gifts are deemed allowed. For example, an advertiser may sponsor professional gatherings only up to the level of covering necessary costs of travel, accommodation and meals, as well as costs of mandatory participation at a professional gathering and costs directly relating to organizing such professional gathering.

Besides there are restrictions relating to type of allowed costs to be covered by an advertiser; there is a time limit for covering such costs which is for the duration of a professional gathering and for maximum of two (2) additional days for related "to" and "from" travel expenses. There is an additional restriction prohibiting sponsorship of accompanying events, such as tourist tours, sporting events and similar events not having the character of a professional gathering.

Sponsoring of professional gatherings shall not be conditioned by requesting or rendering any material or non-material counter-services by the professional public organizing the gathering or by an advertiser. The advertiser shall not influence the content of professional gathering organized by the professional public, but shall be entitled to, at special location destined specified for such activities, beyond the area of principal event, to provide information on a medicine or medical device in compliance with the laws governing medicines and medical devices.

An author, or a person making presentation at a professional gathering organized by the professional public (or a professional gathering at which the professional public participates), regardless of whether the gathering is sponsored by an advertiser or not, shall, before the beginning of a presentation (at the first slide or in another manner which is appropriate, clear and unambiguous) provide the statement on whether such presentation is sponsored by an advertiser.

The advertiser shall be obliged, on its web site in the Republic of Serbia, or on the official web-site abroad, or on other appropriate website, to place the data on professional gatherings it has sponsored (continuously for the current year, as well as for the previous year), including the total amount of funds used for sponsoring each gathering, informing the Ministry in charge of the web site at which it has placed the data, and providing, upon request, such data to the inspection in charge.

Professional associates of an advertiser, engaged in promotion of a medicine, shall be allowed to provide to the professional public, as a gift, only the items which do not have a substantial value, i.e. items with symbolic value relating to medical, dental or pharmaceutical practice, or activities of an employer where the professionals are employed (e.g. pencil, notebook, calendar and similar small value items), which, pursuant to the law are not deemed to be advertising.

Promotion of a medicine to the professional public shall not include encouraging to prescribe, issue, supply, recommend use or purchase of a medicine, by offering and giving an award or incentives in money or gifts, or by giving or procuring any other property or non-property gain, benefit or award.

Also, it is not allowed without a clear medical indication to encourage the professional public to replace one medicine from the same therapy group by another; to present claims or conclusions on the effectiveness of medicine being the subject of clinical trials in the country and abroad, except in case of post-marketing, non-intervention clinical trial; and providing information through the media, for purpose of advertising of medical institutions, private practices, veterinary organizations and specialized shops.

When promoting a medicine or a medical device it is not allowed to diminish the importance of warnings on precautions or undesired reactions to a medicine, specified in brief information covering medicine characteristics in the instructions for use; to diminish therapeutical value of another medicine that has a license; or in any other way as to encourage doubts in respect to value of another medicine; to use the material protected by any form of intellectual property protection, without previous consent of the owner; to use postcards, or any other form of written consignments (the contents of which might be available or readable to other persons apart from the professional public), and use telephone numbers or e-mail addresses of the persons within the circle of the professional public, which advertise or provide information on their work in such a manner, without their previous explicit written consent.

IX Production and wholesale license

Licenses for production and wholesale are issued for indefinite period of time. Medicine production includes the complete production process or certain parts of the production process, active substance production, raw material procurement, medicine quality control and market release of the medicine batch, medicine storage and distribution. The production process is any procedure applied in the production, from the receipt of raw materials, production, packing in interior packaging, up to the labeling and exterior packaging of medicines.

The production may be performed only by a legal entity meeting requirements with respect to space, equipment and staff, in addition to other requirements specified by the law and bylaws, i.e. only a legal entity having the production license granted by the Ministry in charge, irrespective of whether the said medicine is intended for local market, or for exportation.

The medicine producer is obliged to perform the production and quality control in compliance with the law, provisions of the Rulebook, the production license, the guidelines of good production practice and the guidelines of good distribution practice.

One of the main obligations of the producers is keeping of documentation on each produced batch for at least one (1) year following the expiry of term of use of a medicine, or five (5) years as of release of batch, while the documentation on each batch of the medicine, intended for clinical trials, shall be kept for at least five (5) years after the last clinical trial in which the batch was used.

In addition, a producer shall have the plan for an urgent withdrawal of a medicine from the market; such plan shall ensure efficient withdrawal from the market upon request of the Ministry in charge. For purposes of performing and coordinating the withdrawal procedure from the market, a producer shall nominate a person in charge, independent from sales and marketing department, who shall be available at all times.

The production license shall be issued under a resolution of the Ministry in charge, such resolution specifying production location and pharmaceutical form produced at each particular point of production. The Ministry in Charge shall, ex officio, register the medicine production license holder with the issued Medicine Production Licenses Register, following issuance of the production license.

The Agency, when granting release of medicines to the market shall observe the provisions of international agreements covering obligations relating to market release of a medicine that is meeting all of the high quality and efficiency standards; increased worldwide trade in false medicinal products and the resulting necessity of its prevention, as well as international obligations relating to illegal trade in unregistered medicinal products. In order to ensure that Serbian population and medical personnel have the best possible conditions for prevention, diagnostics, treatment and rehabilitation, it is necessary for a wide range of high quality, safe and efficient medicines to be available on Serbian market.

The Agency shall grant approval for market release of the non-registered medicines, when it is medically indicated and legally permitted.

The legal entity which has been granted the medicine and medical device marketing license for wholesale (Wholesaler) shall only sell them upon having the license or the resolution on registration with the Register for Medical Devices, issued by Agency, as well as the medicines and medical devices not having a marketing license, but their importation having been approved by the Agency.

The Wholesalers shall procure the medicines and medical devices only from legal entities in possession of the production license, wholesale medicines and medical devices license, and a license issued by the Ministry in charge.

The Wholesalers shall be obliged, in case of an emergency, upon request of the health institution/private practice, or veterinary organization, to deliver the required amount of the medicine/medical device on wholesale and in shortest term possible, such that lives and health of population are not put at risk.

The Wholesalers shall be obliged, for the sake of continuous supply of medicines and medical devices for which they have been granted the wholesale license by the Ministry in charge, to ensure required stocks, timely supply, import and analysis certificates issued by the Agency, so that there is no interruption of market supply of medicines and medical devices for which they have been granted a license by the Ministry in charge.

The Wholesale may be performed only by legal entities which satisfy the requirements with respect to space, equipment and staff, as well as other requirements specified by the law.

X Intellectual property

The innovative activity in pharmaceutical industry relates to development of new and improvement of existing medicines, as well as development of existing medical equipment. The companies are basing their operations on research and development and tend to protect their intellectual property in order to ensure profit from their inventions and return on their investments during research and development phase. Being familiar with the intellectual property protection system is of key importance for pharmaceutical industry operations.

The patent registration for medicines is different from the patent registration in other industries for two principal reasons:

- Development of a medicine requires a very long period of time;
- Costs of developing a new medicine are very high.

For these reasons, a strong patent protection is necessary in order to ensure return on investment in developing of a new medicine. Having in mind these specific features, pharmaceutical companies protect their intellectual property in two ways:

1. Classic intellectual property protection in the form of patent, trade mark, business secret or in some other form, by which companies acquire exclusive exploitation rights over new medicinal products and other types of creative work. This protection is exercised through the Intellectual Property Protection Bureau and is the usual mechanism of intellectual property protection applied by other industries.

2. By registration of the data in form of exclusivity of the data, i.e. the market exclusivity; it ensures that no other pharmaceutical company is entitled to file the application for registration during the registered period. This registration shall be performed through the Agency and represents the additional system of intellectual property protection in the procedure of the registration of a new medicine.

The pharmaceutical company filing the patent application shall also submit clear and complete data on its discovery, so that persons in charge of assessing the documentation are able to render a technically complete decision.

XII Conclusion

The area of human health has always been the topic of crucial importance for every society. Therefore, it is necessary to have on the other hand clear regulation which will reduce the risks of legal uncertainty as well as to protect the costumers, but also on the other hand the regulation which will not be burdensome and which could not disable the research and development in crucial area such as this.

To meet all these challenges pharmaceutical companies need, on the one hand additional resources to cope with peak workload and, on the other hand, expert knowledge and local experience to face the demands of new regulatory environments and requirements. That It is why it is of special importance for pharmaceutical companies to obtain timely, precise, correct and high quality legal advice with respect to various legal issues in pharmaceutical industry.

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