

PATENTS IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry is characterized by dynamic development, the existence of big multinational companies and a global market. Such development of the pharmaceutical industry was highly influenced by the introduction of patent protection and compliance with intellectual property regulations. One of the most important international obligations is the TRIPS Agreement.

The patent protection of pharmaceutical products is fundamentally important to the pharmaceutical industry, which consists of two sectors: the innovative sector and the genetic sector. Investments in the research and development of new products and technologies are extremely high, but the production is profitable. The innovative pharmaceutical industry is totally dependent on patents and on a strong and effective patent protection system. The benefits of the industry for the patents is clear. It is known that a new compound (new chemical entity, NCE), as a candidate for medicine, required many hundreds of million US\$ to develop a product for the market and that took more than 10 years. Consequently, the patent must cover the product which is to be placed on the market, protecting the NCE and a pharmaceutical composition containing the medically active compound.

INTERNATIONAL TREATIES AND NATIONAL PATENT PRACTICE

The pharmaceutical industry is present on the world market and, therefore, international treaties are of special interest. One of the most important international obligations, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS, 1994) requires all World Trade Organization (WTO) Member Countries to adapt their laws to the minimum standards set by the Agreement [1]. How to implement the provisions of the TRIPS Agreement into national legislation, particularly related to the protection of intellectual property rights (IPR) of pharmaceutical products present a challenge for developing countries. The required legislative reform may have a significant impact on the public – health – sensitive policy.

TRIPS allows patentability for any invention, whether products or processes, in all fields of technology, if they are new, involve an inventive step and are capable of industrial application. In the meantime, Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect public order or morality, including to protect human, animal or plant life or health or avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law. Also, Members may exclude from patentability: diagnostic, therapeutic and surgical methods for the treatment of humans or animals (Article 27) [1].

According to the the Convention on the Grant of European Patents (European Patent Convention, EPC) patents shall be granted for any invention which are susceptible to industrial application, which are new and which involve an inventive step ("useful" and "non-obvious" are synonymous applied in the United States of America); but, methods for the treatment of the human or animal body by surgery or therapy and diagnostic methods practise on the human or animal body shall not be regarded as inventions which are susceptible to industrial application and this provision shall not apply to products, in particular substances or compositions, for use in any of these methods (Article 52) [2].

The industrial applicability model option defines that an invention shall be considered as susceptible to industrial application if it can be made or used in any kind of industry, including agriculture. This formulation is applied in European and the patent laws of many other countries. The "usefulness" model, applied in the United States, has a broader concept. In the meantime, the patent practice of the European Patent Office (EPO) and its Guidelines for examination show that a new use of a medicinal product is a very important cause for patentability [3]. Pharmaceutical patents rarely relate to new chemical entities, new active ingredients. Now a

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days, a great number of pharmaceutical patents protect processes of manufacture, formulations, systems of delivery, and new uses of a known product. In Europe, the first medical indication, "first medical use" has been dealt with as a product claim, whereas the second (or further) medical indication, "second medical use" as a process claim. A claim to a known substance or composition for the first use in surgical, therapeutic and/or diagnostic methods should be in a form such as: "substance or composition X for use as a medicament", or as an "antibacterial agent" or "for treatment of malignant tumors"... whereas a second medical use claim is not the form: "Use of a substance or composition X for the manufacture of a medicament for therapeutic application Y" [3]. The United States have adopted a more restrictive approach to the protection of new uses, because "method-of-use" patents do not encompass protection of the product as such.

In any case, it may be concluded that nothing in the TRIPS Agreement obliges Member countries to introduce additional protection for new uses (the first and the second medical indication). According to Articles 27.1 and 28, the TRIPS Agreement obliges Member States to protect the product, to prevent third parties not having the owner's consent from the acts of: making, using, offering for sale, selling, or importing for these purposes that product; and to protect a process, to prevent third parties not having the owner's consent from the act of using the process, and the acts of: using, offering for sale, selling, or importing for these purposes at least the product obtained directly by that process.

The TRIPS Agreement related to the term of patent protection states that the protection shall not end before the expiration of a period of twenty years starting from the filing date. According to that provision, US patents for which applications were filed after June 7, 1995 will last 20 years from filing, not 17 years from issuance as it used to be calculated. Additionally, it is important that an applicant keeps in mind that, unlike the rest of the world, US patent practice is a "first-to-invent" rather than "first-to-file" system.

Because the filing of a patent application on a new chemical entity takes place at the laboratory research level, generally in vitro testing and it takes about 12 years from that filing for the patented NCE to become a marketed product, the Effective Patent Life (EPL) is less than half the original patent term. Consequently, the USA in 1984, Japan in 1987 and EU Member States in 1993 brought into effect patent term restoration (by Council Regulation EC No. 1768/92 for medicinal products and EC No. 1610/96 for plant protection products). The supplementary Protection Certificate (SPC) regulation, which has the same properties as a patent, comes into effect as soon as the patent expires and has a maximum 5 year term. The European Patent Convention amended by the act revising Article 63, which entered into force on July 4, 1997 (Official Journal

EPO) allows "patent term extension" if the subject-matter of the European patent is a product or a process of manufacturing a product or a use of a product which must undergo an administrative authorisation procedure required by law before it can be put on the market in the State (Article 63b) [2]. But, nothing in the TRIPS Agreement obliges Member countries to introduce additional protection, "patent term extension" for up to 5 years [1].

EXCEPTIONS TO PATENT RIGHTS

A patent is a monopoly for a period of time (e.g. 20 years), limited geographically, which gives the patentee the right to exclude others from making, using, selling or offering to sell the patented invention. On the other hand, a patent does not oblige the patentee to practice the invention. The patent owner also has the right to assign, or transfer by succession, the patent and to conclude licensing contracts. It is well known that the patent protection of a new compound ("product patent") represents absolute protection and the absolute right in relation to next novel inventions pertaining to that compound. The process patent of obtaining can also protect the product directly obtained by that process, which represents relative protection. So, the owner of the process patent would, in order to produce and market (commercial exploitation) a compound, have to obtain a license (by license agreement) from the owner of the patent for that compound. Can national law limit patent monopoly and what are possible exceptions to patent rights? The TRIPS Agreement states: Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account the legitimate interests of third parties (Article 30). This Article creates different interpretations by national patent laws. What does "unreasonable conflict by a patent" exactly mean in practice? Should scientists (and other inventors) be allowed to carry out research using a patented process (obtaining patented compound) without either a licence or the permission of the patent owner (holder)? Many of the national patent laws have a provision which states that work carried out for "experimental purposes" on patented subject matter does not constitute an infringement of the patent concerned. What does experimental purposes mean? Does it only involve fundamental research, or it is research including efforts to modify or improve the invention with or without commercial goals in mind? Are scientists (or other inventors) allowed to demonstrate to a potential customer that a new invention "works" or to demonstrate that, according to the results of clinical trials, a product is safe and effective?

In the United States the research exception means: "experimental or other non profit purposes". The

exception, known as the "Roche-Bolar", specifically applicable to pharmaceutical patents relates to using an invention without the patentee's authorization for the purpose of obtaining approval of a generic product before the patent expiration date and marketing of a generic version promptly after the patent expires. The "Roche-Bolar" exception (early working) was first introduced in the United States by the US Drug Price Competition and Patent Term Restoration Act (1984), and until now has been explicitly adopted by Canada, Australia, Israel, Argentina and Thailand. European patent practice recognizes it by a case law based on the exception of experimental use but it is not sufficiently clear and needs a judicial ruling. For example, a clarification would specify that activities such as validation tests and clinical trials should not be considered to infringe a patent [4].

Some of these questions were considered by the UK court of Appeals and ruled that trials carried out either to discover an unknown effect, or to test a hypothesis, can be regarded as experiments. However, trials carried out to demonstrate to a third party that a product "works", or to collect information to satisfy either a customer or regulatory body, were not acts performed for "experimental purposes" [5].

One of cases of the UK High Court that focused on the "research exception" was the case: Murex Diagnostics Ltd. and Organon Teknika Ltd. vs. a patent monopoly US biotechnology company Chiron on making and selling test kits for the hepatitis-C virus. Murex had been developing an assay for serotyping the hepatitis-C virus when it was sued by Chiron for patent infringement. Murex wanted to continue research and development on this particular assay, even though its commercial use would infringe Chiron's patent. Murex had to reach an agreement with Chiron while awaiting the hearing or its appeal on the first charge [5].

The TRIPS Agreement in Article 31 states the "other use without authorization of the right holder", a use other than that allowed under Article 30. We would like to stress provision 31.1: "where such use is authorized to permit the exploitation of a patent ("the second patent") which cannot be exploited without infringing another patent ("the first patent"), the following additional conditions shall apply:

(i) the invention claimed in the second patent shall involve an important technical advance of considerable economic significance in relation to the invention claimed in the first patent;

(ii) the owner of the first patent shall be entitled to a cross-licence on reasonable terms to the use invention claimed in the second patent; and

(iii) the use authorized in respect to the first patent shall be non-assignable except with the assignment of the second patent".

PROTECTION OF UNDISCLOSED INFORMATION

It is known that the procedure of patent protection demands the disclosure of the invention and the granted patent is a monopoly. How does one protect undisclosed information? The TRIPS Agreement regulates this question to cite the provision of the Paris Convention (1967). Accordingly, in the course of ensuring effective protection against unfair competition, a WTO Member shall protect undisclosed information in accordance with Article 39, particularly if a secret has commercial value because it is secret. It is determined what it meant for the purpose of this provision "a manner contrary to honest commercial practices": It "shall mean at least practices such as breach of contract, breach of confidence and inducement to breach, and includes the acquisition of undisclosed information by third parties who knew, or were grossly negligent in failing to know, that such practices were involved in the acquisition". It is very important that the TRIPS states that "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origin of which involves a considerable effort, shall protect such data against unfair commercial use" [1].

GENERIC MEDICINES

Generic companies manufacture and market very important pharmaceutical products, at lower prices for the consumers and provide improved affordability of medicines. Generics are pharmaceutical products which are not protected by a patent in force, and which are commercialized under a non-proprietary name ("commodity generics") or branded ("brand generics"). According to the independent market analyst Datamonitor, the fact is that by 2005, medicines, which now have annual sales of approximately 100 billion US (based on 1999) will lose patent protection [6]. This represents a great opportunity for generic companies. In the United States generic drugs (medicines) are on center stage as the White House proposed to revise generic drug patent policy and the Food and Drug Administration's (FDA's) Office of Generic Drugs was tackling administrative and policy issues to help speed generic therapies to the market [7]. It is known that US legislation permits generic companies to file an abbreviated new drug application (ANDA), in the case when the original patent is expended. At the same time, the Hatch-Waxman Act (1984) permits patent holders to delay the marketing of a new generic product for 30 months pending resolution of a patent infringement case brought by the innovator against a generic challenger. Which patents are relevant for 30 months market delaying? The FDA's Office proposes a change to clarify requirements for listing patents in the FDA Orange Book. The aim is to prevent an innovative company from delaying generic competition by filing later-issued and frivolous patents. The new FDA's rule specifies that manufacturers should list patents for drug substances

(active ingredients), drug product (formulation and composition) and method of use. The manufacturers cannot list process patents and patents claiming packaging, metabolites or intermediate forms of a drug. Besides, the FDA proposed rule on generic drugs that permits brand-name firms to file patents on polymorphs in the Orange Book [7].

SPECIAL PATENT CASES IN PHARMACEUTICALS

These issues are important for implementing national regulations and/or guidelines for patent offices in the developing countries [4].

Selection Patents

A selection patent relates to a selection invention, which subject-matter is a choice (a selection) from within subject-matter already known from a prior art document. A selection invention occurs more frequently in chemistry than elsewhere. Substantial differences exist in the treatment of these patents, including between the EPO and some national offices in Europe. Yugoslav patent practice allows this means of patent protection.

Analogy Processes

Some patent offices have permitted the patentability of non-novel processes if the resulting chemical is novel and displays unexpected properties. These patents are frequent in biotechnology.

Polymorphism

Some therapeutically active compounds are present in polymorphic forms. They may crystallize in divers forms, which may have different properties that are more or less significant in terms of their therapeutic use. Such forms are deemed as the prior art – and, therefore, non – patentable in some patent offices, but Yugoslav patent practice has allowed the patentability of these inventions.

Compositions

Pharmaceutical composition claims protect a formulated product containing an active ingredient and appropriate additives. Compositions may refer to combinations of known ingredients. But, it is important that the composition solves the "objective technical" problem and produces a new and inventive pharmaceutical product. Such patents are very much present in Yugoslav patent practice.

Optical Isomers

A compound that is an optically active enantiomer of a compound previously known only in racemic form is a special patent case frequently occurs in therapeutically active compounds. It is generally accepted that one

optical isomer will typically have a much higher activity than the other, and could be of different toxicity and other characteristics and this is also patentable.

Active Metabolites

In some cases, an applicant protects the active metabolite that produces the desired effect in the body and attempts to block competition in the market after the primary patent has expired. This is deemed to be an unacceptable attempt to extend patent protection.

Prodrugs

In the case when a previously inactive compound metabolised in the body can produce a therapeutically active ingredient, it is called a "prodrug". There is no determining practice whether the patent for the original compound covers the prodrug.

YUGOSLAV PATENT LEGISLATION AND PRACTICE

The Yugoslav pharmaceutical industry has developed successfully in cooperation with world companies [8]. The main pharmaceutical companies have research centres and inventions protected by patents, although the patent protection of medicines in Yugoslavia started in 1993. It is not sufficiently known that Yugoslavia has a long and prominent tradition in the field of industrial property protection from legal continuity based on the activities of the Kingdom of Serbia, which is one of the eleven countries founders of the Paris Union, i.e. the party of the Paris Convention for the Protection of Industrial Property (1883). FR Yugoslavia (Serbia and Montenegro) has harmonized industrial property laws with international legislation since 1995. Four laws have been passed in accordance with the World Intellectual Property Organization (WIPO) recommendations: the Patent Law, Trademark Law, Law on Industrial Design and Law on Geographical Indications of Origin [9]. The Patent Law enables the protection of inventions in the field of pharmaceuticals: a product (protection of a substance, composition, microorganism, plant or animal cell culture); process, as well as the use of a product or a process; but not the protection of inventions for a surgical or diagnostic procedure or treatment applied directly on the human or animal body. Apart from the above mentioned, the Patent Law is in accordance with the TRIPS Agreement and with the European Patent Convention. It should be pointed out that the Patent Law and Yugoslav patent practice allow the protection of an invention as the first medical use and the second medical use [10,11]. However, Yugoslav legislation has not yet amended a patent term extension (the Supplementary Protection Certificate) and it is known, that the TRIPS Agreement does not oblige the Member countries to do so.

CONCLUSION

The pharmaceutical industry is dependent on intellectual property protection, particularly, on patent protection. As the pharmaceutical industry is present on the world market, international treaties are of the special interest. One of the most important international obligations is the TRIPS Agreement. Yugoslavian (Serbia and Montenegro) industrial property laws are in accordance with international legislation (the TRIPS Agreement and the European Patent Convention) since 1995. Yugoslav practice is also in accordance with European patent practice.

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REFERENCES

- [1] Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), WIPO, Geneva (1995).
- [2] Convention on the Grant of European Patents (European Patent Convention) of 5. October 1973, (text as amended

and revised until to 10.Dec. 1998), Intellectual Property Laws and Treaties, EPO, November, 1999.

- [3] Guidelines for Examination in the European Patent Office, EPO, Feb. 2001.
- [4] S. Jovanović, "Patentna zaštita u oblasti farmaceutskih proizvoda", Savezni zavod za intelektualnu svojinu, Beograd, oktobar 2001.
- [5] S. Cohen, "Time to relax research use of patents", Science and the Law, Nature, **376** (1995) 622.
- [6] K. Robinson, "A rocky road for generics", Market Views, BioPharm International, January (2003), 24-26.
- [7] J. Wechsler, "Generic drugs on centre stage", Washington Report, Pharmaceutical Technology Europe, Dec. (2002), 20-22.
- [8] S. Jovanović, "Pronalazačka aktivnost u farmaceutskoj industriji", Savezni zavod za intelektualnu svojinu, Beograd (1996).
- [9] Zakon o patentima; Zakon o žigovima; Zakon o modelima i uzorcima; Zakon o geografskim oznakama porekla, "Službeni list SRJ", br. 15/95.
- [10] S. Jovanović, "Osnovni elementi zaštite intelektualne svojine", Hem. ind. **50** (1996) 28-32.
- [11] V. Tešankić, O. Đenović, S. Jovanović, "Zaštita pronalazaka u oblasti hemije, biotehnologije i farmacije – prihvatljiva forma patentnih zahteva", Glasnik intelektualne svojine, **6** (1998) 1273-1278

REZIME

PATENTI U FARMACEUTSKOJ INDUSTRIJI

(Stručni rad)

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Farmaceutska industrija, koju karakteriše specijalna vrsta proizvoda, visoka ulaganja u istraživanje i razvoj i posebne mere kontrole kvaliteta, izuzetno je zavisna od stepena zaštite intelektualne svojine. Moglo bi se reći da razvoj farmaceutske industrije direktno zavisi od industrijske svojine, a naročito od jačine patentne zaštite. Kako je farmaceutska industrija prisutna na svetskom tržištu, za nju su važne odredbe međunarodne zakonske regulative. Od posebnog značaja je TRIPS sporazum koji obavezuje sve članice Svetske trgovinske organizacije. Farmaceutska industrija u Srbiji i Crnoj +ori (FR Jugoslavija) se razvijala u saradnji sa velikim svetskim kompanijama uz poštovanje principa zaštite industrijske svojine. Zakonska regulativa Srbije i Crne Gore (Jugoslavije) u ovoj oblasti je od 1995., uglavnom, usaglašena sa međunarodnom regulativom, pre svega TRIPS sporazumom i Konvencijom o evropskom patentu. Jugoslovenska patentna praksa sledi praksu Evropskog zavoda za patente.

Ključne reči: Patent • Farmaceutska industrija • Intelektualna svojina • Industrijska svojina • Međunarodna obaveza • TRIPS sporazum • Zakon o patentima • Key words: Patent • Pharmaceutical industry • Intellectual property • Industrial property • International obligation • TRIPS Agreement • Patent Law •