Intellectual Property for Pharmaceuticals

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Why should a medicinal chemist care about intellectual property? There are specialists dealing with the matter of patents and trademarks, so let us concentrate on "true" science! But: Intellectual property protection is paramount for the pharmaceutical industry. With increased globalisation and global competition as a consequence thereof, only companies with a constant flow of innovative products and services will survive. The better you can protect this innovation the better off your company is.

Intellectual property protection has also grown in importance for universities. Nowadays it is more difficult than ever to secure funds for research. If the results of research could be commercialised, and at the same time a royalty stream generated from it, many financial problems of research groups at universities could be alleviated. The general public will also profit from such a development when the fruits of academic research are more often translated into practical products and made generally available.

Intellectual property rights get more and more attention in the general media. In the past few years a lot of awareness has been created on the emotional side, with slogans such as "no patents for life", or in the context of healthcare costs, prices for pharmaceuticals and parallel imports. It is therefore important that scientists working in research, development, production, marketing and administration know the basic aspects and principles of intellectual property, and have an idea of the burning questions that intellectual property specialists are dealing with [1].

The success of today's pharmaceutical industry very much depends on adequate protection of intellectual property. Under the term intellectual property one understands many different forms of protection titles such as patents, trademarks, designs, plant variety protection, protection of geographical indication and other related titles, but also protection of undisclosed information, know-how, and copyright. Protection of inventions by patents, protection of (generally undisclosed) information required for registration of pharmaceuticals, and trademarks supporting effective marketing are all very important, but one can properly state that *patents* form the lifeline for the research-based pharmaceutical industry. Investment of, at present, more than USD 500 million for research and development of one new medicine which reaches the market can only be justified because intellectual property protection grants a limited term of exclusivity for the commercial exploitation of such an invention. Yet, patents are and will probably continue to remain a contentious issue.

There is an inherent tension between the limited monopoly of a (pharmaceutical) patent, which gives the successful innovator a fair chance to recoup his investments, and the interest of governments in containing health care cost. Likewise the use of trademarks in marketing efforts of pharmaceutical industry is under attack, mainly because some governments and political circles believe that trademarks are misused to partition markets and to indirectly extend the period of exclusivity granted by a patent.

What is a Patent?

A patent is an exclusive right granted by the state for a limited time in respect of a new and useful invention [2]. This right is usually limited to the territory of the state granting the patent. If protection is desired in a number of countries, patents must be obtained in all of them, either through national patent offices or through a regional multinational body such as the European Patent Office.

For a patent to be granted for an invention, the invention must be novel and involve an inventive step, that is, must be non-obvious. Novelty and non-obviousness are determined with respect to the "state of the art", which (somewhat simplified) means everything in use or published before the patent application was first filed or before the invention was made.

It is important to realise that a patent does not give the right to practise the invention, but only the right to exclude others from doing so. For example, owning a patent for a new drug does not give the right to market the drug without permission from the regulatory authorities, nor does it give the right to infringe an earlier existing patent. The patent owner may enforce his exclusive right in the courts, stop the activities of an infringer and make him pay damages. The patent owner may also grant licenses allowing a licensee to use the invention (if he fulfils all the other non-patent requirements), usually in return for financial compensation such as royalties on the sale of products.

The exclusive right given by a patent is granted for a limited period only, usually 20 years from the filing date. Some countries allow extensions of the patent term for pharmaceuticals to make up for the fact that marketing is delayed by the need to obtain regulatory approval. Once the patent term has expired or the patent has lapsed by non-payment of the renewal fees, anyone is free to use the invention. The public is able to do so because the patent specification is published (usually 18 months after the first filing date) with a description which enables the invention to be carried out by a skilled person.

International Agreements

Basis for the "globalisation" of patent rights is the International Convention for the Protection of Industrial Property (Paris Convention) dating back more than 120 years [3]. The most important practical aspect of the Paris Convention is that, if an application for a patent is made in one country, corresponding applications may be filed in other countries within one year from the first filing date. These later filings will be treated as if they were filed on the same day as the first application.

As a consequence, publications and use relating to the invention after that first filing date will not influence the patentability of later filed identical patent applications in other countries. This allows an inventor to first test and develop an invention before spending all the money for world wide filing. It is still desirable to postpone planned publications until patent applications have been filed world wide, since additions to the subject matter included in those later world wide patent applications are not shielded from the impact of prior art surfacing in these first 12 months called "priority year".

The Paris Convention not only covers patents, but also other industrial property rights, notably trademarks. Another important aspect of the Paris Convention is the fact that foreigners and nationals of the state where an intellectual property right is applied for are treated equally except for formal requirements.

A simplified mechanism for world wide patent applications is offered by the Patent Cooperation Treaty (PCT) [4]. The PCT is now in force for over 120 countries, covering all important markets in North America, Europe and Asia, except e.g. for Taiwan. Argentina, Chile and some other countries in Latin America, Arabic countries in the Middle East and also some countries in Africa are not yet members of PCT. The PCT, like the Paris Convention, is administered by the World Intellectual Property Organization (WIPO), a UN organization with its headquarters in Geneva. It does not create a supranational patent office, nor does it grant a "world patent", but it does simplify the process of filing patent applications simultaneously in a

number of countries. Under the PCT, a single application may be filed securing rights for all PCT contracting states. A search is made for relevant prior art together with a first assessment of patentability, and the application is published, together with the search report, 18 months after the priority date. The applicant then has 12 more months (i.e. a total of $2^{1/2}$ years from the first filing date) in which to prepare all necessary translations and documents for national filings in the designated countries. This again allows a patent applicant to further evaluate the commercial value of the invention before making investments in world wide filings. The search results and the preliminary assessment of patentability also reveal if prior art is known which prohibits the grant of a valid patent.

The agreement on Trade Related Aspects of Intellectual Property Rights (TRIPs) is a further important agreement which had considerable impact on patent, trademark and other intellectual property rights available to pharmaceutical companies [5]. This agreement evolved form the GATT Uruguay Round and is part of the package of agreements which had to be accepted and implemented by all World Trade Organization (WTO) member states. The TRIPs agreement covers the whole range of intellectual property issues including patents, trademarks, geographical indications, industrial designs, integrated circuits, copyright and trade secret protection, as well as general provisions concerning basic principles, intellectual property enforcement, and dispute resolution between WTO member states.

TRIPs requires WTO member states to introduce strong patent protection, the most important elements of which are: A minimum term of 20 years from filing; patent protection to be available for all chemical compounds, including pharmaceuticals; patent rights to be without discrimination as to whether products are locally made or imported; and enforcement procedures to be effective, fair, equitable and not unnecessarily costly. Further to that the WTO offers a convenient and comparatively fast dispute settlement procedure for disputes between WTO member states about whether TRIPs (and other GATT/WTO agreements) are properly implemented and properly interpreted.

Prior to the TRIPs agreement a number of countries discriminated against pharmaceutical patents by allowing automatic compulsory licences in this field. This meant that the patent owner could not use the patent to exclude others, but only to collect royalties from imitators, the royalties often being fixed at arbitrarily low levels. Under TRIPs, compulsory licenses are allowed only under strict conditions, and on an individual basis. The question of compulsory licences are again on the table in the political discussions around TRIPs, as could be seen in the Doha and Cancún Ministerial Conferences. Many developing countries believe that the problems with their national health systems could be alleviated by importing pharmaceuticals from other countries under compulsory licences. A complicated system of rules has now been set up, which should make sure, e.g., that the compulsory licence system will not be misused and that the pharmaceuticals imported into developing countries under such a compulsory licence will not be re-exported to first world countries [6].

Formal Aspects of a Patent

A patent application consists of a description of the invention, which may include figures (and in pharmaceutical applications usually chemical formula and examples), the claims, and an abstract. The abstract is technical information only, is used chiefly for search purposes, and has no legal effect.

A patent description is a legal as well as a scientific document, which serves a different purpose from that of a paper in a scientific journal, and should be read in a different way. The description must be sufficiently clear to enable a skilled person to reproduce the invention. In pharmaceutical cases it will normally contain a number of examples. Academic scientists are sometimes distrustful of patents as sources of scientific information because many patents contain what are called "paper examples" which were never actually carried out. The inclusion of a "paper example" as a cookbook recipe in a patent is not a false representation that the compound has been made; it is an honest representation that it is predictable that the compound can be made in that way.

The claims serve the important legal purpose of defining the scope of the exclusive rights given by the patent. Claims in patent applications as filed are often much broader than claims in a patent as granted after examination in a patent office, and only the latter have to be observed. It is an infringement of the patent to make or do something which is covered by the scope of the claims, as interpreted by the responsible court. The scope of the claims is not limited to the literal wording, but to some extent also includes equivalents of the literal wording. The claims must be supported by the description, but will often be broader in scope than the specific embodiments of the invention described in the examples. On the other hand, claims may only cover part of what is described in the patent, since examination of the claims by a patent office may reveal that original claims as filed in the application do not fulfil the legal requirements.

Patents usually contain a number of claims starting with a broad claim to a large group of compounds or a very general process, going on to more limited (dependent) claims to particular sub-groups, and ending with specific claims to individual preferred compounds or particular conditions of a process. These dependent claims are supposed to give a fall-back position in the event that the broadest (or a broader) claim is later found invalid by a court.

Patent claims may be classified into product claims and process claims. Product claims claim a physical entity, for example a chemical compound, a crystal form, a compound mixture or a pharmaceutical formulation. Process claims (sometimes called method claims) cover the act of doing something, for example manufacturing a (new or old) product, using a product in a particular way, or even treating a disease. A compound claim is infringed by someone making, using or selling the compound, irrespective of how it is made. A claim to a process for making the compound is infringed not only by carrying out the process, but also by using or selling the product of the process.

Once a compound is sold, the patent rights are exhausted, which means that the purchaser may use or re-sell it without limitation. Since a patent is a territorial right, this exhaustion is – in principle – limited to the patent territory. The patent owner can therefore stop the import of a patented product even if the patent rights to this product are exhausted in the exporting country. There is a notable exception to the mentioned principle of national exhaustion within the European Economic Area, where the free flow of goods is the rule. Patents can only be enforced once when a product is first put on the European market, a situation called regional exhaustion. Parallel trade within the European Union is a continuous concern for the pharmaceutical industry since national health authorities regulate marketing and pricing, thereby creating considerable price differences for pharmaceuticals between different member states of the EU. These price differences are then used (or rather misused) by parallel traders shifting products from one country to another, and re-labelling or re-packaging the products. Patent (and also trademark) rights cannot be used to stop parallel trade, except under special circumstances.

Patentability Requirements in Europe

Although formal aspects of patent applications and patents are pretty much harmonized throughout the world actually as a consequence of the PCT discussed above and the Patent Law Treaty [7] signed recently, there are still differences in the substantive patentability requirements, most notably between the United States and the rest of the world. In the following we will first present the situation in Europe.

The European Patent Convention (EPC) [8] now comprises 28 member states, in particular the 25 countries of the European Union (EU) with the exception of Latvia, Lithuania and Malta (which will have to join the EPC as well), and also Bulgaria, Romania, Turkey, Monaco, Switzerland and Liechtenstein [9]. As an alternative to filing separate patent applications at each national patent office, the EPC provides for the grant of patents in some or all of the member states by means of a single patent application written in English, French or German. The patent application is examined for patentabi-

lity by the European Patent Office in Munich and Den Haag. Once the European patent is granted, it has to be translated into the national official languages and falls apart into a bundle of national patents subject to national laws on validity and infringement. Although an EU ("Community") patent is in discussion since 1975 no unitary EU patent is available and probably will not be in the near future. Such unitary EU patent would be highly desirable for industry, but the projects for an EU patent failed so far because of the translation requirements, the projected costs for the patent applicant, and inadequate proposals for the judicial arrangements for validity and infringement of such patents.

According to the EPC, inventions can only be patented if they are new, are based on an inventive step, and are industrially applicable [10]. Novelty is determined in relation to the "state of the art", which comprises everything that is known to the public by written or oral publication, use or any other way, in any country in the world, before the priority date of the invention. Earlier filed patent applications, even if they are not yet published, are also taken into account for novelty purposes. The novelty requirement makes sure that nothing is patented which is already in the public domain and freely accessible.

A so-called "inventive step" is present if the invention is non-obvious to "the person skilled in the art", i.e. to a person familiar with the technical field which is a competent worker but lacks imagination or inventive capability. For chemical patents the person skilled in the art normally is an average qualified industrial chemist. For complex inventions such as in the field of biotechnology the person skilled in the art may be considered to be a team of qualified scientists from different branches of science. Whether or not a claim will be regarded by the examiner or the judge as involving an inventive step is sometimes difficult to predict, since to some extent judgment of what is obvious or non-obvious is a matter of subjective interpretation.

In considering obviousness, it is of no relevance how the invention was made, whether as a result of planned research, a flash of inspiration, or even pure chance. An invention may be simple without being obvious. Producing a simple solution to what appears to be a complex problem is often highly inventive. With the benefit of hindsight an invention very often seems to be simple, derived from the prior art as a series of logical steps, but it does not necessarily follow that the invention was obvious at the time of filing the patent application. Further indication of non-obviousness of an invention may be commercial success, a solution to a long-time need, or success where many others failed. The inventive step requirement makes sure that simple and obvious modifications of prior art should remain free to use by everybody.

The third basic requirement of the EPC is that the invention should be susceptible of industrial application. Industrial application comprises making or using the invention in any kind of industry, including agriculture. According to the EPC, methods of medical treatment or diagnosis performed on the human or animal body are regarded as being incapable of industrial application and therefore not patentable. However, substances invented for use in such medical treatment and diagnosis may be patented. An old compound not previously known to have any medicinal property can be protected as a drug claiming "Substance X as a pharmaceutical". The invention that a known drug has a new and unrelated medicinal benefit can be protected by a claim of the type "Use of substance X in the manufacture of a medicament for the treatment of disease Y", commonly known as a "Swiss-type" claim because the Swiss patent office was the first to accept claims of this type. The reason for the exclusion of medical and surgical treatment from patenting is the understanding that doctors should be free to treat their patients without having to worry about whether they are infringing a patent.

The EPC makes further specific exceptions to patentability. For example, artistic works, aesthetic creations, scientific theories, mathematical methods, the presentation of information, business methods, and computer programs as such are all unpatentable. Discussions about the patentability of computer inventions are presently going on, and these inventions may be patentable if they do not relate to computer programs as such. Animal and plant varieties are also not patentable. Plant varieties

can be protected by plant breeders' rights. However, any invention relating to plants which is not restricted to a variety (and for that reason not protectable under plant breeders' rights) should be patentable, if new and non-obvious.

Further excluded from patentability are inventions the publication or exploitation of which would be contrary to "ordre public" or morality. This provision, designed to ensure that patents would not be granted for inventions such as improved letter bombs, has been seized upon by opponents to gene technology, in their attempts to prevent patenting of nucleic acids and living organisms. The European Communities recently approved the Directive on the Patenting of Biotechnological Inventions which more closely defines what should be regarded as contrary to ordre public and morality. The subject matter of the EU Directive is incorporated into the Implementing Regulations of the EPC [11]. It is now clear that processes for cloning human beings, processes for modifying the germ line genetic identity of human beings, uses of human embryos for industrial and commercial purposes, and processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes, are not patentable. On the other hand it is now clearly stated that biological material which is isolated from its natural environment or produced by means of a technical process is patentable (if new and non-obvious), even if it previously occurred in nature. However, discussions about patentability of biotechnological inventions are far from being settled, which is illustrated by the controversy about patenting of stem cell inventions and the fact that leading EU countries such as Germany and France have so far failed to implement the EU Directive on the Patenting of Biotechnological Inventions.

Patent laws of many non-European countries contain similar patentability requirements and exclusions from patentability as the EPC. Some countries offer a "grace period" for publications of the inventors. This means that a publication of the inventor(s) or derived from the inventor(s) will not be regarded as prior art, if the first filing date or the filing date in that particular country is not later than a specified period of months, usually 6 or 12 months, after the first publication date. An inventor publishing his invention in a scientific journal or presenting the subject matter at a public seminar still can file a patent application in these countries. It must, however, be taken into account that under the EPC no valid patent can be granted for European countries if the first filing date is after the publication date!

Patents in the US

Whereas the rest of the world uses the "first-to file" system, in which the date of the first patent filing (the priority date) is important, the USA adheres to the "first-to-invent" system [12]. Here the critical date is the date of invention, and if two inventors independently make the same invention, the patent goes to the one who can prove the earlier invention date in a complex process called "interference". Accordingly, for a US patent, prior art is what was known before the invention date, rather than before the filing date, but with the proviso that if there has been a publication of the invention, the US patent must be applied for within 12 months of the publication date, corresponding to the so-called "grace period" explained above. Furthermore the law in the US does not take into account if an invention is used outside the United States at any time before filing a patent application in the US. Printed publications from anywhere in the world, however, are invalidating a patent as in other constituencies. US law requires that the invention should be "useful", which to some extent corresponds to the industrial applicability requirement under the EPC, but represents a higher hurdle for patentability. In the US, unlike under the EPC, methods of medical and surgical treatment, business methods, and computer programs are patentable.

Trademarks

A trademark is used to identify a product or service and to indicate the source. It serves to differentiate a product or service of one company from same or similar products or services of other companies. Trademarks allow consumers to select products and services from companies they know and trust. Trademarks are exclusive rights granted by the state and limited to the territory of that

state. Again it is not possible to have one registration for a trademark for the whole world, but through registration in each country, or group of countries such as the European Union. The term of a trademark right is generally ten years and renewable indefinitely.

Trademarks are usually words (brands, names), combinations of letters and/or numerals, but they can also be signs, symbols, and even colours, shapes, smells and sounds. When registering, classes of application (groups of goods or services) have to be designated for which a registration is sought.

There is no "novelty requirement", but a trademark is registered in the name of an applicant only if there are no conflicting older trademark rights, i.e. trademarks that are identical or confusingly similar and registered by others before the registration date, or in use by others and widely accepted, or famous trademarks. Trademarks are examined with respect to whether they do not monopolize words of general usage and whether they do not conflict (being identical or confusingly similar) with earlier trademarks.

The Paris Convention and the TRIPs Agreement mentioned above also apply to trademarks. The Paris Convention provides that a priority of a trademark registration in one country is accepted in all other countries within 6 months. The Trademark Law Treaty [13] harmonizes formal aspects of trademark applications and trademark registration. The Madrid Agreement concerning the International Registration of Marks and its Protocol allow a simplified registration procedure in Madrid Union member states based on registration in the home country [14]. The Nice Agreement concerns the International Classification of Goods and Services for the purpose of registration of trademarks [15].

Domain names are to some extent related to trademarks. For domain names, however, a first come first served principle applies, and they cannot be used to exclude others from using the name. Conflicts between trademark owners and domain name owners can often be solved by an efficient arbitration system offered by WIPO, but sometimes regular courts have to decide.

Know-how

Know-how can also be regarded as a special form of intellectual property. To keep know-how secret may be important to retain or gain an advantage vis-à-vis a competitor not disposing over similar knowledge. However, if the secret know-how is (intentionally or accidentally) made public or independently developed by somebody else, all the advantage of secret know-how is lost. For this reason a know-how owner should always make a learned decision whether to keep the know-how secret or to patent it. If it is patented, it cannot be kept secret, but the patent gives a right to exclude others from the use of the patented knowledge.

The TRIPs agreement discussed above also foresees that "undisclosed information" should be protected by law [16]. A special form of undisclosed information are clinical test data required by registration bodies as a condition for approving the marketing of pharmaceutical products. Such data shall be protected against disclosure, and steps taken to ensure that the data are protected against unfair commercial use. In practical terms this means that a competitor (e.g. a generic producer) is not allowed to make use of this information when trying to get marketing approval for a copy product, at least for a period of years. In Europe, registration exclusivity is 6 or 10 years depending on the country and the type of product, and 5 years in the US.

Impact of patents and trademarks on the pharmaceutical industry

The rapid pace of modern developments is accentuating the significance of the drug trademark. In technical terms, the trademark of a respected company stands for quality. The drug trademark conveys to the authorities, doctors, pharmacists and patients a guarantee of safety and therapeutic efficacy for the whole product, and not just for the active substance, as is the case with generics. In commercial terms, it is useful for all parties – above all, patients – to sell a drug under a trade name, rather than using complicated chemical or generic denominations. With an easily memorized trademark and the associated guarantee of quality, the pharmaceutical

manufacturer is invoking the reputation of the company as a whole. Of course, defects must be avoided at all costs, to prevent fatal damage to the company's reputation. In economic terms, the trademark carries a high value-adding potential in the pharmaceutical market [17].

Strong worldwide patent protection is essential to support innovation in the pharmaceutical industry. The great majority of medicines would not have been developed or commercially introduced if patent protection had not been available. The huge cost of research and development for a new chemical entity or for a new indication of an existing pharmaceutical, and the relative ease of copying a medicinal product provide an explanation for the importance of patent protection for major pharmaceutical companies. For drugs introduced in the nineties of the last century, it is estimated that R&D costs are approximately USD 500 million per drug put on the market. And these figures are even higher today. On the other hand costs for demonstrating bioequivalence of a generic copy of a medicinal product is approximately USD 1 million [18].

Yet, the relevance of strong intellectual property protection goes far beyond major multinational pharmaceutical corporations. Guaranteeing the protection of intellectual property in research using the modern tools of molecular biology is essential for many start-up biotech companies to survive. Many of these firms do not yet have products for sale, and for them it is essential to protect their intellectual property as the only real capital they have.

In the context of the controversy surrounding the international trade debate, there are a lot of myths surrounding the issue of patents. A first such myth is that patents create monopolies. In reality, patents offer protection only for a limited time. Due to the time required for market introduction, the actual exclusivity is limited to eight to ten years, in spite of a patent term of 20 years. In countries with patent term extension the exclusivity may last up to five years more. Furthermore, most new medicines protected by patents compete with similar products, both protected and off-patent. Competition is fierce in almost all therapeutic areas, and even new chemical entities which introduce a novel therapeutic concept are followed by competitor products within a short time period. A second myth is that patents are a significant factor in escalating health care costs. This argument ignores the fact that there is a clear and established link between patent protection and the rate of innovation, but no such link between the strength of intellectual property protection and price levels. Innovation has an impact on health care cost: Many pharmaceuticals shorten treatment and hospitalisation time and costs. On the other hand they improve treatment, prolong life, and thereby cause costs which we all think are justified by the results obtained.

Patents are a main driver for future pharmaceutical innovation which will help alleviation, early detection and prevention, and cure of disease.

references

[1] A more comprehensive discussion of Intellectual Property for non-specialists may be found in Chimia 2000, *54*, No. 5 (pages 272 –324)
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