PATENT PROTECTION POLICY IN THE THERAPEUTIC GROUP OF STATINS

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ABSTRACT
This study aimed to analyze the patent protection status at the worldwide level of the medicines in the therapeutic class HMG-CoA reductase inhibitors (statins) and their patent strategies for the period 1995-2008. The three step internet patent database search methodology was developed and applied for published patents during the period 1995 – 2008. Performing the three step patent publications searching methodology, we found and classified 71 patents from 7 patent classes for 5 international non-proprietary names (INN). There were 31 patents for atorvastatin, 18 for fluvastatin, 11 for pravastatin, 32 for simvastatin and 32 for rosuvastatin. Typically for the group, the patents had been granted either for therapeutic activity or application, very often combined with diuretics, produced by other innovators, owners of the patents. All of the patents were protected with European patents, USA, Australian patents and countries outside the World Trade Organisation (WTO), which have not recognised the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement).
The intensity of patent protection policy for the analysed INNs within the statins group during the years after the first granted patent showed that the period of the first six or seven years was relatively calm and the patent activity was slow. Then the patent activity started to increase tremendously around the time of expiration of the first granted patent and in the last two years it declined for some of the molecules insignificantly, while for others, sharply as in the case of atorvastatin and pravastatin respectively.
The study showed that a variety of factors influence the patent protection policy of pharmaceutical manufacturers, such as the time of discovery, application of product, disease priority, technologies, chemical structure of the molecules etc. We found that therapeutic competition is more important than the generic ones for creating the patent profile of an INN, which is in contrast with the beliefs that the patent protection policy affects mainly generic companies.


Keywords: medicines patents, patent protection policy, statins

Introduction
The development of new chemical entities and formulation of the innovative medicinal products ensures new therapeutic option for poorly treated conditions or diseases (17). At the same time the entrance of generic medicines after patent expiration of the innovator supports the sustainability of healthcare provision and contribute to maintaining control over the pharmaceutical expenditures. The patent protection policy of pharmaceutical manufacturers is a critical milestone for both types of manufacturers (innovative or generic) in terms of market penetration, product lifecycle and patients’ access to effective and affordable medicines (9, 10, 17).

In 1995 with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), the patent period was extended to 20 years and began to influence the pharmaceuticals patent protection policy. In respect with this regulatory measure the peoples’ access to medicines started to be widely discussed in the pharmaceutical literature (1, 4).

The pharmaceutical patent protection policy has been researched from different aspects. One of them is the real life protection of the main patent, usually issued to main active formulation and the chemical class to which it belongs. Other aspects of studying are the patent policy of the companies or differences among the countries and their influence on the generic entries (5, 16, 22). A lot of studies are focused on the effect of the generic medicines entry on the pricing and reimbursement of medicines (8, 23) and on the utilization of medicines after the patent expiration (2, 18, 19, 20).

From the pharmaceutical perspective, the real life of a new medicine starts after the establishment of its therapeutic posology during the clinical trials and granting the international non-proprietary name (INN) through the World Health Organisation (WHO) procedures (25). Before that, the product is not recognized by the pharmaceutical companies as potential competitor due to usage of coded names of the main active formulation instead of the INN. Due to this fact, the patent search and detection of any additional protection policy of the originator or therapeutic competitors is sometime complicated and not pharmaceutically reasonable.

During the last three decades a tremendous progress has been made in the antihyperlipidemic therapy through the introduction of new therapeutic classes (3). The faster development of new molecules has created whole medicine families and increased the competitiveness, thus posing challenges to the originator and generic manufacturers to create sophisticated patent protection on the one hand, and
on the other, to quickly penetrate the market and to increase patients’ access to low-priced generics (7, 13, 14, 15).

Therapeutic strategies for the prevention of atherosclerosis are essentially based on the correction of major risk factors, such as elevated plasma lipid levels or arterial blood pressure. Hypercholesterolemia is one of the major risk factors for coronary heart disease. In the last years, a new class of agents was developed that specifically inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. A number of clinical studies have demonstrated that HMG-CoA reductase inhibitors (statins), either alone or in association with other hypolipidemic drugs, can induce regression of vascular atherosclerosis, decrease the incidence of coronary heart disease, and improve survival in coronary heart disease patients.

Statins are one of these therapeutically interesting groups of medicines with increasing market sales all over the world and a lot of brands with well established chemical and pharmacological characteristics (7, 24).

In this study we aimed to analyze the patent protection status at the worldwide level of the medicines in the therapeutic class HMG-CoA reductase inhibitors (statins) and their patent strategies for the period 1995-2008.

The main research questions addressed in this study are the following:

1. What types of companies (originators and generics) are claiming the patents for the INNs from the observed group?
2. Is there any difference among the originator and generic companies patents claims?
3. What is the intensity of patent policy before and after the first patent expiration?
4. What is the specificity of the patent policy according to the International Patent Classification (IPC) and territory?

Materials and Methods

The three step internet patent database search methodology was developed and applied for patents published during the period 1995 – 2008.

The first step was searching the “Orange Book” (21) to clarify the date of issue of the first patent and DrugPatentWatch database for checking the date of valid patents’ expiration (11). The second step was searching the Worldwide Patent Database via the options provided in the European Patent Database (EPO) (12) by using the INNs of the observed medicines in the therapeutic group as a key word. The third search step was an expanded search via the INPADOC patent family system of the European database for clarifying the additional publications of the patents per territory. The INPADOC system connects EPO with more than 70 countries and legal status data for more than 40 patent authorities.

The information for the appearing patents was then systematized according to the following criteria – the description title of the patent, inventor, applicant, IPC class, publication number of patent/publication date, and all INPADOC publications connected with the first description title.

The collected information was analyzed by classifying the patents according to the IPC classification code into the following groups – formulation patents (C07D – chemical active substance), formulation or process patents, chemical or pharmaceutical technology (C07C, C07D, C07K, C07F, C12K), application patents (A61K – preparations for medical, dental or toilet purposes), therapeutic activity (A61P – therapeutic activity of medicinal preparations or chemical compounds). Most of the patents are for more than one IPC code or subgroup due to the complexity of structures or processes.

For all patents the year of first publication was compared with the year of the first patent issued, territory covered, and date of patent expiration for particular INNs.

Results and Discussion

Performing the three steps patent publications searching methodology, we found and classified 71 patents from 7 patent classes for 5 INNs. There were 31 patents for atorvastatin, 18 for fluvastatin, 11 for pravastatin, 32 for simvastatin and 32 for rosuvastatin (Fig. 1).

Fig. 1. Total number of issued patents per INN.

For atorvastatin there were granted a total of 31 patents assigned to the following IPC classes: 42 patents to class A61K (Preparations for medical, dental or toilet purposes), 5 patents to A61P class (Therapeutic effect), 25 patents to class C07D (Heterocyclic compounds) and 8 patents to other classes. The granted patents found protected the chemical structure (n = 5), method for synthesis of atorvastatin (n = 6), its precursors (n = 5) and pharmaceutically tolerable salts (n = 7), crystalline and amorphous forms of atorvastatin (n = 10), methods for obtaining them, pharmaceutical formulations (n = 12) and others. There were patents for therapeutic activity as the entire class of statins, and second applications and combinations with
Ca-antagonists. Most patents had been issued from more than one class.

According to the patent territorial scope 11 patents were issued by the World Intellectual Property Organization (WIPO); 20, by the European Patent Organisation (EPO); 8, by the U.S. Patent and Trademark Office (USPTO). Six patents were issued by the Bulgarian Patent Office (BPO). Most of the patents found were held by Pfizer (USA) – for the main ingredient (n = 2), and for combinations with other therapeutically active ingredients (n = 4).

Eighteen patents had been granted for fluvastatin. Out of them, 30 patents were from class A61K, 6 patents were from class A61P (Therapeutic effect), 10 patents were from class C07D, and one patent, from another class. The patents found protected the chemical structure (n = 5), method of synthesis of the crystalline form (n = 3), amorphous form (n = 4), pharmaceutical formulations (n = 3) and others. There were patents for combined pharmaceutical formulations, and patents for therapeutic use (n = 3).

According to the territorial scope of the patents for fluvastatin, 6 of the patents had been issued by the WIPO; 8, by the EPO; 9, by the USPTO. No patent had been issued by the Bulgarian Patent Office. The largest number of patents were held by Ciba SC Holding AG (n= 6) – the innovator producer, and by TEVA Pharmaceuticals (n= 4) – the generic producer.

For pravastatin there was a total of 11 issued patents. Out of them, 9 patents were from class A61K, 6 patents from class C07C (Acyclic or carbocyclic compounds). No patents were found in class A61P (Therapeutic activity of chemical compounds or medicinal preparations) or class C07D (Heterocyclic compounds), but 5 patents had been granted in class C12P (Fermentation or enzyme-using process to synthesize a desired chemical compound or composition or to separate optical isomers from racemic mixture). The patents found protected the chemical structure (n = 3), methods of isolation and purification of pravastatin (n = 2), pharmaceutical formulations (n = 3), and other therapeutic indications.

According to the territorial scope of the patents for pravastatin, 7 of the patents had been issued by the WIPO; 14, by the EPO; 5, by the USPTO; and 1, by the Bulgarian Patent Office. The largest number of patents was owned by Bristol Myers Squibb Co, as innovator producer and three other generic companies.

For simvastatin there were granted a total of 32 patents. Some of them covered more than one category and thus separated per classes, there were 45 patents from class A61K, 25 patents from class C07D (Heterocyclic compounds), 4 patents from class A61P, one patent from class A44C, two patents from class C07C and one patent from class C07F (Acyclic, carbocyclic or heterocyclic compounds containing different elements). The patents protected the synthesis (n = 10), purification (n = 4), process of preparation of methyl analogues (n = 2), formulations for prolonged release (n = 3), therapeutic use of combined formulations with telmisartan, amlodipine, ezetimide and fenofibrate (n = 5). According to the territorial scope, 16 patents had been issued by the WIPO; 17, by the EPO; 17, by the USPTO, and 3 patents, by the Bulgarian Patent Office. The biggest number of patents was owned by the innovator Merck & Co., Inc., as well as by generic company TEVA.

Fig. 2. Number of issued patents per territory of protection.

For rosuvastatin there had been issued 32 patents. Of these, 24, from patent class A61K; 9 patents, from class A61P; 2 patents, from class C07C; 44 patents, from class C07D; 5 patents, from class C12P. The granted patents were mainly for chemical structure (n = 4), methods of synthesis of the basic structure and patents for the synthesis of precursors (n = 16), patents for crystalline and amorphous form of rosuvastatin

<table>
<thead>
<tr>
<th>IPC class</th>
<th>atorvastatin</th>
<th>fluvastatin</th>
<th>pravastatin</th>
<th>simvastatin</th>
<th>rosuvastatin</th>
<th>Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>A61 K</td>
<td>42</td>
<td>30</td>
<td>9</td>
<td>45</td>
<td>24</td>
<td>30 (14.54)</td>
</tr>
<tr>
<td>A61 P</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td>9</td>
<td>6 (2.16)</td>
</tr>
<tr>
<td>C07 C</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>3.67 (2.08)</td>
<td></td>
</tr>
<tr>
<td>C07 D</td>
<td>25</td>
<td>10</td>
<td>25</td>
<td>44</td>
<td>26 (13.92)</td>
<td></td>
</tr>
<tr>
<td>C12 P</td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>5 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td></td>
<td>1</td>
<td></td>
<td>4.5 (4.95)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1

Number of issued patents per IPC class

BIOTECHNOL. & BIOTECHNOL. EQ. 25/2011/4
(n = 6). Of particular interest are patents for formulation and therapeutic activity, such as rosuvastatin combined with beta-blocker for the treatment of atherosclerosis (n = 4). According to the territorial scope rosuvastatin had 17 patents issued by the WIPO; 9, by the EPO; 20, by the USPTO. The first patent was granted in 2003 to Astra Zeneca (GB), which was the company with the biggest number of patents.

Typically for the group, the patents had been granted either for therapeutic activity or application, very often combined with diuretics, produced by other innovators, owners of the patents. All of the patents were protected with European patents, USA, Australian patents and countries outside the WTO, which have not recognised the TRIPS agreement (Fig. 2).

The intensity of patent protection policy for the analysed INNs within the statins group during the years after the first granted patent is presented in Fig. 3. The period of the first six or seven years was relatively calm and the patent activity was slow. Then the patent activity started to increase tremendously around the time of expiration of the first granted patent and in the last two years it declined for some of the molecules insignificantly, while for others, sharply as in the case of atorvastatin and pravastatin respectively.

In the beginning of the observed period and for the older products the generic companies were usually grated patents for application (A61K). During the last years after 2000 we observed that the generic companies started to follow the originators’ policy and to increase the research and protection of different types of derivatives like salts, intermediates, polymorph forms etc. of the main formulation near to patent expiration period. This is due to the solubility of the derivatives, which is important for the technology process of the dosage forms, or probably due to the results of the clinical trials for bioavailability of derivatives. Thus the competition is transferred to therapeutic competitor which was exactly the situation observed in our study.

The highest number of patents granted for IPC class A61K (preparations for medical dental or toilet purposes) was probably due to the fact that this class is related to the possibility of the formulations to treat not only one symptom. Therapeutic activity (A61P) began to be protected since 1998 which could explain the small number of patents granted in this IPC class.

Per territory protection the activity was similar with regard to the preference countries and followed the market dynamics and emergence. All products have been claimed for protection in the US, EPO, India, China, Australia, Canada, and Japan. The countries outside the WTO (Russia, South Africa etc.) became patent priority in the last 10 years.

The therapeutic competitors, which are the products similar to the first original molecule, appeared to be more important than the generic ones within the statins group. The first therapeutic alternative appears earlier than the generic competitors. Thus the real life time of the main patent is therapeutically shortened and market monopoly is limited not on the basis of the competition but due to the intensive work of the other innovators.

For some of the products, additional factors might have played an important role in formulating the company patent protection policy. Further studies are necessary to explore the effects of the market indicators on the patent protection policy.

The study limitation is the search in the EPO database for worldwide patent presence by using the INN of the products, thus omitting some of the main patents. To overcome this limitation we searched in addition the Orange Book and Patent watch databases.

The macro level of comparison among the molecules within the group allows to reveal the specificity and similarities in the patent protection policies of the pharmaceutical manufacturers. Specificity in the behavior of the originator companies is that they are more oriented towards protection of therapeutic combinations among the active substance and possible therapeutically compatible products, as well as towards the protection of new therapeutic use. The generic manufacturers are oriented towards the protection of new pharmaceutical formulations of the main active substance.
as well as towards protecting the changes in processes of synthesis or manufacturing.

The similarities refer to the fact that both types of companies became more active in patent protection in a little while before the main patent expiry.

Conclusions
Our study showed that a variety of factors are influencing the patent protection policy of pharmaceutical manufacturers, such as the time of discovery, application of product, disease priority, technologies, chemical structure of the molecules etc.

We found that therapeutic competition was more important than the generic one for creating the patent profile of particular INN, which is in contrast with the beliefs that the patent protection policy affects mainly generic companies.

We also confirmed the results from similar studies that around the date of main patent expiration usually the activity of both originators and generic companies for granting new patents increases, probably due to the attempts to increase the market monopoly of the product or to prevent other companies from market penetration.

REFERENCES
1. Agreement on Trade-Related Aspects of Intellectual Property (15 April 1994) LT/UR/1C/1IP/1art.