Drug Discovery Today • Volume 00, Number 00 • October 2014 PERSPECTIVE

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Drug repurposing and the prior art patents of competitors

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Drug repurposing (i.e., finding novel indications for established substances) has received increasing attention in industry recently. One challenge of repositioned drugs is obtaining effective patent protection, especially if the 'novel' indications have already been claimed by competitors within the same drug class. Here, I report the case of patents relating to phosphodiesterase type 5 (PDE5) inhibitors. Patentees of later-filed patents on novel indications (even when they could not observe prior patenting of their direct competitors) filed patents for which patent examiners did not see the prior-filed patents of the competitors as relevant prior art, whereas these follower patent applications often failed because of other reasons.

Introduction

Searching for new uses and/or indications for established drug substances is known as redirecting, repositioning, reprofiling, or repurposing of drugs [1]. The latter term is used here. The benefits of such an approach are straightforward: given that the substances have passed safety tests and have shown desirably pharmacokinetic and pharmacodynamic characteristics [2], time-to-market and the costs involved are lower compared with developing new molecular entities (NMEs, i.e., novel substances that have not been approved for human treatment), as costs for NMEs increase, while the amount of approved NMEs remains about constant [2,3]. Eighty-four percent of all drugs sold in the USA address more than one indication, whereas an additional 6% have novel indications under development [4]. In addition, there are numerous examples of successful drug repurposing (e.g., [1,5–7]). Overall, drug-repurposing approaches were estimated to be accountable for industry revenues of approximately US$20 billion in 2012 [8].

Given the high costs involved in clinical drug development, patent protection is particularly relevant [2,6,9]. Companies typically file a range of new patents over the life cycle of a product to extend their exclusivity, often through line extensions (e.g., novel formulations addressing older patients in contrast to pediatric patients) and repurposing [10–12]. In the latter, they can even claim the substances made by their competitors from the same drug class* to block the development activities of those competitors [12].

The patent system and patenting for repurposing

Before assessing the impact of such approaches on drug repurposing, a few clarifications about the patent system are in order.† Patentees define an invention via so-called 'patent claims', which describe the invention as a combination of features, jointly defining the scope of the patents. A patent application remains secret for 18 months before it is published, and patent examination usually then occurs. During patent examination, examiners assess the novelty of the claims and their nonobviousness (i.e., the invention might not be obvious to the 'skilled person in the art'). In case of very similar patent filings, the earlier one would be granted. Often, patent applicants try to maximize the breadth of their patent by claiming topics broadly, which are then narrowed significantly during examination. To do this, patent examiners search prior art (i.e., patents, scientific literature, etc.) to assess the novelty and nonobviousness, building

* A drug class refers to structurally similar molecules with similar physiological effects.

† Although patenting rules differ among countries, the following procedures broadly describe the practice in the USA and Europe.

1359-6446/06/$ - see front matter © 2014 Published by Elsevier Ltd. http://dx.doi.org/10.1016/j.drudis.2014.09.016

Please cite this article in press as: Sternitzke, C. Drug repurposing and the prior art patents of competitors, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.09.016

on published sources (and unpublished ones that might be on file with the same patent office), referencing back to them in their examination reports.

Although patenting the same invention twice is forbidden, a later patent might be covered by the claims of an earlier one.[‡] An illustrative example is a substance patent and a patent filed later claiming the use of that substance for a medical indication. Although both patents belong to different parties, the substance patentholder is unable to use the substance for the particular indication described in the later patent, and the owner of the later patents is unable to use the substance from the earlier patent without permission (regardless of the indication).

For many companies, being limited in their operations by owning such dependent patents is undesired, and it can deter them from commercializing their affected products. One way to assure freedom to operate is early defensive publishing and/or strategic disclosure, that is, publishing topics broadly (giving, for instance, many examples of use) either anonymously or attributably (linked to the publisher) to create prior art. This can occur in an easily accessible form (as a scientific publication, database entry, etc.) or hidden (e.g., as a dissertation in a foreign language) [13,14]. As a consequence, only more specific, and narrower, patents filed later (by competitors or by the same company) might get granted, with limited exclusionary power, which can then be circumvented more easily.

Looking at patent practice in pharmaceuticals, and into activities occurring within a class of drugs, a patent claiming the use of a particular substance for a specific indication might be nonobvious if the use of another substance from the same class has been described for the same indication before. In fact, '[. . .] many composition of matter compound patents claim a very large number of uses for the compound, even indications well beyond those initially demonstrated by the data, and therefore the 'new' indication may be previously disclosed in the compound patent simply by referring them as possibilities.' ([15] p. 43). Hence, these earlier filings assure freedom to operate, and eventually enable broad patent protection to be obtained.

However, owners of such follow-on drugs inside a class might change the formulation or dosing of repurposed drugs [5,6,15,16] and, by doing so, assure their novelty and nonobviousness. Proactively adjusting the formulation or dosing to outmaneuver earlier prior art from direct competitors could mean that followers might frequently receive patents on their inventions even in light of earlier patents claiming the same indication inside the same drug class. However, should companies become proactive, or do they 'naturally' file such patents?

Methodology, field of research, and data

The assessment of proactive versus 'natural' filing behavior can be accomplished by taking into account the time-lag of 18 months, during which a patent application remains unpublished. If two competitors file patents for the same indication within 18 months of each other, and patent examiners do not consider the earlier-filed application as constituting prior art, then this would favor the 'natural' filing hypothesis.

The data for the analysis build on [12] who found the above-mentioned blocking activities, and relate to PDE5 inhibitors. Only substances were considered for the analysis that had been approved in the USA by 2011, namely sildenafil, vardenafil, and tadalafil. These substances were searched in the Chemical Abstracts (CA) database using the CAS number, which is a unique ID for these substances that is supposed to be assigned to any chemical patent document, to identify all relevant patent filings. To elicit which content was in fact claimed (unbiased by examination results), the analyses were primarily based on patent applications for assessing the patentability of the later patents, and on granted earlier patents to assess the legal dependence of the follower patents.

The results from the search in the CAS database were transferred to the Minesoft PATBASE database to determine which of the patents found belonged to the same patent family (i.e., were based on the same idea). Manual data cleaning took place, eliminating patents that, for example, mentioned these substances coincidentally. Patent claims were investigated in more detail for each published US patent document and the first patent document of a patent family [either an application at the European Patent Office (EPO) or via the Patent Cooperation Treaty (PCT)] to identify the nature of the claims (focusing on substances, dosing and/or formulations, indications, etc.). From a total of 72 patent families stemming from Pfizer, Lilly, and Bayer, 58 patent families comprised indications and were analyzed. In addition to the above-mentioned steps, examination reports from the Patent Application Information Retrieval (PAIR) system of the USPTO (where not available, from the EPO) were screened for the selected documents to elicit references made by examiners from later applications to earlier ones to assess their patentability.

To further investigate the indications mentioned within the patent documents, the indications found were manually structured according to the hierarchical MeSH classification (Medical Subject Headings, a controlled thesaurus provided by the US National Library of Medicine). The MeSH thesaurus provides alternative terms and/or synonyms for identical indications, while its hierarchical structure also enables one to assess whether the terms used refer to narrower or broader indication categories, such as cardiovascular diseases in contrast to its subcategory heart failure. Taking such a hierarchy into account is important for assessing the novelty of an indication. For instance, when treatment of diseases has been claimed on a superior level, it is unlikely that treatment of a disease on a lower level can be still claimed successfully. However, this is not the case the other way round, because higher-level diseases can involve more mechanisms that are relevant to a disease. In some instances, applicants used a continuation-in-part application (CIP), which enables one to add novel matter to an older, still pending patent from the same patent family. However, examiners do not consider older content from the same patent family as novelty destroying or nonobvious; therefore, the new priority date for the newly added content was used, as indicated with the term 'CIP' in the patent number column in Table 1.

Results

In total, approximately 180 different indications were mentioned in the data set with, on average, approximately six indications in every US patent document (which have at least one indication), and each indication is mentioned in approximately 2.5 patent families. Four patent families had more than 40 indications and might have been filed defensively to establish freedom to operate, because none of them was granted. Fifty indications were mentioned by at least two competitors, from which ten patent–patent pairs for eight indications were filed within a timeframe shorter than 18 months (Table 1), with one involving autoimmune diseases and depression simultaneously (as indications overlap, the latter relation is indirectly also represented by the last two patent pairs). Three early patents occurred twice, whereas among the follower patents, one appeared four times in this role.

In eight of the ten patent–patent pairs, the follower patent was not granted. Overall, Table 1

[‡] As long as the later invention is novel and nonobvious in light of the earlier one, the Patent Office is not concerned with this situation.

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