Current patenting trends for biologics versus small molecules

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Various factors are making it even more difficult for the pharmaceutical industry to develop small molecules that can be subsequently brought onto the market as drugs [1]. Accordingly, as is well documented, the pharmaceutical sector has increasingly focused attention elsewhere in the search for alternative approaches [2], notable examples of which include antibodies, novel vaccines, genetic medicines and protein-based alternatives to small molecules. Yet, in spite of such advances, small molecules still appear to be dominating the market place. This raises the question as to why more biological-based treatments, or ‘biologics’, do not appear to be on the market. As patent protection is key for the commercial viability of a drug, it is worth considering whether or not the answers to this question lie in the patent databases.

Patenting process

While different patenting strategies are used by different organizations, there are several common elements to the conventional patent filing mechanisms adopted by pharmaceutical organizations. In particular, with many companies conducting research in similar fields, it is important to identify potentially valuable candidates early and file patent applications as soon as possible. While this stops competitors exploiting such research for commercial purposes, patent applications are filed well before an approvable product has been developed. Consequently, in the relatively small number of overall cases where a drug does make it to market, much of the drug's patent lifetime has expired. As a result of this, promising treatments that take too long to develop may be abandoned, since without a patent monopoly, research costs cannot be recouped.

Therefore, it is not only important to identify new compounds early, but also to get those compounds to a sellable, final product as quickly as possible. As such, any technology that is particularly well suited to swift optimization will likely be a great source of interest to pharmaceutical innovators. Such factors must play an important role in the allocation of funding to particular technologies and may be reflected in the number of patent filings.

Although the shift towards biologics has been known for some time, it is unclear whether or not this shift is being reflected in the filing of patent applications. As such, various patent databases have been analyzed to see what changes, if any, seem to be happening in the filings of patents for small molecules and biologics.

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Methodology

First, in order to distinguish between the subject matter of those patent applications relating to ‘small-molecule’ drugs and those patent applications relating to ‘biologics’, we defined each of these titles in term of the appropriate International Patent Classification codes (IPCs) [101]. During the prosecution of a patent application, the invention for which protection is sought is searched to assess to what extent a patent should be granted, and is assigned by the patent office one or more IPCs that describe the particular technological fields to which the invention relates. We created a list of relevant IPCs for both ‘small-molecule’ drugs and ‘biologics’ and analyzed the resulting applications.

As the development of a drug can take many years, data were collected from as far back as the late 1980s, typically looking at the annual number of filings in the relevant categories. In order to improve the relevance of patent filing data acquired, we also restricted our search to those applications with an equivalent US, European or international patent application.

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Our results suggested that the number of patent applications filed by leading pharmaceutical companies for biological drugs has exceeded those for small molecules for at least the last 15 years, but it also showed that this gap has appeared to be widen since 2005.

Investigation into patent filing activity between 2005 and 2009 has revealed that despite an overall decline in the number of patents filed, the gap between the numbers filed for biologics and small molecules has widened significantly – by approximately 60%. In 2008, there were around 9000 patents filed relating to biologics compared with just over 2700 for small molecules.

When we looked into some of the pharmaceutical industry’s largest organizations according to turnover [102], this showed that the number of patents filed for biological drugs fell by an average of 20% in the 3 years to the end of 2009, compared with an average fall of over 40% for small molecules.

Discussion

These data are interesting as despite more patents being filed overall in the biological field, the presence of biological treatments on the market is still overshadowed by small molecules. This may be explained by many factors, including the way IPC classifications are allocated. Additionally, as patent applications are not

published earlier than 18 months after their filing date, it is possible that more applications are being filed, but are being allowed to lapse prior to publication. This may be due to the technology having no commercial promise, or a change of heart on the part of the applicant who may decide to keep information secret.

The decrease in small-molecule filings could stem from a variety of reasons. As the number of molecules already in the published literature (patent and non-patent) has exploded over the last few decades, it will have become harder to find clear chemical space in which to design potentially patentable, drug-like molecules. In addition, the high attrition rate of small-molecule candidates may have dissuaded big pharma from investing as much in small-molecule programs in the past. It is also possible that biologics are now seen as a more important development focus for big pharma, perhaps because biologics are more difficult for generics to copy once the patents expire.

Small molecules still dominate the market, although this dominance is likely to decrease over time. Biological drugs are still in their relative infancy, but the pipelines of big pharma are increasingly focused on such products – this focus should feed through into the market over the next decade. Another reason for the sustained prevalence of small molecules is that the industry has built up significant infrastructure and human resources geared towards the development and production of such drugs. This will not disappear overnight. Big pharma also has the potential to ‘muscle-in’ on the generics market for small molecules, and we are beginning to see increased blurring of the innovator/generic split, as erstwhile innovators set up (or acquire) their own generics operations.

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Additionally, the major patent offices are becoming more stringent in their examination of the inventiveness of small molecules. It is often the case that some unexpected benefit needs to be shown compared with known compounds, and this hurdle of ‘unexpectedness’ is becoming harder to get over. It is also probable that the degree of exemplification of groups of small molecules required demonstrating a ‘class effect’ is increasing; this increases costs and often tends to lead to a restriction of the breadth of patent claims. The change in biologics filings is likely to be related to the significant advances in molecular biology/pharmacology over the last couple of decades, including the human genome project and the

rise of genetic medicine. A far greater understanding of receptor–target structure and function has been amassed, and improved techniques for preparing biopharmaceutical candidate molecules have provided the ability to screen large numbers of possible biologics candidates. Big pharma has increasingly been investing in such programs, and a greater number of biopharmaceutical candidates have inevitably led to more patent filings.

Conclusion

It is very difficult to make accurate predictions based on these findings, especially in high technology areas such as drug discovery where significant shifts can occur unexpectedly. Instinctively, one would expect the gap to widen further in favor of biologics filings, simply because there is likely to be more ‘virgin snow’ in this area. Further, as the regulations governing drug approval have historically been geared towards small molecules, there are likely to be changes in the regulatory system to accommodate for diverse, new biologicals (impacting on patent filings).

Such an increased regulatory burden and the increasing demands in showing patentability are likely to further increase development costs. This may lead to more consolidation in the industry, as pipelines are ‘bolted-on’ to reduce costs. It seems logical to conclude that, in time, patent filings in the biologics area will encounter similar challenges to those seen with small

molecules (i.e., where the published literature becomes more extensive, making it more difficult to show inventiveness). This is already beginning to affect some fields, such as antibody technology.

One important twist to such predictions, at least for UK-based companies, is the forthcoming ‘patent box’ legislation [103]. This will enable pharmaceutical companies to benefit from a significantly reduced rate of UK corporation tax on profits derived from patented products. This could lead to increased patent filings for relatively narrow subject matter (small molecule or biologics), simply to ensure that the eventual product can benefit from the reduced tax rate. Another factor to consider is that more and more people around the world are entering the ‘middle classes’, and the health-care demands and expectations of this group are high [3]. As such, demand for effective new pharmaceuticals should remain high, and this should help to underpin patent filing activity across ‘big pharma’.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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