International

Patent protection for new uses of known drugs

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"The most effective way to move from target identification to the clinic is to identify already approved drugs with the potential for activating or inhibiting unintended targets."
(S Dakshanamurthy *et al, J Med Chem*, 2012, 55(15), pp6832–6848.)

Introduction

Research into new medical uses of known drugs offers the most cost-effective avenue for discovering new therapies today. A famous example of inventions in this category is the case of Viagra (sildenafil citrate): originally developed as a drug for treating pulmonary hypertension and angina, it was only during Phase I clinical trials that unexpected side effects in male patients were observed. This led to the development of Viagra for treating erectile dysfunction — a chance discovery that secured almost $2 billion a year in net sales for Pfizer before loss of exclusivity (http://on.pfizer.com/ylTLXn).

While serendipity can often play an important part in such discoveries, more systematic efforts are now being made to determine possible new uses for known drugs.

If a drug has already been tested safely on animals and found to be non-toxic for humans, it can offer research opportunities with reduced risk. A 2011 publication from the Biotechnology Industry Organisation reported that over 35% of drugs being developed for use in humans fail toxicology screening or Phase I clinical trials; therefore, focusing research on drugs which have already cleared those hurdles has obvious attractions.

However, as with all research in the pharmaceutical field, robust patent protection is essential to ensure a reasonable return on research investment. This chapter explores how well the patent system has risen to this challenge.

A fragmented global picture

Although the World Trade Organisation Agreement on Trade-Related Aspects of IP Rights swept away many bars to the patenting of pharmaceutical products *per se* (eg, in India, Pakistan and Brazil), there has been little subsequent effort to harmonise the availability of patent protection for new uses of known drugs. Rather, pharmaceutical and biotech companies are presented with a fragmented global picture. Most countries allow such patents, but a small minority are hostile.

In most developed countries, robust patent protection is available for new uses of known drugs. The European Patent Office (EPO) has allowed patents for such inventions since the 1980s. A similarly sympathetic view is taken in many countries throughout the world, including Australia, Canada, China, Japan, South Korea, Indonesia, Israel, Mexico, Nigeria, New Zealand, the Philippines, Russia, Singapore, South Africa, Taiwan, Thailand, Ukraine and the United States.

Some developing countries, however, remain firmly opposed to patent protection for new uses of known drugs. India has emerged as the standard bearer for such countries, with a statutory prohibition (Section 3(d) of the Indian Patents Act). In Brazil, approval from the national health surveillance agency is required before a patent can be granted in the pharmaceutical field, and the agency has not allowed patents for new uses of known drugs since 2004. A similarly unsympathetic

approach to such inventions is taken in Argentina, the present and former countries of the Andean Community (Bolivia, Colombia, Ecuador, Peru and Venezuela) and the states of the Gulf Cooperation Council.

Despite these restrictions on patent protection in some emerging economies, the availability of patent protection in developed countries can enable a decent return on investment in this area. Further, as discussed below, many developed countries are actually increasing the scope for patents of this nature, which may create attractive new areas of research.

Patent protection for more incremental developments?

There is a welcome development in this field that opens up new opportunities. Many developed countries are now extending the availability of patent protection beyond situations where a known drug is developed to treat a new disease. Increasingly, patent protection is becoming available for modifications to existing therapies, such as variations in the frequency, size and timing of the treatment.

The leading case in Europe in this regard is Decision G2/08 from the EPO Enlarged Board of Appeal, the EPO's highest judicial body. In that case the board held that in principle, a patent should be available for the use of a known drug in treating a disease for which it has already been used, provided that there is a new and non-obvious aspect to the means by which treatment is effected. The board set out a non-exhaustive list of potentially patentable developments in this area:

- a new and inventive dosage regime;
- a new and inventive mode of administration;
- treatment of the same disease by targeting a different etiology; and
- a new patient group, which can be treated by the known substance or composition.

These four potentially patentable developments are discussed in more detail below.

Dosage regime

The dosage regime associated with a particular therapy can have a profound effect on the efficacy of the treatment. The regime may include, for example, the amount of drug administered, frequency of administration and time of day administered. In the case above, the only novel aspect of the invention was that the drug was to be administered "once per day prior to sleep". The board confirmed explicitly that this feature could, in principle, form the basis of a valid patent.

Following that case, Merck & Co Inc sought to enforce a patent based on a new dosage regime for finasteride for treating androgenic alopecia. The novel feature claimed by Merck's patent was that the finasteride is provided in a dosage amount between approximately 0.05 milligrams (mg) and 1.0mg.

In 2008 the Court of Appeal of England and Wales upheld Merck's patent. The equivalent judgment of the German Federal Court also concluded that a dosage regime could, in principle, be patentable (although it found Merck's patent invalid for other reasons). In parallel litigation proceedings in France, the civil courts came to the opposite view, finding that a dosage regime was not patentable because it was "plainly not" a second therapeutic application. However, it may well turn out that in future national tribunals in Europe will defer to the opinion of the EPO Enlarged Board of Appeal.

On the whole, the availability of patent protection for new dosage regimes is becoming well established in Europe. Such patents are also granted by patent offices in many other developed countries, including the United States, Japan, Russia, Australia and New Zealand. Research-based pharmaceutical companies should consider carefully whether and when to protect the results of clinical research into dose optimisation.

Mode of administration

An example of a patentable invention along these lines is that found to be allowable by EPO Board of Appeal Decision T51/93. In that case a patent was upheld for a known drug for treating a known condition by subcutaneous administration, where the drug had previously been applied only by intramuscular administration for that condition.

Patent protection should therefore be considered whenever it is found that a known drug can advantageously be delivered in a new way, even when there is no change to the formulation.

Targeting different etiology

Etiology refers to the cause or origin of a medical condition. It has long been the case that merely identifying the mechanism by which a known drug achieves a known effect cannot constitute a patentable invention. However, a finding that a known drug can target a known disease via a different etiology can yield a patentable invention if the finding leads to new considerations which will apply when diagnosing the disease.

One case which illustrates this point is EPO Technical Board of Appeal Decision T836/01. In that case, human interferon-ß2 was claimed for use in influencing tumour/cancer cell growth and differentiation. A prior publication disclosed the use of interferon-ß2 for the purpose of stimulating the immune system of patients undergoing chemotherapy (ie, the same drug for treating the same disease). However, the claimed method involved direct treatment of the cancer cells with interferon-ß2, whereas the previously disclosed method involved an indirect effect via the immune system.

The board upheld the patent at issue on the basis that the particular therapy claimed could lead to commercial applications which were truly new, since it identified a completely new clinical situation. Subsequent EPO decisions have taken a similar approach (eg, T1642/06).

Therefore, patent protection should be considered whenever ongoing research provides new information about the biological activity by which a known drug achieves its therapeutic effect.

Patient group

The possibility of having claims granted for the use of a known drug in treating a specific patient group offers significant scope for commercially valuable patent protection.

As early as the 1980s, a patent for an attenuated virus for use in protecting maternally immune (sero-positive) pigs against Aujeszky's disease was found to be allowable by the EPO (T19/86). A similar therapy had previously been used to treat sero-negative pigs. The therapy claimed was considered to be treatment of the same disease but in an immunologically different population, and therefore patentable.

Subsequent EPO decisions have confirmed the principle that a new patient group can constitute a patentable invention. In particular, in a more recent decision (T1399/04) a patent was allowed for a combination therapy for treating chronic hepatitis C in previously untreated patients with a specific virus load and particular form of the virus. Treatment of hepatitis C with the particular combination of drugs was already known. Following T19/86, the board upheld the patent, even though it seemed likely that the known treatment of chronic hepatitis C might inevitably have involved the treatment of some patients covered by the new patent.

Patent protection for the treatment of new patient groups is therefore available at the EPO. Patents for such inventions can often also be obtained in the United States, Japan, Australia, New Zealand and possibly China.

The possibility of patent protection in this area has the potential to be extremely valuable. It is increasingly found that drugs have different efficacies in different patient groups. Advances in the field of pharmacogenomics mean that specific genetic mutations in patients can now be linked with their susceptibility to certain diseases and/or their response to certain courses of treatment.

An example here is the drug gefitinib. This drug has particular efficacy in treating non-small cell lung carcinoma patients with a specific mutation in their epidermal growth factor receptor gene. This mutation is found in only 10% to 15% of non-small cell lung carcinoma patients, particularly Asian, female patients. Testing for the specific mutation allows selective targeting of patients who will respond well to gefitinib. Patients without this mutation fare better on standard chemotherapy.

No discussion on this topic would be complete without mention of the March 2012 decision of the US Supreme Court in *Mayo Collaborative Services v Prometheus Laboratories, Inc*, in which patent claims for methods for optimising the dose of a drug were held to be ineligible as claiming 'laws of nature'. At the time, there was concern that this reasoning might extend to patents for identifying patient groups. However, there is good reason to believe, both from the *Prometheus* decision itself and from subsequent case law, that enforceable patents centred around patient

groups may in fact continue to be available in the United States.

The possibility of patent protection for the treatment of particular patient groups offers significant scope for companies to protect the results obtained from costly clinical trials. It will also facilitate research designed at targeting drugs on specific patient groups where they will be of maximum benefit.

Conclusion

The ability of the patent system to keep pace with the latest research methodologies and clinical strategies is tested by its ability to protect new uses of known drugs. Differing approaches apply by jurisdiction, although robust protection is available in most developed countries and some other major markets. Further developments in pharmacogenomics and personalised medicine are likely to stretch the system further. Regardless, investigation of new uses for known drugs provides a comparatively low risk – and potentially highly profitable – approach to the classical drug discovery paradigm. *iam*

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Ravi Srinivasan is a partner of J A Kemp. He specialises in pharmaceutical work and has many years' experience of devising and implementing patent strategies for pharmaceutical companies around the world.

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The *IAM Patent 1000: The World's Leading Patent Practitioners* identified Mr Srinivasan as a recommended individual for his expertise in pharmaceuticals.

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He joined J A Kemp in 2006 and handles patent work in all aspects of chemistry, including pharmaceuticals, nutraceuticals (particularly lipids), industrial minerals and electroluminescent polymers. Mr Newman also has experience filing and prosecuting supplementary protection certificates, and advises on related regulatory issues. He was recently involved in referrals in this area to the European Court of Justice.