When public policies collide: the battle to enforce second medical use patents for drugs in Europe

Mike Snodin discusses recent decisions on second medical use patents in Europe and the important points that innovators can take from those decisions.

New therapeutic uses of known drugs represent an important way in which patients can gain access to safe and effective new treatment options. This is not least because of the safety benefits that stem from the fact that the therapeutic window of an already marketed drug (as opposed to that for an innovative drug) will be reasonably well understood.

As methods of medical treatment are not patentable in Europe, the patent offices, courts and legislators in the EU have sought to identify ways in which new therapeutic uses of known drugs can be patented. This is because the ability to rely upon such patent protection is crucial to incentivising pharmaceutical companies to continue developing such potentially important new uses.

The solution settled upon has been the protection provided by claims in so-called "second medical use" formats. However, whilst such claims have been widely used by innovators for about 30 years, there has been remarkably little case law on the scope of protection that they provide.

This means that there is not always a straightforward answer to the question of whether, and to what extent, a patent to a second medical use is enforceable against a generic competitor. This question has now come to the fore in recent disputes in the UK (involving pregabalin[1]) and the Netherlands (involving zoledronic acid[2]), in which innovators have sought to enforce second medical use patents against so-called "skinny label" generic products (ie products with labels that do not mention the patented indications).

The judgements issued so far in both disputes have provoked heated debate. Whilst that debate is far from being settled (not least because of an appeal that will be heard in the UK in late April), there are already a number of practical lessons that innovators can learn from the decisions about how to maximise the chances of their second medical use patents being enforceable against skinny label generic products.

Second medical use claim formats

Two claim formats

It is tricky to identify a claim format in Europe that can protect a new therapeutic indication of a known drug. This is because any claim to the new indication must not encompass either:

(i) methods of medical treatment using the drug (as such methods represent unpatentable subject matter in Europe); or
(ii) previously known uses of the drug (as those uses would destroy the novelty of the claim).

However, two different solutions have been found, which are:

(a) the so-called "Swiss" format, "Use of a substance or composition X for the manufacture of a medicament for therapeutic application Y"; and
(b) the EPC2000 format, "Substance or composition X for use in the treatment of disease Y".

The Swiss format has been widely used since the mid-1980s, when the Enlarged Board of Appeal of the European Patent Office issued decisions[3] that approved the use of such claims. By way of contrast, the EPC2000 format only became available when a revised European Patent Convention came into force on 13 December 2007.

Recent developments[4] mean that the EPO will no longer allow claims in the Swiss format (if those claims have a priority date of 29 January 2011 or later). Nevertheless, that format will remain highly relevant for many years to come. This is not least because a large proportion of European patents to second medical uses (ie those that were granted before 13 December 2007) will contain claims in the Swiss format only.

Although originally intended to provide equivalent protection to claims in the Swiss format, the EPC2000 format has now been acknowledged by an EPO Board of Appeal[5] to provide a different scope of protection. Indeed, viewing things simplistically, it is easy to see why a use-limited process claim (eg in Swiss format) might provide a narrower scope of protection than a use-limited product claim (eg in EPC2000 format). This is a potentially very important point, as it could well mean that the courts in Europe will treat Swiss and EPC2000 format claims differently for enforcement purposes.

Assessing validity

The validity of claims in either of the two second medical use formats can only be assured if special claim interpretation rules are applied.

For example, unless "*for*" in the phrase "*for therapeutic application Y*" is interpreted to mean "*suitable* ***and intended*** *for*" (as opposed to merely "*suitable for*"), "Swiss" format claims would lack novelty over prior disclosures of the use of the same medicament for completely different therapeutic applications.

Similarly, the EPC2000 format represents a special exception to the normal principle that the intended use of a product does not confer novelty upon that product.

The skinny label products under dispute

Pregabalin

The drug pregabalin is marketed by Pfizer company Warner-Lambert under the name Lyrica. A commercially very important product, Lyrica generated more UK sales in 2013 than any other of Pfizer's drugs.

Actavis sought a marketing authorisation for a skinny label pregabalin product, to be marketed under the name Lecaent. The product label for Lecaent was "skinny" because it listed epilepsy and generalised anxiety disorder (for which all relevant intellectual property protection had expired) but excluded neuropathic pain, which is the subject of a Swiss format second medical use patent (EP 0 934 061 B3) that remains in force.

Zoledronic acid

Novartis markets zoledronic acid under two different names, Zometa and Aclasta. The two names reflect two different strengths of intravenous solution, with Zometa comprising a more concentrated solution (4mg per 5mL) than Aclasta (5mg per100 mL). The authorised indications for Aclasta are osteoporosis and Paget's disease.

Sun Pharmaceuticals obtained a marketing authorisation for a generic version of Aclasta. Sun's authorization was amended to remove all references to osteoporosis, the sole indication for which any relevant second medical use patent protection remained in force in the Netherlands (via EP 1 296 689 B3, which contains only claims in the "Swiss" format).

The essence of the disputes

The skinny label generic products produced by Actavis and Sun do not indicate that they are intended for use in the treatment of the patented indications. However, that does not necessarily mean that they are incapable of infringing the second medical use patents held by Warner-Lambert and Novartis, respectively.

This is not least because prescribing practices in the UK and the Netherlands

permit the dispensing of a product (generic or otherwise) for an indication that is absent from the product label. This leads to a risk of so-called cross-label prescribing, whereby the generic product is dispensed for an indication that has been omitted (for patent reasons) from its label – thus effectively circumventing the patent protection.

Indeed, such cross-label prescribing is particularly likely to happen in the UK, due to:

- the widespread practice of prescribing by international non-proprietary name (INN) (instead of by brand name), without any mention of the indication for which the drug is prescribed; combined with
- the existence of an incentive (increased profit margin) for pharmacists to fulfil such prescriptions by dispensing a generic product (if available).

The situation in the Netherlands is slightly different, where the current tendering practices of healthcare insurers represent an additional reason why cross-label prescribing might occur.

For both Lyrica and Aclasta, a large proportion of total sales relates to the patented indications. Thus, with large revenues at stake, both Warner-Lambert and Novartis sought to ensure that their second medical use patents were respected.

Because of the different practical circumstances in the two cases, Warner-Lambert and Novartis used different tactics in seeking to enforce their patents. However, in short, both companies wanted their generic competitors to do much more to prevent (or at least minimise) cross-label prescribing than just hide behind the essentially ineffectual wording of the skinny labels.

Colliding public policies

The disputes in the UK and the Netherlands raise very tricky issues.

On the one hand, patentees can point to the importance of ensuring that the legislative intent behind the provision of patent protection for second medical uses is honoured by enabling the enforcement of that protection such that it provides a meaningful monopoly.

On the other hand, generic companies can emphasise the importance of ensuring that there is a free market for sales of medicinal products for indications for which all relevant intellectual property protection has expired.

Whilst these points alone would have made it challenging for the UK and Dutch courts to decide how best to balance the competing interests, the facts were complicated still further by the involvement of public policies on the provision of healthcare (eg policies on prescribing practices and/or the use of healthcare insurers). This is because those policies introduce third parties:

- who are responsible (in whole or in part) for the occurrence of cross-label prescribing, and hence for losses suffered by the patentee; but
- who are independent parties under the control of neither the patentee nor the generic competitor.

Of course, an obvious solution might be for a patentee to seek relief from the third parties involved in cross-label prescribing. However, there are further legal and practical issues that make it difficult to establish exactly how (or even whether) this can or should be done.

The UK and Dutch decisions

The UK

On 21 January 2015, Justice Arnold refused to grant relief sought by Warner-Lambert that would have imposed a number of conditions upon the marketing of Lecaent going well beyond the mere omission of neuropathic pain from the product label.

Whilst there has already been much commentary on that decision[6], this article will focus upon what appear to this author to be two key reasons behind Justice Arnold's decision.

The first reason was Justice Arnold's view (based upon commentary in a UK Court of Appeal judgement from 2008[7]) that a Swiss format second medical use claim was a process claim that:

> *is not aimed at and does not touch the doctor – it is directed at the manufacturer.*

This view led to the inevitable conclusion that, when considering whether Lecaent was "suitable and intended for" the treatment of neuropathic pain, it was only the manufacturer's intention that mattered, and not that of any other (downstream) party dealing with Lecaent.

The second reason was that Justice Arnold accepted submissions from Actavis' counsel that the public policy behind Swiss format claims meant that the intention had to be *subjective*.

To illustrate why this should be so, counsel for Actavis drew attention to a hypothetical situation in which a compound is marketed by a first party for a first indication and then the same compound is subsequently patented (and marketed) by a second party for a second indication. In the UK, a foreseeable consequence in this scenario is the first party's product would be dispensed for the treatment of the indication patented by the second party.

It was argued by Actavis that nothing less than a requirement for subjective intention would shield the first party from allegations of infringement of the second party's patent. Justice Jacob agreed with this, as well as the contention that the same principles should apply to a third party who sells the same compound for the same indication as the first party.

Adopting the standard of subjective intention meant that the UK High Court needed only to assess the manufacturer's state of mind, ie decide upon whether their actions were targeted or aimed at achieving use of their product in the treatment of the patented indication. On this standard, Justice Jacob held that the evidence presented by Warner-Lambert failed to establish that Actavis had a subjective intention to sell Lecaent for the treatment of neuropathic pain. He therefore decided that Actavis was not guilty of direct infringement of Warner-Lambert's patent.

Justice Jacob also concluded that Actavis did not indirectly infringe the patent, although this was primarily upon the grounds of his belief that there is no downstream party that performs the manufacturing process that is the subject of a Swiss format claim.

Nevertheless, Justice Jacob accepted that this was an important and developing area of the law, and that he could be mistaken in his conclusion on direct infringement. Therefore, following a third hearing between the parties[8], he granted relief (based on an extension of principles established in two other cases[9]) sought by Warner-Lambert that aimed at compelling NHS England to issue guidelines indicating that pregabalin should only be prescribed for the treatment of neuropathic pain under the brand name Lyrica.

Whilst no doubt going a long way to address Warner-Lambert's concerns about likely cross-label prescribing, this relief was only granted on the basis of the possibility that Justice Jacob's views on infringement were incorrect and that, as a result, NHS England could potentially be viewed as "an innocent party who is mixed up in the wrongdoing of others".

The Netherlands

The evidence before the Hague Court of Appeal made it much more straightforward for that court to conclude that Sun Pharmaceuticals *intended* to market a generic zoledronic acid product for the treatment of the patented indication (osteoporosis).

For example, the indicators pointing to such intent included the following.

- Osteoporosis is very common and is usually treated by multiple (annual) administrations of zoledronic acid. In contrast, the only indication on the label of Sun's generic product (Paget's disease) is a rare disorder that is typically treated by a one-off administration of zoledronic acid.
- The court accepted Novartis' estimate of the annual volume of product sales for the treatment of Paget's disease, which estimate

was exceeded by the volume of sales achieved by Sun in only two months.
- Sun won a tender from a health insurer (VGZ) that placed no conditions upon the disorders for which Sun's zoledronic acid product could be prescribed. In the light of the dispensing practices under VGZ's preference policy (in which even a prescription for Novartis' brand would be fulfilled with Sun's product), it was inevitable that Sun's product would be dispensed for the treatment of osteoporosis.
- Sun did not seek to impose any obligation upon VGZ to dispense their product solely for the treatment of Paget's disease.

Curiously, however, the Hague Court of Appeal only held Sun to be guilty of *indirectly* (as opposed to directly) infringing Novartis' second medical use patent.

Commentary

There are many interesting and important aspects of the above-mentioned decisions of the UK High Court and the Hague Court of Appeal. However, the comments in this article will be limited to issues relating to the scope and enforceability of Swiss format second medical use claims, as well as practical lessons that can be learnt from the decisions.

The scope and enforceability of Swiss format claims

Whether (or to what extent) a Swiss format claim will be enforceable against a skinny label generic product will depend largely upon the standard that the courts use to assess the intent of the generic manufacturer.

The standard of subjective intent used by the UK High Court could well make such enforcement very difficult. However, it remains to be seen whether the UK Court of Appeal (or any courts outside of the UK) will adopt the same standard or will find persuasive reasons to reach a different conclusion.

Other key points for enforceability will be the views of the courts upon:

1. whether a downstream party is capable of directly infringing a second medical use patent; and, if so
2. whether the supply of a skinny label generic product can *indirectly* infringe a second medical use claim.

These are points where the conclusion for claims in EPC2000 format could be different from that for claims in Swiss format. Whilst we do not yet have any judicial guidance on these very interesting points, clear differences of opinion are already emerging on the answers for claims in Swiss format.

That is, whilst the Hague Court of Appeal found a Swiss format claim to be indirectly infringed by Sun Pharmaceuticals' supply of a skinny label medicament, the UK High Court essentially decided that there cannot be any indirect infringement in such circumstances. This must mean that the Hague Court of Appeal disagreed with the UK High Court and reached the conclusion that Swiss format claims are directed at more parties than just the manufacturer. However, as the court did not discuss this point, their reasons for reaching this conclusion remain unclear.

This is disappointing, not least because, in the UK, the only type of relief granted to Warner-Lambert (against NHS England) will cease to become available in future cases if the UK Court of Appeal merely confirms Justice Jacob's views on infringement. Thus, for innovators, much may depend upon persuading the courts in Europe to reach a contrary view and to accept that Swiss format claims can indeed be infringed by parties downstream from the generic manufacturer (eg pharmacists or bodies involved in crafting and issuing prescribing policies).

Whilst this author can imagine at least one interpretation of Swiss format claims that could support such a contrary view, it remains to be seen whether any claim interpretation can overcome Actavis' arguments as to why a generic manufacturer is liable for infringement only if they have a subjective intention for their product to be used in treating the patented indication. Thus, it may be that alternative interpretations of Swiss format claims will be more useful in supporting enforcement action against downstream parties than against generic manufacturers.

Practical lessons to be learned

There are a number of practical tips that the holders of second medical use patents can glean from the decisions in the UK and the Netherlands.

Firstly, and as illustrated by the most recent decision in the UK, it may be that the most effective relief will be provided by enforcing patents against downstream parties – who after all may be either wholly or partly responsible for the cross-label prescribing of a skinny label product.

Whilst patentees may be reluctant to sue such downstream parties (eg because of their involvement in decisions to use or purchase the patentee's own products), they might ultimately have little choice to do so.

Secondly, all of the above-mentioned decisions point to the importance of ensuring (at least for the time being) that any enforcement action relating to a skinny label generic product is supported by evidence demonstrating the subjective intent of the generic company. Whilst there are clear difficulties in proving what was in the mind of the generic company, the courts ought to allow reasonable inferences about intent to be drawn from the generic company's behaviour.

Finally, a related point is that a generic company would be hard pressed to resist a finding of subjective intent if their skinny label product had a pharmaceutical form (or strength) matching that of a unique innovator product for which all of the authorised indications were protected by a second medical use patent.

Thus, provided that there is sufficient technical and regulatory justification to do so, innovators may wish to seek to develop unique formulations, eg based upon a unique pharmaceutical form and/or a unique dose, for each (group of) indication(s) protected by a second medical use patent.

This last point reinforces the conclusion that the lifespan of an innovative drug is most likely to be optimised if IP practitioners are involved in all aspects of product development that could lead to a regulatory filing.

References

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