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Enforcement Of Second Medical Use Patents: Landmark Case Sets The Scene For Future Battles

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MIKE SNODIN discusses the UK Court of Appeal's recent decision on second medical use patents and "skinny label" generic products that, whilst containing encouraging signs for the innovative pharmaceutical industry, leaves open key questions that can only be answered in further disputes.

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On Oct. 13, 2016, the UK Court of Appeal issued a judgement that found Warner-Lambert's patent to the use of pregabalin for the treatment of pain to be invalid on the grounds of insufficiency[1].

Whilst that judgement likely spells the end of a landmark case on second medical use patents, many issues relating to the enforcement of such patents remain unresolved.

This article discusses a selection of challenging issues that the courts will need to address in future cases. It also points to proactive tactics that innovators could adopt with a view reducing the chances of second medical use patents being infringed by so-called "skinny label" products.

Legal Context

Intellectual property laws in Europe contain a prohibition against patenting methods of medical treatment. However, in recognition of the important role that patent protection plays in encouraging the development of new uses of known drugs, European courts and legislators have validated the use of claims in so-called second medical use formats. Such claims avoid the prohibition against patenting methods of treatment whilst still providing useful protection for innovators.

During the 1980s, developments in case law in Europe resulted in the widespread acceptance of claims in so-called Swiss format (although Swiss form claims are no longer accepted in Europe in applications having a priority date of 29 January 2011 or later). Such claims are directed towards a manufacturing process and typically take the following form: *"Use of a substance or composition X for the manufacture of a medicament for therapeutic application Y"*.

In order to recognize the validity of such claims, it was necessary for the courts to draw distinctions between those medicaments intended for the new use and those intended only for previously known uses. This was done by interpreting *"for therapeutic application Y"* to mean *"suitable **and intended** for therapeutic application Y"*.

Whilst essential for validity purposes, this interpretation does pose challenges when it comes to determining infringement. That is, if a claim in Swiss format can only be enforced against a manufacturer who *intends* for their medicament to be used in the therapeutic application mentioned in the claim, how does one determine the intention of the manufacturer?

The answer to this question is straightforward if the manufacturer sells the medicament with a label listing the relevant therapeutic application. In that situation, the manufacturer would clearly be infringing.

However, the situation is much less clear-cut for those generic medicaments that have a "skinny" label, where patented therapeutic applications are omitted or "carved out" from the product label. This is because prescribing and dispensing practices in many countries in Europe make it likely that the generic product will be used to treat the indication(s) omitted from the skinny label.

The Dispute

Whether or not a skinny label generic product can infringe a claim in Swiss format was a central issue in a landmark dispute in the UK between Warner-Lambert

and Actavis. That dispute arose after Actavis sought a marketing authorization for a skinny label pregabalin product, to be marketed under the name Lecaent.

Warner-Lambert's pregabalin product, Lyrica, had three indications – epilepsy, generalized anxiety disorder and neuropathic pain. Actavis sought approval for only the first two uses, not for the pain indication, which still had patent protection (Lyrica is now Pfizer's product following that company's acquisition of Warner-Lambert in 2000).

In essence, Warner-Lambert sought to force Actavis to take various actions to help reduce the chances of Lecaent being used for the commercially valuable indication of treating neuropathic pain. That indication was the subject of a "Swiss" format claim of an in-force patent (EP 0 934 061 B3), which Warner-Lambert alleged would be infringed by the sale of Lecaent.

In response, Actavis argued that the proposed sale of Lecaent would be non-infringing, and that Warner-Lambert's patent was invalid.

In previous judgements relating to the same dispute, both the High Court and the Court of Appeal refused to grant a preliminary injunction preventing sale of Lecaent. After a full trial on issues of infringement and validity, the High Court found the patent to be invalid (on the grounds of lack of sufficiency) and not infringed.

Warner-Lambert subsequently made a conditional application to amend the claims of the patent, to limit them to the subject matter found by the High Court to be sufficiently disclosed. The High Court refused permission to enter that amendment, on the grounds that it was submitted too late (after the end of the full trial) and so represented an abuse of process.

The Decision

The decision of Oct. 13, 2016 combined Warner-Lambert's appeals against the High Court's findings of invalidity, non-infringement and abuse of process.

Validity

In explaining the unanimous judgement of the Court, Lord Justice Floyd observed that the requirement for an invention to be sufficiently disclosed in the specification as filed was *"A test designed to prevent speculative claiming"*, which test *"need go no further than requiring the patentee to show that the claim is not speculative"*. Lord Justice Floyd also rejected the use of alternative tests for sufficiency that require the specification as filed to provide *"any greater degree of confidence in the patentee's prediction"*.

Whist Lord Justice Floyd commented that the test for sufficiency *"represents a very low threshold"*, he nevertheless confirmed the High Court's finding that the claims were insufficient. In essence, the judgement of the Court of Appeal was that the claims were speculative to the extent that they covered the treatment of central neuropathic pain (as opposed to peripheral neuropathic pain). The Court reached this conclusion after first determining that the claims covered both types of pain, and after having received expert testimony on the issue of the information that would have been common general knowledge at the time the patent was filed.

Lord Justice Floyd also confirmed that Warner-Lambert's application to amend the claim represented an abuse of process, essentially on the grounds that the amendment could and should have been put forward at a much earlier stage (in order to provide Actavis with a proper opportunity to address the amended claim during the trial before the High Court).

Infringement

Having confirmed that the patent was invalid, the Court of Appeal need not have considered the issue of infringement. However, in electing to tackle this task, Floyd explained that:

"The issue which this aspect of the case raises is, and remains, one of great difficulty. The law is struggling on the one hand to give the patentee a proper reward for his contribution to the art by elucidating the new use for the drug, whilst at the same time not excluding the competing manufacturer from making and marketing the drug for its known purpose. The issue is complicated by the interaction with the law relating to, and the practices of the market in, prescription medicines. The solution adopted by this court in Warner-Lambert CoA was an attempt to strike the right balance by not placing insuperable obstacles in the path of the patentee, whilst at the same time recognising in very clear terms that the remedies available for infringement will have to be moulded so as to achieve fair and proportionate relief tailored to the very special circumstances of this type of case."

Lord Justice Floyd then proceeded to explain the standards he believed should be applied when determining both direct and indirect infringement of Swiss form claims by a skinny label product. Notably, the standards on both issues differed markedly from those applied by the High Court.

With respect to the issue of direct infringement, Lord Justice Floyd reaffirmed his comments in the court's earlier judgement (on the issue of a preliminary injunction) by setting a test based upon the *foreseeability* of the use of the skinny label product in the treatment of the patented indication. In this respect, Lord Justice Floyd observed that[2]:

"From an objective standpoint ***one would normally regard a person to intend what he knows or can reasonably foresee as the consequences of his actions…***

… If that is the basic test to be adopted, what is sufficient to negative the existence of intention? In my judgment ***the absence of the patented indication from the label cannot conceivably be sufficient to negative the intention*** [emphasis added]."

Whilst this approach clearly poses challenges for manufacturers of skinny label products, Lord Justice Floyd did point to a way in which patent infringement might be avoided:

"The intention will be negatived where the manufacturer has taken all reasonable steps within his power to prevent the consequences occurring. *In such circumstances his true objective is a lawful one, and one would be entitled to say that the foreseen consequences were not intended, but were an unintended incident of his otherwise lawful activity* [emphasis added]."

On indirect infringement, Lord Justice Floyd observed that this hinged upon the provision of "means for putting the invention into effect." Further, with regard to the additional requirement for the invention to be put into effect (by a downstream party), he warned against reading this as a requirement for a "downstream act of manufacture" of a medicament and commented that:

"The invention in the present case is the use of pregabalin in the preparation of a pharmaceutical composition for treating pain. As the example of labelling by a pharmacist shows, that process is not completed when the pregabalin has been formulated into a pharmaceutical composition by a manufacturer. ***The process of preparing the composition can continue through any packaging step performed by the manufacturer and includes the labelling step performed by the pharmacist…***

… I have already concluded when considering direct infringement that ***the significance of a packaging step is only that it demonstrates the necessary intention. I am therefore unable to understand why other acts of the pharmacist in preparing the composition for delivery to the patient cannot also be regarded as relevant acts of preparation, if done with the necessary intention.*** *I cannot agree with the judge that there is no relevant act of preparation by pharmacists, nor any prospect of such an act* [emphasis added]."

Commentary

Whilst Warner-Lambert will no doubt be disappointed that its patent has been revoked, key aspects of the Court of Appeal's decision are likely to be welcomed by the innovative pharmaceutical industry. However, with unresolved issues remaining in at least four areas, courts will face significant challenges in resolving future disputes over skinny label products.

Plus Points For Innovators

Although sufficiency of disclosure will always be assessed upon the basis of the (scientific) facts pertaining to each case, it is clear that the Court of Appeal has set the bar relatively low for the level of disclosure needed to pass the test for sufficiency. This is because the threshold for sufficiency will be passed if the specification discloses the invention in a manner that merely renders it "plausible" (as opposed to a stricter test, such as "more likely than not").

However, the most significant aspect of the decision is the commentary on the tests for infringement of a Swiss form claim. In particular, reaffirmation of the "foreseeability" standard for assessing direct infringement is likely to facilitate the enforcement of patents to new medical uses of known drugs.

A particularly important implication of this relative ease of enforcement is that it should enable patentees not only to take action against (direct or indirect) infringers, but also to obtain so-called *Norwich Pharmacal* relief

against "innocent" third parties who are *"mixed up in the wrongdoing of others"*.

Obtaining court orders requiring "innocent" third parties to take (or avoid taking) certain actions may well prove to be the most effective way of ensuring that skinny label generic products are not used for the treatment of patented indications. Indeed, when Warner-Lambert persuaded the High Court to grant *Norwich Pharmacal* relief against NHS England, Justice Arnold commented that[3]:

"I consider that the issuing of guidance by NHS England is the most efficacious, dissuasive and cheapest solution to the problem which confronts Warner-Lambert."

Challenge 1: How Can Direct Infringement Be Avoided?
Generics companies seeking to launch skinny label products now know that they should take *"all reasonable steps"* within their power to try to prevent their product being used to treat patented indications. However, the Court of Appeal did not explain which (combinations of) steps might suffice to avoid a finding of patent infringement.

This leaves both innovators and generics in a decidedly uncertain situation. This is because it can be very difficult to determine when a generics company has done enough to avoid infringement, a point that is illustrated by Justice Arnold's comments at the beginning of the Warner-Lambert saga[4]:

"A final point to note at this stage is that counsel for Warner-Lambert did not concede that Actavis would not infringe the Patent if it took all the steps required by Warner-Lambert's proposed order despite being invited to do so by counsel for Actavis. It is inherent in Warner-Lambert's case that, to the extent that those steps were ineffective, Actavis would still infringe the Patent and would still have to pay damages or account for profits in respect of their infringing sales."

Greater insight into the precise location of the boundary between lawful and unlawful (infringing) behavior is therefore likely to emerge only through further court cases involving skinny label products.

Nevertheless, it is worth noting that the Court of Appeal's judgement appears to imply that that sale of skinny label products may be deemed lawful even in circumstances where it remains foreseeable that the product will ultimately be used for the treatment of a patented indication. This is because Lord Justice Floyd explicitly acknowledged the possibility for a lawful activity to have an *"unintended incident"*, which in this case would be an unintended downstream use of the product.

Thus, it may well be that generics companies need merely take *"all reasonable steps"* within their power to *try* to prevent skinny label products from being used in the treatment of patented indications. There may be no requirement for them to actually *succeed* in preventing such use (which, after all, may well occur for reasons that are largely outside of their control).

Challenge 2: How Can Indirect Infringement Be Avoided?
Under UK law, indirect infringement can occur when there is unauthorized supply of a *"means, relating to an essential element of the invention, for putting the invention into effect"*. The view of the Court of Appeal appears to be that, for an invention relating to a new medical use, the *"means"* might be a medicament supplied by a manufacturer who does **not** intend it to be used in the patented indication. In that circumstance, a downstream party putting the invention into effect might be, for example, a pharmacist who applies to the product a label that lists a patented indication.

Whilst this all makes perfect sense to this author, it does raise the possibility that the manufacturer of a skinny label product that does not *directly* infringe a Swiss form claim might nevertheless be found liable for *indirect* infringement of that claim.

Indirect infringement may be found when a person supplies relevant *"means"* in circumstances *"when he knows, or it is obvious to a reasonable person in the circumstances, that those means are suitable for putting, and are intended to put, the invention into effect in the United Kingdom"*. For the supplier of a skinny label product, the assessment of indirect infringement will therefore hinge upon the question of whether the medicament is *intended* to put the invention into effect.

For indirect infringement, intention may well be assessed under a very different standard than that used by the Court of Appeal to determine direct infringement

of Swiss form claims. This is because the UK courts have previously decided that, for indirect infringement, it is the intention of the *end user* that counts (as opposed to the intention of the supplier, which is the decisive factor for direct infringement). This principle was most clearly expressed by the Court of Appeal in *Grimme v Scott*[5]:

"The question is what the supplier knows or ought to know about the intention of the person who is in a position to put the invention into effect – the person at the end of the supply chain...

... In short, the knowledge and intention requirements ... are satisfied if, at the time of supply or offer of supply, the supplier knows, or it is obvious in the circumstances, that ultimate users will intend to put the invention into effect. That is to be proved on the usual standard of balance of probabilities."

Therefore, with indirect infringement appearing to hinge more upon the *knowledge* than the intention of the supplier, it is perhaps possible that the manufacturer of a skinny label product will be found liable for (indirect) infringement even if they have taken *"all reasonable steps"* within their power to try to prevent their product being used in the treatment of the patented indication.

Challenge 3: Off-Label Uses

New uses of known drugs are frequently patented in Europe. In this respect, it is not uncommon for a situation to arise where:

(a) a patent to a new indication for a known drug is awarded to an entity unconnected to those responsible for marketing the drug; but

(b) clinical trials are never conducted upon that new indication, which remains *unauthorized*; and

(c) that indication is therefore not listed on any product label for the drug in question.

The views expressed by Lord Justice Floyd may well mean that the facts of point (c) above are irrelevant to the issue of infringement. Therefore, depending upon the relevance that the courts ascribe to factors such as point (b) above, it is possible that even *off*-label uses of a drug may create liability for (direct and/or indirect) patent infringement. Indeed, there may well be circumstances in which a manufacturer is able to foresee that his product will be used to treat an unauthorized indication.

Moreover, the Court of Appeal's approach to infringement has the consequence that the grant of a patent to a new use can render unlawful (i.e., infringing) the repetition of acts (such as supplying a drug) that were previously lawful[6]. This is because the patent itself changes the conditions under which the supply takes place, by making it possible (for the first time) to foresee that the drug will be intentionally used for the treatment of the patented indication.

Thus, continuing to sell a drug after the grant of a second medical use patent might generate liability for infringement, even if the patent in question was filed *after* the drug was first marketed (with an identical product label).

At this point, it is unclear whether *off*-label uses could generate the same kinds of obligations (to take all reasonable steps to prevent infringement) as arise in respect of *cross*-label indications. Again, greater clarity on this point is only likely to emerge from further court cases relating to infringement of claims in second medical use format.

Challenge 4: Remedies For Infringement

The biggest challenge faced by courts in future cases may well relate to identifying the relief that should be granted to the holder of a patent (to a new medical use) that has been infringed by sale of a skinny label product. Particularly tricky questions are likely to include the following.

(1) Should the court grant an injunction preventing *all* sales of a skinny label product found (at full trial) to be infringing?

(2) Should the court award damages based upon the cost of lost sales for the patentee, or instead upon profits accrued by the infringer?

(3) Should damages be reduced to account for the fact that not all of the product will be used to treat the patented indication(s)?

Based upon hints dropped in the judgements of the Court of Appeal in the Warner-Lambert case, the answer to question 3 may well be "yes". However, it remains to be

seen what the courts will make of questions 1 and 2, if and when those questions arise in other cases.

Conclusions

The Court of Appeal's confirmation of invalidity of the Warner-Lambert patent will no doubt be a bitter blow to Pfizer, as generic versions of pregabalin should now be able to compete against Lyrica for sales in all authorized indications, including pain.

However, even Pfizer is likely to take a crumb of comfort from other aspects of the Court of Appeal's judgement, such as the "pro-patentee" tests proposed for sufficiency and (direct and indirect) infringement. Whilst the court's commentary on infringement is not strictly binding, it represents a unanimous judgement reached after full arguments on the points. Therefore, at least the lower courts are likely to find the infringement tests proposed by the Court of Appeal to be highly persuasive.

Nevertheless, many challenges remain in connection with the enforcement of second medical use patents against skinny label generics. This is because there is still great uncertainty with regard to the precise boundary between lawful and unlawful (infringing) behaviors, as well as the remedies that will be available if a second medical use patent is determined to have been infringed by a skinny label product.

In the light of such uncertainties, it appears to this author that innovators may wish to give thought to proactive tactics aimed at *preventing* (cross-label) use of generic products for the treatment of patented indications. Measures that could be considered include those previously suggested by this author, namely[7]:

- enforcing patents against downstream parties who are wholly or partly responsible for (increasing the likelihood of) cross-label prescribing of a skinny label product; and/or
- subject to technical and regulatory constraints, developing unique formulations for each (group of) indication(s) protected by a new medical use patent.

Whilst both of these options are associated with additional cost burdens for innovators, it appears to this author that they are likely to remain the most effective strategies for minimizing erosion of sales for products where patent protection for some (but not all) indications has expired. Indeed, the granting of *Norwich Pharmacal* relief to Warner-Lambert (requiring NHS England to issue prescribing guidance) shows that at least the courts in the UK are perfectly prepared to entertain such effective solutions.

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Mike Snodin is the founder and director of Park Grove IP, a UK-based patent attorney firm that provides advice to companies in the chemical, pharmaceutical and life sciences fields. The views expressed in this article are the personal views of the author. Email: mike.snodin@parkgrove-ip.com.