Warner Lambert v Actavis: Supreme Court Considers Medical Use Claims

The Supreme Court in the UK handed down its decision in *Warner-Lambert v Actavis* on 14th November 2018 (and a copy of the complete decision is available here). The Supreme Court considered the following issues in its judgment:

1. how much data is required in the application as originally filed to support a second medical use claim; and
2. the circumstances under which "cross label use" for the patented indication of a drug sold by a competitor company can constitute infringement of a second medical use claim.

"Second medical use" claims in Europe

The *de novo* discovery of effective and safe pharmaceuticals is a challenging process, and many new drugs do not ultimately show sufficient efficacy against their target disease to secure regulatory approval. For this reason, there is an extensive and growing list of drugs which have shown an acceptable safety profile in human trials, but which have failed late stage clinical trials, and which are therefore no longer under development.

Increasingly, unmet medical needs are being met by "repurposing" of such old medicines for new diseases. Generally, much less investment is needed for clinical investigation of the activity of such an old medicine against a new disease than would be required to develop a wholly new drug to treat the disease at issue. Nevertheless, considerable resources are still required to carry out the necessary clinical trials to assess whether or not known drugs have activity against new target diseases.

For this reason, a finding that a known drug has efficacy against a new disease target has long been thought to be a finding which merits patent protection. To that end, since the 1980s, the European Patent Office (EPO) has been willing in principle to grant claims in "second medical use" format. The original claim format for a second medical use claim was the "Swiss-style" claim format, approved in Decision G5/83, published in the Official Journal of the EPO in March 1985. Then, following the changes to the EPC which took effect in 2007, second medical use claims were granted in "product for use" format[1].

The two claim formats are set out below.

"Swiss-style" claim: Use of [known drug] in the manufacture of a medicament for use in [treating new disease target]

"Compound for use" claim: [Known drug] for use in [treating new disease target]

The question then arises as to how such claims can be infringed. Commercial sale of most medicinal products in the EU is governed by Directive 2001/83/EC. Under this Directive, no medicinal product may be placed on the market of a member state unless a marketing authorisation has been issued. A summary of the product characteristics (SmPC), which includes therapeutic indications and dosages, must be submitted as part of the application for a marketing authorisation. Subsequently, when the medicinal product is marketed it must be accompanied by a package leaflet. That package leaflet must specify, *inter alia*, the therapeutic indications and dosages set out in the SmPC.

Article 10 of Directive 2001/83/EC permits generic pharmaceutical companies to secure marketing authorisation for a drug simply by demonstrating that the drug is a generic version of a reference medicinal product which has been approved following a full set of clinical trials. Under such circumstances, the SmPC for the generic product will be identical to the SmPC which accompanied the initial marketing authorisation for the reference product, but with one important exception. Article 11, final paragraph, of the Directive specifies that:

"those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included".

Thus, generic manufacturers may adopt a so-called "skinny SmPC", which omits patented indications and dosages. It has been a matter of debate whether or not sale of a drug covered by a second medical use claim under such a "skinny SmPC" can infringe the second medical use claim under circumstances where the generic product ends up being used, to greater or lesser extent, to treat the patented indication in patients.

Warner-Lambert v Actavis: The dispute

The dispute between Warner-Lambert and Actavis concerned the drug pregabalin. This drug was marketed by Warner-Lambert under the tradename Lyrica® for three indications (epilepsy, generalised anxiety disorder and neuropathic pain). Patent protection for pregabalin per se expired in October 2013, and an SPC covering the product had been allowed to lapse. However, Warner-Lambert held a second medical use patent containing "Swiss-style" claims covering one of the three indications (neuropathic pain). The relevant claims are set out below:

Claim 1: Use of [pregabalin] or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating pain.

Claim 3: Use according to claim 1 wherein the pain is neuropathic pain.

Dispute on validity

The dispute on validity was focussed on claim 3. It was common ground that pregabalin did in fact have efficacy in treating neuropathic pain. However, the parties differed on whether or not that activity was made plausible from the results in the patent specification as originally filed.

The patent specification contained credible animal data showing that pregabalin had efficacy against inflammatory pain (a different pain type to neuropathic pain). Before the Supreme Court, it was accepted that inflammatory pain and neuropathic pain could arise from different biological mechanisms, but that both pain types could in principle arise from central sensitization. Thus, central sensitization was a biological mechanism which could in principle (but need not necessarily) mediate both inflammatory pain and neuropathic pain.

Warner-Lambert argued that, given that (a) the patent specification contained credible results showing efficacy against inflammatory pain and (b) there was one mechanism in common between inflammatory pain and peripheral neuropathic pain, it was plausible from the results in the patent specification that pregabalin would indeed have efficacy against peripheral neuropathic pain. It further argued that claim 3 should be interpreted as limited to peripheral neuropathic pain, or alternatively that support for peripheral neuropathic pain should be sufficient to support a claim to neuropathic pain generally.

Actavis, in contrast, argued that the results in the patent specification showing activity against inflammatory pain did not prove that pregabalin was targeting central sensitization. It could be working via an entirely different mechanism, which is relevant only to inflammatory pain, and not to peripheral neuropathic pain. The results in the patent specification were not therefore sufficient to support a claim to neuropathic pain.

Dispute on infringement

Several generic companies, including Actavis, had sought and obtained authorisations to market pregabalin for non-pain indications under a "skinny SmPC" which indicated only the anxiety and epilepsy indications. However, Warner-Lambert was concerned that Actavis' product was in fact being used for the pain indication in the UK.

The problem which Warner-Lambert faced is that doctors in the UK usually prescribe drugs with reference to the international non-proprietary name of the active ingredient. The prescription would not therefore refer to the innovator's brand name: there would simply be a reference to "pregabalin", not to "Lyrica®". Further, the prescription does not generally indicate the disease which is to be treated. The pharmacist receiving the prescription will not therefore know what disease is being treated, and will accordingly often supply the generic version of the drug even when the patient is suffering from the patented disease state (here, neuropathic pain).

The dispute on infringement centred on what test should be applied to assess whether the generic manufacturer is liable for infringement. Is it sufficient if it is foreseeable that at least some of the generic product will end up treating patients suffering from neuropathic pain? Alternatively, is it necessary that the generic company must have the subjective intention when manufacturing their product that the drug will be used for the patented indication? Another option considered was whether or not it is necessary for a finding of infringement that the generic product manufactured by Actavis carries some indication visible from the product itself which refers to the patented indication.

Findings on validity

It is a well established principle, applied at the EPO and by English courts, that the disclosure in a patent specification must be such as to render "plausible" the efficacy specified in a medical use claim. The Supreme Court therefore had the task of determining whether or not the animal data in Warner-Lambert's patent specification met that threshold.

When considering whether or not the data in the patent as originally filed was sufficient to support claim 3 as granted, all of the judges in the Supreme Court looked closely at the relevant EPO case law. Specifically, they reviewed the Board of Appeal cases from the EPO which concerned European patents and applications which were based on a finding that a specified therapeutic product has some sort of desirable biological activity. Those cases have long established that the patent specification as originally filed must contain a "plausible" disclosure of the relevant biological activity. It is perhaps fair to say, though, that that case law is not wholly consistent (indeed, the Supreme Court judges themselves did not agree on the conclusions reached in the EPO case law).

In particular, some of the reasoning in the relevant Board of Appeal Decisions suggests that to satisfy the requirement for a "plausible" disclosure of efficacy, it is necessary that the patent specification must contain some technical information indicating that the biological activity ascribed to the claimed product does in fact arise[2]. Other reasoning suggests that all that is necessary for a "plausible" disclosure of efficacy is a statement of efficacy which is *prima facie* credible, i.e. where there is no reason to believe that the biological activity ascribed to the claimed product does not in fact arise[3].

As noted above, the Supreme Court judges could not agree on the correct approach to take in this regard. Lord Hodge and Lord Mance favoured the latter approach, whereby a credible statement of efficacy should suffice. The majority of the judges, however, took a contrary view. Thus, Lords Sumption, Reed and Briggs held, by 3:2 majority, that a "plausible" disclosure of efficacy requires at least some technical information in the original patent specification which indicates that the biological activity ascribed to the claimed product does in fact arise.

The leading judgment on this topic, which was approved by a majority of the judges and therefore constitutes binding precedent in the UK, was given by Lord Sumption. Lord Sumption pointed out that the patent system involves, at its heart, a bargain between the state and the inventor, whereby the inventor obtains a limited monopoly in return for disclosing an invention and dedicating it to the public for use after the monopoly has expired. Lord Sumption also reviewed a previous case from the Supreme Court (in its previous incarnation as the House of Lords) which held that a patent can be invalid for insufficiency if the monopoly conferred was not commensurate with the technical contribution to the art made by the patentee[4].

Applying these principles to the question of what should contribute a "plausible" disclosure of efficacy to support a medical use claim, Lord Sumption held that something more is needed than a mere statement of efficacy, even under circumstances where there is nothing to cast doubt on such a statement. He indicated that

"It must always be necessary for the patentee to demonstrate that he has included in the specification something that makes the claim to therapeutic efficacy plausible" (paragraph [33])

Lord Sumption then went on to set out, in paragraph [37], the following conclusions for assessing whether or not a claim for a therapeutic product is supported by a "plausible" disclosure in the patent specification:

1. The proposition that a product is efficacious for the treatment of a given condition must be plausible.
2. It is not made plausible by a bare assertion to that effect, and the disclosure of a mere possibility that it will work is no better than a bare assertion.
3. The claimed therapeutic effect may well be rendered plausible by a specification showing that something was worth trying for a reason.
4. Although the disclosure need not definitively prove the assertion that the product works for the designated purpose, there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true.
5. That reasonable prospect must be based on […] 'a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se'[5].
6. The effect on the disease process need not necessarily be demonstrated by experimental data. It can be demonstrated by *a priori* reasoning.
7. Sufficiency is a characteristic of the disclosure, and these matters must appear from the patent.

The test for plausibility is still said to be "*relatively undemanding*". However, Lord Sumption emphasised that it "*cannot be deprived of all meaning or reduced … to little more than a test of good faith*" (para [37]). A helpful summary of the new test for plausibility in the UK was perhaps provided by Lord Mance, who summarised Lord Sumption's test as follows:

"Lord Sumption's test amounts on its face to, or certainly risks being read as, a requirement that the plausibility of the claim must appear to be established prima facie through scientifically cogent reasoning or experimental evidence set out in the specification" (paragraph [195])

When applying this reasoning to the dispute before them, the majority of the Supreme Court judges held that there was no credible disclosure in the patent specification of the efficacy of pregabalin against peripheral neuropathic pain. Although the activity observed against inflammatory pain could have been mediated by an interference with the central sensitization mechanism (in which case activity against peripheral neuropathic pain would also be expected), it could equally well be mediated by some other mechanism unconnected with peripheral neuropathic pain. Under these circumstances, it was held that there was not a sufficiently unambiguous link between the data provided and the claimed therapeutic activity. Claim 3 of the patent was therefore held invalid for insufficiency.

Findings on infringement

The findings of the Supreme Court on infringement are not formally binding in the UK. That is because (a) the findings were *obiter dicta*, given that the patent had already been found to be invalid, and (b) there was no clear majority in favour of a single test to determine infringement. Further, the claim under consideration was a "Swiss style" claim, whereas many claims likely to be litigated in the future will be in the more modern "compound for use" claim format.

When considering the "Swiss-style" claim, all of the Supreme Court judges held that only direct infringement was relevant: nobody in the supply chain other than the generic manufacturer could be said to be using pregabalin "for the preparation of a pharmaceutical composition". Thus, supply of the pregabalin drug to pharmacists, etc., could not lead to liability under the contributory infringement provisions.

When considering direct infringement, however, the judges could not agree on the circumstances whereby a generic manufacturer preparing a medicament should infringe a "Swiss style" claim, and in particular when a pharmaceutical composition is prepared by a generics company "for use in treating pain". All of the judges agreed that this utility requirement is not satisfied merely because it was foreseeable to the generics manufacturer that some of the generic product would ultimately be used in the treatment of pain. However, they came to different conclusions as to exactly how infringement should be assessed. A summary of their conclusions is set out below.

- Two of the judges (Lord Hodge and Lord Briggs) held that there is infringement of a "Swiss-style" claim where the relevant medicament is prepared by a third party who has the subjective intent of targeting patients suffering from the patented disease.
- Two of the judges (Lord Sumption and Lord Reed), rejected the notion of subjective intent and held that manufacture of the relevant medicament would only infringe a "Swiss-style" claim under circumstances where there is some indication on the product itself that it is intended for the patented indication.
- The last judge (Lord Mance) lent towards the "outward presentation" test propounded by Lords Sumption and Reed, but articulated concerns that this could in some circumstances lead to an unjust outcome, for example where a generics company actively encourages use of the generic product in the patented indication.

These conclusions are not all that helpful to patentees holding medical use claims. However, generic manufacturers would be unwise to draw much comfort from these findings. There are at least two reasons for that.

First, as noted above, these conclusions are not binding, and it should be noted that there was no patent specialist among the Supreme Court judges hearing this case. Going forwards, a patent specialist (Lord Kitchin) will sit on the Supreme Court, which may well affect the outcome of any future case on this topic.

Second, all of the Supreme Court judges took great pains to emphasise that their decision applied only to claims in "Swiss-style" format, and that their reasoning could not be applied to the more modern "compound for use" medical use claim format[6]. As discussed further below, it is possible that it would be considerably easier for a patentee to establish infringement of a "compound for use" claim under comparable circumstances.

Second medical use claims going forward

The decision of the Supreme Court on validity, although no doubt unwelcome to Warner-Lambert, may not significantly impact the practice of applicants in this area going forwards.

As noted above, the governing EPO case law was arguably inconsistent on the issue of what is required for a "plausible" disclosure of efficacy. However, other jurisdictions (e.g., Canada, China and Japan) have strict requirements that a medical use claim be supported by technical evidence indicating that the activity ascribed to the claimed therapeutic product does in fact arise. Given that the majority of patent applications in this field are designed to be filed widely around the world, prudent patentees have for some time been including in relevant patent applications data and/or cogent scientific reasoning to support the medical use specified in the claims.

As regards infringement, the majority of cases likely to be litigated going forwards will contain the modern "compound for use" claims, rather than the "Swiss-style" claims considered in this decision. As discussed above, the reasoning of the various judges in this decision was explicitly directed to "Swiss-style" claims. Further, although all of the Supreme Court judges rejected a test based on "foreseeability", it is possible that a "compound for use" claim could indeed be infringed by manufacture of a generic product on the basis that it is foreseeable that at least some of the generic product will end up treating patients suffering from the claimed indication. This is discussed further below.

Foreseeability test for "compound for use" claims

A "compound for use" claim is a claim to a product, unlike a "Swiss style" claim which is directed to a process. It therefore seems difficult to escape the conclusion that a patient who takes a generic medicament to alleviate the claimed indication is practicing the subject matter of the claim.

In particular, under the circumstances outlined above, the patient will usually have a subjective intention to treat his or her disease symptoms by taking the medicament. Further, even if a more demanding test is imposed, requiring some "outward manifestation" referring to the patented indication, the product in hand of the patient might satisfy this requirement. Thus, a prescription medicine supplied to a patient will generally carry a label instructing administration "as directed by your doctor". The doctor's instructions will, of course, have been given with reference to the patient's condition. Thus, arguably there is some outward manifestation on the final medicament which cross-references directly to the patented indication.

If we assume that the patient is indeed practicing the subject matter of the "compound for use" second medical use invention, then a generic manufacture is likely to incur liability for contributory infringement under circumstances whereby the manufacturer can foresee use of the generic medicament by patients suffering from the patented indication. Liability here arises under Section 60(2) of the UK Patents Act. That Section reads as follows:

"Subject to the following provisions of this section, a person (other than the proprietor of the patent) also infringes a patent for an invention if, while the patent is in force and without the consent of the proprietor, he supplies or offers to supply in the United Kingdom a person other than a licensee or other person entitled to work the invention with any of the means, relating to an essential element of the invention, for putting the invention into effect ***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.***" (emphasis added).

Although the patient is of course exempt from any infringement action, the patient is not a "person entitled to work the invention". It therefore follows that supply to the patient can in principle contravene Section 60(2) where the generic manufacturer knows, or where it would be obvious to a reasonable person, that the generic drug would ultimately be used by patients to treat the patented indication.

Further, the existing case law governing Section 60(2) has made it clear that foreseeability of anybody in the supply chain is sufficient to establish liability for infringement. The foreseeability test is not limited to the party purchasing drugs directly from the generics supplier.

A leading case in this regard is *KCI Licensing v Smith & Nephew*[7]. This case concerned a medical apparatus having an inlet tube. The claim required a clamp on the inlet tube. The defendant supplied an apparatus with a stopper on the inlet tube in place of the clamp. It did not suggest or induce any modification of this apparatus by replacing the stopper with a clamp. Nevertheless, the Court of Appeal found infringement under Section 60(2) of the UK Patents Act. It was sufficient that the defendant knew (or ought to have known) that some of the end users (medical personnel in a hospital) would make the modifications necessary to bring the apparatus within the scope of the claims.

Applying this reasoning to the supply of a generic medicine, if it is held that the patient is indeed putting the claimed invention into effect, then supply of a generic medicine should infringe under Section 60(2) if the generics manufacturer can foresee the relevant cross label use.

This analysis demonstrates that the approach taken by the Supreme Court in *Warner-Lambert v Actavis*, which rejects a "foreseeability" test to govern infringement of a medical use claim by a generic manufacturer, may well not apply to claims in "compound for use" format. Generics companies would therefore perhaps be unwise to conclude that securing a "skinny SmPC", and avoiding any outward indication of the patented disease state in their generic product, will be sufficient to avoid infringement of a "product for use" claim in the UK.

Footnotes

1. The EPO no longer grants second medical use claims in "Swiss-style" format in applications with a priority date after 29 January 2011. Only the "compound for use" format is therefore available in new European patent applications.
2. See for example references to the need for evidence/data in reasons 4.5, 4.6.2, 4.6.4 and 4.9 of T488/16
3. See for example reason 15 of T578/06
4. Biogen v Medeva [1996] UKHL 18
5. Lord Sumption was quoting here from Decision T609/02 from the EPO
6. See for example paragraphs [63], [86], [123] and [199] of the Supreme Court judgment

7. KCI Licensing Inc and others v Smith and Nephew plc and others [2010] EWCA Civ 1260

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