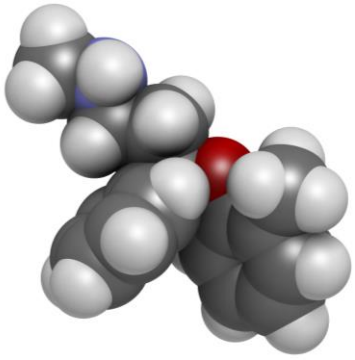

Actavis v Eli Lilly

How Eli Lilly avoided being caught in a squeeze between obviousness and insufficiency.

An often-used argument when seeking revocation of a patent, where it is alleged that the patent discloses little more than the prior art, is that the patent is obvious and if it not obvious then it is insufficient. In *Actavis v Lilly*[1], Mr Justice Henry Carr rejected this squeeze between obviousness and insufficiency in a judgement where cross examination of the expert witnesses proved both crucial and surprising.

Background

Actavis sought revocation of EP (UK) 0 721 777 (the patent) based on a lack of inventive step in view of two prior art documents and also alleged that the patent is insufficient or obvious on the basis that the disclosure lacks plausibility. The patent was set to expire in January 2016 and Lilly obtained a Supplementary Protection Certificate which expires on 29 May 2019. Claim 1 of the patent is a Swiss-form second medical use claim directed to the "use of tomoxetine for the manufacture of a medicament for treating attention-deficit/hyperactivity disorder." Lilly counterclaimed for threatened infringement as Actavis had brought this claim to 'clear the way' for the launch of a generic product before the expiration of the SPC that would infringe the patent if it was found to be valid.

Tomoxetine is commercially available in the form of the R-stereoisomer (atomoxetine)and had been sold by Lilly under the brand name Strattera™ for the treatment of attention-deficit/hyperactivity disorder (ADHD) since 2004, and its annual sales in the UK are in excess of £10 million. Actavis submitted that there was a squeeze between lack of inventive step and lack of plausibility. Their argument was that the patent discloses no more than a bald assertion of the effectiveness of atomoxetine to treat ADHD and that this was known from the prior art:

"... if the skilled person was unconvinced by the prior art, he/she (hereafter "he") would be equally unconvinced by the patent."

Lilly's submissions were that no hint of atomoxetine for treating ADHD was given in the prior art citations which were both published over a decade before the priority date of the patent. Furthermore, the teaching of these documents was that atomoxetine could be used to treat depression and that there was no evidence at the priority date that it could be used in the treatment of ADHD. In addition, the patent expressly referred to credible evidence, later confirmed by the sales of Strattera™, that atomoxetine was a safe and effective treatment of ADHD.

The Skilled Team

It was common ground between the parties that the 'skilled person' in this case was actually a team and would include a clinician and a child and adolescent psychiatrist with expertise in treating and a research interest in ADHD who was also interested in developing new treatments for ADHD at the priority date. Carr J also found that it would include a 'basic' pharmacologist[2], given that there were no psychopharmacologists with clinical expertise in ADHD at the priority date.

[1] Actavis Group PTC EHF & Anor v Eli Lilly and Company [2015] EWHC 3294 (Pat)

[2] A pharmacologist without clinic training, as distinct from a 'clinical' psycopharmacologist

Common General Knowledge

The leading treatments for ADHD at the priority date were stimulants, primarily sold under the brand name "Ritalin", however tricyclic antidepressants (TCAs) were also used. Stimulants and TCAs both had their disadvantages and in particular Carr J found that clinicians were more cautious about prescribing TCAs for treating ADHD due to a number of sudden infant deaths in the early 1990s. Actavis submitted that the known disadvantages created a strong motivation to develop alternative treatments at the priority date, whereas Lilly submitted that there was a long felt want for alternatives which was satisfied with the launch of Strattera™.

Carr J agreed that there was motivation to develop alternative treatments to TCAs and that this motivation had existed for many years before the priority date and had increased by the unexplained sudden deaths. However, Carr J also found that the motivation was not as strong as the desire to find alternative stimulants that did not suffer from the disadvantages of known stimulants.

Actavis submitted that the therapeutic effect of TCAs in ADHD was the inhibition of "noradrenaline (NE) reuptake" and that another drug that had the same pharmacological action would be expected to produce the same therapeutic effect. However, Lilly submitted that the picture was less clear, and that it could not be assumed that this was the means that TCAs worked in ADHD. Having regard to the common general knowledge of the skilled team, Carr J's findings were that:

(i) the skilled pharmacologist would be aware of TCAs as antidepressants and that the action of TCAs would most likely result from selective inhibition of NE reuptake; and

(ii) the skilled clinician would view it as a reasonable hypothesis that TCAs would be effective to treat ADHD as a result of selective inhibition of NE reuptake.

Construction

Actavis drew on Floyd LJ's conclusion in *Warner Lambert v Actavis*[3] that the word 'for' in Swiss form medical use claims meant 'suitable and intended for' in that the use was known or could be reasonably foreseeable by the manufacturer. Actavis contended that this construction is relevant when considering plausibility in the context of sufficiency but it was concluded that, drawing on Aldous LJ's judgement in *Bristol-Meyers Squibb v Baker Norton*[4] and Floyd J's judgement in *Teva v Merck*[5], that the phrase 'for treating ADHD' in claim 1 does not mean that the treatment must be successful for or cures every patient – this will never be the case for a medical use claim as patients respond differently to treatments.

Obviousness

Carr J noted that a particular step in a claim may lack inventiveness due to trends in the field at the priority date or recent publication of prior art. Several witnesses had acknowledged the difficulty of avoiding hindsight as so much has changed in the general knowledge in the field, the priority date was over two decades ago, and it was now known that atomoxetine is a successful treatment for ADHD.

When considering the question of obviousness, Carr J stated that *"it is important not to become confused between the extent of disclosure of the specification and the invention specified in the claims... the correct question is whether the alleged invention defined in the claims was obvious."* Lord Hoffman stated in *Conor v Angiotech*[6]:

"...the invention is the product specified in the claim and the patentee is entitled to have the question of obviousness determined by reference to his claim and not to some vague paraphrase based upon the extent of his disclosure in the description. There is no requirement in the EPC or the statute that the specification must demonstrate that the invention will work or explain why it will work."

Although 'obvious to try' is not an independent ground of invalidating a patent it is one factor considered in an assessment of inventive step, and must be coupled with a fair expectation of success (as Floyd J summarised in *Omnipharm Ltd. v Merial*[7]). However, Carr J noted the "Catch 22" problem with the obvious to try approach, as

[3] Warner-Lambert Company, LLC v Actavis Group Ptc EHF & Others [2015] EWCA Civ 556

[4] Bristol-Meyers Squibb v Baker Norton [2001] RPC 1

[5] Teva v Merck [2010] FSR 17

[6] Conor v Angiotech [2008] RPC 28

[7] Omnipharm Ltd v. Merial [2011] EWHC 3393

referred to in a commentary[8] by Sir Hugh Laddie, that he higher the reward for find a solution to the problem, the more worthwhile all potential avenues will be examined and therefore it will be harder for more commercially attractive solutions to avoid an obviousness attack.

The Prior Art

The patent cited a paper by Gehlert et al. which referenced a paper by Wong et al. The experts agreed that both of these publications were addressed to a psychopharmacologist. The patent was alleged to lack inventive step in view of "Chouinard" combined with Wong and "Zerbe" combined with Wong, and both combinations were accepted by Carr J. Wong describes a molecule that inhibits NE uptake in rats and has potential as an antidepressant.

Chouinard

Chouinard described a six week open-label early phase II clinical trial of atomoxetine in ten depressed patients. Actavis' 'obvious to try' attack was that it was known that TCAs were effective to treat ADHD by inhibiting NE reuptake, and that there was a precedent for using antidepressant drugs, and in particular TCAs, as a second-line treatment for ADHD. Actavis also alleged that that was a need for an alternative to TCAs due to the deaths it had been linked to. Chouinard completed their argument as it describes atomoxetine as a selective inhibitor of NE reuptake and concludes that it is effective as an antidepressant (Chouinard also cited Wong in support). As Chouinard suggested that atomoxetine would be effective in the treatment of depression (and avoid it unwanted side effects), Actavis submitted that it would be relatively simple, with the knowledge that antidepressants (TCAs) were effective in treating ADHD, to perform a basic phase II trial to test atomoxetine on ADHD patients.

Carr J, applying the *Pozzoli*[9] approach, noted that the difference between claim 1 and Chouinard was that Chouinard did not suggest the use of atomoxetine in the manufacture of a medicament to treat ADHD. He stated that there was an "attractive simplicity" to Actavis' arguments, and during cross-examination even Actavis' expert witness, Dr. Steingard, agreed with the other experts (including Lilly's expert Prof. Hill) that it was not obvious in view of Chouinard to try atomoxetine in the treatment of ADHD. Carr J agreed that it was not obvious to try atomoxetine for treating ADHD in view of Chouinard.

Zerbe

Zerbe described a phase-I trial that administered atomoxetine to healthy humans twice a day for a week and concluded that tomoxetine should be a clinically effective antidepressant at the doses which specifically inhibit NE uptake. As with Chouinard, however, Lilly's expert Prof. Hill noted that there was nothing in Zerbe regarding ADHD or the use of atomoxetine in ADHD, and expressed the view that depression and ADHD were very different illnesses. Carr J found that if it was obvious to progress Zerbe any further it would only be as an antidepressant. Even Actavis' expert, Dr. Steingard, agreed that little could be deduced from Zerbe without further studies in depressed patients. Carr J therefore concluded that it was not obvious to try atomoxetine for treating ADHD from Zerbe, particularly given that Zerbe was published ten years before the priority date when atomoxetine had not gained regulatory approval for depression.

Fair expectation of success

Even if it were obvious in view of either Chouinard or Zerbe to try atomoxetine in treating ADHD, Carr J found that the skilled team would not have had a fair expectation that the drug would be "discernibly effective." He concluded that the skilled clinician would consider the hypothesis that the effectiveness of TCAs to treat ADHD was the result of selectively inhibiting NE reuptake to be reasonable, and therefore the skilled team may have a fair expectation that atomoxetine could be an effective treatment of ADHD. However, Carr J's view was that the picture of ADHD at the priority date was complex, and that *"a number of other contributory causes were possible"*. This degree of doubt was also reflected by Dr. Steingard who said that it was *"more indicative of an interesting project with uncertain results than a fair expectation of success."*

Insufficiency

Carr J stated that:

[8] "Patents - what's invention got to do with it?" (Chapter 6 in Intellectual Property in the New Millennium, p.93)
[9] Pozzoli SpA v BDMO SA [2007] FSR 37

"For the purpose of obviousness, the skilled person should be able to make a fair prediction that the alleged invention will, not might, succeed. A question arises as to whether the same is true in relation to sufficiency, or is the standard of "plausibility" different."

Actavis submitted that the tests were the same, citing *Regeneron*[10] in which Kitchen LJ referred to the EPO Technical Board of Appeal (TBA) in *Salk*[11]. Kitchen LJ said that the patentee must show that the product has an effect such that the claimed therapeutic effect is plausible. The TBA in *Salk* emphasised that the mere assertion of a therapeutic effect may not be enough:

"It is required that the patent provides some information in the form or, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease... Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account but only to back up the findings in the patent application... and not to establish sufficiency on their own."

Finally, Actavis contended that the word 'for' in the claim requires that it must be at least *"reasonably foreseeable"* from the disclosure of the patent that atomoxetine will be effective in the treatment of ADHD.

Lilly pointed out that lack of plausibility is not a ground of invalidity, and that the issue of plausibility only arises "*as a check on over-breadth of claim."* Lilly also submitted that even if plausibility arises in the absence of over-breadth of claim, the threshold for plausibility is lower than that for obviousness (otherwise patents would only be granted to inventions that were *"implausible"* over the prior art). Lilly submitted that Lord Hoffmann's judgement in *Conor*[12] proceeded on the basis that lack of plausibility arises for speculative patents whose breadth of claim meant that the invention was *"inherently improbable"*[13].

[10] Regeneron v Genentech [2013] EWCA (Civ) 93, [56]
[11] T 609/02 Salk Institute
[12] Conor v Angiotech [2008] RPC 28
[13] In Conor v Angiotech [2008] RPC [28] the patent said very little and offered no proof about how or why taxol would be effective to prevent restenosis, but Lord Hoffman found that this did not render the patent implausible.

Expert Evidence

Although the written evidence of Actavis' experts, Prof. Cowen and Dr. Steingard, supported their case, during cross-examination it was revealed that Prof. Cowen considered the patent's disclosure of atomoxetine as a selective inhibitor of NE reuptake to be supported by Gehlert and Wong; and Dr. Steingard *"was in no doubt that the disclosure of the patent was credible"*. Lilly's experts, Profs. Hill and Sharp, also considered the disclosure credible, but interestingly they held the mistaken belief that the patent was *"an authoritative document, and that statements would not be made in such a document without underlying evidence"*. However, Carr J ruled that this mistaken belief was only one of several reasons why Prof. Hill would consider the patent plausible.

Assessment

In Carr J's assessment he accepted that *Regeneron*[14] and *Salk*[15] were concerned with plausibility across a wide claim scope, but he did not accept that plausibly only applied to claims with wide scope. He summarised:

"In my judgement, the policy considerations underlying plausibility for sufficiency are different from those underlying fair expectations of success for obviousness, which indicates that the standard for assessment of plausibility is not the same as assessment of obviousness. For obviousness, a fair expectation of success is required because, in an empirical art, many routes may be obvious to try, without any real idea of whether they will work. The denial of patent protection based upon the "obvious to try" criterion alone would provide insufficient for research and development... and would lead to the conclusion that a research program of uncertain outcome would deprive a patent of inventive step. The reason why... the invention of a patent should be plausible is different. It is to exclude speculative patents, based on a mere assertion; where there is no real reason to suppose that the assertion is true."

In the present case, the patent disclosed for the first time the effectiveness of atomoxetine to treat ADHD as a selective NE reuptake inhibitor. Carr J stated that the

[14] Regeneron v Genentech [2013] EWCA (Civ) 93, [56]
[15] T 609/02 Salk Institute

skilled clinician would consider the hypothesis that TCAs' efficacy in treating ADHD was due to selectively inhibiting NE reuptake, and would also consider the position in relation to ADHD to be more complex. Nevertheless, the skilled team would consider the invention credible. Carr J also considered that widespread administration of the drug confirming that atomoxetine is safe and efficient to treat ADHD to be admissible and important post-published evidence. Subject to this, and the evidence of the experts, Carr J concluded that the patent was plausible, and rejected the squeeze between obviousness and insufficiency.

The claim for revocation was therefore dismissed and the counterclaim for threatened infringement succeeded.

Conclusion

It is interesting how the cited cases were interpreted by Carr J in his conclusion that the patent was both not obvious and plausible. It is a welcome reminder that, for the assessment of obviousness, the invention is defined according to the scope claims and not by the level of any supporting data or evidence in the specification. It is also a welcome conclusion for patentees that plausibility is only a threshold test that is not the same as a 'fair expectation of success,' and that if a claimed invention is credible it may be plausible even in the absence of supporting empirical data in the specification. The outcome of this case may likely have been different if the judge had considered the tests for plausibility and fair expectation of success to be the same.

It will be interesting to see how the Court of Appeal rules on these points of law, as this decision is thought likely to be the subject of a future appeal.

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