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Overactive bladder patent upheld on a-PEE-al

Kate O'Sullivan (Bristows) · Wednesday, August 2nd, 2023

On 25 July 2023, the Court of Appeal handed down its decision in *Teva & Sandoz v Astellas**[1]*** concerning the validity of Astellas' patent to mirabegron for use in the treatment of overactive bladder ("**OAB**"). At first instance, Meade J had held the patent valid and infringement by the generics' proposed acts was not separately contested. On appeal, Teva and Sandoz contended that the judge had erred in the application of the law as to obviousness. The Court of Appeal dismissed the appeal, with Lord Justice Arnold giving the leading judgment and Lord Justice Stuart-Smith and Lady Justice Falk in agreement.

First Instance decision

In 2020, Teva and Sandoz issued proceedings seeking to revoke Astellas' European Patent (UK) 1 559 427 B1 (the "**Patent**") and associated SPC. The Patent claims priority to November 2002 and, as noted above, protects mirabegron for use in the treatment of overactive bladder. Mirabegron is a ?3-adrenoceptor ("**?3-AR**") agonist which results in relaxation of the bladder smooth muscle, expanding the bladder's capacity and relieving patient symptoms. Astellas market mirabegron under the name Betmiga® and Teva and Sandoz wished to clear the way (having accepted that there would be infringement if the Patent was held to be valid).

By trial, the main issue in dispute was whether the Patent was obvious over one piece of prior art: Australian patent application 199889288 ("**AU 228**"). AU 228 discloses a series of compounds according to a Markush formula which are described as being therapeutic agents for diabetes mellitus and having anti-obesity and anti-hyperlipemia actions due to selective stimulation of ?3-AR (i.e. agonism). While the compounds are defined by Markush formula, six example compounds are disclosed: compound 5 is mirabegron. The only numerical data provided are in relation to compound 6 which is tested in a hyperglycaemic mouse model. There is no discussion of OAB and no numerical data demonstrating the selectivity of the compounds for ?3-AR.

Teva and Sandoz argued that it was common general knowledge that selective ?3-AR agonists had potential to treat OAB. Further, there was a shortage of human, selective ?3-AR agonists. Accordingly, the skilled team would be interested in the ?3-AR agonists in AU 228 and test them in the appropriate OAB model. Upon obtaining positive results, the skilled team would then take mirabegron into clinical trials with an expectation of success. Astellas' case was that ?3-AR agonism was one of a number of potential ways to treat OAB. There was no clinical evidence that ?3-AR agonism would work to treat OAB; in fact, a ?3-AR agonist had failed in human clinical trials to treat obesity. AU 228 is silent as to OAB and mirabegron's activity (i.e. selectivity and

potency). Even if ?3-AR agonism were to be pursued, there were many other compounds to choose other than mirabegron.

As regards the CGK, Meade J found that whilst there was "momentum" in the idea of using ?3-AR agonists in the treatment of OAB, it was known that certain ?3-AR agonists had failed in obesity clinical trials. Further, it was established that not all ?3-AR agonists behaved the same way, only a handful were human-selective and their potency varied. The evidence also showed that, at the priority date, there were a number of other approaches being considered to treat OAB. Meade J found that the generic companies had overstated the confidence that the skilled team would have in treating OAB with ?3-AR and had oversimplified the situation, in that they argued that the skilled team would consider *any* ?3-AR agonist would be likely to succeed as a treatment. In Meade J's view, the skilled team could not draw any conclusions about the efficacy of the compounds in AU 228 without further testing. Given the failed obesity clinical trials involving ?3-AR agonists, their known unpredictability and the absence of data in AU 228, there was no reasonable expectation of success of mirabegron as a treatment for OAB. Accordingly, the obviousness attack based on AU 228 failed.

Appeal

On appeal, Teva and Sandoz contended that the judge had erred in the application of the law as stated in *Pozzoli**[2]* and *Philips**[3]*, in particular the premise that in order to be inventive the patent must solve the problem to which is it addressed. On the basis that the Patent only provides data from rat models for OAB (i.e. no human clinical trial data or data from human tissue assays), the generics argued that Meade J's reasoning depended on two uncertainties that the Patent had failed to solve: (1) the uncertainty regarding ?3-AR agonism to treat OAB without human clinical trial data; and (2) the uncertainty as to whether mirabegron was a human ?3-AR selective agonist or a sufficiently potent agonist.

Arnold LJ did not accept these arguments for two reasons. First, it was not the case that Meade J had held the Patent to be inventive by overcoming the technical problem of side effects associated with cross-reactive ?3-AR agonists; indeed, at first instance, Astellas had accepted that the Patent does not disclose mirabegron's selectivity for ?3-AR. Instead, Meade J had found that, having read AU 288 in light of the common general knowledge, it was not obvious to try mirabegron as a treatment for OAB with a reasonable expectation of success. This was due, in part, to the skilled team's lack of confidence in ?3-AR agonism as a potential therapy for OAB and the lack of disclosure in AU 288.

Second, citing *Conor Medsystems**[4]*, the question of obviousness does not depend on the amount of evidence presented in the specification. Provided that the Patent makes it plausible that mirabegron is efficacious for the treatment of OAB (which the generics accepted), then obviousness should be assessed in the normal way, i.e. whether AU 288 read with the common general knowledge made it obvious to try mirabegron as a treatment for OAB with a reasonable expectation of success. Arnold LJ considered that Meade J had done so and thus saw no reason to interfere with his judgment, thereby dismissing the appeal.

Comment

As UK patent litigators will know, obviousness attacks at first instance before the English Patents Court hinge on a multi-factorial evaluation of all the available evidence – both the evidence given

in writing by expert witnesses in their reports and also the oral testimony in cross-examination. There is no cross-examination of witnesses in the Court of Appeal and fresh evidence is hardly ever permitted. As a result, the Court of Appeal is generally reluctant to interfere with the findings of the first instance judge absent an error of law or principle. In this instance, permission to appeal was granted on the basis of an arguable tension between the law on obviousness in *Conor Medsystems* and in *Pozzolli/Philips* and in particular about the assessment of the technical contribution of the patent. However, by the time the appeal reached Arnold LJ, the generics accepted that there was no conflict between the cases and instead ran the argument that the judge erred in principle because he did not correctly apply the law as stated in *Pozzoli* and *Philips*. After having noted the generics faced an obstacle in that Meade J's judgment "*contains a very careful, detailed and nuanced consideration of the evidence and issues*", Arnold LJ's decision succinctly deals with the generics' appeal. This decision is therefore a reminder of the challenges facing litigants attempting to appeal a finding on obviousness. In short, unless a real error of principle can be identified, appellants will face an uphill battle to persuade the Court of Appeal that a first instance judge has erred in their assessment of inventive step.

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[1] [2023] EWCA Civ 880

[2] [2007] EWCA Civ 588

[3] [2019] EWCA Civ 2230

[4] [2008] UKHL 49

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