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Mirabegron's food effect sufficiently fixed by new formulation – Astellas v Teva and Sandoz

David Hemming (Bristows) · Friday, November 3rd, 2023

A hefty judgment was recently handed down by Mellor J concerning a patent for a modified release formulation of mirabegron. The patent was held to be valid and not infringed by Sandoz, while infringement with respect to Teva (which had admitted infringement with an earlier version of its product but sought a declaration of non-infringement in relation to a new version) remains to be decided. A link to the judgment, which considered a number of grounds including a detailed analysis of insufficiency and plausibility, can be found [here](#).

Background

The compound patent for mirabegron, a drug for the treatment of overactive bladder syndrome (“OAB”), had previously been challenged by Teva and Sandoz but was held to be valid and infringed (see judgment of Meade J, [2022] EWHC 1316 (Pat) [here](#)). At the date of trial in the present matter, Teva and Sandoz had obtained permission to appeal but had been enjoined from launching their generic products. This appeal ([2023] EWCA Civ 880) was later dismissed – see [here](#).

The present case started as a claim for infringement brought by Astellas Pharma Inc (“Astellas”) against Teva and Sandoz (the “Defendants”). As noted above, Teva admitted infringement in relation to its original mirabegron product, but subsequently amended its formulation to a new product and sought a declaration of non-infringement (“DNI”). The parties agreed that due to time constraints, Teva's DNI could be heard at a later date. Sandoz did not admit infringement and this was one of the issues considered at trial.

Both Teva and Sandoz counterclaimed for invalidity (on the grounds of obviousness, insufficiency and added matter).

On insufficiency two attacks were made – the main one being excessive claim breadth. In particular, Teva and Sandoz said that it was not plausible that the invention of the Patent works (in the sense of reducing the food effect – see below) with substantially all the products falling within at least claim 1, and that this claim scope exceeded the technical contribution of the Patent.

The Skilled Team and the CGK

The parties agreed that the skilled team would include a clinician and a formulator, but there was significant debate between the parties as to the degree of involvement by a skilled

pharmacokineticist. Astellas' case was that the skilled formulator would have some pharmacokinetics knowledge, but that on having concerns about accumulation of the drug, they would immediately reject an extended release formulation and would go no further in consulting a PK expert. The judge, siding with the Defendants, held that the skilled pharmacokineticist would in fact be a key part of the team and would be involved from the beginning. Either way, this point did not affect the CGK given to the skilled team as a whole.

The key teaching in the specification was of a formulation of mirabegron which would cause the dissolution rate (i.e. the rate of drug release) to be the rate limiting step for absorption. This in turn lowered the effect of food on the drug. The dissolution parameters were defined by various numerical limits within the claims.

Construction of the Patent

As in many patent disputes, there was a debate about construction. In this case, the judge noted that the insufficiency arguments led to a "heated" debate over what certain parts of the specification mean and this in turn became crucial to the construction of the words "*a pharmaceutical composition for modified release*" in claim 1 (referred to as "**Integer A**"). This phrase was defined in the specification of the patent, but the correct interpretation of this definition in context, and the limits of that definition, were in dispute. In particular, the extent to which the claim required a particular reduction in food effect to be demonstrated. Noting that there is a difference between being over-meticulous and merely being careful, the Judge came to a view on construction which was favoured by the Defendants and in which some reduction in food effects is a requirement of the claim as properly construed.

Insufficiency – excessive claim breadth

The Defendants argued that the data in Example 3 (the only PK data in humans) did not support the scope of claim 1 (i.e. it was not plausible that the invention works with substantially all the products falling within the claim) and consequently the claim scope exceeded the technical contribution of the Patent. Further, they said that conditional amendments proposed by Astellas would have the same issue. There was a second claim breadth attack which fell away with an unconditional amendment to the claim.

The starting point for Mellor J's analysis was Kitchin LJ's judgment in *Regeneron v Genentech* [2013] EWCA Civ 93. In particular, he noted the fourth principle from that case, that it must be possible to make a "reasonable prediction" that the invention will work with substantially everything falling within the scope of the claim (i.e. be credible) and that if this is not possible, then the monopoly exceeds the technical contribution made by the patent to the state of the art.

Also relying on a passage from the Supreme Court's judgment in *Warner Lambert v Generics (UK)* [2018] UKSC 56 ("*the specification must disclose some reason for supposing that the implied assertion of efficacy in the claim is true*"), Mellor J noted that while the parties construed integer A differently (efficacy being express in the Defendant's construction rather than implied), the threshold for plausibility was the same on either construction, with the key wording from that test being "*some reason for supposing*", which must be disclosed by the specification of the patent. He also referred to the Court of Appeal's decision in *FibroGen v Akebia* [2021] EWCA Civ 1279, in which Birss LJ clarified the test for "*reasonable prediction*".

The Defendants argued that the key question in the present case was whether it was possible to

make a reasonable prediction that compositions which satisfy the structural features of claim 1 and which also satisfy the relevant functional feature (an in vitro dissolution profile), will be capable of reducing the food effect that is seen in conventional tablets of mirabegron. Astellas did not dispute that this was the appropriate question to address.

After considering expert evidence on this point and both sides' submissions (the Defendants' that the limits of an integer were arbitrary, and that it was not credible that every formulation within the dissolution range would show a required reduction in food effect, versus the Claimant's contention that the evidence established that products with the dissolution profile required by the claim and made with the excipients disclosed in the claim would all be expected to alleviate the food effect to some degree, on the basis that the Defendants' proposed profiles were hypothetical), the judge held that the Defendants' arguments were flawed. First, they had misunderstood the teaching of the Patent, and second, their argument ignored the normal shape of release curves which had been proposed.

Regarding the arbitrary limits, the judge noted that the Patentee had to place some boundary on the scope of its claim and that from an insufficiency perspective, there was nothing wrong with what appears to be an arbitrary limit, provided that the promise of the Patent is in fact delivered. On the test from *Akebia*, Mellor J said that the invention would work if the formulation reduced the impact of a food effect. Based on the teaching from the Patent, it was therefore possible to reasonably predict that the reduced food effect could be achieved across the scope of the claims. Accordingly, the Defendants' arguments on lack of technical contribution and *AgrEvo* obviousness also fell away.

The judge also rejected an argument on uncertainty insufficiency.

Obviousness

Ultimately, following a thorough statement of the applicable principles on the law of obviousness, and a lengthy analysis of a number of issues relating to each of three pieces of prior art, Mellor J held that on the correct construction of Integer A, Claim 1 was not obvious (interestingly, he said that on Astellas' own proposed construction, Claim 1 would have been obvious).

Infringement by Sandoz

Sandoz took the position that infringement of its product would turn on the construction of Integer A of Claim 1 – i.e. whether its product was a “pharmaceutical composition for modified release” (it accepted that its product fell within the claim regarding the required dissolution profile). If Astellas' construction was favoured, then Sandoz admitted that its product fell within the claim; if Sandoz' construction was favoured then it said infringement was not proven. Given that Astellas did not establish that a “reduction in food effect” was demonstrated by Sandoz' mirabegron product, then on the Judge's construction of Claim 1 there was no infringement. In making this finding, the judge noted that plausibility is a different standard from that required to prove infringement – even though the Patent makes it plausible that a reduction in food effect is achieved across the breadth of claim, to prove infringement at least some reduction in food effect must be demonstrated.

Comment

This was a very lengthy judgment covering a wide range of the patentability requirements and their

interplay with issues of construction and infringement. However, it ultimately proves (yet again) how crucial issues of construction can be.

In the context of the recent EPO decision on plausibility (G2/21) and a flurry of interest in this issue, it is also interesting to read a further case from the English Patents Court in which they grapple with this issue and find the patent sufficient. In addition, it will be interesting to hear the outcome of Teva's upcoming DNI, assuming that it continues to pursue this approach in light of this judgment.

As an aside, the judge apologised for the time taken to render the judgment, citing a backlog as a result of his mammoth FRAND judgment in *InterDigital v Lenovo*. Given the length of this judgment soon after, this author hopes that Mellor J's keyboard is still in working order!

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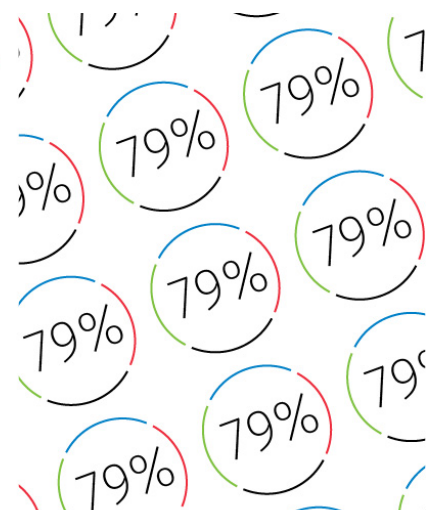
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