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Actavis v ICOS

Will dosage regime patents stand up in the UK courts?

ICOS's patent EP 1173181 is directed to a dosage regimen of the phosphodiesterase type 5 (PDE5) inhibitor tadalafil, which is marketed by Lilly under the brand name CIALIS™ (for male erectile dysfunction). The product has enjoyed considerable commercial success with UK sales of $99 million in 2014. The relevant claims specify tadalafil in a unit dosage form for oral administration up to a maximum total dose of 5mg per day, when used to treat sexual dysfunction.

An advantage of tadalafil over other PDE5 inhibitors like sildenafil (VIAGRA®) is that the effective use of tadalafil at a maximum dose of 5mg per day can reduce side effects such as headaches, backaches, myalgia and flushing (in contrast with sildenafil which is marketed in doses of 25mg, 50mg and 100mg).

Actavis, TEVA and Mylan began proceedings to revoke the patent and "clear the way" ahead of the marketing of their own generic tadalafil product. ICOS and Lilly counterclaimed that the claimants were threatening to infringe the patent. In the High Court, Birss J held that the relevant claims were valid and infringed. The judge gave the claimants leave to appeal.

Although various questions of construction and validity were in issue on the appeal, what makes this case of interest is the question as to whether a specific dosage regime that was not taught or suggested by the prior art and represented a surprising result, nevertheless lacks inventive step, because a skilled person could have arrived at it through routine experimentation. Specifically, the prior art taught a PDE5 inhibitor at a concentration of 50mg and the patentee argued that there was no reasonable expectation that a dose of 5mg, which is considerably lower than 50mg, would be efficacious at all or would have the benefits it has. At first instance, Birss J upheld the claims on the basis that the skilled team could not have expected that a dose of 5mg would be effective, notwithstanding his finding that there would have been a motivation to conduct routine dose-ranging studies to investigate whether such a lower dose would work and that there was a reasonable expectation that a lower dose would work.

In a very thorough judgment from the Court of Appeal, Kitchin LJ examined all of Birss J's findings of fact before disagreeing with his conclusion, saying: "*The judge has lost sight of the fact that, on his own findings, the claimed invention lies at the*

end of the familiar path through the routine pre-clinical and clinical trials' process. The skilled but non-inventive team would embark on that process with a reasonable expectation of success and in the course of it they would carry out Phase IIb dose ranging studies with the aim of finding out, among other things, the dose response relationship. It is very likely that in so doing they would test a dose of 5mg tadalafil per day and, if they did so, they would find that it is safe and efficacious. At that point they would have arrived at the claimed invention."

Floyd LJ, agreeing with Kitchin LJ, put it another way: "*It is true that the judge made a finding that the skilled team would be surprised by the result, namely efficacy at 5 mg/day. However it is a result which on his findings would be arrived at by the standard, routine enquiries into dose response which are required by Phase IIb clinical trials. The surprising result, once uncovered, does not make these routine enquiries inventive.*"

In summary then, the Court of Appeal has held that an unexpected result is not enough to support an invention if it is the result of a routine enquiry carried out with an expectation of a positive outcome. Does this mean the end for dosage regimen patents in the UK? In argument Actavis relied heavily on the comment of Jacob LJ in *Actavis UK Ltd v Merck & Co Inc* [2008] RPC 26 in which he said: "*So holding is far from saying that in general just specifying a new dosage regime in a Swiss form claim can give rise to a valid patent. On the contrary, nearly always such dosage regimes will be obvious – it is standard practice to investigate appropriate dosage regimes*." However, Kitchin LJ in *ICOS* was keen to emphasise that this does not mean that investigations into appropriate dosage regimens cannot yield patentable inventions, pointing out, as Jacob LJ had previously recognised, that: "*research into new and better dosage regimens is clearly desirable and that there is no policy reason why the discovery of a novel and non-obvious dosing regimen should not be rewarded by a patent.*"

Indeed, it is not difficult to think of situations in which arriving at a particular dosage form requires something more than routine experimentation, even if the investigation of dosage regimens is routinely carried out in any event during the course of a product's route to regulatory approval. However, this was not such a case.

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