ON THE OTHER HAND: IS THIS THE LAST WORD ON PATENTING ENANTIOMERS?

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The judgment of the Court of Appeal in *H Lundbeck a/s v Generics UK Ltd and others*[1] may turn out to be the last word on the important issue of the patentability of individual enantiomers. This is perhaps more likely to be the case than it would usually be for a decision of the Court of Appeal, on account of Lord Hoffmann taking the highly unusual step of joining two Lord Justices of Appeal, Smith and Jacob LLJ, and giving the leading judgment. The interpretation and application of the law by these eminent judges cannot be faulted. Yet no chemist would hesitate to declare the result to be bizarre. How then has this happened?

The Danish pharmaceutical company Lundbeck invented a drug, citalopram, which is an anti-depressant in the class known as selective serotonin reuptake inhibitors. Lundbeck's patent for citalopram expired several years ago, since when generic citalopram has been sold by a number of manufacturers. However, Lundbeck subsequently obtained the grant of a patent for the (+) or 'S' enantiomer of citalopram alone, generally known as escitalopram. This patent, EP(UK) 0347066 ('the patent') claims not only a method for resolution of citalopram (claim 6), but also escitalopram itself and pharmaceutical compositions containing it (claims 1 and 3).

Background Chemistry

A little background chemistry may be helpful. Certain chemical compounds exhibit a property known as chirality, which means that they can exist in two molecular structures which are mirror images of each other, but are non-superimposable (and therefore not identical). Many naturally occurring compounds are chiral but, unless special steps are taken during preparation, synthetic versions of them will exist as a 50:50 mixture of the two enantiomers. Such mixtures are termed racemic mixtures or racemates. It is possible to separate the two enantiomers from a racemate by a process termed resolution, although doing so may be difficult.

The individual enantiomers of a chiral compound exhibit identical physical properties such as boiling points and react in an identical manner (and at identical rates) with non-chiral molecules. However, individual enantiomers differ in two key respects. First, they rotate the plane of polarised light in opposite directions: they are optically active. The direction in which the individual enantiomers rotate light is often notated by a (+) or (–) sign, meaning that light is rotated to the right and left respectively. Secondly, and importantly from the point of view of pharmaceutical chemistry, the reactions of the separate enantiomers with other chiral molecules are often dramatically different. Most drug targets within the human body (for example, proteins) are chiral. Consequently, if a chiral drug is administered as a racemate, typically only one of the enantiomers will display the required pharmaceutical activity, while the other may be inactive or may even display undesirable side effects. Consequently, the preference in recent times has been for chiral drugs to be prepared and administered as a single enantiomer.

Novelty

A number of manufacturers of generic pharmaceuticals took action to revoke the patent. In the proceedings in the Patents Court before Kitchin J,[2] the claimants did not argue that the prior art disclosed the single enantiomer, escitalopram, but contended that the scope of claim 1 extended to the single enantiomer when present (in a 50:50 mixture with the other enantiomer) in the racemate. Lundbeck conceded the existence of a prior enabling disclosure of racemic citalopram, but contended that claim 1 of the patent was limited to the single enantiomer in question, excluding the racemate. Applying the approach to patent construction set out in *Kirin-Amgen*,[3] that is, what would a person skilled in the art understand the patentee to have used the language of the claim to mean, the judge, after hearing expert evidence, held that the patent claimed only the isolated enantiomer and that the racemate did not fall within claims 1 or 3. The attack on the grounds of anticipation therefore failed.

In their judgments on the appeal, both Lord Hoffmann and Lord Justice Jacob dismissed very swiftly any argument of lack of novelty, and agreed with Kitchin J that the skilled person would not have understood claim 1 of the patent to have encompassed the unresolved half of the racemate.

1) [2008] EWCA Civ 311.

2) *Generics (UK) Limited and others v H. Lundbeck A/S* [2007] EWHC 1040.

3) *Kirin-Amgen Inc. v Hoechst Marion Roussel Limited* [2005] 1 All ER 667.

Inventive Step

The claimants also argued that the patent lacked an inventive step, because it was obvious to try to separate the enantiomers of citalopram, and at the priority date (1988) it was obvious to use the method of resolution disclosed in claim 6. The judge accepted that in 1988 it had been an obviously desirable aim to prepare and test the single enantiomer, but then held that the fact that there was no known means to effect the separation meant that the product claims were not obvious.

The method of claim 6 is not a direct resolution of the racemic mixture, but relies instead on the separation of the enantiomers of the precursor of citalopram (using the usual synthetic route) which is referred to as the diol, followed by conversion of each enantiomer of the diol to citalopram separately. The judge held that the critical issue was whether it would have been obvious to the skilled person that the diol could be converted to escitalopram without losing its stereochemistry. This particular issue was hotly disputed, with each side's experts disagreeing over the expectations of the skilled person in 1988. Kitchin J agreed with the patentee, holding that the skilled person would have believed that the attempted conversion of the chiral intermediate to the final product would yield a racemic mixture, rather than the single enantiomer (escitalopram). The attack on claim 6 on the grounds of obviousness therefore also failed.

Jacob LJ had no hesitation in agreeing with Kitchin J's finding of lack of obviousness, because he agreed that the skilled man would have had no expectation that the method of resolution that was ultimately successful would have worked. Lord Hoffmann went into greater detail, but came to the same conclusion. He made the point that although the diol was prior art, as was its conversion to citalopram, there was no teaching of how to separate the enantiomers of the diol, nor how to convert them into the individual enantiomers of citalopram. The separation could be achieved by known and tried methods, but the potential problem of the conversion to citalopram without loss of stereochemistry remained. Depending upon which of two types of reaction mechanism occurs, the stereochemistry may either be preserved to give a single enantiomer, or lost to give the racemate. The generic manufacturers had accepted that no one would have known whether the method was going to work, but the opinion of their expert witness, Dr Newton, was that the reaction looked promising, so the skilled man would have tried it. In support of this, Dr Newton said that the skilled man would have known from guidelines set out in two papers by Sir Jack Baldwin (known as 'Baldwin's Rules') that the type of reaction mechanism that preserves stereochemistry (known as an S_N2 reaction) would be favoured. Ironically, it was these very rules that led to Kitchin J finding that the method was not obvious, a finding followed by Lord Hoffmann and Jacob LJ. This came about because Lundbeck's expert witness, Professor Davies, disagreed with Dr Newton's interpretation of Baldwin's Rules. In Professor Davies' opinion, which was accepted by the judge, Baldwin's Rules suggested that the desired reaction was unfavourable, and would be expected to proceed instead by the alternative S_N1 reaction mechanism, in which stereochemistry is lost. As we now know, irrespective of what Baldwin's Rules might have predicted, the desired reaction clearly was favoured, because that is what happens, and it is very easy to do.

Professor Davies eventually provided an explanation for his 'correct' application of Baldwin's Rules giving an incorrect prediction. However, that can hardly be relevant. If it takes even Oxford's Waynflete Professor of Chemistry two attempts to get the prediction right by applying Baldwin's Rules, they are not going to be much help to the average addressee of the patent. That is the point. In the real world of the industrial laboratory rather than the court room, the practical chemist is unlikely even to have bothered to think about Baldwin's Rules. Separating enantiomers may be notoriously difficult, but everyone knows that eventually it is going to be done. It has long been well known that one way of making a single enantiomer of a compound is to start with a precursor that is already a single enantiomer, and then make the desired compound from it in a way that preserves the stereochemistry. If a resolution is proving particularly intractable, it must therefore be obvious to go back a step in the synthetic route, and try separating the enantiomers of the immediate precursor, in the present case the diol. The method for the crucial reaction described in the patent uses known reagents, and, above all, was very quick and easy to try, so the average skilled chemist would have found it quicker and simpler just to try the reaction.

The principal reason for the judges all failing to find obviousness was their acceptance of the rather surprising evidence of an eminent professor, who was rather more qualified than the intended addressee of the patent. However, they may still have come to the same conclusion on the basis of the new test in *Saint-Gobain*,[4] that has been followed in cases such as *Angiotech*,[5] which requires that for a result to be obvious, it must be more or less self-evident that it will work. The chemist might have looked at the question differently: to him it was obvious because he had no doubt that one or other of the standard methods in his repertoire would work, and if the first one he tried didn't, then he would

4) *Saint-Gobain v Fusion Provida* [2005] EWCA Civ 177.

5) *Angiotech Pharmaceuticals Inc. v Conor Medsystems* [2007] RPC 20.

have tried another until he found one that did. Prior to *Saint-Gobain* the English Patents Court was sometimes thought to make it too easy to find obviousness. Now the Patents Court has become more friendly to patentees by going to the other extreme. Wherever the line for what is obvious is drawn, strange results will sometimes emerge.

Sufficiency

The final attack made by the generic manufacturers was that the product claims (1 and 3), which claimed escitalopram however obtained, were far too broad to be supported by the disclosure and were therefore invalid for insufficiency. Kitchin J held that it was obviously desirable, as at 1988, to separate the enantiomers of citalopram. The inventive step was not in deciding to separate the enantiomers, but in finding a way it could be done. He then considered the House of Lords' decision in *Biogen v Medeva*,[6] in which Lord Hoffmann held that the patent specification must enable the invention to be performed to the full extent of the monopoly claimed and that a patentee who has found a way of achieving an obviously desirable goal should not be permitted to monopolise every other way of doing so. The patent does not teach any general method of preparing the single enantiomers, other than by the single method described in claim 6. In consequence, whereas he held claim 6 to be valid, he found claims 1 and 3 to be too broad, and thus invalid.

It was on the issue of sufficiency that the Court of Appeal differed from Kitchin J's decision, and upheld the validity of the claims in the patent to escitalopram and pharmaceutical compositions containing escitalopram. It had generally been understood, not least by Kitchin J, that the principle of what has become known as 'Biogen insufficiency' has general applicability. Lord Hoffmann himself, however, explained that this was not so, and that, in general, a product claim is fully enabled so long as one method of making that product is disclosed. Lord Hoffmann went on to explain that the position in Biogen itself had been different because the DNA molecule for which the inventor had disclosed one method of preparation, had previously existed, albeit not isolated but as a mixture together with many other substances in people suffering from hepatitis B. One could forgive Kitchin J for believing that the same reasoning applied in the present case, in which the product, namely escitalopram, was already known and had previously existed, albeit as a mixture with its other enantiomer.

Jacob LJ elaborated somewhat on the consequence that when a patentee successfully has a product claim granted, then he actually gets rather more than he has invented. First, such a claim will have the effect of covering all ways of making the product, including ways which may be inventive and quite different from the patentee's route. Secondly, it would give him a monopoly over all uses of the patented compound, including uses that he has never thought of. However, Jacob LJ saw nothing wrong in the fact that compound claims may give a patentee 'more than he deserves', which, he considered, had not in practice proved to be much of a problem.

Once again, the chemist might find the judgment surprising. In the case of the isolation of a naturally occurring compound for the first time (for example, from a plant) and the discovery that such a compound has a useful pharmaceutical effect, it has long been accepted that if the relevant compound had not previously been known, the patentee would be entitled to an absolute monopoly of that compound and its use for any purpose. The position is rather different when a single enantiomer is isolated from a racemic mixture. A patentee who has isolated a compound from a plant extract may have little idea that any particular compound (among, possibly, thousands present) will have any useful quality, whereas it was known that at least one of the two enantiomers present in racemic citalopram was an effective anti-depressant. Indeed, nobody, including the prospective patentee, knows *a priori* what compounds are even present in the plant extract, and even less what their structures are. By contrast, the fact that escitalopram was present in racemic citalopram was known, its structure was known, and all of its properties were known except for the way in which it rotated a beam of polarised light, and how it reacted with other chiral compounds.

Conclusion

As we said in the opening paragraph, this may turn out to be the last word on the patenting of enantiomers. However, the result may, in practice, not make much difference, because there will not be many cases in which the method used to resolve the racemate is not held to be obvious.

A somewhat surprising consequence of the decision of the Court of Appeal in this case is that the patentee's contribution to the art (for the purposes of considering sufficiency) is not necessarily the same as the inventive step underlying a patent. As Lord Hoffmann explained, if a product claim satisfies the requirements of section 1 of the 1977 Act, the technical contribution is the product and not the process by which it was made, even if that process was the only inventive step.

6) [1997] RPC 1.

The requirements of section 1 include novelty and inventive step, which probably explains the discrepancy between the judges' conclusion and that of the chemist referred to in the opening paragraph. The average chemist would, we believe, have some difficulty in regarding one of the enantiomers of a known racemic mixture as being novel and inventive. The enantiomer, he would say, has been known for years, and it has been sold by the ton, albeit as a 50:50 mixture with the other enantiomer. The law, however, is made by lawyers, and legal cases are argued and decided by lawyers.