Patent decisions on patents for chiral compounds

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A chiral compound is one which has at least one asymmetric carbon centre. As a result, there are at least two forms of the compound called enantiomers or steroisomers. Different enantiomers normally have different functions and activities in the human body. The importance of chirality in the pharmaceutical field came to the foreground following the experience with thalidomide. Thalidomide was marketed in 1960s as a mild sedative and antiemetic. Thalidomide is chiral and has two enantiomers one of which was a nonteratogenic sedative and the other of which was teratogenic. As a result of being taken by pregnant women, thalidomide caused widespread deformities in the children of those women. As an aside, thalidomide is atypical in that each of the two enantiomers reverts over time to a mixture of the two enantiomers i.e., they self-racemise. Thalidomide has been found to be useful for treating other diseases but is of course now contraindicated for various classes of patients including pregnant women.

The first patented chiral compound to be litigated fully in the English courts was atorvastatin in the mid-1990s (Ranbaxy v Warner-Lambert). The Patents Court decision was handed down in October 1995 and the Court of Appeal decision in June 2006. This case has been followed in the past couple of years by two further cases, the first concerning escitalopram (Generics v Lundbeck) and the second concerning **levofloxacin** (Generics v Daiichi). The Patents Court decision in the **levofloxacin** case was handed down last year and the House of Lords decision in the escitalopram case was handed down in January of this year.

In this article, we consider the issues raised in these cases arising out of the chiral nature of the compounds the subject of the patents in suit. The decision on the sufficiency issue argued in the House of Lords in the escitalopram case, however, is applicable to all patents and not

just those concerning chiral compounds.

Infringement

Two patents were in dispute in the atorvastatin case. The second was held invalid for lack of novelty and obviousness at first instance and the finding of lack of novelty was upheld on appeal. The validity of the first patent (referred to as the basic patent) was not in issue. The defendant Ranbaxy however had requested a declaration of non-infringement of the basic patent. The basic patent claimed the chemical compound atorvastatin defined by reference to the structure of the compound. Thus, claim 1 was to "A compound of structural formula" (1).

Apart from the structure, the only reference in the basic patent to stereochemistry was in the following passage:

> *"The compounds of structural formula 1 above possess two asymetric carbon centres, one at the 4-hydroxy position of the pyran-2-one ring and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. The asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis- isomers and the other two of which are the R-trans- and the S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula 1 above."*

Ranbaxy wished to sell the therapeutically active enantiomer and argued that the claim covered the racemate but not each of the two trans-enantiomers separately.

At first instance, Pumfrey J, construing the claim through the eyes of the notional skilled addressee and in the context of the specification, held that the claim covered not merely the racemate but also each of the two trans-isomers separately. He therefore refused to grant the declaration. His decision was upheld on appeal to the Court of Appeal.

Pumfrey J's decision on the issue was based on his findings of fact as regards the common general knowledge of the skilled addressee at the date of the basic patent in 1986 and in particular the fact that the skilled addressee would have appreciated that (1) the compound comprised

a number of enantiomers, (2) one of the enantiomers was likely to be considerably more therapeutically effective as a cholesterol lowering drug than the other (a feature of this class of drug) and (3) the racemate was resolvable into its constituent enantiomers using conventional techniques.

Novelty

The issue which arose for the first time in the **levofloxacin** case was whether a claim to an enantiomer was anticipated by the prior disclosure of the racemate (as well as the way of making the racemate). The defendant in the **levofloxacin** case accepted that the claim in issue did not extend to the racemate i.e., it covered only the enantiomer. The prior art relied upon as anticipating the claim was a prior patent and a prior paper, both of which disclosed ofloxacin (the racemate) and also a way of making it.

Kitchin J held, relying on the House of Lords decision in Synthon v SKB (2005 UKHL 59) that the claim was not anticipated. As Lord Hoffman had made clear in the Synthon case "… anticipation requires prior disclosure of subject-matter which, when performed, must necessarily infringe the patented invention" Kitchin J held as a matter of fact that neither of the two pieces of prior art taught or suggested resolution of the racemate (ofloxacin) into its two constituent enantiomers (one of which was levofloxacin).

In reaching this conclusion, Kitchin J took comfort from the obiter dicta made by Lord Hoffmann in the Court of Appeal decision in the escitalopram case. In the **levofloxacin** case, the defendant accepted that the prior art did not anticipate the isolated enantiomer. Lord Hoffmann had commented on the fact that this approach was consistent with the settled jurisprudence of the EPO namely that the disclosure of the racemate does not in itself amount to a disclosure of the enantiomers. The point did not arise for a decision in the escitalopram case because the defendant had argued that the claim to the enantiomer in that case covered not merely the isolated enantiomer but also the enantiomer as part of the racemate. The anticipation attack in the escitalopram case therefore turned on the construction of that claim i.e., whether it included the enantiomer as part of the racemate. Kitchin J held that it did not and his decision on this issue was upheld by the Court of Appeal.

As an aside, it is worth noting that in the **levofloxacin** case Kitchin J declined to follow several decisions of the German Patents Court which had come to a different conclusion on the same issue on the basis that they had conflated the issues of novelty and obviousness. In January of this year, in the appeal in the olanzapine case in Germany, the German Supreme Court in fact overturned one of those decisions of the German Patents Court finding that the test applied by the German Patents Court was too broad. In the light of that decision, it is expected that the German Supreme Court will also overturn the German Patents Court decision on novelty in the German escitalopram case. Overall, it seems that the German courts are moving towards the more "photographic" approach to novelty traditionally applied by the English courts.

Obviousness

Obviousness is an issue which turns on the specific finding of facts made by the Court based on the opinions of the experts giving evidence on behalf of the parties.

In the atorvastatin case, obviousness was in issue as regards the second patent which was directed to the hemicalcium salt of the therapeutically active enantiomer of atorvastatin. At first instance, Pumfrey J held that the second patent was invalid for both anticipation (over an intervening reference) and obviousness (over the basic patent). As the anticipation attack was upheld on appeal, the Court of Appeal did not hear argument on the issue of obviousness.

In the **levofloxacin** case, Kitchin J held that the patent was not invalid for obviousness. The obviousness attack was based on common general knowledge alone as well as three papers emanating from Riker. As regards common general knowledge alone, Kitchin J held that as at 1985 the priority date of the **levofloxacin** patent (1) the notional skilled addressee would have considered investigating whether the enantiomers of ofloxacin could be separated fairly easily but if they could not then he would have redirected his efforts elsewhere and (2) the enantiomers could not be separated easily – resolution would have involved a research programme of uncertain outcome. Accordingly, he held the patented invention of **levofloxacin** not obvious over common general knowledge alone. As regards the three papers emanating

from Riker, he held that the disclosures in each of them would not have made the resolution of the enantiomers any easier and therefore that the claim to **levofloxacin** was not obvious over any of them together with common general knowledge.

Finally, in the escitalopram case, Kitchin J held that the patent was not invalid for obviousness. The obviousness attack was based on two prior published patents both of which disclosed the racemate and methods to make the racemate but did not disclose either the enantiomers nor the means of making them i.e., the means of resolving the racemate.

Kitchin J held that whilst the skilled addressee would have had an incentive in 1988 to resolve the racemate, it would not have been a straightforward exercise – resolution would again have involved a research programme of uncertain outcome.

In both the **levofloxacin** and escitalopram cases, the same Judge at first instance had to consider whether the patentee was entitled to rely on the unexpected benefits of the invention in support of nonobviousness. In the escitalopram case, Kitchin J held that unless the unexpected benefits were disclosed or at least foreshadowed in the specification then the patentee was not entitled to rely upon them. In the **levofloxacin** case, the unexpected benefit was described in the specification as filed but not in the priority document. He upheld the patentee's claim to priority but held that the patentee was not then entitled to rely on a discovery made after the priority date and not described or foreshadowed in the priority document.

As a further aside, it is interesting to note that earlier this year, the District Court of The Hague held that the Dutch part of the escitalopram patent was invalid on the ground of obviousness.

Sufficiency

In the escitalopram case, claims 1, 3 and 6 of the patent were in issue. Claim 1 was directed to the enantiomer itself (escitalopram), claim 3 was directed to the pharmaceutical composition containing escitalopram and claim 6 was directed to the process of making escitalopram.

Kitchin J decided at first instance that claims 1, 3 and 6 were novel and nonobvious. However, he held claims 1 and 3 invalid for insufficiency on the basis that they covered escitalopram howsoever made and yet the patent itself disclosed only two ways of making it. Relying on the House of Lords decision in Biogen v Medeva, he held that because it was obvious to try to make escitalopram but the difficulty lay in doing so, the technical contribution made by the patent only extended to escitalopram made using the (two) methods disclosed in the patent and therefore the monopoly conferred by the patent should be confined to that invention.

The Court of Appeal upheld Kitchin J's findings on novelty and non-obviousness but reversed his finding on insufficiency. Interestingly, Lord Hoffmann who normally sits in the House of Lords, came down from the Lords to sit on the Court of Appeal panel hearing the appeal. The crucial distinction drawn by Lord Hoffmann was that the claims in issue in Biogen were "product by process" claims whereas those in the escitalopram case were mere "product" claims. He went on to point out that the Judge had wrongly equated the "technical contribution" with the "inventive step". He considered that the invention in the escitalopram case was the way of making the enantiomer whereas the technical contribution was the enantiomer itself.

It is of interest that in a separate Judgment, Jacob LJ qualified to some extent what Lord Hoffmann had said in order to show that a claim covering more than one product could in certain circumstances still be vulnerable to an insufficiency attack.

> *"So, for example, if a man finds a particular way of making a new substance which is 10 times harder than diamond, he cannot just claim "a substance which is ten times harder than diamond." He can claim his particular method and he can claim the actual new substance produced by his method, either by specifying its composition and structure or, if that cannot be done, by reference to the method … but no more. The reason he cannot claim more is that he had not enabled more – he has claimed the entire class of products which have the known desirable properties yet he had only enabled one member of that class. Such a case is to be contrasted with the present where the desirable end of indeed fully enabled – that which makes it desirable forms no part of the claim limitation."*

Of even more interest given that Lord Hoffmann had himself been a member of the tripartite panel of the Court of Appeal hearing the appeal, the House of Lords gave permission to the defendants to petition against the decision of the Court of Appeal. The House of Lords decision was handed down in late February.

The House of Lords in effect rubberstamped Lord Hoffmann's Court of Appeal decision – in relation to a simple product claim i.e., a claim to a new product (not defined by reference to the way in which it is made), the claim is enabled provided that the patentee discloses one way of making it. The claim is not therefore invalid for insufficiency even if there are other ways of making the product that owe nothing to the technical contribution to the art made by the patentee (i.e., the one way of making it) which is disclosed in the patent.

Validity of SPCs for enantiomers

In the **levofloxacin** case, the validity of the SPC for **levofloxacin** was attacked on the basis that the relevant marketing authorisation was not that for **levofloxacin** itself but rather the earlier marketing authorisation for the racemate ofloxacin.

Kitchin J distinguished the ECJ decisions in BASF which concerned the products differing only in respect of their impurity levels and the MIT case which concerned the combination of an active and nonactive excipient. On the basis that the ofloxacin (the racemate) and both enantiomers were in effect different drugs having different therapeutic effects, he held that the relevant marketing authorisation was not that for ofloxacin but rather the one on which the SPC had been based namely that for levofloxacin.

Bird & Bird - Neil Jenkins