

PATENTING ENANTIOMERS – THE HOUSE OF LORDS' DECISION IN *LUNDBECK v GENERICS* AND A COMPARISON WITH THE DECISION OF THE DISTRICT COURT OF THE HAGUE

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In an earlier article¹, the authors discussed the Court of Appeal's decision in *H Lundbeck a/s v Generics UK Ltd & others*². Notwithstanding the presence of Lord Hoffmann in that Court, who gave the leading judgment, the House of Lords has now reconsidered the case and handed down its judgment³ at the end of February. In affirming the Court of Appeal's decision, the law relating to the patentability of individual enantiomers and, more widely, the general applicability of the so-called doctrine of "Biogen insufficiency" can now be stated with confidence.

Background

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.

Citalopram is a chemical compound that exhibits a property known as chirality, which means that its molecules can exist in two forms, the structures of which are mirror images of each other, but are non-superimposable (and therefore not identical) in the same way as a person's left and right hands. Each form is known as an enantiomer, whilst a 50:50 mixture of the two enantiomers, which is generally the product of synthesis, is known as a racemate. It is possible to separate the two enantiomers from a racemate by a process termed resolution, although doing so may be difficult. Although the individual enantiomers of a chiral compound exhibit identical physical properties, and react in an identical manner (and at identical rates) with non-chiral molecules, they may react differently, or at different rates, with other chiral compounds. Consequently, the enantiomers of a chiral drug often have dramatically different physiological effects, because most drug targets within the human body (e.g. proteins) are chiral: one may be inactive or may even display undesirable side effects. It is therefore preferable for chiral drugs to be prepared and administered as a single enantiomer.

Lundbeck subsequently achieved the resolution of citalopram and 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).

Novelty and Inventive Step

The authors discussed the High Court's and Court of Appeal's decisions with regard to novelty and obviousness in some detail in their previous article. These issues were not pursued before the House of Lords, so the judgments of their Lordships are confined to the question of sufficiency, which was the sole ground of the appeal to them. Of note, however, is Lord Scott's observation that he found the issue of novelty in this case "less easy to understand if the claimed invention is of a chemical product where, as here, the existence of the product is known, its chemical and molecular structure is known and, up to a point, its characteristics are known". Lord Scott satisfied himself, on the basis of EPO jurisprudence⁴, that a single enantiomer of a compound previously known only as one half of a racemic mixture is indeed novel, even though, as explained by the Technical Board of Appeal, it is

1) Bio-Science Law Review 9: 156-159 (2008).

2) [2008] EWCA Civ 311.

3) [2009] UKHL 12.

4) Case T 0296/87.

theoretically possible, and desirable, to resolve a racemate⁵. Accordingly, there can now be no doubt that this is the case under both English law and EPO procedure. We do, however, return below to the question of inventive step, which may be the key to understanding the decision in this case, and was central to the judgment of the District Court of the Hague⁶ on the Dutch part of the same European Patent as the Patent.

Sufficiency

The sole ground relied upon by the generic manufacturers before the House of Lords was that the product claims (claims 1 and 3), which claimed escitalopram however obtained, were too broad to be supported by the disclosure and were therefore invalid for insufficiency.

Kitchin J had 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*⁷, 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.

The Court of Appeal disagreed, holding that the principle of what has become known as “Biogen Insufficiency” does not have general applicability, and in particular is not relevant to simple product claims. Lord Hoffmann himself (sitting, unusually, in the Court of Appeal) explained that in general a simple product claim is fully enabled so long as one method of making that product is disclosed, and that the position in *Biogen* itself had been different because of the complicated nature of the patent claims (which is discussed further in the Conclusion section below).

Lord Mance characterised the question put before their Lordships as follows:

“Where a patent claim relates to a product, rather than a method, is the patent liable to revocation on the ground of insufficiency ... if the only inventive step involved in the product consists in the method by which it is made available and if its description and specification disclose only that inventive method and

superior methods are found by others which owe nothing to that method? Can such a claim be said to have been supported in its full width by the description given, in the sense identified as necessary by Lord Hoffman in Biogen?”

Essentially, once novelty and inventive step were no longer in issue, the question for their Lordships came down to nothing more than whether the product claimed in the Patent complied with sections 1(1) and 14(3) of the Patents Act 1977. Section 1(1) imposes only the conditions that a claimed invention be new, involve an inventive step, be capable of industrial application, and not be expressly excluded from patentability, whilst section 14(3) requires that the specification disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art. Once the questions of novelty and inventive step had been decided (which they had prior to this appeal), all that remains is to decide whether the claimed product is capable of industrial application (which it is) and whether a method is described which enables a person skilled in the art to make the (single) enantiomers. The one process described does work, so there was therefore no real prospect that the House of Lords could reach any decision other than that the product claims of the Patent to the single enantiomers are valid.

The only issue which occupied the judges was that raised by the spectre of insufficiency in the sense described in *Biogen*. This, as explained by Lord Walker, appears to relate more closely to section 14(5)(c) of the Patents Act 1977, which requires the claims of a patent to be “supported by the description”, but, as he went on to explain, sections 14(3) and 14(5)(c) operate together to spell out the need for an enabling disclosure, the former relating to the specification as a whole, and the latter to the claims which define the monopoly sought by the inventor.

The judges carried out a detailed analysis of the reasoning in *Biogen*, and also of other case law relating to insufficiency, including the EPO decision in *Exxon*⁸ which was cited by Lord Hoffmann in *Biogen*. The correct position, as identified by their Lordships, can be summarised as follows:

- From *Exxon*, the underlying purpose of the requirement for a claim to be sufficient is “to ensure that the patent monopoly should be justified by the actual technical contribution to the art”. Similarly, “the extent of the patent monopoly, as defined by the claims, should correspond to the technical contribution to the art in order for it to be supported, or justified” (authors’ underlining).

5) Case T 1046/97.

6) Case Nos 08-1827, 08-2142 and 08-2172.

7) [1997] RPC 1.

8) Fuel Oils/EXXON T409/91 [1994] OJEP 653.

- “Technical contribution to the art” is not necessarily the same as the “inventive concept” underlying the patent. According to Lord Walker, “Inventive concept is concerned with the identification of the core (or kernel, or essence) of the invention – the idea or principle, of more or less general application which entitles the inventor’s achievement to be called inventive. The inventor’s technical contribution to the art is concerned with the evaluation of its inventive concept – how far forward has it carried the state of the art?”.
- Whilst “technical contribution to the art” is not a statutory term, as a general rule the monopoly to be granted to the patentee is to be assessed by reference to the technical contribution made by the teaching of the patent (Lord Neuberger). However, the technical contribution in any particular case may be more or less than the inventive concept, although this is difficult to reconcile with the wording of the decision in *Exxon*.
- In a claim to a product, such as the (+) enantiomer of citalopram, the patentee’s technical contribution to the art is to make available a product that was previously unavailable. This is so even though the actual inventive concept may be (as in this case) a single method of preparation of the product.
- Lord Hoffmann’s statement in the Court of Appeal decision that “when a product claim satisfies the requirements of section 1 of the 1977 Act, the technical contribution to the art is the product and not the process by which it was made, even if that process was the only inventive step” is therefore correct.
- This is in line with the extract from the *Exxon* decision, on which Lord Hoffmann relied in *Biogen*, which stated “this case differs from those where a class of chemical compounds is claimed and only one method of preparing them is necessary to enable a skilled person to carry out the invention i.e. to prepare all compounds of the claimed class. Rather, the present case is comparable to cases where a group of chemical compounds is claimed, and not all of the claimed compounds can be prepared by the methods disclosed in the description or being part of the common general knowledge”.
- Accordingly, it is the case that a claim to a single enantiomer of a known compound is valid, even if the patent discloses only a single method of preparation of the enantiomer.

Conclusion on escitalopram

For the reasons set out above, the final appeal in respect of the Patent has been dismissed, and all claims found valid in the United Kingdom. As the authors pointed out in their consideration of the decision of the Court of Appeal, the result, now confirmed by the House of Lords, is no doubt legally correct (and indeed even if it was not, it now is coming

as it does from the UK’s highest court). It is, nevertheless, a decision that would be likely to be thought surprising to the practising organic chemist, who would more likely take the view that the individual enantiomers of a racemic citalopram had been known and characterised many years ago, and could eventually be resolved by one of the standard methods of resolution, as all racemates eventually are.

Perhaps not surprisingly in the circumstances, the position is not the same in all countries in Europe, even though the patents granted in those countries are all part of the same EP 0347066. In Germany, for example, the Bundespatentgericht held that claims 1 to 5 were invalid for lack of novelty, whilst claim 6 was invalid for lack of inventive step. Similarly, the action by generics manufacturers against the Dutch part of EP 0347066 resulted in all claims being held invalid for lack of inventive step. In neither of these decisions did the Court find it necessary to consider the question of sufficiency (although it was raised by one of the parties before the Dutch Court.)

The reasoning of the judges in the District Court of the Hague is particularly instructive, and is worth considering briefly as it probably helps to explain the discrepancy between the legal decision and the chemist’s view. The Dutch Court first considered novelty, and quickly concluded, principally on the basis of the EPO decisions that we have already referred to, that the product claims were novel. It was on the question of obviousness that the Dutch Court took a drastically different view. The judges agreed with Kitchin J that the average person skilled in the art, with racemic citalopram in his possession, had sufficient motivation to try to resolve it in order to obtain the enantiomers. Where they differ from Kitchin J, however, is in finding that such a person would have been able to do so at the priority date on the basis of his common general knowledge without inventive intellectual effort. The Dutch Court gave full and detailed consideration to the various methods commonly used for resolution at the priority date, and concluded that:

“...by means of fractional crystallisation making use of obvious citalopram derivatives and common chiral acids and solvents, with routine and systematically executed experiments, would have obtained enantiomer-pure escitalopram within an acceptable time and thus without undue burden.”

The Dutch judges totally rejected the claims by Lundbeck that it had tried many methods at great length without success. In fact, on the basis of experimental evidence submitted by one of the claimants, they went so far as to say that:

“Lundbeck did less than the average skilled person would have done by application of his common general knowledge when searching for the enantiomers of citalopram.”

This would have been sufficient to decide that the claims to escitalopram as a product were invalid, but the Court went on to consider the inventiveness of the process for resolution claimed in claim 6, and this formed the largest part of the judgment. The essence of the claimed method is to resolve the racemic immediate precursor in the usual synthetic route to citalopram (referred to as the diol) and then convert those enantiomers by a process that preserves the stereochemistry, rather than losing it to produce racemic citalopram, as happens in the normal process. This, Lundbeck found, could be done by using a different, but well-known, reagent to effect the reaction. The reason that this works is that the reaction proceeds via a pathway in which stereochemistry is maintained (i.e. a pure enantiomer is formed), rather than by the other possible pathway in which stereochemistry is lost (i.e. the racemic mixture is formed). The two possible pathways are well known to organic chemists, who refer to them as S_N2 and S_N1 respectively. As a guide to which of these pathways will be followed, chemists often use the so-called Baldwin Rules, which, as the expert for one of the generics companies explained to Kitchin J in the High Court, actually predict that the reaction would follow the S_N2 pathway, thus resulting in the stereochemically pure (+) enantiomer of citalopram. Those who have read the judgment of the Court of Appeal (or the authors’ earlier article) will know that Kitchin J accepted the evidence of Lundbeck’s expert Professor Steve Davies, that the average skilled person would not deem the Baldwin Rules applicable to a molecule such as the diol. Interestingly, the generics companies in the Dutch proceedings instructed Professor Baldwin, the author of the Baldwin Rules, as an expert. This may in part explain why the Judges of the Dutch Court said that they “respectfully disagree” with the English judgment on this point.

To emphasise the point, the Court of the Hague drew attention to several references that form part of the common general knowledge, all of which confirm that the Baldwin Rules would be expected to apply to a molecule such as the diol. Not only does the judgment carefully dismiss all of the numerous arguments and objections raised by Lundbeck, but it alleges that Professor Davies created an impression with one of his diagrams that was incorrect, and held:

“In the opinion of this court, the conclusion which Kitchin J attached to that inaccurate assumption – induced by Davies – cannot be maintained ...”

It is the opinion of the authors that most practising chemists to whom the Patent is addressed would not have taken too much notice of what the Baldwin Rules predicted in any event, but would simply have tried the reaction to see if it worked,

and found that it did, and gave the desired single enantiomer as the product. Whether or not this would render the process obvious depends, so far as the English Courts would be concerned, upon the interpretation of obviousness under the test given in *Saint-Gobain*.⁹

Once the process used by Lundbeck to resolve citalopram was found to be obvious, it follows that the product claims would also have been non-inventive and invalid, even if they had not already been found to be so by the Dutch Court on other grounds. In view of the fact that the product and process claims were all found invalid, the Dutch Court decided that it was not necessary for it to consider the question of insufficiency, and simply ordered the Dutch patent to be revoked. Presumably, if Kitchin J had come to a similar conclusion with regard to obviousness, then the whole question of Biogen insufficiency would not have been reconsidered at the present time.

What is left of *Biogen* insufficiency?

Where, then, does this leave the decision in *Biogen* in UK jurisprudence, in which the patent was revoked on the grounds that the breadth of the claims exceeded the technical contribution to the art? This form of attack, which subsequently became known as the doctrine of “Biogen insufficiency” was never a free-standing reason for revocation of a patent, as stressed by the Court of Appeal in *Kirin-Amgen*¹⁰. In that case, the court gave a reminder that the sole ground on which a patent can be revoked for invalidity in respect of insufficiency was that laid down in s 72(1)(c) of the Patents Act 1977 i.e. “the specification of the patent does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art”. “Biogen insufficiency” is therefore a sub-category of the wider class of insufficiency as defined in the Act.

The decision in *Biogen* has certainly not been overruled – Lord Walker described it as a “tour de force” and Lord Neuberger stated that “it applied in the light of the very unusual nature of the claim in that case”. Furthermore, the doctrine has recently been applied (by Kitchin J again) in *Novartis v Johnson & Johnson*¹¹, in which a patent claiming a type of extended wear contact lens was revoked on the grounds of insufficiency.

However, it is clear that the doctrine itself has been severely circumscribed. Lord Neuberger referred to Kitchin J’s “mistaken view that the reasoning in *Biogen* is of much wider application, and in particular that it applies to any product claims”, admitting that he himself made the same mistake in *Kirin-Amgen*¹², in which he was the trial judge.

9) *Saint-Gobain v Fusion Provido* [2005] EWCA Civ 177.

10) [2003] RPC 3.

11) [2009] EWHC 1671 (Pat).

12) [2002] RPC 1.

In *Biogen*, the claim under consideration was to a product identified partly by the way in which it was made (“recombinant DNA”) and partly by what it did (“characterised by ...”). The patentee could claim neither the product itself, as it already existed in nature, nor the process by which it was made, given that recombinant DNA technology was a known method. In *Novartis v Johnson & Johnson*, Kitchin J said “Inventions which are claimed by reference to the results to be achieved often provoke a good deal of suspicion that they are merely an attempt to monopolise all ways of solving a known problem”. However, it is now clear that a straightforward product claim, even to an obviously desirable product, simply does not fall within the scope of *Biogen*. Furthermore, it is difficult to envisage how the *Biogen* doctrine could now be applied outside the scope of a claim similar in form to that in *Biogen* itself i.e. a hybrid claim specifying both physical characteristics and desired results, as was the case in *Novartis*.

The normal principle is that a patent claiming a product but disclosing only one method of making that product covers the product, however made. It is now clear that this is of general application, even in circumstances where (to use Lord Neuberger’s phrase) the product is a “known desideratum”. This will be welcomed by patentees, who may now be able to

extend the term of patent protection for chiral compounds by patenting individual enantiomers (provided of course that the method of preparation is novel and inventive). More widely, provided that product claims are drafted without reference to how the product is made, it seems likely that the doctrine of *Biogen* insufficiency will not be of assistance to a party seeking to revoke the patent and *Biogen* insufficiency may never be applied again in respect of straightforward single product claims.

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