



Patent and enantiomers: the court in Ranbaxy holds up a mirror to the law

The recent decision of the High Court in *Ranbaxy UK Limited & Arrow Generics Limited v Warner-Lambert Company*¹ gives, perhaps ironically, encouragement both to patentees and to generics manufacturers in the pharmaceuticals sector.

Ranbaxy sought a declaration of non-infringement in respect of Warner-Lambert's patent EP(UK) 0247633 ('633) which covers a class of compounds which includes atorvastatin, a cholesterol synthesis inhibitor. The calcium salt of atorvastatin is sold by Pfizer (Warner-Lambert's parent company) as Lipitor and is currently the world's top-selling drug, with global sales in excess of US\$12 billion.

In separate actions, which were heard together with the first action, Ranbaxy and Arrow sought to revoke the patent EP(UK) 0409281 ('281), a later patent which specifically claims a single enantiomer of atorvastatin calcium.

In refusing the declaration of non-infringement for '633 but finding '281 invalid for anticipation and obviousness, Pumfrey J. provided some useful clarification as to the UK courts' current approach to patent construction and validity of selection patents. This article sets out to summarise the decision and to analyse whether it is in fact correct and the implications for generics manufacturers in the pharmaceuticals sector.

1. Some background

Before considering the patents, some background chemistry is required. Certain chemical compounds exhibit a property known as **chirality**, whereby the compound exists in two molecular forms which are mirror images of each other but which are non-superimposable (and therefore non-identical). Such compounds are said to be **chiral**, and the two forms of the molecule are called **enantiomers**. A simple example of such a pair is shown in figure 1. Many naturally occurring compounds are chiral, but unless special steps are taken during preparation, synthetic versions of such compounds will exist as a 50:50 mixture of the two enantiomers. Such mixtures are termed **racemic** mixtures or **racemates**. It is however generally possible to separate the two enantiomers from a racemate by a process termed **resolution**.

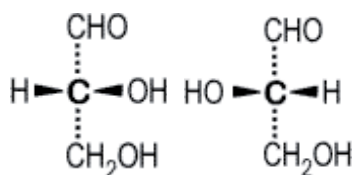


Fig 1 – simple pair of enantiomers. The figure attempts to render three-dimensional objects in two dimensions: dashed lines point beneath the plane of the paper whereas wedged lines point towards the viewer. The two forms are mirror images of each other, but cannot be superimposed by rotation and/or translation.

Enantiomers exhibit identical physical properties such as boiling points etc, and react in an identical manner (and at identical rates) with non-chiral molecules. However, the properties of the separate enantiomers are typically dramatically different when reacting with other chiral molecules. This is of great importance in pharmaceutical chemistry, as most drug targets within the human body (e.g. 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, and the other enantiomer will be inactive, or may even display undesirable side effects such as toxicity. Consequently, the preference in recent times has been for chiral drugs to be prepared and administered as a single enantiomer, and Lipitor itself is a single enantiomer of atorvastatin calcium.



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2. Patents and enantiomers: the decision

The issue with regard to '633 was purely a matter of patent construction. The patent claimed a class of compounds with a given structural formula and a range of substituents. The structural formula in the patent appeared to show a single enantiomer of the claimed range of compounds. However, it was common ground that the method of preparation set out in the patent specification would yield the racemate, rather than a single enantiomer. Ranbaxy argued that the patent therefore claimed only the racemate, relying on the fact that a structural formula of a single enantiomer is often used by chemists when in fact a racemate is being described. If so, Ranbaxy argued that a formulation consisting of a single enantiomer would fall outwith the patent. Warner-Lambert, on the other hand, argued that the skilled man would recognise that only one of the enantiomers would in fact be pharmacologically active, and would also know that the relevant enantiomer could be isolated by known methods of resolution.

As is well known, the courts in countries which have adopted the European Patent Convention ("EPC"), which includes the UK, are required to construe patents in a manner "which combines a fair protection for the patentee with a reasonable degree of certainty for third parties"². The House of Lords in *Kirin Amgen v Hoechst Marion Roussel Limited*³ held that the correct approach to construction of a patent claim, in order to achieve the requirements of the EPC, is to decide what the person skilled in the art would have understood the patentee to be using the language of the claim to mean. In other words, whilst the language used in the claim is of critical importance, the court should not use a literal approach when considering that language, but should instead adopt a purposive approach.

Applying this approach, Pumfrey J. held that although the structural formula in the patent was used to denote a racemate, the skilled man would recognise that "there is a single enantiomer that is the effective compound, and that he can resolve the racemate using conventional techniques in order to extract that enantiomer". The claim therefore covered both the racemate and the individual enantiomers, and the declaration of non-infringement was accordingly refused.

3. Patents and enantiomers: is the decision correct?

In considering the correctness of the decision, it is worthwhile first considering whether Warner-Lambert would be entitled to be granted a further patent claiming a single enantiomer. The sole reported case on this issue in the UK courts is *ICI (Howe's) Application*⁴. This case concerned an appeal by the applicant from a rejection of its patent application on the grounds of obviousness. The patent application was for a single enantiomer of a propranolamine derivative with useful therapeutic properties. The prior art consisted of a number of journal articles, dating from a decade or more prior to the application, which disclosed the racemate of the relevant compound. It was common ground (as in the Ranbaxy case) that the skilled man would realise that it was possible to obtain, by conventional methods, a single enantiomer from the racemate. However, the judge held that the prior art did not establish that the racemate had shown any particular promise as a pharmaceutical compound, and that it would not have been obvious that producing a single enantiomer would produce a beneficial result. The appeal was therefore allowed.

It is submitted that this decision, although correct on its particular facts, would in fact preclude Warner-Lambert (and other proprietors of patents for a racemic pharmaceutical) from obtaining a patent for a single enantiomer. This is because the pharmacological properties of the racemate would already be known to be favourable, unlike the situation in *Howe* where the racemate did not appear to be a promising candidate. As this is so, it would be obvious to the skilled man that a single enantiomer is likely to be responsible for the observed pharmacological properties, and it would be obvious to isolate and test the individual enantiomers. An application for a single enantiomer would therefore fail for want of an inventive step. This is certainly in line with the EPO's approach (e.g. *Hoechst/Enantiomers*⁵), which permits a single enantiomer to be patented only if the discovery of the claimed benefits of an individual enantiomer compared with the corresponding racemate involves an inventive step. In *Hoechst*, the applicant argued that the fact that the single enantiomer exhibited four times the activity of the racemate (as against the allegedly expected twofold improvement) was sufficient to establish an inventive step. The EPO disagreed, holding that it would be obvious to the skilled man to isolate and test the single enantiomers in order to increase activity, thereby rendering the "invention" obvious.

Given the above, there are obvious arguments in favour of the position that the decision is correct. Provided that the relevant enantiomer can be isolated by standard techniques, without the need for an inventive step, it is arguably fair to extend the protection afforded by a patent for a racemate to the individual enantiomers, particularly given that the patentee itself would almost certainly be precluded from obtaining a further patent for an individual



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enantiomer. Furthermore, if such analysis is correct, the rights of third parties are protected by the requirement that the racemate can be resolved using conventional techniques. If, in the instance of a particular drug, resolution of the enantiomers proved not to be possible by conventional techniques, a single enantiomer would presumably fall outwith the patent and/or the patent would be invalid for insufficiency insofar as it sought to claim a single enantiomer without disclosing how to prepare it. The decision therefore arguably achieves the aim set out in the Protocol.

However, that is not to say that Ranbaxy's case on appeal is impossible. On the contrary, its argument could be that the patentee chose not to claim expressly a single enantiomer (because it did not include directions to do so, which could very easily have been included), and therefore cannot now seek to extend the scope of the patent to cover the single enantiomer. In this regard, it is worth noting that UK law by no means provides a seamless level of protection for putative intellectual property rights – see for example (in the context of copyright/design right) the decision in *Lambretta Clothing Co Ltd v Teddy Smith (UK) Ltd*⁶. According to this analysis, the fact that Warner-Lambert could not obtain a subsequent patent claiming the single enantiomer is irrelevant to the issue of whether the first patent in fact claims the enantiomer – in effect by drafting the patent as it did, the patentee has lost the right to protect the single enantiomer.

Ranbaxy has indicated that it will appeal, and it remains to be seen which approach the Court of Appeal will take.

4. Selection patents

Appeals involving patents have ramifications beyond the interests of the parties to the appeal, as the validity or otherwise of the patent can potentially affect parties unconnected with the appeal. The Court of Appeal's decision in *Halliburton* therefore provides a welcome confirmation that public interest matters must be taken into account by the courts when considering patent validity.

The claimants alleged that '281 was invalid for (i) anticipation by Warner-Lambert's application under PCT number WO 89/07598 ('598); and (ii) lack of inventive step over the application for '633. In considering anticipation, the judge briefly considered the authorities, concluding that the prior disclosure relied upon must "be clearly shown to have planted [its] flag at the precise destination before the patentee" i.e. it is not sufficient that the prior disclosure merely contains a direction which is capable of being carried out in more than one way, only one of which would infringe the patent claim. The judge held that '598 gives specific directions to make three compounds, one of which (the relevant enantiomer of atorvastatin) falls within claim 1 of '281, and '281 is accordingly invalid for lack of novelty

Of more interest is the obviousness attack, relying upon the application for '633 ('633A). '633A gives a specific example of the sodium salt of racemic atorvastatin, and also a general disclosure in respect of a range of compounds containing "a hydroxy acid or pharmaceutically acceptable salt thereof". The latter is said in '633A to consist of salts formed with sodium, potassium, calcium, magnesium, aluminium, iron and zinc ions.

Warner-Lambert contended that the calcium salt of a single enantiomer of atorvastatin was not obvious, given the disclosure in '633A. The judge held that, given that resolution of the racemate formed part of the common general knowledge at the relevant date, the selection of a single enantiomer could not constitute an inventive step. This is of course in line with his decision on construction, as set out above. Furthermore, it cannot be inventive to use the calcium salt when that salt, along with six others, was expressly disclosed in '633A.

The judge then went on to consider the requirements for a selection patent i.e. a patent claiming a subclass of a previously disclosed class of compounds. Summarising the rules laid down by previous cases, particularly *IG Farbenindustrie AG's Patents*⁷ and *E. I. Du Pont de Nemours (Witsiepe's) Application*⁸, the judge held that the necessary (albeit not sufficient) conditions, for a patent application claiming a selected subclass (or even a single compound) of a previously disclosed larger class, to meet the requirements for novelty and inventive step are:

- 1 The prior disclosure is of a class, rather than a disclosure of the individual members of that class;
- 2 The members of the sub-class have advantageous properties over the larger class;
- 3 All the selected members of the sub-class possess the advantage;
- 4 The later specification discloses what the claimed advantage is; and
- 5 The prior publication of the wider class does not refer to that advantage.



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These requirements were not satisfied in the present case, as '281 did not claim any advantages over and above those claimed in '633A. It is submitted that this part of the decision is certainly correct: even if (which seems unlikely) the judge was wrong on the issue of obviousness, the novelty attack on '281 seems clear cut and beyond argument.

Summary

In summary, the decision on construction will be viewed favourably by patentees generally, as the patent was construed in a relatively wide and generous manner. However, the judgment also makes it clear that the rules on selection patents are applied strictly by the UK Courts, and that it is not permissible for a patentee to extend its protection simply by selecting a subclass of a previously disclosed class of compounds, without setting out clearly what new advantage is claimed for the subclass.

Authors



Richard Kempner
☎ (+44(0) 113 209 2370
✉ richard.kempner@addleshawgoddard.com



Stuart Jackson
☎ (+44(0) 113 209 2391
✉ stuart.jackson@addleshawgoddard.com



Brian Whitehead
☎ (+44(0) 113 209 2330
✉ brian.whitehead@addleshawgoddard.com

Notes

- ¹ [2005] EWHC 2142 (Pat), handed down on 12 October 2005
- ² Protocol on the Interpretation of Article 69, EPC ("the Protocol")
- ³ [2005] R.P.C. 9
- ⁴ [1977] R.P.C. 121
- ⁵ [1990] E.P.O.R. 337
- ⁶ [2005] R.P.C. 6
- ⁷ [1930] 47 R.P.C. 289
- ⁸ [1982] F.S.R. 303

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