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Case No: A3/2010/0126/CHPCF

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM Chancery Division, Patents Court
Mr Justice Floyd
[2009] EWHC 2952 (Pat)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 08/04/2011

Before :

THE CHANCELLOR OF THE HIGH COURT
LORD JUSTICE RICHARDS
and
LORD JUSTICE PATTEN

- -

Between :

MERCK SHARP & DOHME CORP (formerly known as MERCK & CO INC) (a company incorporated under the laws of the state of New Jersey, United States)	**Appellant**
- and -	
TEVA UK Ltd	**Respondent**

- -
- -

Peter Prescott QC & Thomas Hinchliffe (instructed by Rouse Legal) for the Appellant
Simon Thorley QC & Thomas Mitcheson (instructed by **Bird and Bird**) for the Respondent

Hearing date: 15 March 2011

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Approved Judgment

The Chancellor:

Introduction

1. Glaucoma is the name given to a group of disorders of the eye characterised by the intraocular pressure ("IOP") being so high as to damage the nerve fibres in the retina and optic nerve as it leaves the eye. On 11th April 1991 the Association for Research in Vision and Ophthalmology ("ARVO") published as part of its Abstract Program Book for its annual meeting to be held between 28th April and 3rd May 1991 in Sarasota, Florida a paper submitted by George Nardin and others (including 3 representatives of the appellant, Merck Sharp & Dohme Corp ("Merck")). The paper ("Nardin") related to the additive effect in reducing IOP of administering an eye-drop including 2% of a drug then known as MK 507 some ten minutes after the administration of an eye-drop containing 0.5% of a drug called timolol. The paper suggested, on the basis of experimental tests carried out on humans over a period of 8 days, that such consecutive administration improved reduction of IOP by about 17%. On 14th April 1992 Merck filed its application for a patent in respect of "ophthalmic compositions comprising combinations of [MK 507] and [timolol]" for the treatment of glaucoma. The priority date for the patent EP 0 509 752 B1 granted later ("the Patent") was 17th April 1991, namely some six days after the publication of Nardin.

2. On 19th August 2008 the respondent, Teva UK Ltd ("Teva"), instituted proceedings in the Patents Court seeking a declaration that the Patent is and has at all material times been invalid and an order that it be revoked. The grounds of invalidity relied on were want of novelty, lack of an inventive step, insufficiency and added matter. Merck sought to meet these objections by applying on 11th May 2009 for an order under s.75 Patents Act 1977 permitting the amendment of the Patent. The action was tried by Floyd J on four days between 27th October and 2nd November 2009. For the reasons given in his judgment handed down on 20th November 2009 Floyd J concluded that the Patent both as originally granted and as proposed to be amended was invalid for lack of an inventive step. In addition he made certain alternative findings in the event that he was wrong on his principal conclusion. On 11th December 2009 Merck applied again for an order permitting amendment of the Patent under s.75 in certain additional respects. By his order made on 16th December 2009 Floyd J dismissed both applications to amend the Patent, ordered that it be revoked and refused permission to appeal.

3. On 18th January 2010 Merck issued an appellant's notice. It sought permission to appeal and for an order reversing that of Floyd J on 14 grounds. The application came before Jacob and Lloyd LJJ on 11th May 2010. They gave Merck permission to appeal on grounds 1 to 6 (both inclusive) and 14 only. Those grounds relate only to claim 18 of the Patent as proposed to be amended and take issue with the judge's conclusion on obviousness (ground 14) and added matter (grounds 2 to 6). Thus the issues before us were limited to those two objections to that claim. The parties agreed that if we upheld the judge's conclusion on obviousness then the issue on added matter would not arise. Having heard full argument from both sides on obviousness we concluded that the judge was right and that argument on added matter was unnecessary. Accordingly we did not hear argument on that issue. My judgment is, therefore, limited to the

issue of obviousness in relation to amended claim 18. Before I deal with that issue it is necessary to describe in a good deal more detail the common general knowledge and prior art at the priority date, the specification and claims in the Patent and the judgment of Floyd J.

Common general knowledge and prior art

4. The technical background is set out with conspicuous clarity by Floyd J in paragraphs 4 to 23 of his judgment. The description which follows is taken from those paragraphs. Glaucoma, which I have already described in paragraph 1 above, is caused by an increase in IOP. The most common type results from impedance to the flow of aqueous humour through the exit routes from the eye, causing the IOP to rise. It results in progressive loss of field of vision. Treatments of glaucoma rely either on reducing the rate at which aqueous humour enters the eye, or increasing the rate at which it leaves.

5. The process by which aqueous humour is created is dependent on the enzyme carbonic anhydrase. Inhibition of this enzyme, by means of a carbonic anhydrase inhibitor ("CAI") reduces the production of aqueous humour. At the priority date, chronic simple glaucoma was treated with four main classes of drug, namely, miotics, sympathomimetics, beta blockers and CAIs. Of these the beta blocker timolol was the most widely prescribed. It was the "first line" treatment and regarded as the gold standard. It had no major side effects in the majority of patients. Apart from timolol all the other drugs had some unpleasant side effects. Pilocarpine, a miotic, was known to cause constriction of the pupil or "brown out", as well as stinging on application and headache. The beta blockers led to reddening of the eye, stinging or burning and vaso-constriction leading to discomfort or disfigurement.

6. All but the CAIs were administered topically (eyedrops). CAIs were given by mouth. Diamox was the trade name of a clinically approved oral CAI. This had the effect of inhibiting the enzyme in the whole body, with the consequence that the side effects were experienced systemically. It could cause tingling in the extremities, depression, loss of libido and other undesirable side effects. It was well recognised that a topical CAI would be likely to reduce and localise any side-effects. Accordingly, much research had been done by the priority date into identifying and obtaining approval for a CAI which could be administered topically. A number of compounds had been suggested in the literature, but none had yet obtained clinical approval. The front runners at the priority date were MK 507, sezolamide and a compound called MK 927. MK 507 was Merck's name for the compound which became known as dorzolamide. A review of the literature would have shown MK 507 or dorzolamide.

7. Clinically, glaucoma would be treated first with a single drug. It was common practice, where a single drug was not proving effective, for a second drug to be prescribed. About 50% of glaucoma patients required a second drug. Some would be on more than two drugs. If a patient was required to take doses of both drugs at the same time, he or she would be advised to wait 5 to 10 minutes

between the instillations of the different drugs. The parties' clinical experts agreed that in 1991 the treatment options for glaucoma were limited.

8. Adjunctive therapy is the term used by Floyd J to describe the therapy in which the patient takes a number of medicaments for the same complaint. Where the patient takes doses of the two medicaments at effectively the same time (i.e. separated by the 5 minute interval) he used the term concomitant administration. Adjunctive therapy is to be distinguished from a product where two active ingredients are formulated together in the same eye drop solution. The judge referred to this as co-formulation. At the priority date a number of co-formulated drugs had been marketed, but none with any great success. Other methods of treating glaucoma included surgery (trabeculectomy) and laser surgery (trabeculoplasty).

9. An extremely important problem associated with glaucoma treatment in 1991 was the lack of patient compliance. This was for at least three reasons. First, ocular hypertension is asymptomatic, so the patient is unaware of the IOP lowering effects of the drugs. Secondly, many of the drugs have unpleasant side effects including stinging, irritation and discomfort upon instillation. Thirdly, the physical act of administering the drug is difficult, particularly in the elderly and those suffering from poor vision.

10. All or nearly all commercially available drugs in 1991 were designed so that only one drop needed to be administered at any one time. The reason is again that the act of placing the drop in the eye is difficult. The problem is exacerbated where the drug causes discomfort. The taking of concomitant medication at 5-10 minute intervals was also seen as a significant inconvenience for some patients.

11. At the priority date the commercial formulation of timolol that was on the market was available at concentrations of 0.25% and 0.5%. The dose was administered twice a day. It was recognised that 0.5% twice a day was at the top of the dose response curve. In other words no added benefit could be obtained by increasing the concentration or repeating the dose more frequently. It was formulated at a pH of 6.8. It was well known that the degree of corneal penetration of a drug depended on its degree of ionisation: un-ionised drugs being better at penetrating the cornea. In consequence the degree of penetration was known to be dependent on pH. However, the degree of penetration did not depend solely on pH. In particular it was well known that the degree of penetration could, if necessary, be increased by the inclusion of a viscosity modifying agent, so as to prolong the contact time of the drug with the eye and therefore give it more opportunity to penetrate.

Prior Art

12. The prior art on which Teva relied for its claim of want of novelty or inventive step was, in the context I have described, Nardin. That document was entitled "Activity of the topical CAI MK-507 bid [sc. bis in die or twice daily] when added to timolol bid." After setting out the names of the contributors and the organisations to which they belonged it continued:

> "The topical carbonic anhydrase inhibitor MK-507 at 2% has demonstrated IOP lowering in patients treated three times daily. This was a 4 center, double-masked, randomised, placebo-controlled parallel study of the degree of additional IOP-lowering activity of 2% MK-507 q12hr given to patients with elevated IOP receiving 0.5% timolol q12hr. Entry criteria included bilateral primary open angle glaucoma or ocular hypertension with IOP > 22 mmHg after a 2-3 wk run-in on 0.5% timolol (8am – 8pm). After a 12 hr diurnal IOP curve on timolol alone, patients began dosing with 2% MK-507 (n=15) or Placebo (n=15) at 8:10 pm – 8:10 am (10 min post timolol dose) for 8 days. IOP was measured 8am & 9am on Day 2 with a 12 hr diurnal curve on day 8. MK-507 q12 hr demonstrated a clinically and statistically significant additive effect, ranging from 13%-21% based on a worse eye analysis."

The paper then set out the preliminary IOP data.

13. In relation to Nardin, Floyd J commented on a number of significant features. They included the following:

> (1) The trial was designed to test for an additive effect on IOP lowering of 2% MK 507 given twice a day on patients receiving 0.5% timolol twice a day.
>
> (2) The tests were performed on humans.
>
> (3) The patients were given their MK 507 dose ten minutes after their timolol dose for 8 days.
>
> (4) The results were statistically significant, meaning that they were very unlikely indeed to be due to chance; and clinically significant which meant that the improvements in IOP translated into real benefit for the patients.
>
> (5) The two drugs were being concomitantly administered, despite the fact that this meant that MK 507 was being administered at less than the three times a day dosing that is referred to in the first sentence.

The Patent

14. The Patent explains the medical context I have summarised in paragraphs 4 to 11 above. The specification notes that topically effective CAIs had been disclosed though none was available for clinical use and continues at [0010]:

> "Thus, when a carbonic anhydrase inhibitor is combined with a beta adrenergic antagonist, there is experienced an

> effect that reduces the intraocular pressure below that obtained by either medicament individually."

The specification as sought to be amended then continues in [0013]:

> "The combination disclosed herein is effective ~~either~~ by co-administration of the medicaments in one solution ~~or as a combined therapy achieved by prior administration of either the carbonic anhydrase inhibitor or the β-adrenergic antagonist followed by administration of the other solution.~~ The use of a single solution containing both active medicaments is ~~preferred.~~ disclosed."

The specification continues with an explanation of various concentrations of timolol and dorzolamide and includes three examples, the third of which is identical to Nardin.

15. Claim 1 as proposed to be amended and substituting their full chemical names with dorzolamide and timolol would read:

> "1. Use of
>
> (a) 0.05 to 5% (w/w) of dorzolamide, or an ophthalmologically acceptable salt thereof; and
>
> (b) 0.01 to 1.0% (w/w) of timolol, or an ophthalmologically acceptable salt thereof;
>
> for the manufacture of a medicament for the treatment of ocular hypertension or glaucoma in a patient who is insufficiently responsive to β-adrenergic antagonists, wherein said medicament takes the form of a single solution adopted for topical administration."

16. Claims 2 to 7 were dependent on unamended claim 1. The proposed amendment deleted claims 8 and 9. Unamended claim 10 is to:

> "An ophthalmic formulation for the treatment of ocular hypertension or glaucoma in a patient population the members of which are insufficiently responsive to β-adrenergic antagonists, which comprises:
>
> (a) 0.05 to 5% (w/w) of dorzolamide, or an ophthalmologically acceptable salt thereof;
>
> (b) 0.01 to 1.0% (w/w) of timolol, or an ophthalmologically acceptable salt thereof; and
>
> (c) an ophthalmologically acceptable carrier."

Unamended claims 11 to 18 were dependent on claim 10.

17. Unamended claims 19 and 20 were to a process for a formulation as claimed in any of unamended claims 10 to 18. Unamended claim 20 would become amended claim 18 in the following form:

> "18. A process as claimed in claim ~~19~~ 17, for obtaining an ophthalmic formulation in the form of a solution, which comprises:
>
> (1) suspending or dissolving in water:
>
> (a) 0.05 to 5% (w/w) of dorzolamide or an ophthalmologically acceptable salt thereof; and
>
> (b) 0.01 to 1.0% (w/w) of timolol, or an ophthalmologically acceptable salt thereof;
>
> together with non-toxic auxiliary substances which may go with an ophthalmologically acceptable carrier; and
>
> (2) adjusting the pH of the composition obtained to ~~5.0~~ 5.5-6.0 by the addition of a suitable reagent."

In its unamended form it was dependent on claim 19 paragraph (2) being the additional integer. Thus the argument in this case has centred on amended claim 18 and the alteration of the lower end of the range of the pH of the composition from 5.0 to 5.5. Floyd J held that unamended claim 20 and amended claim 18 were both invalid for added matter but went on to consider both novelty and obviousness. For reasons I have explained in paragraph 3 above I am not concerned with the added matter objection.

Judgment of Floyd J

18. For the reasons given in paragraphs 81 to 86 the judge concluded that claims 1 to 6 and 8 and 9 were all invalid for want of novelty. Merck did not seek to appeal from that conclusion. The judge then considered the narrowest use claim in claim 6 on the basis, as expressed in paragraph 115, that all other claims relied on were of equivalent width or broader or were not claimed to be independently valid. In paragraph 118 he said:

> "The question I must ask is whether it would be obvious to the skilled team on reading Nardin to use a co-formulation of the two drugs within claim 6 for treating glaucoma in patients for whom timolol is not good enough."

He concluded in paragraph 161 that that claim was obvious and thereby invalidated the patent as a whole. He did so by reference to a product called Ganda, an earlier patent granted to Merck and common general knowledge at the time. In its notice of appeal Merck sought permission to appeal from that conclusion on grounds 7 to 13 to the effect that the judge had wrongly found that at the priority date the co-formulation of timolol and dorzolamide in the amounts specified in claim 6 was obvious either as part of the common general knowledge or by reference to Ganda.

19. As I have already indicated, permission to appeal on those grounds was refused. Accordingly, it is necessary to consider the rest of the judgment of Floyd J on obviousness by reference to amended claim 18 alone. In paragraphs 87 to 99 Floyd J directed himself as to the law on obviousness by reference to the well known passages in **Hallen v Brabantia** [1989] RPC 307; **St Gobain v Fusion Provida** [2005] EWCA Civ 177 and **Conor v Angiotech** [2007] UKHL 49. It is common ground that such direction was entirely correct. It is said that he did not properly apply it to the facts of the case. His approach was to follow the four steps suggested by the Court of Appeal in **Pozzoli v BDMO** [2007] EWCA Civ 588, namely:

> "(1)
>
> (a) Identify the notional 'person skilled in the art'.
>
> (b) Identify the relevant common general knowledge of that person.
>
> (2) Identify the inventive concept of the claim in question or, if that cannot readily be done, construe it.
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed.
>
> (4) Ask whether, when viewed without any knowledge of the alleged invention as claimed: do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"

20. In paragraphs 100 to 113 the judge considered the first question. In paragraphs 114 and 115 he concluded that:

> "114. ...the skilled person would know as part of the common general knowledge that co-formulation was a valuable and appropriate measure where the circumstances justified it. It would always bring with it the advantage of patient compliance. It would be particularly suitable where the two drugs can be administered concomitantly at the same dosage interval.

The inventive concept

> 115. There is no sense in fudging the issue of the inventive concept of claim 1. It is using a co-formulated solution of dorzolamide and timolol for treating glaucoma in patients for whom timolol is not good enough. For that purpose I will consider the narrowest use claim advanced, claim 6. If that is obvious, the patent does not survive – all the other claims relied on are of equivalent width or broader, or are not contended to be independently valid."

21. The judge then considered the differences between Nardin and that inventive concept. He considered that there were only two, namely the identification of MK 507 and co-formulation. He considered that the skilled man would readily and rapidly discover what MK 507 was. The remaining question posed in paragraph 118 was:

> "...whether it would be obvious to the skilled team on reading Nardin to use a co-formulation of the two drugs within claim 6 for treating glaucoma in patients for whom timolol is not good enough."

22. The case for Teva in respect of that question, which he accepted, was in two parts. The first part set out in paragraph 119 was:

> "(i) Additive therapy was commonplace;
>
> (ii) Timolol was the first line, gold standard treatment. When it was not good enough, a variety of unsatisfactory drugs were prescribed as adjunctive therapy. There was no satisfactory adjunctive compound;
>
> (iii) Co-formulations were well known in ocular treatment in general. Clinical approval had been obtained for some co-formulations;
>
> (iv) The desirability of one-drop medication for compliance reasons was well known;
>
> (v) Workers in the field wanted a topical CAI to gain the advantage of the reduction of aqueous humour formation which was known to be achieved when administered orally;
>
> (vi) It would accordingly be natural to investigate whether any potentially useful CAI had an additive effect when co-administered with timolol, particularly when administered twice daily as timolol was habitually administered;
>
> (vii) The skilled reader would readily understand, therefore that this is what Nardin was doing with MK 507, the best bet at the time for a topical CAI;

> (viii) The results shown in Nardin, namely an additive effect when administered twice daily (not three times daily) would have been credible and interesting;
>
> (ix) The skilled reader would understand that the fact that there was an additive effect rendered moot any debate about whether the CAI mechanism of action could add anything to an optimum timolol dose;
>
> (x) The importance of twice daily administration would not be lost on the reader: to spell it out the patient would have to apply two drops (as with all adjunctive therapy) but in this case would be able to apply them on the same two occasions and no others; and
>
> (xi) The results in Nardin would therefore naturally and non-inventively suggest a co-formulation."

23. Floyd J accepted all these steps and concluded in paragraph 128:

> "In my judgment the idea of co-formulating MK 507 and timolol would occur to the notional skilled team if they read Nardin with interest. There is no doubt that the Nardin disclosure would have been seen as an important and exciting one. I do not think, as Merck submits, that it would only become a natural consideration once the dorzolamide mono-therapy had been more extensively worked on, or once co-administration had, as [counsel for Merck] puts it, been "bottomed out". Once the essential facts are appreciated as they would be, namely (a) additivity to timolol's best dosage regime and (b) concomitant administration at the same dosage times and intervals, a co-formulation would be a startlingly obvious thing to consider. The skilled team would plainly have seen, without any hindsight prompting, the bonus that a co-formulation would offer."

24. The judge then recorded the second stage of the argument for Teva as follows:

> "(i) Armed with the results from Nardin the skilled team would know that a development programme would be necessary which could be time consuming and expensive. A question therefore arises as to whether the team would abandon it at that stage.
>
> (ii) Nothing in Nardin would lead the skilled team to abandon the project before it began.
>
> (iii) On starting the project, the team would discover that one cannot dissolve enough dorzolamide in a 0.5% solution of timolol at the pH at which timolol is formulated, pH 6.8.

> This would rapidly lead to the knowledge that a pH of around 6.0 was required.
>
> (iv) The skilled team would recognise that lowering the pH at which timolol was formulated could lead to a decrease in the bioavailability of timolol.
>
> (v) This knowledge would not cause the skilled team to abandon the project. The skilled team would still want to obtain animal data or, if it paused to consider theory, would appreciate that the reduction in bioavailability is not likely to be great.
>
> (vi) Thereafter the project is a normal drug development program."

25. He accepted propositions (iii) and (iv) as being well established by the evidence and continued in paragraph 130:

> "The real questions are whether the skilled team would embark on the project at all, whether, after starting the project, the pH/bioavailability problem would lead to abandonment, and whether, if not, the team would eventually arrive at an effective formulation for use."

He then proceeded to answer each of those questions. For the reasons given in paragraphs 131 to 135 he considered that the project would not be abandoned before it was begun. He referred to the evidence of the parties' respective professors in ophthalmology and concluded that:

> "…the skilled team would be highly motivated to produce the co-formulated product, given the quantitative results in Nardin and the patient compliance benefits of a co-formulation. The quantitative results obtained at bid would lead the team to expect success. Of course the skilled team would realise that something might go wrong on the way, but nothing concrete was suggested which would have affected the skilled team's prognosis at the outset."

26. Floyd J then considered in paragraphs 136 to 148 whether the pH problem would cause the project to be abandoned. He concluded in paragraph 147 that:

> "…the problem might cause the skilled team to appreciate that there might be a problem en route to their ultimate goal which they had not appreciated at the outset. But I do not think it is realistic to suggest that it would have caused the team to abandon the project. The motivation to obtain a co-formulation would remain unaltered, making abandoning it in favour of pursuing co-administration alone an unattractive proposition. Other drug combinations had not been suggested in Nardin. Moreover the pH problem did

> not mean that the co-formulation would not work. Nardin predicted a 13 to 21% increase in efficacy. The actual reduction in bioavailability might be very small indeed, or non-existent, given the distance from the pKa value. There would also be a question as to whether any reduction in timolol availability would matter clinically. The clinician on the team would know that the 0.5% timolol dose was at the top of the dose response curve, and that there was not much evidence of any difference in effect as compared to 0.25% so the reduction in bioavailability might well not matter. The possible effect would not cause the skilled team to abandon the project."

27. Finally Floyd J considered whether the evidence established that the project would be successful. In paragraphs 149 to 159 he considered whether the skilled team starting from Nardin would be able to carry the project through to actual use. He concluded that it would. In paragraph 161 he concluded:

> "I need, at the end to take a step back. [Counsel for Merck] reminded me that I must be careful not to allow hindsight to colour my judgment when considering the fourth step [in Pozzoli], particularly when an "obvious to try" case is being run. Many cases have stressed this. Nevertheless, I am driven to the conclusion that the use of the co-formulation to treat glaucoma as claimed in claim 6 does not involve an inventive step. The skilled team would have been highly motivated to achieve such a use. They would have entertained throughout a fair expectation of success and would have arrived at their goal without any invention. None of the other claims can survive these findings."

28. In the light of his conclusions on obviousness the judge did not have to deal with the objection based on insufficiency. He concluded that the patent as sought to be amended was invalid for want of an inventive step. In addition he considered that unamended claims 1 to 6, 8 and 9 also lacked an inventive step. Had the patent been otherwise valid he would not have allowed the amendment to unamended claim 20 (amended claim 18) anyway on the ground that it added matter.

The appeal - submissions and conclusion

29. The permissible grounds of appeal are grounds 1 and 14. The effective ground is ground 14. In view of some of the submissions made to this court I find it necessary to set out that ground in full. But the reader must bear in mind that when originally formulated it was in the context that co-formulation, as claimed in claim 6, was not obvious. Ground 14 is as follows:

> "Further the learned judge failed to deal adequately or at all with [Merck]'s case that the step by step project proposed by [Teva] as the obvious way forward would not arrive at a

> formulation with the features called for by the independently valid claims, even if it was not abandoned outright. In particular the learned judge addressed the possibility that the skilled person would abandon the project but he failed to consider the impact on the later steps in [Teva]'s step by step approach of the outcomes of the tests [Teva] contended would be performed at earlier steps. [Teva] needed to establish that the outcome of its step by step approach would be a formulation formulated at a pH range of 5.5-6.0 required by proposed amended claim 18 and (or) with the amounts of the two drugs such that the concentrations fell within the scope of the claims, and in particular claim 6. [Teva] failed to do so. Although the judge expressed the conclusion that the use of a formulation within claim 6 does not involve an inventive step his reasoning does not adequately support that conclusion. The correct conclusion is that the claims are not obvious on this basis."

30. The effect of the decision of this court in allowing permission to appeal on ground 14 but not grounds 7 to 13 is that the only permissible ground left to Merck is that expressed in the middle of ground 14, namely, whether Teva had established that the outcome of its step by step approach would be a formulation of timolol and dorzolamide in the proportions specified in claim 6 at a pH range of 5.5-6.0 as required by proposed amended claim 18. Counsel for Merck submits that the proper conclusion on that issue is in the negative. He relies on the following propositions:

> (1) As Nardin said nothing about how to suspend or dissolve both timolol and dorzolamide in water so as to constitute a co-formulation the skilled team would have to find that out in the six days which elapsed between the publication of Nardin and the priority date.
>
> (2) Notwithstanding his correct self-direction on the law the judge wrongly applied hindsight in concluding that the skilled team starting with Nardin would end up with a co-formulation within amended claim 18.

31. In support of his first proposition counsel for Merck emphasised the regulatory environment involved in the introduction of new medicinal products. He pointed out, correctly, that all those steps could not possibly be completed in six days. Indeed he questioned whether the skilled team would even find out in that period that dorzolamide would not dissolve in water with timolol at the concentration for which claim 6 provided without making some adjustment to the pH. He accepted that discovering what that adjustment was is a matter of trial and error and does not involve any inventive step but suggested that the trials and errors would take a substantial period of time.

32. In relation to his second proposition counsel for Merck contended that the judge had wrongly employed hindsight in concluding that the skilled team would ever start out on a project for the co-formulation of timolol and dorzolamide. If, as the judge had decided, the development of such a co-formulation would not qualify

for patent protection why spend the time and money necessary for its development. This part of his argument involved a challenge to the reasoning and conclusion of the judge on the first of the questions he posed for himself in paragraph 130 I have quoted in paragraph 25 above.

33. Counsel for Merck then went on to suggest that even if the skilled team had set out on trying to provide a co-formulation of timolol and dorzolamide their subsequent realisation of the problems of solubility of dorzolamide at the pH at which timolol is formulated would lead them to abandon the project. This part of his case appears to me to involve a challenge to the reasoning and conclusion of the judge in respect of the second of the questions suggested in paragraph 130 of his judgment quoted in paragraph 25 above.

34. Both propositions were disputed by counsel for Teva. He contended, by reference to Patents Act 1977 ss.1(1), 2(1) and (2) and 3 that the test of obviousness does not involve any express or implied time limit. In relation to the second he contended that the characterisation of the judge's approach as a classic step by step analogy, which is recognised as possibly involving hindsight to an impermissible degree, was not correct. Rather the judge reached essential conclusions of fact on the basis of the evidence before him.

35. I will deal with the two propositions in turn. The tests for novelty and obviousness both depend on the statutory definition of 'state of the art' in s.2(2) Patents Act 1977. That is in the following terms:

> "The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way."

By s.2(1) an invention is to be taken to be new if it does not form part of the state of the art. The only element of time is that the relevant state of the art is that which exists on the priority date.

36. The test of obviousness is prescribed by s.3 in these terms:

> "An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above…"

There is no additional time requirement in that case either. If by reference to the relevant state of the art the invention is obvious then it matters not that it may take time to perform the necessary routine tests. It is a matter of simple comparison between the relevant art and the claimed invention.

37. That this is so is consistent with the decision of this court in **Actavis UK Ltd v Merck & Co. Inc.** [2008] EWCA Civ 444 [2008] RPC 26. In that case it was asserted that the invention had been obvious but had been rendered inventive because of some supervening publications. That submission was upheld by the judge and the Court of Appeal. In paragraph 119 Jacob LJ noted that:

> "…superficially one might think this conclusion is a bit odd given that the invention was once obvious – one might assume that when an invention becomes obvious it must remain so thereafter. But such an assumption would be wrong: obviousness must be determined as of a particular date. There is at least one other well-known example showing how an invention which might be held obvious on one date, would not be so held at a later date. That is where there has been commercial success following a long-felt want. Time can indeed change one's perspective. The perspective the court must bring to bear is that of the skilled man at the priority date and not any earlier time."

If an earlier date is excluded then so must be a later date. The only relevant date is the priority date. In addition, problems or time taken to obtain regulatory approval are not relevant to the question of obviousness. This is clear from the statement of Aldous LJ in **Richardson Vick's Patent** [1997] RPC 888, 896 and of Lewison J in **Ivax Pharmaceuticals UK Ltd v Akzo Nobel BV** [2006] EWHC 1089 (Ch) [2007] RPC 3 paras 41 to 43.

38. But that is not the end to the objections to which this submission gave rise, namely that this point was not raised in the court below, nor, for that matter in the grounds of appeal. Had it been raised in the court below some evidence would have been necessary to indicate how long it would have taken for the skilled man to appreciate the necessity for and the extent of the adjustment of the pH of the formulation to ensure the solubility of the dorzolamide. There was none. Indeed I understood counsel for Merck to accept that it would have been obvious to the skilled man that some such adjustment would be required and it was a mere matter of trial and error to discover what it was. Accordingly I conclude that this point is not open to Merck, permission to raise it should not be given, and that it is in any event incorrect as a matter of law.

39. I turn then to the second proposition. Counsel for Merck submitted that the reasoning of the judge involved no fewer than 23 steps, 17 from the first stage and 6 from the second. He claimed that such a quantity was unparalleled and itself indicative of the use of hindsight. I would reject this submission. The first ten in the first stage are different elements in the relevant state of the art and the eleventh is the conclusion the judge drew from them. It seems to me that the first stage involves one step only, namely embarking on the project which Nardin suggested.

40. The judge considered this in detail in paragraphs 131 to 135. In paragraphs 133 and 134 he evaluated the evidence of Professors Serle and Rennie, the ophthalmological experts for Merck and Teva respectively, and preferred the latter as the more realistic. On this aspect he considered that the conclusion that co-

formulation would be considered well worth while investigating was inescapable. He concluded in paragraph 135:

> "It is worth reviewing at this stage the factors which should be borne in mind in any assessment of obviousness. So far as motivation is concerned, I consider that the skilled team would be highly motivated to produce the co-formulated product, given the quantitative results in Nardin and the patient compliance benefits of a co-formulation. The quantitative results obtained at bid [twice daily administration] would lead the team to expect success. Of course the skilled team would realise that something might go wrong on the way, but nothing concrete was suggested which would have affected the skilled team's prognosis at the outset."

I see nothing in this section to suggest that impermissible hindsight had crept in. Nor do I accept the submission of counsel for Merck that if a step is obvious it will not be taken because no patent protection will arise at the end. The true test is whether the improvement involves an inventive step, not a commercially attractive one.

41. Similarly the six steps suggested to form the second stage appear to me to involve only one namely appreciating the need to adjust the pH of the formulation and then conducting the routine tests required to discover to what pH it needed to be adjusted. Indeed when pressed counsel for Merck accepted that there were only two steps in respect of which the judge used hindsight, namely embarking on the project in the first place, with which I have already dealt, and continuing it after appreciating the need to adjust the pH of the formulation. This was the issue with which the judge dealt in paragraphs 136 to 148.

42. On this issue the judge accepted (paragraph 137) the evidence of Dr Wilson, the expert pharmacologist for Teva, that "the pH route to achieving the necessary solubility was the most obvious one". In addition it was supported by the contemporaneous documents produced by Merck to the effect that any drop in bioavailability due to the lowering of pH would be slight. He rejected the contrary submission of Merck on the ground that the works on which it relied were not part of the common general knowledge at the time. On this aspect of the case he did not consider that:

> "...it is realistic to suggest that it would have caused the team to abandon the project. The motivation to obtain a co-formulation would remain unaltered, making abandoning it in favour of pursuing co-administration alone an unattractive proposition."

43. I detect no hint of impermissible hindsight being used here either. The judge's conclusion was based firmly on his evaluation of the evidence, both oral and documentary, adduced before him. It is accepted that the judge correctly directed himself. Further he was conscious of the dangers of hindsight creeping in. He stood back and reconsidered his conclusions with the consequence recorded in

paragraph 161 quoted in paragraph 27 above. Indeed given the facts that Nardin, Ganda and the need to adjust pH to ensure solubility were all part of the common general knowledge or relevant state of the art he could not sensibly have arrived at any other conclusion. I see no error on the part of the judge which could entitle this court to interfere with his conclusion. I would dismiss this appeal.

Lord Justice Richards

44. I agree.

Lord Justice Patten

45. I also agree.