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Case No: A3/2011/2970

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGH COURT OF JUSTICE
CHANCERY DIVISION (PATENTS COURT)
THE HON MR JUSTICE FLOYD
[2011] EWHC 2403 (Pat)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 12/12/2012

Before:

LORD JUSTICE MUNBY
LORD JUSTICE LEWISON
and
LORD JUSTICE KITCHIN

- -

Between:

Novartis AG **(a company incorporated under the laws of Switzerland)**	**Appellant/ Defendant**
- and -	
Generics (UK) Limited **(trading as Mylan)**	**Respondent /Claimant**

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- -

Iain Purvis QC and Miss Anna Edwards-Stuart (instructed by Bristows)
for the Appellant
Daniel Alexander QC and Henry Ward (instructed by Taylor Wessing LLP)
for the Respondent

Hearing date: 14 November 2012

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Judgment

Lord Justice Kitchin:

Introduction

1. This is an appeal against the judgment of Floyd J dated 30 September 2011 and his consequential order made on 20 October 2011 revoking Supplementary Protection Certificate SPC/GB98/038 ("the SPC") and its basic patent, UK Patent No. 2,203,040 on the basis that claims 1 to 9 of the basic patent were invalid.

2. The SPC and the patent are owned by the appellant, Novartis, and protect a drug called rivastigmine which is used for the treatment of Alzheimer's disease. Novartis markets rivastigmine under the trade name Exelon.

3. In these proceedings the respondent, Mylan, sought revocation of the SPC and claims 1 to 9 of the patent in order to market a generic version of rivastigmine which it accepts falls within the product claims and is the direct product of the process claims of the patent. The trial was therefore only concerned with validity.

4. Rivastigmine is the (-)-enantiomer of N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl–carbamate. This is a racemic compound which was made and tested in about 1985 by a team of scientists led by Professor Marta Weinstock at the Hebrew University of Jerusalem and was disclosed by them in two prior publications relied upon in these proceedings, European Patent Application No. 0, 193, 926 ("the Weinstock application") and an article published in the proceedings of the thirtieth OHOLO conference on Alzheimer's disease and other related neuropsychiatric disorders ("the Weinstock article"). The racemic compound is referred to in these publications as RA_7. As the judge explained, RA_7 was one of a number of compounds proposed by Professor Weinstock for the treatment of Alzheimer's disease, but the publications did not suggest that it should be resolved into its individual enantiomers. The issue at trial was therefore whether, in the light of either of the Weinstock publications, it would have been obvious to a skilled team working in the pharmaceutical industry to select RA_7 and resolve it into its individual enantiomers and use the (-) enantiomer as a medicinal product for the treatment of Alzheimer's disease.

5. The judge concluded there was nothing inventive in deciding to resolve and test RA_7 to see if there were advantages or disadvantages associated with one of its enantiomers. Further, a pharmaceutical composition for the treatment of Alzheimer's disease comprising rivastigmine was conceptually obvious. It followed that the narrowest of all the claims relied upon by Novartis, namely rivastigmine in pharmaceutically acceptable form for use in the treatment of Alzheimer's disease, was invalid for lack of inventive step.

6. Upon this appeal, Novartis contends that the judge's finding was based on a number of errors of law and fact. Mylan responds that, on analysis, Novartis is simply inviting this court to reverse the judge's evaluation of the facts, something this court should be very cautious about doing for the reasons explained by Lord Hoffmann in *Biogen Inc v Medeva plc* [1997] RPC 1 at 45.

Technical background

7. The judge set out the technical background to the patent in his judgment at [6] – [25]. Novartis does not challenge any part of this description. Nor does it contest the judge's finding that all of this background formed part of the common general knowledge of the skilled team to whom the patent is addressed.

8. For the purpose of this appeal, I would emphasise the following. Alzheimer's disease is a degenerative and irreversible brain disorder. Patients suffer a progressive decline in cognitive function and exhibit various behavioural symptoms, many of which can be particularly stressful for the patients' families and carers. Even today, it has no cure.

9. By March 1987, the priority date of the patent, there was a consensus that the cognitive symptoms associated with Alzheimer's disease were due, at least in part, to a deficit of cholinergic transmission in the central nervous system. Studies had shown that patients suffering from the disease exhibited reduced synthesis and release of acetylcholine (ACh) and reduced activity of acetylcholinesterase (AChE), the enzyme primarily responsible for its hydrolysis. These studies suggested that ACh replacement or enhancing therapies might prove beneficial, the so-called "cholinergic hypothesis". As the judge explained at [11], of the possible ways of achieving enhancement, the most promising was a proposal to use chemicals called cholinesterase inhibitors to block the active site of AChE and so inhibit its activity. If ACh cannot bind to AChE, it cannot be broken down and its level can be maintained.

10. Other than the compounds described in the Weinstock publications, only two cholinesterase inhibitors had shown some therapeutic promise for the treatment of Alzheimer's disease by the priority date. One was physostigmine, a naturally occurring compound found in the Calabar bean. It had shown some efficacy in limited experimental trials. But it was known to be far from ideal as a treatment because it suffered from the drawbacks of having a short duration of action and a small therapeutic window, meaning that intolerable side effects are observed at or close to a therapeutic dose. In addition, it has variable bioavailability and is chemically unstable. Another compound, tacrine, had generated interest in the light of a study published in the New England Journal of Medicine in 1986 which indicated that its oral administration resulted in a significant cognitive improvement in Alzheimer's disease patients without causing side effects.

11. It was, in the end, common ground at the trial that the cholinergic hypothesis presented the most promising line of research into the treatment of Alzheimer's disease at the priority date. Tacrine was the first potential treatment to emerge from this hypothesis, but there was a need for others.

12. Finally, I should say a word about chirality. As the judge recorded at [24], it was also common ground at the trial that the skilled team reading the patent would have had an expectation that the activity of a drug molecule would be affected by chirality. It is unusual to find that the activities of the (+) and (-) enantiomers of a racemic compound are the same. In some cases one enantiomer is completely inactive, but usually one enantiomer is more active than the other.

The patent

13. The judge summarised the disclosure of the patent at [29] – [43]. The specification explains that the invention relates to rivastigmine which it describes as a novel phenyl carbamate with anticholinesterase activity. It recognises that the racemic mixture of which rivastigmine is the (-) enantiomer was known from the Weinstock application but continues:

> "It has now surprisingly been found that the (-) enantiomer of formula I and its pharmacologically acceptable acid addition salts exhibit a particularly marked and selective inhibition of the acetylcholinesterase.
>
> These findings are unexpected, particularly since it is not believed that the dialkylaminoalkyl side chain, which contains the optically active centre, is mainly responsible for the acetylcholinesterase inhibiting activity of the phenyl carbamates."

14. However, as the judge held at [32], the evidence showed that the skilled team would not entirely agree that the findings were unexpected because it was common ground that the chiral part of the molecule would be expected to influence the activity and hence the potency of the compound.

The skilled team

15. The judge described the addressee of the patent at [46]. The patent is, he found, addressed to a team of skilled researchers in a pharmaceutical company with an interest in developing drugs for use in the treatment of Alzheimer's disease. Such a team would include a medicinal chemist and a pharmacologist who would likely be a neuroscientist.

16. Both parties therefore called two experts, a medicinal chemist and a neuroscientist with experience of Alzheimer's disease. Mylan called Dr Roger Newton and Professor David Smith; Novartis called Dr David Cavalla and Professor Paul Francis.

17. Until his retirement in 1996, Dr Newton was employed by Glaxo and Allen & Hanburys as a medicinal chemist, ultimately directing their global research into respiratory diseases. Professor Smith is Professor Emeritus of Pharmacology and Honorary Associate Director of the MRC Anatomical Neuropharmacology Unit at the University of Oxford. He has had a particular interest in Alzheimer's disease since the late 1970s.

18. Dr Cavalla was, like Dr Newton, employed by Glaxo for a number of years as a medicinal chemist. After the priority date he moved to the Napp Research Centre in Cambridge. Professor Francis is a Professor of Neurochemistry at King's College London where he leads a research team studying the biochemistry of dementia. He has more than 25 years' experience in the study of Alzheimer's disease.

19. As the judge recorded (at [56]), all of these witnesses gave their evidence fairly and genuinely intended to assist him on the technical aspects of the case. But as between the two medicinal chemistry experts, the judge observed:

> "I formed the view that Dr Newton had more of the practical scientist about him, preferring to test things in the laboratory rather than engaging in any extended theoretical or mechanistic discussion. Dr Cavalla's approach was more analytical, preferring to think deeply about the rationale for any experiment before conducting it."

Prior art

20. The Weinstock application and the Weinstock article are different publications. However, for the purpose of this appeal, Novartis accepts that nothing turns on the differences between them and so there is no need to consider them separately. They disclose a number of novel phenyl carbamates, most of which are chiral.

21. The judge described the disclosure of the Weinstock publications in detail from [58]-[77]. I need only refer to Professor Weinstock's conclusions in the Weinstock application:

> "The most preferred compounds of the RA series are RA_4, RA_5, RA_6, RA_{15}, RA_{14}, RA_7 and RA_8, all of which produce inhibition of brain acetylcholinesterase after parenteral administration of significantly longer duration than that induced by physostigmine or miotine. These compounds also have a greater safety margin (therapeutic ratio) than physostigmine. RA_4, $_6$, $_7$ and $_8$ also show better bioavailability after oral administration than physostigmine. In addition, the acute toxicity (lethality) induced by RA_7 can be decreased more than 10-fold and that of RA_{14} more than 8-fold by the antidote atropine, compared to only a 3-fold decrease for physostigmine and miotine."

And that:

> "The compounds of the invention are therefore useful for the treatment of … Alzheimer's disease …"

22. There was no real dispute that the notional skilled team would have taken the Weinstock publications seriously. As the judge found at [79], their disclosure was sufficiently promising to encourage workers to pursue Professor Weinstock's work further, notwithstanding the interest in tacrine generated by the article in the New England Journal of Medicine.

The judgment

23. The judge began his assessment of obviousness by directing himself as to the correct legal approach. Most importantly, he referred to the guidance given by Lord Hoffmann in *Conor v Angiotech* [2008] RPC 28, [2008] UKHL 49 at [42]:

> "In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case in which there was a fair expectation of success. How much of an expectation would be needed depended upon the particular facts of the case. As Kitchin J said in *Generics (UK) Ltd v. H Lundbeck A/S* [2007] RPC 32, para. 72:
>
> > "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success.""

24. The judge then identified the difference between the invention and the disclosure of the Weinstock publications in these terms at [92]:

> "In the end no one suggested that the case could be decided differently depending on whether one started from the Weinstock Application or the Weinstock Article. The steps from Weinstock to the inventive concept are, putting the matter in the most generous way to Novartis: (a) the choice of RA_7 (b) its resolution into its enantiomers and (c) the preparation of a pharmaceutical containing the (-) enantiomer. It is of course implicit in Weinstock that the ultimate target is a pharmaceutical for the treatment of AD."

25. This brought the judge to the key question whether, viewed without any knowledge of the invention, these differences constituted steps which would have been obvious to the person skilled in the art at the priority date. He reminded himself (at [93]) that one must be particularly careful to avoid hindsight and that although he had to consider each of the differences, in the end the statutory question must be asked in relation to the invention as a whole.

26. The judge therefore turned to consider the first of these steps, namely the selection of RA_7. The judge began by noting a difference of opinion between the medicinal chemistry experts as to the approach the skilled team would take in the light of the Weinstock publications. Dr Newton took the view that Professor Weinstock's work provided an adequate basis for taking one or more of her compounds into development. Dr Cavalla, on the other hand, thought this work represented an incomplete investigation into the structure-activity relationship of these compounds and would therefore have carried on synthesising and testing new compounds. It was on the basis of Dr Cavalla's evidence that Novartis contended that the obvious approach was to carry on with Professor Weinstock's

investigations, and that to stop that process and move into development was not obvious.

27. The judge considered that Novartis' submission was based on a false dichotomy. He accepted that one obvious course was to continue investigating the structure-activity relationship and synthesising new compounds. But it did not follow that the other course of selecting one or more of Professor Weinstock's compounds for development was not obvious. Indeed, the judge thought it was also obvious for the reasons he gave at [96]:

> "Weinstock had carried out an investigation of structure/activity, albeit a limited one, and reached some very positive conclusions. The compounds are disclosed as having promise, and meeting her criteria for an improvement over physostigmine. It does not require any insight or invention to go on and investigate whether that promise translated into a useful therapeutic effect."

28. The judge then had to consider the question of which compounds it was obvious to develop. As to this, he held there was, in the end, little dispute that RA_7 was one of those showing the most promise. Professor Francis described it as the "top pick". Nobody suggested any good reason for excluding it. It followed that RA_7 was an obvious compound to take forward.

29. That brought the judge to the second step, namely the resolution of RA_7 into its enantiomers. The judge disposed of two points at the outset. He noted (at [101]) it was common ground that the skilled team would consider the question of resolution of its lead development compound. He also noted (at [102]) that the actual resolution of RA_7 did not involve any problematic chemistry. He recognised that the skilled team would be aware that resolution could, in some cases, represent a difficult task but he was not persuaded that in 1987 this would make the skilled team hesitant about trying. The question therefore turned on whether the skilled team would take the decision actually to resolve RA_7. This, the judge considered, would be a decision lying in the province of the medicinal chemist.

30. Once again Dr Newton and Dr Cavalla took very different positions. The judge summarised Dr Newton's evidence as being that the processes involved when a chiral drug is taken are so many and so varied that it is impossible to predict in advance that there will be no advantage in resolving it and administering only one of its enantiomers, and that the skilled team would therefore try to resolve it to see whether that was the case.

31. Dr Cavalla did not disagree with the first aspect of this evidence but expressed the view that, in any individual case, the skilled team would conduct an analysis on a theoretical basis to see whether there would be an expectation of an improvement if the drug was administered as an individual enantiomer. In the particular case of RA_7, he thought there would be no expectation of a benefit.

32. The experts agreed that the skilled team would expect a difference in potency between RA_7 and one of its enantiomers because the chiral end of the molecule is involved in the initial binding to the enzyme. An increase in potency may improve

the therapeutic window. But, if the toxic effects of a drug are caused by the same mechanism as the therapeutic effect, an increase in potency may cause a reduction in both the therapeutic dose and the lethal dose, and so result in no change in the therapeutic window. The judge accepted that, applying this logic, the skilled team would not see an improvement in therapeutic window as a likely outcome of the resolution of RA_7.

33. Nevertheless, the judge thought that the skilled team would consider resolution a worthwhile thing to do for the following reasons. First, they would consider there might be a difference between the enantiomers in terms of their metabolism. Second, they would be aware that the process of penetration of the blood brain barrier could be stereo-selective. Third, they would be aware that delivering a drug as a resolved enantiomer avoids the possibility of unknown, stereo-specific side effects emerging downstream. The judge concluded (at [111]) that, since the reduction or elimination of any risk was a high technical priority, there was nothing inventive in deciding to resolve and test RA_7 to see if there were advantages or disadvantages associated with one enantiomer. Indeed, it would have been a routine thing to do.

34. The third and final step is the preparation of a pharmaceutical containing rivastigmine. The Weinstock publications teach the utility of the disclosed compounds in the treatment of Alzheimer's disease. It followed that, once a skilled team had resolved RA_7, it would have been obvious to formulate it as a pharmaceutical composition.

35. The judge arrived at his overall conclusion at [115]:

> "I think the correct analysis is that a pharmaceutical composition for treatment of AD comprising rivastigmine was conceptually obvious in the light of Weinstock and would immediately occur to the skilled team. The team would consider that resolving RA7 would be a worthwhile step to take for good technical reasons. The team would find that the chemistry involved is trivial. Applying the principles outlined above I have no doubt that the inventive concept is obvious in the light of Weinstock."

The appeal

36. Upon this appeal, the parties have been represented as they were before the judge, Novartis by Mr Iain Purvis QC and Ms Anna Edwards-Stuart, and Mylan by Mr Daniel Alexander QC and Mr Henry Ward.

37. Mr Purvis began by attacking the judge's approach to the first step, namely the selection of RA_7 for development which, he submitted, revealed errors of law and fact. In summary, Mr Purvis submitted that it was common ground that extensive further testing was required before any of the compounds disclosed in the Weinstock publications could be selected for development. He continued that it was also common ground that resolution of candidate compounds would not be carried out until the development phase. Although the Weinstock publications disclosed RA_7 as a candidate compound for further research, whether it would have

emerged as a compound suitable for development was a matter of complete speculation.

38. Mr Purvis developed his submission by reference to the nature of the process of drug discovery and development at the priority date. This, he argued, followed a clearly defined series of steps which were summarised by the judge at [47] – [50] in these terms:

> "47. As at 1987 the process of drug discovery and development followed a number of stages which could include (i) identification of the target pathway; (ii) generation of novel compounds; (iii) identification of lead compounds; (iv) optimisation of lead compounds; (v) further rounds of (ii) to (iv), including parallel series of lead compound discovery; (vi) pre-clinical development; (vii) clinical trials. This is of course an idealised pathway: the evidence showed that not every company pursued such an extensive investigation of compounds.
>
> 48. The neuroscientist would be concerned with the identification of the target pathway. The generation of novel compounds aims to manipulate or mimic known compounds in order to obtain novel compounds that retain the benefits associated with the known compounds but do not suffer from the drawbacks. The drug research and development team would identify suitable compounds. Promising (or lead) compounds would be identified and provided to the neuroscientist for testing. The team would then consider the results of these studies together. The neuroscientist would be able to identify suitable candidates based on the results of the biochemical and pharmacological properties, whilst the medicinal chemist might be able to attribute these properties to particular chemical groups on the compound, and make suggestions for further compounds for synthesis.
>
> 49. Once suitable lead candidates have been selected, further testing will be carried out on a decreasing number of compounds with the less suitable candidates being eliminated at each stage. In the case of CNS drugs, this further testing would include cognition tests in animal models. At the end of stage (v) the team would have selected one compound to progress to preclinical research (stage (vi)), together with a back-up candidate should the first candidate fail.
>
> 50. The pre-clinical research programme consists of further animal, *ex vivo* and *in vitro* experiments. However, these experiments are carried out in accordance with the

> requirements of the regulator and to obtain regulatory approval in order to test the compounds in humans."

39. Mr Purvis contended, and I accept, that this summary does not draw a clear distinction, at least in terms of nomenclature, between "drug research or discovery" and "drug development". The first five stages identified by the judge at [47] constitute drug research or discovery and it is only at stage (vi) that drug development begins, during which a single suitable candidate is subjected to pre-clinical testing in accordance with the relevant regulatory guidelines. The distinction is important, submitted Mr Purvis, because it was common ground that resolution would only be performed once the drug development stage was reached.

40. At this point I must explain a little more about what stages (iv) and (v) involve. As explained by Professor Francis, promising or lead compounds are identified in stage (iii) and then passed to the neuroscientist. In the first part of stage (iv), he carries out a series of biochemical and pharmacological assays intended to identify the drugs with the most suitable profiles. The results are considered by the neuroscientist and the medicinal chemist to identify suitable lead candidates. These are then carried into the second part of stage (iv) which, in the case of drugs for use in conditions involving the central nervous system, involves cognition testing in animal models, detailed observation of the incidence and intensity of side effects and advanced pharmacological and biochemical tests to look for enzyme-receptor specificity. In stage (v), further rounds of stages (ii) - (iv) take place with the result that, at the end of stage (v), the team will have selected one compound to progress to pre-clinical research in stage (vi), together with a back-up candidate should the first candidate fail.

41. Professor Francis and Dr Cavalla considered that the Weinstock publications really fell into the first part of stage (iv). The neuroscientist would be likely to select at least seven of the compounds Professor Weinstock had disclosed for further experiments intended to provide a better understanding of the important characteristics of those various compounds. Such experiments would include *ex vivo* pharmacokinetic analyses in animal models to determine bioavailability, half-life and variability; *in vitro* pharmacokinetic analyses on human AChE; systematic and semi-quantitative studies of side effects; and further studies in animal models to ascertain the activity and suitability of the compounds for administration.

42. Mr Purvis submitted that all these tests comprise a serious and detailed set of experiments, the outcome of which would have been entirely speculative and that none of the experts suggested that resolution of the candidate compounds would have been an obvious step to take before these tests had been carried out. So, Mr Purvis continued, even on Mylan's case, it cannot be suggested it was obvious to resolve RA_7 in the light of the Weinstock publications. Rather, it can only be said to have been an obvious response to further experiments performed in the light of the Weinstock publications and on the assumptions: (i) RA_7 had been chosen to take forward as part of a research project for further testing along with other drugs; and (ii) RA_7 had survived that testing and (iii) RA_7 had been selected for drug development. These were matters which the judge failed to take into account.

43. It follows, submitted Mr Purvis, that, had the judge properly considered the matter, he would have been forced to conclude that, given the small numbers of racemic

compounds apparently tested by Professor Weinstock and the limitations of her experiments, the expectation of the skilled team for any of those racemic compounds, let alone the enantiomers of RA_7, in terms of likelihood of ultimate success would have been low. Indeed, as I understood Mr Purvis, the expectation of success would have been so low, and the prospect of success so speculative, as necessarily to render the invention non obvious.

44. Attractively though these submissions were presented, I am unable to accept them. First, the Weinstock publications clearly teach that all of the preferred compounds, including RA_7, inhibit AChE for a significantly longer period and have a better therapeutic ratio than physostigmine. Further, four compounds, including RA_7, were shown to have better bioavailability after oral administration that physostigmine. Professor Weinstock therefore had a plausible basis for claiming that the compounds she disclosed would be useful for the treatment of Alzheimer's disease.

45. Second, both Professor Francis and Dr Cavalla accepted that the results shown by Professor Weinstock were encouraging and that they rendered RA_7 an attractive candidate for the treatment of Alzheimer's disease. Thus, Professor Francis stated in his first report at [188]:

> "The results shown in the Weinstock Application are encouraging. As with the Weinstock Article a number of the compounds appear to have a longer duration of action and increased tolerability as compared with physostigmine, with little change in AChE inhibition. However there is no analysis of cognitive function at all and the instance and severity of side effects is poorly reported."

46. Despite these qualifications, Professor Francis concluded:

> "… the skilled addressee would consider the data in the Weinstock Article to have been sufficiently interesting to carry out further investigation of these compounds."

47. Dr Cavalla also accepted that RA_7 was at least an attractive candidate in the light of the Weinstock publications and that it would be reasonable to look at it and propose its use as a treatment for Alzheimer's disease. As he said in the course of his cross-examination on day 2 at 175:

> "Q. You would at least agree with this, I know there is a big dispute about it, that of the compounds disclosed in the Weinstock article and the Weinstock application, RA7 was at least one of the attractive candidates by reference to important criteria?
>
> A. Yes.
>
> Q. So you would accept that at least in March 1987 there would not have been anything surprising if someone were to

> look at that material and propose the use of RA7 as a treatment for Alzheimer's?
>
> A. I would propose it but not necessarily be that confident that it would work.
>
> Q. Okay, but so far as it goes, propose it as a serious candidate, that would be a reasonable thing to do?
>
> A. Is that not what the Weinstock application makes clear?"

48. A little later, at page 176, he accepted that Professor Weinstock's work was lead optimisation, albeit limited:

> "Q. But you would accept this, that the Weinstock material is itself a lead optimisation campaign?
>
> Q. An extremely limited one."

49. In his second report, Dr Cavalla said, at [25], that pre-clinical development followed lead optimisation. It naturally followed, as he accepted in cross-examination on day 2 at page 185, it was obvious to investigate these compounds further:

> "Q. But are you suggesting that in this programme that the skilled team, you say, would have taken forward that they simply would not have found time to investigate the characteristics of the existing compounds and resolve them?
>
> A. I am not saying that. I am saying given sufficient resources one would like to do a range of things. But I do believe that as a matter of preference one would want to pursue further chemical variation in the RA series rather than resolve one of the enantiomers of the more active compounds.
>
> Q. But it would have been perfectly reasonable for a skilled team to say I want to work on the compounds that have been specifically disclosed and if they reached that conclusion to then investigate those compounds further. One obvious thing to do would be to investigate the chirality.
>
> A. One obvious thing might be to do that, but I return to what I said some time ago, that the pursuit of stereochemical variation is at odds with the teaching of the Weinstock article and the Weinstock application where it is its physiochemical variation which has delivered successful results."

50. Reverting to the judgment, it is clear from [47] – [49] the judge had well in mind the different stages of drug discovery and development and the various tests involved in taking candidates through to the end of stage (v). Then, at [94] – [97], having identified the false dichotomy to which I have referred, the judge observed that the fact that one obvious approach in the light of the Weinstock publications

was to continue making more compounds did not mean that the alternative course of establishing the viability of the compounds Professor Weinstock had disclosed was not obvious. He clearly thought that was a self-evident thing to do, concluding (at [100]) that RA_7 was an obvious compound to take further. By this I understand him to mean, taking it through any remaining necessary stages and into development. The judge then specifically rejected the submission now advanced at [114]:

> "Mr Purvis stressed the fact that this was not a case where the racemic compound was already in clinical trials, or on the market. He contrasted the present case, where there is only limited *in vivo* and *ex vivo* testing of a number of potential development candidates, with the position in the other decided cases I have mentioned where the compound was further advanced. There is no doubt that this is a factor to be taken into consideration. But I do not think this takes Novartis very far, given the very clear teaching in Weinstock about RA_7."

51. It follows that the judge did not omit from his consideration steps (iv) and (v) of the whole drug discovery and development process. Further, in the light of the evidence to which I have referred, I have no doubt that the judge had ample material upon which he could properly come to the conclusion that it was obvious to take RA_7 into development.

52. Mr Purvis next contended that the findings of the judge amounted to an overall finding that it was obvious to try an undisclosed chemical entity (rivastigmine) for a particular therapeutic purpose (the treatment of Alzheimer's disease). In order to make such a finding the judge was obliged to consider whether the skilled team would have had a fair expectation that the undisclosed chemical entity would successfully treat Alzheimer's disease, and that he did not do.

53. Mr Purvis developed his submission as follows. Although the judge referred to the opinion of Lord Hoffmann in *Conor* at [44], he failed to apply it because he did not consider the expectation of success at all. Moreover, Mr Purvis continued, the "obvious to try" test only applies where it is more or less self evident that what is being tested ought to work and in this regard referred us to the judgment of Jacob LJ in *Saint Gobain v Fusion-Provida* at [35]:

> "None of this to my mind remotely makes the idea of using Zn/Al alloy for pipes obvious — as something which is simply self-evident to the unimaginative man skilled in the art. Mere possible inclusion of something within a research programme on the basis you will find out more and something might turn up is not enough. If it were otherwise there would be few inventions that were patentable. The only research which would be worthwhile (because of the prospect of protection) would be into areas totally devoid of prospect. The "obvious to try" test really only works where it is more-or-less self-evident that what is being tested ought to work."

54. It follows, submitted Mr Purvis, that had the judge considered the correct question, namely whether or not, in the light of the Weinstock publications, the skilled team would have had an expectation that rivastigmine would be a successful treatment for Alzheimer's disease (as opposed to RA_7 being one of a number of promising compounds worthy of extensive further testing) the judge would have been forced to conclude that there was no such expectation. Moreover, although it was common ground that there was enough in the Weinstock publications to justify taking forward a number of the disclosed compounds (including RA_7) for further testing, the results of that testing were entirely speculative. There was therefore no material before the court to conclude the Weinstock publications demonstrated a fair expectation of success that the racemate RA_7 (let alone the enantiomer rivastigmine) would work as a treatment for Alzheimer's disease. Speculation as to the results of a research programme is not a sound or appropriate foundation for a finding of obviousness.

55. I of course accept that a patentee is entitled to have the issue of obviousness assessed by reference to the invention he has described and claimed. This was made clear by Lord Hoffmann in *Conor* at [19]. In deciding whether the invention was obvious to the skilled but unimaginative addressee at the priority date the court will have regard to all the circumstances of the case including, where appropriate, whether it was obvious to try a particular route with a reasonable or fair expectation of success. What is a reasonable or fair expectation of success will again depend upon all the circumstances and will vary from case to case. Sometimes, as in *Saint Gobain*, it may be appropriate to consider whether it is more or less self-evident that what is being tested ought to work. So, as this court explained in that case, simply including something in a research project in the hope that something might turn up is unlikely to be enough. But I reject the submission that the court can only make a finding of obviousness where it is manifest that a test ought to work. That would be to impose a straightjacket upon the assessment of obviousness which is not warranted by the statutory test and would, for example, preclude a finding of obviousness in a case where the results of an entirely routine test are unpredictable.

56. The correct approach was recently explained by this court in *MedImmune v Novartis* [2012] EWCA Civ 1234. I put it this way at [90]-[93]:

> "90. One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them

worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.

91. For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way. Lord Hoffmann summarised the position in this way in *Conor* at [42]:

> "In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation would be needed depended on the particular facts of the case."

92. Moreover, whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account. In *Generics (UK) Ltd v H Lundbeck*, [2008] EWCA Civ 311, [2008] RPC 19, at [24] and in *Conor* [2008] UKHL 49, [2008] RPC 28 at [42], Lord Hoffmann approved this statement of principle which I made at first instance in *Lundbeck*:

> "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

93. Ultimately the court has to evaluate all the relevant circumstances in order to answer a single and relatively simple question of fact: was it obvious to the skilled but unimaginative addressee to make a product or carry out a process falling

within the claim. As Aldous LJ said in *Norton Healthcare v Beecham Group Plc* (unreported, 19 June 1997):

> "Each case depends upon the invention and the surrounding facts. No formula can be substituted for the words of the statute. In every case the Court has to weigh up the evidence and decide whether the invention was obvious. This is the statutory task."

57. Lewison LJ said at [178]-[182]:

> "178. These articles [Arts. 52 and 56 EPC] find their domestic equivalent in sections 1 and 3 of the Patents Act 1977. As Jacob LJ pointed out in *Actavis UK Ltd v Novartis AG* [2010] EWCA Civ 82 [2010] FSR 18 (§ 17):
>
> > "So at bottom the question is simply whether the invention is obvious. Any paraphrase or other test is only an aid to answering the statutory question."
>
> 179. The same point is made in *Johns-Manville Corporation's Patent* [1967] RPC 479, which is the starting point in domestic law of the idea of "obvious to try". In that case Diplock LJ said:
>
> > "I have endeavoured to refrain from coining a definition of "obviousness" which counsel may be tempted to cite in subsequent cases relating to different types of claims. Patent law can too easily be bedevilled by linguistics and the citation of a plethora of cases about other inventions of different kinds. The correctness of a decision upon an issue of obviousness does not depend upon whether or not the decider has paraphrased the words of the Act in some particular verbal formula. I doubt whether there is any verbal formula which is appropriate to all classes of claims."
>
> 180. In the same case Willmer LJ said:
>
> > "I would, however, desire to associate myself particularly with what Diplock, LJ said as to the undesirability of coining phrases for the purpose of paraphrasing the words of the Act."
>
> 181. These sentiments seem to have been largely ignored by the profession. It cannot be said too often that the statutory question is: was *the invention* obvious at the priority date? It is not: was it obvious to try? In my judgment too much elaboration of the statutory question has been attached to it. The questions of the degree of expectation of success and the length of time thought to be needed to undertake a trial have taken on lives of their own. I think that this happened in our

> case. Insistence on the statutory question is not a novel thought. It is also an obvious one: see *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2007] EWCA Civ 5 [2007] RPC 20 (§§ 44, 45 per Jacob LJ, approved on appeal: [2008] UKHL 49 [2008] RPC 28 § 42 per Lord Hoffmann; § 49 per Lord Walker; § 55 per Lord Neuberger). In *Generics (UK) Ltd v H Lundbeck A/S* [2007] EWHC 1040 (Pat) [2007] RPC 32 (§72) Kitchin LJ (as he then wasn't) said:
>
> > "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."
>
> 182. This statement of principle was also approved by the House of Lords in *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc*. One of the important points, to my mind, is that all these considerations interact with each other. In short, it all depends. MedImmune's argument proceeded on the basis that Novartis needed to establish (a) a fair prospect of success (b) within a reasonable time, as if these were two independent conditions that had to be satisfied. They are not successive hurdles to be jumped; they are no more than aspects of the statutory question: was the invention obvious? We should stick to the statutory question, which has to be applied in all sorts of circumstances and in all sorts of different fields of endeavour."

58. I believe that in this case the judge directed himself correctly as to the law and in a manner which is entirely consistent with the principles explained by this court in *MedImmune*. As I have said, he referred to Lord Hoffmann's opinion in *Conor*. He also referred to the guidance given by the Technical Board of Appeal of the EPO in case T 0939/92 *Agrevo* at [2.4.2] that the skilled person does not act out of idle curiosity but with a technical purpose in mind. He noted too the reliance placed by Mr Purvis on the decision of this court in *Saint Gobain.* He then applied these principles to the facts of the case and assessed first, whether it was obvious to take RA_7 into development; and second, whether it was obvious to attempt to resolve it. He answered both these questions in the affirmative. As for the former, it required no insight or invention to follow the teaching of Professor Weinstock, to take the compounds she disclosed as having promise and meeting her criteria for an improvement over physostigmine and to investigate whether that promise translated into a useful therapeutic effect. As for the latter, the skilled team would consider that resolution of the racemate might bring practical benefits and would see resolution as a routine step. The approach adopted by the judge reveals no error of law. To the contrary, he approached the matter entirely properly. I would therefore reject this ground of appeal.

59. Mr Purvis then turned his attention to the assessment by the judge of the evidence of Dr Cavalla and Dr Newton and focused on the judge's reasoning at [103]-[104] and [110]:

> "103. It can be seen therefore that much turns on whether the skilled team would take the decision actually to resolve their development candidates, including RA_7. This decision would be in the province of the medicinal chemists. I hope I do not treat Dr Newton's evidence unfairly if I summarise it by saying that, in his view, (a) the processes involved when a chiral drug is taken are so many and so varied that it would be impossible to predict in advance that there would be no advantage in resolving it and administering only one of the enantiomers, and that therefore (b) the skilled team would resolve the compound to see whether that was the case.
>
> 104. Dr Cavalla's evidence did not disagree in general with Dr Newton's first proposition. However, his view was that, in any individual case the skilled team would conduct an analysis on a theoretical basis as to whether there would be an expectation of an improvement if the drug was administered as an individual enantiomer. He contended that in the particular case of RA_7 there would be no expectation of a benefit.
>
> …
>
> 110. In the end I found Dr Cavalla's reasoning less convincing. Mr Alexander QC, who appeared for Mylan with Mr Henry Ward, characterised it as something of an exercise in hindsight. Although that is a submission normally directed at the evidence attacking a patent, I think it has some force here when directed against the very theoretical evidence of Dr Cavalla. Not enough was known at the priority date to justify the conclusions which he sought to draw."

60. I must return to the details of the evidence given by Dr Cavalla and Dr Newton later in this judgment, but Mr Purvis submitted they can be summarised as follows. Dr Cavalla's evidence was that the skilled team at the priority date would not have embarked on the process of seeking to resolve the enantiomers of RA_7 because they would have had no expectation that to do so would have been worthwhile. Dr Newton's evidence was that the skilled team would have embarked on the process regardless of any expectations, because there was always a chance that something surprising might be found. The only expectation of a technical difference between the enantiomers in this case would have been in terms of absolute potency, which was agreed to be irrelevant. However, continued Mr Purvis, the judge (at least implicitly) concluded that this was no bar to a successful obviousness attack because in the pharmaceutical industry the reduction or elimination of risk was a

high technical priority. This entirely generalised attack was, he submitted, the wrong approach as a matter of law. If it were right, then any step, however obscure, which might conceivably throw up some information of interest would have to be found to be obvious. In the context of single enantiomer claims, this would mean that, save for cases where the actual process of resolution could not be achieved without invention, all such claims must necessarily be invalid. It is always the case that some unexpected effect in terms of toxicity associated with one particular enantiomer cannot be excluded - even where, as here, no toxic effect, other than that associated with the therapeutic action, had been observed for the racemate.

61. It seems me that this is a different way of putting the submission with which I have just dealt. It also involves a mischaracterisation of Dr Newton's evidence. Dr Newton did not say the skilled person would embark on a programme of experimentation on the basis that something surprising might be found. His evidence was that enantiomers frequently exhibit different activities, involve different systems of metabolism and have different toxicities. These are a consequence of their chiral structure and the chiral environment of the body in which they act. These differences are impossible to predict but it is important to determine whether they exist. Resolution of enantiomers is often relatively easy and so it is good science to get on and do it. This is not a matter of experimentation in the hope that something may turn up; it is experimentation driven by rational technical considerations. Moreover, and for the reasons I have given, I reject the submission that the inherent lack of predictability in chiral chemistry precludes a finding of obviousness as a matter of law.

62. This brings me to Mr Purvis' next submission, that the judge erred in his approach to the evidence of Dr Cavalla and Dr Newton. He contended the judge had no proper evidential basis for concluding resolution might bring practical benefits and attacked the judge's factual findings at [108]:

> "However I am unable to accept that the skilled team would fail to see practical benefits in resolution. Firstly, there is the question of the metabolism of the compound. Whilst the very process of blocking the active site on the AChE results in a breakdown of the drug molecule, this is not the only metabolic process to which the drug might be subjected. Those drug molecules which do not interact with the target enzyme could be broken down by other enzymes, for example pseudo-cholinesterase, in a stereospecific way. Dr Newton was clear that metabolism was an area where there might (not would) be a stereochemical effect between enantiomers. Secondly, the skilled team would be aware that the process of penetration of the blood brain barrier could be stereo-selective. Thirdly, delivering a drug as a resolved enantiomer avoids the possibility of unknown, stereo-specific side effects emerging downstream."

63. In my judgment this attack is not sustainable. First of all the judge had ample material upon which to conclude that resolution of compounds taken forward into

development was something the industry did as a matter of standard practice. Indeed he recorded at [101]:

> "Two points can be dealt with straight away. Firstly, it was common ground that the skilled team would consider the question of resolution in relation to its lead compound or compounds taken forward for development. It could scarcely have been otherwise given the fact that, of the chiral medicinal compounds introduced in 1984 and 1985 (excluding semi-synthetic compounds where nature had produced an enantiomerically pure starting point) about 50% were racemates. Burger's Medicinal Chemistry, published in 1970, contained a sentence which said "*Nowadays a study is automatically made of the stereochemical aspects of a novel biologically active molecule*". Although this was accepted to be something of an exaggeration in 1970 if it meant a practical investigation, Dr Cavalla accepted the proposition as of 1987 if it meant a theoretical study."

64. Moreover, Dr Cavalla accepted in the passage of his cross examination set out at [49] above that for a team taking RA_7 forward, one obvious thing to do was to try and resolve it. Further, the skilled team would have expected to see differences in stereochemistry, at least as a matter of generality, as he acknowledged on day 2 at 204:

> "MR ALEXANDER: And it is right to say, and I think we have debated this already, that a skilled team would have expected to see differences based on stereochemistry in at least one of absorption, distribution, metabolism and excretion in general for chiral compounds. That is right, is it not?
>
> A. Yes, but this is a case about a particular compound.
>
> Q. I quite understand, but as a matter of generality that is what the skilled person would have expected.
>
> A. But not necessarily always.
>
> Q. All right, not necessarily always, but as a matter of generality you do not quibble with that, do you?
>
> A. No, I do not."

65. Here there were good practical reasons for attempting to resolve RA_7, as the judge found. First, the skilled team would have perceived that there was a possibility of metabolic differences between the enantiomers, at least in terms of their metabolism by mechanisms other than AChE and, in particular, an enzyme called pseudo-cholinesterase. In this regard, Dr Cavalla accepted that RA_7 metabolism is effected both by AChE and other cholinesterases; and that the full ADME (absorption, distribution, metabolism, and excretion) profile of the enantiomers could only be determined by experiment. This was a matter which would need to

be determined in the course of development, as Dr Cavalla explained on day 2 at 245-246:

> "A. We have talked about metabolism quite a lot. There are a couple of different aspects to it, well, three aspects, one of which is this is acetylcholinesterase mediating metabolism by and large; secondly that the more potent an enantiomer is, it is also expected to be more rapidly metabolised; and thirdly, the metabolism itself is not a good predictor of duration of action because of the two-step nature of the inhibition process.
>
> Q. You may be right on all of those things, but those are in a sense just theoretical predictions, are they not?
>
> A. They are theoretical predictions related to the specific case at hand. Whereas, I think what you are talking about is generalities.
>
> Q. In the specific case at hand, were there to be differences in metabolism that were chirally determined, that would be an important factor to understand at an early stage of development?
>
> A. It would be, it could be an important factor, but it is more likely to go in the opposite way to the way you want it to, or the duration of action not to be stereo selective for the reasons I have expounded.
>
> Q. But none the less it would be an important thing to determine?
>
> A. In the course of development you would need to determine that, yes."

66. Second, the skilled team would have been aware that transportation across the blood brain barrier could be stereo selective, as Dr Cavalla accepted on day 2 at 244.

67. Third, delivering the drug as a resolved enantiomer would avoid the possibility of unknown stereo specific side effects emerging downstream. This finding was based upon Dr Newton's evidence, including this passage of his cross examination from day 1 at 65:

> "If you have two compounds as a mixture and you have not tested them, you cannot have expectations about whether they will be better, worse, what they are going to do. The whole history of resolution is that you keep finding things which are surprising. I went through my report, I showed you all the various things which can vary with stereo chemistry. You do not know and you cannot tell without doing an experiment.

> That is a fact of life, I am afraid, and that is the reason why we always resolve."

68. Finally, although Dr Cavalla's theory that resolution would not have a significant impact on toxicity was founded on the premise that any increase in efficacy for a given enantiomer would be matched by an increase in side effects, the results in the Weinstock publications cast some doubt on this. They showed that some compounds with low activity proved highly toxic, and vice versa. Dr Cavalla accepted that was so on day 2 from 251-252:

> "Q. In both tables. What table 2 is showing is there is low potency effectively of RA13 and in table 3 relatively high toxicity.
>
> A. And in general the Weinstock Article also shows cases where potency and toxicity do not correlate and they do that through affecting physiochemical characteristics.
>
> Q Yes, indeed, but my point is this. There is not anything in the Weinstock material that says, "Oh, here we have an automatic correlation between potency and toxicity which would lead a skilled team to say, well, there is absolutely no point in testing the enantiomers for their characteristics?
>
> A. Well, in my report I think I say that the potency and toxicity are correlated with one another in the absence of any other factors to say the opposite. The Weinstock Article, and the application say the opposite by varying the physiochemical characteristics and the distribution of the molecules. But you will not get that with the enantiomers, except in the rare circumstances that you have an effect on penetration into the brain through an uptake process or through a stereoselective inhibition of protein binding, which I understand is your case. I am just saying, that is a fairly rare likelihood of that occurring.
>
> Q. Yes, my point is this. If one looks at this data, it does not suggest that there is this automatic correlation.
>
> A. No, of course we went through that yesterday."

69. The judge had the advantage of seeing and hearing Dr Newton and Dr Cavalla give their evidence. No basis has been shown for challenging his finding that Dr Cavalla's reasoning was rather theoretical and that Dr Newton's evidence was to be preferred as being more practical. Moreover, I have read the transcripts of their evidence and, for the reasons I have given, I am satisfied that the judge was entitled to come to the conclusion that there were practical benefits in resolution. I would therefore reject this attack on his judgment.

70. Mr Purvis frankly accepted that if he did not prevail on any of the grounds with which I have dealt, he was unlikely to do so in relation to the two which remain. Nevertheless, I will address them, albeit shortly.

71. Mr Purvis argued that in opposing Novartis' application for an interim injunction, Mylan relied heavily on the FDA guidelines of 1987 which, it was said, rendered it virtually obligatory to perform resolution of putative pharmaceuticals. Mr Purvis also submitted that Dr Newton also relied heavily on these guidelines in his evidence at the trial. He then argued as follows. In fact, this was not the true position as explained in the unchallenged evidence of fact from Dr Weissinger who was working at the FDA at the priority date and was subsequently responsible for developing the FDA's policy statement on stereoisomers which was published in 1992. This simply required applicants to provide information and results from all studies carried out on the enantiomers of any racemic compound for which an application was made, and that in general no such information was provided. Mr Purvis submitted that this showed that applicants were not in fact resolving racemic compounds on a routine basis at the priority date.

72. The problem with this submission is that the judge did not find that resolution of a racemic compound was virtually obligatory at the priority date, but he had a good deal of other evidence before him that it was common practice for such resolutions to be carried out. Allen & Hanburys always attempted to resolve racemic compounds and Dr Cavalla accepted that many large companies attempted such resolutions at an early stage of drug development.

73. Finally, Mr Purvis argued that, at the end of his judgment, the judge also considered obviousness on the basis of the problem-solution approach favoured by Boards of Appeal of the EPO. In doing so the judge wrongly characterised the objective technical effect of the invention as "simply that which one would expect from resolution of a chiral compound". He ought to have characterised the objective technical effect as the use of rivastigmine as a treatment of Alzheimer's disease and that was not something that was expected at the priority date.

74. In my judgment there is nothing in this point. The starting point here is the work of Professor Weinstock which suggested the use of RA_7 to treat Alzheimer's disease. On the evidence before him, the judge was right to conclude that the technical effect of the invention was obvious. It was the result of taking the routine step of resolving that racemate.

Conclusion

75. For all the reasons I have given, I am satisfied the judge did not err in principle and there is no good reason for interfering with his assessment of the evidence. I would dismiss the appeal.

Lord Justice Lewison:

76. I agree. This is another case in which a patentee defending his patent has attempted to analyse a single multi-faceted question ("was the invention obvious?") by chopping it up into a series of sub-questions, and then treating each of the sub-questions in isolation. For the reasons explained by this court in *MedImmune* that is the wrong approach. I therefore agree with Kitchin LJ that, for the reasons he gives, this appeal must be dismissed.

Lord Justice Munby:

77. I agree with both judgments.