

Neutral Citation Number: [2011] EWHC 2403 (Pat)

Case No: HC11C00492

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 30th September 2011

Before :

THE HON MR JUSTICE FLOYD

Between :

GENERIC (UK) LIMITED	<u>Claimants</u>
(trading as Mylan)	
- and -	
NOVARTIS AG	<u>Defendants</u>
(a company incorporated under the laws of Switzerland)	

Daniel Alexander QC and Henry Ward (instructed by **Taylor Wessing LLP**) for the
Claimants

Iain Purvis QC and Anna Edwards-Stuart (instructed by **Bristows**) for the **Defendants**

Hearing dates: 5th to 7th September 2011 -

Judgment

Mr Justice Floyd :

1. A Supplementary Protection Certificate (“SPC”) extends the life of a granted “basic patent” in certain circumstances beyond the date on which the patent would otherwise come to the end of its statutory term. Generics (UK) Limited (who trade as “Mylan”) seek declarations of invalidity in respect of such a certificate - SPC/GB98/038 - and also of its basic patent, UK Patent No 2 203 040. The basic patent, and the SPC, protect a drug for the symptomatic treatment of Alzheimer’s disease (“AD”) called rivastigmine. The patentees, Novartis, market rivastigmine under the trade name Exelon. By counterclaim, Novartis allege that Mylan’s threatened marketing of a generic version of rivastigmine will infringe the SPC, and seek appropriate relief.
2. The action has come to trial very quickly. The claim form was issued on 3rd March 2011. Following an application for an interim injunction, an expedited trial of the action was ordered on 30th June 2011. The action was tried over three days from September 5th to 7th, just over six months from the issue of the claim form. Expedition was justified because Mylan intended to launch a product prior to the expiry of the SPC, which will occur on 30th July 2012.
3. Rivastigmine is the modern name for the (-)-enantiomer of N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl-carbamate. In around 1985 a team of scientists led by Marta Weinstock, working at the Hebrew University of Jerusalem, made and tested a compound named RA₇, which is the unresolved racemic compound of which rivastigmine is the (-) enantiomer. RA₇ was one of a number of compounds proposed by Weinstock for the treatment of AD, but her publications made no mention of resolving it into its individual enantiomers. The sole question which arises in this action is whether a relevantly skilled pharmaceutical development team, in ignorance of the patent in suit, would find it obvious in the light of the Weinstock publications to resolve the racemic mixture of RA₇ into its individual enantiomers.
4. The only ground of attack on the patent is therefore lack of inventive step. An insufficiency argument which was expressed to be conditional on a factual argument being run by the patentee was not pursued. No separate issues arise on the counterclaim.
5. This is not the first patent action in recent years in which the question of inventive step has involved consideration of whether it is obvious to resolve a chiral compound, already used or proposed for use in therapy, into its individual enantiomers. *Generics v Lundbeck* [2009] UKHL 12 and *Generics v Daiichi* [2009] EWCA Civ 646 are examples. Although both sides attempted to draw comparisons with the facts of those cases, the present case has to be decided on its own facts.

Technical Background

6. The patent in suit assumes that the skilled reader has a certain amount of technical knowledge in the field of AD and general medicinal chemistry. All of what follows in this section of my judgment would be part of the reader’s common general knowledge at the priority date in March 1987.

Alzheimer's disease

7. AD is a form of dementia. It is a progressive, degenerative, irreversible and ultimately terminal brain disorder.

The cholinergic system

8. Acetylcholine (ACh) is a neurotransmitter active in the central nervous system (CNS) where it binds to receptors. Within the CNS, ACh and the associated neurons form the cholinergic system. ACh-containing neurons in the brainstem and basal forebrain deliver ACh to areas of the brain.
9. ACh is synthesised within nerve terminals. When released from the nerve terminals the ACh diffuses across the synaptic cleft. Some ACh will bind to receptors on the pre- and post-synaptic cells, but most ACh will be hydrolysed by the enzyme acetylcholinesterase (AChE) (or in some cases by butyrylcholinesterase (BuChE)) which converts ACh into the inactive metabolites choline and acetate. The choline produced by the action of AChE is recycled to synthesise new ACh molecules.

The cholinergic hypothesis and AD

10. By the priority date, various neurochemical studies had shown an involvement of the cholinergic system in AD. In patients with AD, reduced activities of AChE had been reported, as had a reduced release and synthesis of ACh.
11. These studies suggested that enhancing cholinergic activity could be of benefit to those suffering from AD. Of the possible ways of achieving this enhancement, the most promising was the proposal to inhibit the enzyme AChE by chemical interaction. Initial support for this approach had been gained from preliminary trials using the drugs physostigmine and tacrine.

Cholinesterase inhibitors

12. Both AChE and BuChE are enzymes with an active site that comprises two distinct regions: an anionic site and an esteric site. These active sites interact with different parts of the ACh molecule. The anionic site binds to the (basic) choline moiety and the esteric site reacts with the (acidic) acetyl (or butyryl) group, leading to spontaneous hydrolysis of the substrate.
13. Cholinesterase inhibitors (also called anticholinesterases) act by inhibiting (i.e. by blocking the active sites of) AChE and/or BuChE. The inhibitor binds with the two sites of the cholinesterase molecule so as to prevent access by ACh. If a molecule of ACh cannot bind to the site, it cannot be hydrolysed there, and levels of ACh can be maintained.
14. As at the priority date, drugs for cholinesterase inhibition fell into three categories according to the nature of their interaction with the active site of cholinesterase: short-acting, medium-acting and irreversible. Of these only the medium acting inhibitors showed promise. Medium-acting cholinesterase inhibitors include neostigmine, pyridostigmine and physostigmine. These drugs contain (basic) groups that bind to the anionic site of the cholinesterase and also interact with the esteric site in a way which leads to much slower hydrolysis and a longer lasting effect.

Physostigmine and tacrine

15. Physostigmine is a naturally occurring compound found in the Calabar bean. It was available for clinical use to treat the CNS effects of anticholinergic drug overdoses. Physostigmine had been shown to show some efficacy for treating AD in some limited experimental trials.
16. Physostigmine was far from ideal as a treatment. This was primarily because of its short duration of action (typically 30 minutes) and its small therapeutic window (which meant that intolerable side effects were observed at or close to therapeutic doses). In addition it had variable bioavailability and was chemically unstable.
17. A study published in the New England Journal of Medicine in 1986 by Summers and others indicated significant cognitive improvement, without side effects, amongst people with AD who had been given oral tacrine. This paper attracted significant interest on its publication as it appeared to be the first potential treatment for AD to have emerged from the cholinergic hypothesis.

Brain regions

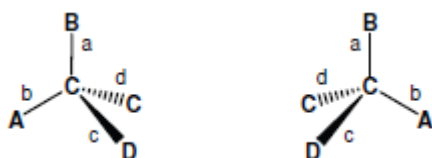
18. Four regions of the brain are known as the cortex, hippocampus, striatum and medulla. Cholinergic degeneration was known to be more pronounced in the hippocampal and cortical regions of the brain in patients with AD and these areas were associated with cognitive impairment.

Other lines of research

19. The cholinergic hypothesis was not the only line of research activity into the treatment of AD at the priority date. But it was, in the end, common ground between the experts that this hypothesis represented the most promising line at the time.

Chirality

20. A molecule is said to be chiral when it is non-superimposable on its mirror image. If a molecule is superimposable on its mirror image, it is termed achiral. For example, the right and left hands of the human body are chiral objects since they are mirror images and not super-imposable. “Chiral” derives from the Greek word for “hand”.
21. If a carbon atom has four different types of atoms or groups bonded to it designated as A, B, C and D in the figure below, then the molecule is chiral:



22. No matter how it is moved about, the molecule on the left side cannot be superimposed on its mirror image shown on the right side. Molecules of this type are referred to as stereo-isomers or enantiomers. Enantiomers have identical physical and chemical properties in every respect, except two. They differ in their optical properties (the direction in which they rotate the plane of polarised light) and

in the fact that they react at different rates with other chiral compounds. Since living beings contain chiral proteins and constitute a chiral environment, the chirality of compounds administered to humans is of importance for therapy.

23. A racemate is an equimolar mixture of a pair of enantiomers. Because a racemate consists of a mixture containing equal amounts of the (+) and (-) enantiomers, it is not optically active (i.e. it does not rotate the plane of polarised light).
24. It was common ground that at the priority date the skilled reader would have an expectation that the activity of a drug molecule would be affected by chirality. Cases where the activities of the (+) and (-) enantiomers were the same would be unusual. In some cases one of the enantiomers may be completely inactive, but in the more general case one would expect to find greater activity in one enantiomer than the other.
25. A skilled chemist will recognise when a molecule has a chiral carbon atom. He or she will understand that the compound will be capable of existing as a racemate, or, subject to the ability to resolve it, as the individual enantiomers.
26. By the priority date drug regulators worldwide were recommending that enantiomers should be made and tested. For example this was a recommendation made in 1985 by the Japanese regulator. Mylan did not suggest that the Japanese regulations would be part of the common general knowledge: only that the regulations reflected good science. I consider that the skilled team would be aware that it was good practice and good science to make and test the characteristics of each isomer.
27. Novartis adduced evidence from a Dr Weissinger, a scientist from the American Food and Drug Administration, principally to establish that there was no mandatory requirement at the priority date to resolve chiral drug substances into enantiomers. Mylan did not challenge this evidence.

Therapeutic ratio and window

28. The therapeutic ratio of a drug is defined as the dose to produce a therapeutic effect divided by the dose to produce mortality in 50% of animals. The therapeutic window is the difference between the dose which is large enough to produce a therapeutic effect and the dose which is small enough to avoid toxic side effects.

The patent in suit

29. The patent has a priority date of 4 March 1987. The specification is entitled “Phenyl carbamate”, and the inventor is identified as a Dr Enz. Dr Enz was a researcher at Sandoz’ laboratories in Basle. The patent application, originally made in the name of Sandoz, was subsequently transferred to Novartis following the merger of Sandoz and Ciba-Geigy to form Novartis.
30. The invention on which the patent is based is rivastigmine and its anticholinesterase activity. The patent recognises that the racemic mixture of rivastigmine with the (+)-enantiomer is known from EPA 193,926 (the Weinstock Application cited as prior art). The specification also expressly recognises that the racemate has been

previously disclosed as an acetylcholinesterase inhibitor in the central nervous system.

31. The patent 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.”

32. The evidence showed that the skilled person would not entirely agree that the findings were unexpected. It was common ground that the chiral part of the molecule would be expected to influence the potency of the compound.

33. The patent also expressly accepts that the free base may be prepared from the racemate by separation of the enantiomers in accordance with known methods.

34. The patent explains a little more of what it means by selectivity at page 3, where it says that the compounds:

“exert a brain region-selective inhibition of acetylcholinesterase activity, hippocampal and cortical enzyme being more inhibited than acetylcholinesterase originating from striatum and pons/medulla.”

35. The patent then contains various tests to demonstrate the pharmacological profile of the compound as compared with the (+) enantiomer and the racemate.

36. The first experiment is an *in vitro* indirect measurement of the level of inhibition of AChE in rat hippocampal tissue slices. The experiment showed that rivastigmine inhibited by approximately 40% as compared to 25% for the racemate. The (+) enantiomer was shown to be inactive in this model.

37. The second experiment measured AChE inhibition in different rat brain regions. The IC₅₀ measurements are shown in Table 1:

IC ₅₀	Cortex	Hippocampus	Striatum
Compound A	2.8	3.7	3.0
Compound B	16.1	14.5	13.8
Racemate C	3.2	3.9	3.2

38. These results are said to show that rivastigmine (compound A) is slightly superior to the racemate C with compound B (the (+) enantiomer) showing some, but much

more limited, activity. This is a different result from the first experiment which showed the (+) enantiomer to be inactive.

39. The third experiment describes AChE inhibition *ex vivo* in different rat brain regions. The results for rivastigmine are as follows:

Time After Administration	IC ₅₀ (μmol/kg) / % inhibition		
	Cortex	Hippocampus	Striatum
30 mins	2 μmol/kg	4 μmol/kg	7 μmol/kg
6 hours	39%	44%	16%

40. Although no data are given for the racemate, the patent says that the IC₅₀ for all examined regions were “about 2-3 times higher” than for rivastigmine in this experiment. The evidence showed that this was not a result on which reliance could be placed to show a greater than expected effect, given the absence of data or anything to indicate statistical significance.
41. From page 6 of the patent a number of *in vivo* studies are then described, although these are all in fact more correctly described as *ex vivo* studies (see below). The first of these assesses influence on dopamine metabolism. No data is given, but it is reported that dopamine metabolism in the striatum is increased following the administration of all three compounds. Rivastigmine is more active than the (+) enantiomer and Racemate C in enhancing the striatal dopamine metabolite concentration. None of the witnesses attached much significance to this test.
42. The second *ex vivo* experiment described is entitled “Muscarinic and nicotinic effects on brain glucose utilization”. The results are not shown but the patent states that after oral application of rivastigmine and the (+) enantiomer significant changes in glucose utilisation in various rat brain regions are observed. It is said that compound A is more potent than that of compound B during the initial 30 minutes. It is said that the most marked changes are found in the visual regions and the anteroventral thalamus and also in the lateral habenula nucleus. These are not areas of the brain that are of particular interest in relation to AD.
43. The final *ex vivo* experiment is entitled “Acetylcholine levels in different rat brain regions”. It is reported that a single oral application of 25 mol/kg increases ACh concentrations in the striatum, cortex and hippocampus. It is also stated that the maximal effect is achieved about 30 minutes after oral application and declines during the next 3-4 hours. The ACh levels in the cortex and hippocampus are said to be still significantly higher at 4 hours compared to controls. The effects are said to be dose dependent. It is said that the influence of the (+) enantiomer is significantly weaker than the racemate, and that the influence of the racemate is significantly weaker than rivastigmine.

The claims in issue

44. Novartis rely on claims 1, 3, 5, 7 and 9 of the patent. Claim 1 is to a process for the production of rivastigmine in free base or acid addition salt form, which includes

the step of separating the enantiomers from the corresponding racemate and recovering the resultant enantiomer in free base or acid addition salt form.

45. Claim 3 is to rivastigmine in free base or acid addition salt form. Claim 5 is to rivastigmine as previously defined in pharmaceutically acceptable form for use as a pharmaceutical. Claim 7 is rivastigmine in pharmaceutically acceptable form for use in the treatment of Alzheimer's disease. Claim 9 is to a pharmaceutical composition comprising rivastigmine in pharmaceutically acceptable form, in association with a pharmaceutical carrier or diluent.

The skilled addressee

46. The patent is clearly addressed to a team of skilled researchers in a pharmaceutical company with an interest in developing drugs for use in treatments for AD. Such a team would include a medicinal chemist and a pharmacologist. The medicinal chemist would be likely to be a generalist, with the ability to apply the skills of medicinal chemistry to any pharmaceutical, including one for AD. The pharmacologist would be likely to be a neuroscientist. There was some debate about who would lead such a team. The evidence established that there would be a continuing dialogue between the medicinal chemist and the pharmacologist/neuroscientist, each supplying direction to the project based on their particular areas of expertise.

Pharmaceutical research and development

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.

The witnesses

51. Both sides called distinguished experts in support of their cases, each relying on a medicinal chemist and a pharmacologist/neuroscientist. Mylan called Dr Roger Newton and Professor David Smith; Novartis called Dr David Cavalla and Professor Paul Francis.
52. Until he retired in 1996 Dr Newton was employed by Glaxo and Allen & Hanburys as a medicinal chemist, ultimately directing their global research into respiratory diseases. During his time at Glaxo, Glaxo discovered and successfully launched the drugs imigran, zofran and serevent. In addition to his work at Glaxo, Dr Newton has held various consultancies and academic appointments, including visiting professorships.
53. Professor Smith is Professor Emeritus of Pharmacology and Honorary Associate Director of the MRC Anatomical Neuropharmacology Unit, both at the University of Oxford. His research from the early 1970s was on the animal central nervous system. In the late 1970s he became interested in AD and showed in 1983 that the level of acetylcholinesterase in the cerebrospinal fluid was much reduced in patients with AD. In 1986 he negotiated a substantial grant from Squibb Inc., part of which was used to establish the Oxford Project to Investigate Memory and Ageing (OPTIMA), a clinic-pathological study of AD and normal ageing. He was a Director of OPTIMA until he retired in 2009. He was the founding Chief Editor of *Neuroscience*, Chief Series Editor of *Methods on Neuroscience* between 1981 and 1998 and the first Chairman of the Scientific Advisory Board of the Alzheimer's Research Trust between 1997 and 2002.
54. Like Dr Newton, Dr Cavalla was employed as a medicinal chemist by Glaxo. In 1983, he was awarded a post-doctoral fellowship at the National Institute of Mental Health in Washington DC, in biochemical neuropharmacology. He returned to the UK in 1985, to work as a medicinal chemist at Glaxo Group Research in Ware. He worked on the brain chemical transmitter, 5-hydroxytryptamine ("5-HT" or serotonin), on projects for the treatment of migraine, cancer chemotherapy-induced nausea, and in other projects for the treatment of hypertension and congestive heart failure. In 1989 he moved to Napp Research Centre, Cambridge and directed a discovery programme for the treatment of asthma. In 1998, he founded Arachnova Ltd, a company engaged in the discovery and early development of secondary uses for existing drugs. He left Arachnova in 2007 and founded Numedicus, a company which collaborates on the identification of new pharmaceutical products based on secondary uses for existing drugs. He is also a director of D4 Pharma limited, which is developing new drugs in the areas of Parkinson's disease, painful muscle spasm and mild cognitive impairment. He is the author of *Modern Strategy for Preclinical R&D – Towards the Virtual Research Company* (John Wiley, 1997) as well as many published papers. He is a former Chairman of the Society for Medicines Research.

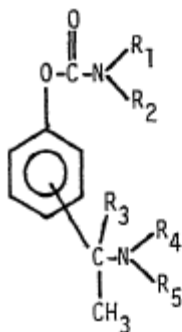
55. Professor Francis is a Professor of Neurochemistry at King's College London, where he leads a research team studying the biochemistry of dementia within the Neurogeneration Group of the Wolfson Centre for Age-Related Diseases. He also teaches on subjects including AD and other dementias. He has more than 25 years' experience in the study of AD and other dementias.
56. None of these experts was subjected to any substantial criticisms as to the relevance of their expertise or the manner in which they gave their evidence. I consider that they all gave their evidence fairly and were genuinely intending to do their best to help me on the technical aspects of the case. Professor Smith made some errors in his first report which he readily acknowledged in cross-examination. As between the two medicinal chemistry experts, 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.

The prior art

57. Two publications by Weinstock *et al* are relied on as prior art. The first is European Patent Application No 0 193 926. The second is an article or chapter in *Alzheimer's and Parkinson's Diseases – Strategies for Research and Development* entitled "Pharmacological activity of Anticholinesterases of potential use in the treatment of Alzheimer's disease". I will refer to these as "the Weinstock Application" and "the Weinstock Article" respectively.

The Weinstock Application

58. The Weinstock Application was published on 10 September 1986. It discloses a class of novel phenyl carbamates which are useful as pharmaceutical compositions having anti-cholinesterase activity. The class described is a series of mono- and di-alkyl derivatives of miotine (a compound previously only used as an insecticide and for eye drops) and is defined by a general structural formula I:



wherein

R₁ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R₂ is hydrogen, methyl, ethyl or propyl, or

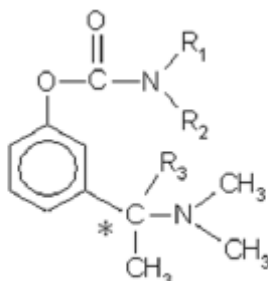
R₁ and R₂ together with the nitrogen to which they are attached
form a morpholino or piperidino radical,

R₃ is hydrogen or lower alkyl,

R₄ and R₅ are the same or different and each is a lower alkyl,
and the dialkylaminoalkyl group is in the meta, ortho or para
position,

or a pharmacologically acceptable salt thereof and a physiologi-
cally acceptable carrier therefor. Hereinafter these compounds
are called compounds of the invention.

59. The general formula shows two substituent groups on the benzene ring. The group at 12 o'clock is the carbamate group. The group shown generally at about 5 o'clock is the dialkylaminoalkyl group. It is shown in this way because it is permitted by the formula to be in any of the three positions relative to the carbamate group: ortho-, meta- or para-.
60. The Weinstock application explains that there is an especially preferred sub-class of the compounds generally defined by formula I. These are where the dialkylaminoalkyl group is in the meta- position and R₄ and R₅ are both methyl groups. The class of preferred compounds is thus shown as follows:



61. The carbon atom on the dialkylaminoalkyl group is shown with an asterisk to indicate chirality. In fact it will only be chiral if R₃ is not methyl (otherwise it will have only three, and not the required four, different groups).

62. Eight specific compounds are identified on page 10 of the application in which R₁ is varied between hydrogen and ethyl and a series of alkyl substituents is placed on R₂. R₃ is always hydrogen. This has the effect of making the carbon atom in the dialkylaminoalkyl group a chiral carbon atom. Most of these compounds are subsequently given numbers in an RA series for ease of identification. The preferred compounds form numbers 4, 5, 6, 7, 8, 14 and 15 in this series.
63. The Weinstock Application draws attention to the unsatisfactory results obtained with physostigmine. It points out that physostigmine has several disadvantages as a therapeutic agent:
- chemical instability;
 - short half life leading to a need for repeated administration;
 - low therapeutic ratio, and a small therapeutic window;
 - irregular and unpredictable absorption from the gut.
64. Accordingly, the Weinstock Application points out that there is a need for new carbamate derivatives which, amongst other things:
- show greater chemical stability than physostigmine;
 - inhibit acetylcholinesterase in the brain for periods of between 3 and 12 hours;
 - have reliable absorption;
 - are relatively less toxic than physostigmine.
65. The Application contains experimental data on 11 of the specially preferred compounds compared with physostigmine and miotine. The tests are categorised as *in vitro* and *in vivo*, although it is common ground that the latter are not true *in vivo* experiments but are better categorised as *ex vivo* or *in vivo/in vitro*. Although the compounds are administered to living animals, the measurements are made *in vitro* after the animals have been sacrificed and the enzyme recovered from brain tissue.
66. The *in vitro* experiments test for anticholinesterase activity. The authors conclude that in general the compounds produce a significant inhibition from about 10⁻⁵ to 10⁻⁸ molar, although they are all less potent than physostigmine.
67. The first of the *ex vivo* experiments measures the ability of AChE extracted from mice brain tissue to hydrolyse ACh, and is therefore a test of potency over time. The mice had previously been dosed sub-cutaneously or orally with the test compounds. The potency of the compounds varied from about 2 to about 90% of that achieved by physostigmine, as can be seen in Table 2. Putting aside RA₁₀ (which scores poorly on duration of action), compound RA₇ was the best after oral administration, but compound RA₅ and RA₁₅ were better than RA₇ after sub-cutaneous administration. RA₇ also scored highest on duration of action after three hours, although compounds RA₆, RA₁₅, RA₁₄, RA₅, RA₁₂ and RA₈ all scored reasonably well on this measure. Later in the Weinstock Application the authors

report that RA₆ and RA₇ still caused significant inhibition after 7 hours, although no data is shown for the other compounds. RA₁₃ and RA₁₀ both stand out as poor performers at this stage.

68. The second of the *ex vivo* experiments assessed the acute toxicity, or the dose which is lethal to 50% of subjects (LD₅₀). The experiment was repeated after the animals had been treated with atropine sulphate, which blocks muscarinic receptors. The purpose of the latter experiment was to show the potential for treatment with atropine in the case of drug overdose. The results are said to enable the assessment of the relative degrees of toxicity of the carbamates which result from excessive activation of muscarinic receptors and from respiratory muscle paralysis which is insensitive to atropine. The incidence and degree of side effects was noted. The results in table 3 show LD₅₀ values between 19 micromoles/kg for RA₅ and >568 for RA₈. High scores are what is needed on this measure. The ranking of the RA compounds (excluding RA₁₀ and RA₁₃) is 8>6>4>14>7>12>15>5. RA₇ is the best compound in relation to the degree of protection afforded by atropine pre-treatment. Table 3 also contains values for therapeutic ratio. RA₇ is again the best here (excluding 10 and 13). Finally the table contains a ratio of LD₅₀ oral over LD₅₀ subcutaneous. The authors suggest that the lower this ratio the greater the bioavailability by the oral route. RA₇ is again the best on this measure.
69. The authors note that the *ex vivo* results show relatively more activity relative to physostigmine than one would expect from the *in vitro* results for compounds 5, 6, 15, 14, 10 and 7. They suggest that this may be due to greater chemical stability, slower metabolism, degradation or excretion, higher lipid solubility enabling a greater proportion of the drug to enter the central nervous system or more efficient absorption from the gut. They point out that it is of little importance whether one has to administer 1-2mg of physostigmine or 2-50 mg of the RA series. What is important is safety and reduction of side effects. Hence, they stress the importance of the therapeutic ratio (LD₅₀/ED₅₀). They observe that this ratio is better than for physostigmine for compounds 4, 5, 6, 7, 8, 10, 14 and 15. Moreover the compounds do not induce any significant side effects whilst physostigmine induces lachrymation, fasciculations and tremor.
70. Overall the authors conclude as follows:
- “The most preferred compounds of the RA series are RA₄, RA₅, RA₆, RA₁₅, RA₁₄, RA₇ and RA₈, 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. RA₄, 6, 7 and 8 also show better bioavailability after oral administration than physostigmine. In addition, the acute toxicity (lethality) induced by RA₇ can be decreased more than 10-fold and that of RA₁₄ more than 8-fold by the antidote atropine, compared to only a 3-fold decrease for physostigmine and miotine.”
71. The authors specifically claim that:

“The compounds of the invention are therefore useful for the treatment of ... Alzheimer’s disease ...”

72. RA₇ is claimed uniquely in claim 7. There is also a claim to a non-chiral compound, in which R₃ is CH₃, for which no data are provided, but which is listed as preferred.

The Weinstock Article

73. The Weinstock Article was published in 1986 in the proceedings of the thirtieth OHOLO Conference on Basic and Therapeutic Strategies in Alzheimer’s and Other Related Neuropsychiatric disorders. The Weinstock Article comes from the same laboratory as the Weinstock Application, and the disclosure is similar. However, the general formula for the class of compounds fixes the values of R₃ to H, and R₄ and R₅ to methyl.

74. The authors again report that the novel carbamates were more active *in vivo* than the *in vitro* experiments would predict, although RA₈ was only weakly active. All the compounds other than RA₁₀ caused significant inhibition for 3 to 7 hours and caused >70% inhibition of brain AChE after oral administration. RA₇ and RA₈ showed good oral bioavailability. The therapeutic ratios of all compounds were similar. RA₇ again scored best on protection by atropine.

75. In the general discussion the authors point out that the discrepancy between *in vivo* and *ex vivo* results is most evident for RA₇ and RA₈ where there is 50-60 times increase in effectiveness. They tentatively attribute this difference to greater chemical stability, slower metabolism or greater lipid solubility. They say this could explain the more efficient absorption from the gut, particularly for RA₇ and RA₈.

76. The authors then say:

“The greater therapeutic ratios of the RA compounds appears at first sight to be surprising since the mortality is a direct result of the AChE inhibition, and is due to the presence of excess ACh[E] in the medulla, which causes respiratory arrest.”

77. The authors also report that they have made an attempt to determine whether the compounds have a selective effect in different brain areas. They found that physostigmine inhibited AChE to the same extent in four areas in the rat brain in spite of the fact that these areas contain different amounts of AChE. RA₆, RA₇ and RA₁₅ caused significantly less inhibition in the medulla. They say:

“The most striking difference was seen with RA₇ which only reduced AChE in the medulla by 10%. Since the ED₅₀ was determined in the whole brain, of which the cerebral cortex contributes a major portion compared to the medulla, this differential effect of the drugs serves to explain their higher therapeutic ratio.”

Reactions to the prior art

78. Professor Smith sought to make rather more of the reaction to Weinstock's work than was justified. Notwithstanding this, it is clear that Weinstock's work was taken seriously. Leon Thal, a neurologist at the University of California followed up the work, as did a group of workers at Warner-Lambert and Parke-Davis in Ann Arbor, Michigan. It is perhaps of some minor significance for the obviousness case that the latter group had gone on to *in vivo* behavioural tests on the compounds, without apparently investigating any further compounds.
79. There was no real dispute that the notional skilled team would also have taken the Weinstock work seriously and regarded it as worth pursuing. It is true that, at the time, the Summers work was attracting more interest, but I do not think that this concurrent interest created much if any disincentive for the skilled team to pursue Weinstock's compounds. Weinstock's disclosure was sufficiently promising to encourage workers to pursue it further, and would have created its own momentum, notwithstanding the interest in tacrine.

The history of the invention

80. Novartis did not call any witnesses to explain the way in which the invention came to be made. They are of course under no obligation to do so. The evidence of the inventor can often give rise to unhelpful satellite disputes about whether the inventor was typical of the skilled person, whether he or she had access to, and only to, the cited prior art, and so on. In the present case Novartis made disclosure of the documents relevant to the making of the invention, a few of which were referred to in the evidence. Mylan sought to draw inferences from the documents.
81. It is clear from the disclosure that Dr Enz had not simply read the Weinstock publications, but was in direct contact with Marta Weinstock, and had been provided with samples of some of her compounds. One cannot be certain from this material how much information Dr Enz was provided with. It may possibly have gone beyond the content of the Weinstock publications.
82. Sandoz made some attempt to verify the results reported by Weinstock in her work. They seem to have focussed immediately on RA₇, confirming Weinstock's results on that compound. They stated in a report in March 1986 that:
- “Further studies will be performed with this and related drugs (e.g. isomers) to elucidate possible interactions between peripheral and central cholinergic system”
83. The reference to isomers does not necessarily imply stereoisomers, but it does appear that from this point Sandoz proceeded more or less immediately to resolve RA₇ into its individual enantiomers. In a report dated August 1986 the researchers state as follows:

“Recently, a novel anticholinesterase agent 114-612 [the Sandoz name for RA₇] has been described, which is claimed to readily reach the CNS after parenteral or oral administration and to have a higher therapeutic ratio than physostigmine, as

well as greater chemical stability and longer duration of action. We have therefore synthesized the optically active forms of [RA₇] and found that the 212-713 hta ((-) form) is superior to 212-712 hta ((+) form). 212-713 hta should be more suitable than physostigmine for the long term treatment of conditions associated with a deficit in cholinergic transmission in the CNS”

84. Although the documents do not throw much light on the obviousness of choosing to develop RA₇ (as opposed to any of the other Weinstock compounds), I think it is fair to conclude that the decision to resolve RA₇, once chosen, into its enantiomers was thought of at the time to be a routine step. It was plainly not thought necessary to explain the reasons for resolving RA₇ to the readers of the report.

The legal approach

85. In *Conor v Angiotech* [2008] RPC 28, [2008] UKHL 49 at [42], Lord Hoffmann summarised the approach to obviousness in this way:

“[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."

86. Mr Purvis QC, who appeared for Novartis with Ms Anna Edwards-Stuart, singled out the question of motive for special consideration in this case. He reminded me of what the Technical Board of Appeal of the EPO had said in T 0939/92 *Agrevo* at [2.4.2]:

“...the notional person skilled in the art is not to be assumed to seek to perform a particular act without some concrete technical reason: he must, rather, be assumed to act not out of idle curiosity but with some specific technical purpose in mind.”

87. The passage from *Agrevo* relied on by Mr Purvis forms part of a larger discussion of the approach taken by the Boards to the issue of obviousness. As the Board explains in [2.4.3], the Boards adopt a “problem and solution approach”, in which the skilled person is assumed to be attempting to solve the problem of how to obtain the results objectively achieved by the claimed invention. As the Board goes on to explain at [2.5.1] to [2.5.3], the results objectively achieved by the invention may have a decisive effect on the legal conclusion of whether an invention is obvious. If the invention is, for example, merely another compound of the same class as the known art, without any technical benefit, then the invention is likely to be held to be obvious. On the other hand, where the invention delivers a hitherto unknown technical effect, the solution to the problem of how to provide that technical effect may prove to be inventive.

88. Mr Purvis also relied on what Jacob LJ said in *Saint-Gobain v Fusion Provida & Electrosteel* [2005] EWCA (Civ) 177 at paragraph 35:

“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.”

89. Expressions of that kind are however quite sensitive to the facts. For example in *Pharmacia v Merck* [2001] EWCA Civ 1610; [2002] RPC 41, Aldous LJ said at [124]:

“A step from the prior art, albeit made without reason, can still be obvious. ... The statutory test is obviousness and any modification which is obvious will not be patentable, whereas one which is not obvious will be. The true test, as made clear in *Windsurfing*, is to ask whether the invention was obvious. Whether or not there is a reason for taking the step from the prior art may well be an important consideration, but that does not mean that it is an essential requirement of a conclusion of obviousness. In any case the judge in these proceedings did consider whether there was a reason for taking the step from the prior art and concluded that there was, namely a natural desire to investigate the analogs and the structural activity relationship of such compounds.”

The inventive concept

90. The inventive concepts of the various claims alleged by Novartis to be independently valid are all different. I propose to take the narrowest of these, namely rivastigmine in pharmaceutically acceptable form for use in the treatment of AD.

The skilled person and the common general knowledge

91. I have identified the skilled person and the common general knowledge above.

The difference from Weinstock

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 RA₇ (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.

Are the differences obvious without knowledge of the invention?

93. It is at this stage that one must be particularly careful to avoid hindsight. The parties made their submissions on each of the differences, but in the end one must ask the statutory question in relation to the invention as a whole.

Selection of RA₇ for development

94. The medicinal chemistry experts differed on the approach that the skilled team would take to the Weinstock work. Dr Newton took the view that the work disclosed an adequate basis for taking one or more of the compounds into development, whereas Dr Cavalla was of the view that Weinstock represented an incomplete investigation into the structure/activity relationship. Dr Cavalla would therefore have carried on synthesising new compounds and subjecting them to tests of the same kind as Weinstock. He said he would be particularly interested in a non-chiral compound mentioned (but not tested) by Weinstock.
95. Mr Purvis submitted that the obvious approach was to carry on with the investigation of structure. It was by making structural changes that Weinstock had observed improvements, and the obvious approach was to carry on investigating the same sort of structural changes as she was making. To halt that process and move into development was not obvious.
96. I think that this submission is based on a false dichotomy. It is undoubtedly correct that one obvious approach in the light of Weinstock is to continue making more compounds. I accept that some medicinal chemists would have followed this course so as to perform an exhaustive investigation into the structure/activity relationship. But it does not follow from that the alternative course of selecting one or more of the specific compounds disclosed for development was not obvious. 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.
97. It is true, as Dr Newton accepted, that there may be compounds which might work better within the scope of the formula disclosed by Weinstock. An investigation into whether that was so can, in my judgment, properly be described as a research project. Newly synthesised compounds which showed objective improvements over Weinstock would qualify for patent protection. It simply does not follow from

this that the alternative course of establishing the viability of Weinstock's compounds was not obvious.

98. Dr Cavalla's evidence that he would wish to investigate the non-chiral compound mentioned but not tested by Weinstock falls into this same category. It does not make the alternative of developing the compounds which had been made and tested by Weinstock any less of a self-evident thing to do.
99. Dr Newton considered that there were some indications in the Weinstock work that she had in fact investigated other aspects of the structure of the molecule, but not reported the results. It is true that, at least in the Weinstock Application, she expresses preferences for groups in some positions when the data does not establish the basis for that preference. That view of the document was not accepted by Professor Smith, and I have not relied on it. Indeed I have accepted that the skilled person would recognise that there was scope for further investigations.
100. Apart from the dispute about whether to develop *any* of the specifically disclosed compounds, there remains the question of *which*. As to this, there was in the end little dispute that RA₇ would be one of those showing the most promise. Professor Francis accepted that RA₇ was the "top pick" from the Weinstock Application, on the basis that one was only going to pick one compound. Nobody suggested any good reason for excluding it, either on the basis of the Weinstock Article or the Weinstock Application. I conclude that the RA₇ would be an obvious choice of compound to take further.

Whether to resolve?

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.
102. Secondly, it was common ground that the actual resolution of RA₇ did not involve any problematic chemistry. RA₇ is easily resolved into rivastigmine using a standard stereochemical resolving agent. Novartis did not seek to make anything out of the practical chemistry involved. They contended that the skilled team would be aware that resolution could, in some cases, represent a difficult task, and that this would make the skilled team reluctant even to attempt a simple resolution. Although I accept that questions may arise as to the extent of resources which a skilled team might be prepared to devote to difficult resolution, I am not persuaded that in 1987 the skilled team would be hesitant about seeing whether a chiral compound could be easily resolved.

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 RA₇. 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 RA₇ there would be no expectation of a benefit.
105. It was common ground that the skilled team would expect a difference in *potency* between RA₇ and one of its enantiomers. This is because the chiral end of the molecule is involved in the initial binding to the enzyme. It follows that the skilled team would conclude that, by resolution, one would obtain a drug which could be administered in smaller doses, simply by eliminating the less potent or inactive enantiomer.
106. Novartis contend that the skilled team would see no advantage in the present case in an improvement in potency. Normally an improvement in potency is desired where there is a narrow or non-existent therapeutic window, so that one is hampered in administering enough of the drug to cause a therapeutic effect without causing undesirable side effects. Mere changes in potency do not necessarily lead to an improvement in therapeutic window, however. As Weinstock explains, if the toxic effects are caused by the same mechanism as the therapeutic effect, a more potent drug may cause both the therapeutic dose and the lethal dose to reduce, without any change in the therapeutic window.
107. I accept that, applying this logic, the skilled team would not see an improvement in therapeutic window as a likely outcome of resolution of RA₇.
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.

109. It is true that none of these reasons carry with it an expectation of improvement. But in the pharmaceutical industry the reduction or elimination of risk was a high technical priority. Dr Newton summarised it in this way:

“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. ...

“Q. If they were doing it, they were not doing it because they thought the FDA wanted it?

A. No, of course not. They were doing it, as I have tried to explain to you, because it is good science and because you do not resolve -- you do not develop a mixture of two compounds which have totally different, perhaps, biological activities; totally different, perhaps, metabolism; totally different, perhaps, toxicities; you need to know about that before you go and spend all your money.

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.
111. I think that by the priority date there was nothing conceivably inventive in deciding to resolve and test RA₇ to see if there were advantages or disadvantages associated with one enantiomer. Whilst not mandated by any regulation, such a decision would be treated as a routine step. To this limited extent the history of the invention at Sandoz is of some assistance to Mylan.

The pharmaceutical composition

112. I have pointed out the passages where the Weinstock publications teach the utility of the disclosed compounds in the treatment of AD. Once a skilled person had resolved RA₇ it would be obvious to formulate it as a pharmaceutical composition.

Overall conclusion on obviousness

113. There was some reference to material in the form of declarations by Dr Enz placed before the United States Patent and Trademark Office many years after the priority date in support of the corresponding United States patent. The material consisted

of an attempt to show increased selectivity of rivastigmine over the racemate. Neither side suggested that it was possible to draw any reliable conclusions from that evidence. Accordingly I have to approach the case on the basis that the advantages of resolving RA₇ are, in fact, no more than those which would be expected.

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 RA₇.
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.
116. I believe that conclusion to be consistent with the “problem and solution approach” employed by the Boards of Appeal. The objective technical effect demonstrated by the patent in comparison with the Weinstock prior art is simply that which one would expect from resolution of a chiral compound. The skilled person would know how to solve the problem of achieving those effects by an application of the common general knowledge about chiral compounds.
117. In the result all the claims relied on are invalid, and the SPC is accordingly invalid as well. It follows that the action succeeds and the counterclaim will be dismissed.