

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 30/06/2008

Before :

THE HON MR JUSTICE FLOYD

Between :

ACTAVIS UK LIMITED	<u>Claimant</u>
- and -	
JANSSEN PHARMACEUTICA N.V.	<u>Defendant</u>

Roger Wyand QC and Piers Acland (instructed by **Bird & Bird**) for the **Claimant**
Daniel Alexander QC and James Whyte (instructed by **Linklaters LLP**) for the **Defendant**

Hearing dates: 14th -15th May, 19th May

Judgment

Mr Justice Floyd :

1. Actavis UK Limited seeks revocation of European Patent No 0 334 429 (“the Patent”) which is in the name of Janssen Pharmaceutica N.V. (“Janssen”). The Patent concerns the stereochemistry of an important blood pressure drug, nebivolol. Janssen has applied to amend certain claims of the Patent. Actavis maintains that the Patent, even if so amended would remain invalid for lack of novelty and lack of inventive step.

The background and the common general knowledge

2. There is very little dispute about the relevant technical background. I set out below the matters which formed part of the relevant common general knowledge.

Hypertension and anti-hypertensive agents

3. Hypertension is the technical name for high blood pressure. Three main classes of agent were used to treat hypertension in 1988: β -blockers, diuretics and vasodilators.
4. **β -blockers** are so named because they block the action of endogenous compounds such as adrenaline on certain receptors in the body, the so-called β -adrenergic receptors. There are two sub types of β -receptor: β_1 and β_2 . The former are to be found in the heart and kidneys; the latter are found in the lungs.

5. Early β -blockers were non-selective in that the drug would block both β_1 and β_2 receptors. This meant that if these early drugs were used to treat angina (in the heart muscle) in patients who also had asthma, there was the potential for serious side effects, as the receptors in the lung (undesired) would be blocked along with the receptors in the heart (desired). The second generation of β -blockers therefore focussed on drugs with β_1 selectivity. Drugs with a high ratio of β_1 to β_2 activity were therefore developed.
6. The precise mechanism of action of β -blockers in lowering blood pressure was not fully elucidated in 1988. It was, however, known that they reduced cardiac output (both heart rate and force of contraction) but were also associated, at least in the short term, with vasoconstriction, which acts as a drag on the blood pressure lowering effect of the β -blocker. So use of a β -blocker might not be associated with an immediate drop in blood pressure.
7. In 1988 the focus of drug development was a third generation of β -blockers, in which the compound has additional pharmacological properties.
8. Labetalol was one of the first of this third generation. It combined non-selective β -blockade with α -adrenergic receptor blockade (blocking the vasoconstrictor effects of noradrenaline). It was marketed as a racemate of four stereoisomers (see below). The α - and β -blockade reside principally in separate isomers. This aspect of the drug attracted particular interest at the time it was launched.
9. **Diuretics** increase the rate at which sodium is excreted from the body in urine. This has the effect of reducing the amount of water and sodium in the body, which reduces the pressure on the walls of the blood vessels.
10. **Vasodilators** dilate blood vessels. The result is that they reduce vascular resistance and hence blood pressure, because the diameter of the blood vessels increases.

Step care management

11. The treatment of hypertension with β -blockers together with a diuretic and/or vasodilator, known as “**step care**” management, was well known. The rationale of this approach is to alleviate the body’s natural response to a fall in blood pressure when treated with β -blockers alone. A vasodilator will counter this effect.

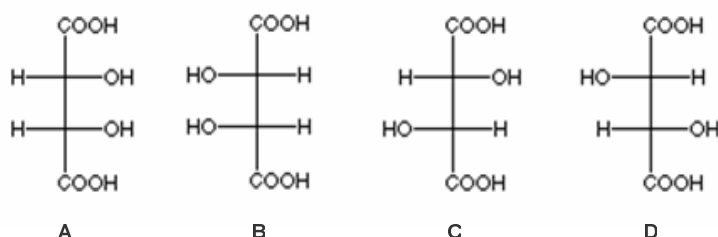
Animal models

12. The standard animal models used for studying hypertension in 1988 included normotensive (normal blood pressure) and hypertensive (raised blood pressure) models. The blood pressure response in normotensive models would be smaller than the response seen in hypertensive models. There were various hypertensive models available. For rats, investigators would often clamp the renal arteries which had the effect of raising its blood pressure due to reducing blood supply to the kidney and increasing release of the hormone renin. Another model was a strain of rat from Japan known as the spontaneously hypertensive rat.

13. Tissue and organ preparations also existed and were used routinely for investigating β -blocker activity. The effect of the candidate drug would be assessed in its ability to counter the effects of a β -agonist on the tissue or organ in question.

Stereochemistry

14. The underlying concepts of stereochemistry have been described in a number of judgments: see e.g. the summary by Kitchin J in *Generics v Lundbeck* [2007] EWHC 1040 (Pat); [2007] RPC 32 at [12]-[17].
15. This case concerns the stereochemistry of compounds with more than one chiral centre. In theory a structure with a number of chiral centres, (say N), will exist as 2^N stereoisomers. So a structure such as that with which we are concerned in this case, with four chiral centres, could in theory have 16 stereoisomers. These stereoisomers consist of pairs of enantiomers, and there will be half of 2^N , or $2^{(N-1)}$ of these pairs. This is not always true, however, because in symmetrical molecules some of the stereoisomers will be the same.
16. A simple example is tartaric acid which has two chiral centres, and would therefore be expected to have four stereoisomers. In fact it has only three. In the diagram below enantiomers C and D are identical, because rotating one about the vertical axis makes it so:



17. Compounds which have chiral centres but which are in fact achiral are called meso compounds.
18. It is common ground that by the priority date there was pressure from the regulatory bodies including the FDA in the United States and the Japanese Ministry of Health to provide information about individual isomers.

The expert witnesses

19. Actavis called two expert witnesses, Professor John Reid and Professor Roger Newton as their expert pharmacologist and medicinal chemist respectively.
20. Professor Reid is Regius Professor of Medicine and Therapeutics and Head of the Division of Cardiovascular and Medical Sciences at the University of Glasgow. From 1987 to 1993 he was Editor in Chief of the *Journal of Hypertension*, a well known international publication in the field of high blood pressure research and its treatment. After qualifying in Medicine from Oxford University in the late 1960s he spent over 10 years at the Royal Postgraduate Medical School/Hammersmith Hospital in London training and conducting research in clinical pharmacology and new drug development. The principal interest of his group was blood pressure treatment and

the investigation and optimisation of β -blockers for the treatment of hypertension and other cardiovascular diseases. He was very well qualified to give evidence on the pharmacological aspects of the case.

21. Professor Newton was employed by Glaxo from 1971 to 1996 as a medicinal chemist in their chemistry division. Whilst at Glaxo, his areas of research included drugs for the treatment of cardiovascular, central nervous system and infectious diseases. For eight years he directed the company's global research into respiratory diseases. He joined Glaxo, as a senior research chemist and eventually became the director of the Chemical Research Division of Glaxo. He was also the Resident Medicinal Chemist in the Chemistry Department at the University of Cambridge from 1996 until 2005 and is Visiting Professor at the University of Sussex. His PhD was in the stereochemistry of compounds with bridgehead nitrogen atoms. Professor Newton has now given evidence in a large number of disputes concerning medicinal chemistry, a fact to which Mr Alexander QC (who appeared for Janssen with Mr James Whyte) drew attention in cross-examination. His evidence is not less useful as a result.
22. Janssen called only one expert, Professor Caldwell, who is the Dean of the Faculty of Medicine in the University of Liverpool. He played an important role in the re-emergence of stereochemistry as a factor in drug development. Since 1980 he has had an extensive consulting practice concerned with aspects of drug discovery and development including several programs related to hypertension and β -blockers.
23. Mr Wyand QC (who appeared for Actavis with Mr Piers Acland) said that there was a contrast between the oral evidence of Professor Caldwell and his expert report. There is some force in that, in that points taken firmly in his report seemed to dissolve under cross-examination. An example is his challenge in his second report to Professor Newton's assertion that the ratio of RSSS to SRRR isomers would be 1:1. Under cross-examination he said that if it were anything other than a racemate it would be surprising. Whilst I have not ignored his report, I have relied primarily on the oral evidence Professor Caldwell gave where there is a dispute between him and Professors Reid or Newton.

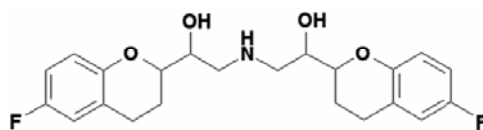
Witnesses of fact

24. Actavis served fact witness statements from Professor Stephen Curry and Mr Martin Barkworth. Only the former was cross-examined (by video-link). He was a good witness.
25. Janssen called Mr Woestenborghs to give evidence about a prior disclosure. He had no real recollection of the relevant events, and was understandably reluctant to accept that he had disclosed the invention, with the consequences that might entail. This led him, I thought, to cling on to somewhat unlikely explanations as to what might have happened.

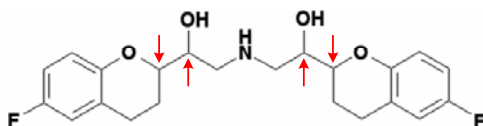
Nebivolol

26. Although not part of the relevant common general knowledge, it is worth noting what nebivolol is.

27. The general chemical structure of nebivolol is as follows:



28. This structure contains four chiral centres:



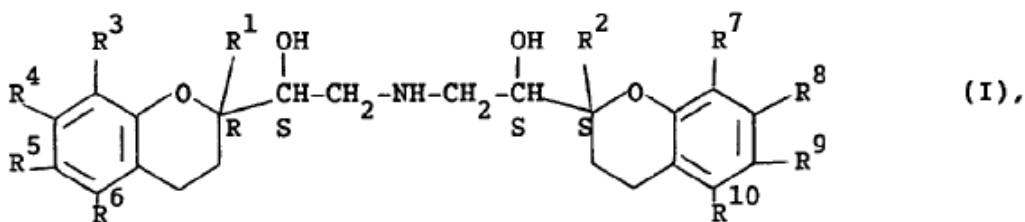
29. If all R and S combinations were distinct, the structure would embrace eight pairs of enantiomers. However, owing to the symmetry of the molecule around the central nitrogen atom, some of these configurations are duplicative. In summary, there are four pairs of enantiomers and two meso forms, a total of ten enantiomers.
30. Nebivolol comprises a 1:1 mixture of two isomers: the SRRR and the RSSS. The former is referred to as *d*-nebivolol and the latter as *l*-nebivolol.

The Patent

31. The Patent has an unchallenged priority date of 23rd March 1988. It is entitled “Agents for lowering the blood pressure”.
32. The Patent begins by saying that United States Patent No 4,654,362 (the “362 patent” cited as prior art in this case) describes a class of 2,2'-iminobisethanol derivatives having β -blocking activities. It identifies the discovery underlying the Patent in the following terms:

It has now been found that a certain class of isomers of said bisethanol derivatives potentiate the activity of blood pressure reducing agents.

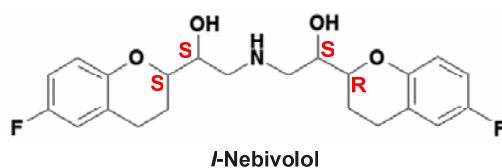
33. There follows a clause describing the invention in similar terms to the “use” claim of claim 1. The compounds for use in the invention are defined by a general formula (I) indicating the stereochemistry of the four chiral centres with the letters R and S:



34. The invention is said to be concerned with the use for the manufacture of a medicament for potentiating the effects of blood pressure reducing agents having

adrenergic and/or vasodilating activity, other than the agents of formula (I), of a compound of formula (I).

35. The complex wording is the result of a desire to claim the invention in so called “Swiss” form. In short it is saying: use of an RSSS to potentiate blood pressure drugs (other than another RSSS).
36. The compounds for use in the invention are therefore the RSSS isomers of the class of compounds. The most preferred compound at page 2 lines 35-36 is the compound in which R⁵ and R⁹ are fluoro-, with the remaining substituents all hydrogen. That compound is l-nebivolol:



37. The specification then proceeds to explain in detail how the compounds of formula (I) can be prepared by stereo-specific synthesis. The final step in the synthesis is to react an RS oxirane with an SS amine (or an SS oxirane with an RS amine). Examples 1-3 describe the synthesis of l-nebivolol.
38. At page 4 line 15 the specification says this:
- The compounds of formula (I) with the exception of (RSSS)- α,α' -[iminobis(methylene)bis(3,4-dihydro-2H-1-benzopyran-2-methanol)] ethanedioate(1:1) are deemed to be novel compounds and constitute in an additional feature to the present invention.
39. The patentee is acknowledging in this passage that one of the RSSS compounds is not novel. The RSSS compound in question is the RSSS isomer of the preferred compound of the 362 patent. That compound is the one in which all the substituents in the general formula 1 are hydrogen. Its RSSS isomer is specifically characterised in 362.
40. The specification gives a long list of blood pressure reducing agents which are potentiated by the compounds of formula (I). A particular group is said to be the compounds of the cited 362 patent. The SRRR enantiomers are singled out and d-nebivolol specifically mentioned.
41. At page 4 line 55 a further aspect of the invention is described, namely a composition comprising an amount capable of potentiating the effects of blood pressure reducing agents of a compound of formula (I) together with a blood pressure reducing agent. A favoured ratio of the two ingredients is said to be 1:1.
42. In addition to examples describing the synthesis of the RSSS compounds, the specification also contains pharmacological examples. These experiments comprised blood pressure and heart rate measurements on the spontaneously hypertensive rat – a well known animal model. They compared the effect of administering (a) l-nebivolol alone (b) known hypertensive agents and (c) the combination. The experiments were done at two dosage rates. The results show that whilst, on the whole, l-nebivolol alone had little or no effect, it greatly improved the performance of the known agents.

The claims

43. Claim 1 is to

The use for the manufacture of a medicament for potentiating the effects of blood pressure reducing agents having adrenergic and/or vasodilating activity, other than the agents of formula (I) as defined hereinafter, of a compound of the formula (I)... or a pharmaceutically acceptable acid addition salt, wherein [definitions follow]

44. I have set out formula (I) above, and nothing turns on the definitions of the various generalised radicals R¹ to R¹⁰.

45. Claim 3 claims the use according to claim 1 wherein the compound used is l-nebivolol.

46. Claim 4 is for

A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a compound of formula (I) as defined in any of claims 1 to 3, and a blood pressure reducing agent having adrenergic and/or vasodilating activity, said agent being other than the said compound of formula (I).

47. Claim 5 claims a claim 4 composition where the blood pressure agent is selected from a list of known agents.

48. Claim 6 claims a claim 4 composition where the agent is d-nebivolol. So here the claimed composition is the RSSS and SRRR enantiomers of the same structural formula.

49. Claim 7 claims the claim 5 or 6 composition when the molar ratio is 1:1.

50. Claim 7, as dependent on claim 6, as dependent on claim 4, as dependent on claim 3 is a claim to a 1:1 mixture of RSSS and SRRR nebivolol. This is the mixture of isomers which is marketed as nebivolol. Only claims 4, 5, 6 and 7 (not claim 3) are defended as independently valid.

Construction

Use ... for potentiating

51. Claims 1-3 are use claims. In G2/88 *MOBIL/Friction reducing additive* [1990] EPOR 73, the Enlarged Board of Appeal of the EPO held that:

In relation to a claim whose wording clearly defines a new use of a known compound, depending upon its particular wording in the context of the remainder of the patent, the proper interpretation of the claim will normally be such that the attaining of a new technical effect which underlies the new use is a technical feature of the claimed invention.

52. Later the Board explained what might be meant by the technical effect being “a technical feature of the invention”. It was that
- “the compound actually achieves the particular effect.”
53. In the present case I see no difficulty in construing claim 1 as restricted to the use of the RSSS isomers in such a way as actually to achieve the technical effect, namely the potentiation of another (non RSSS) blood pressure drug. I would have done so whether the claim related to a “new use of a known compound” or not. That latter issue is something that I consider in its proper place, under the heading of novelty below.
54. The parties also debated the meaning of “potentiating”. I think “potentiating” probably means no more than “improving the effect of”. Obviously the blood pressure reducing drug is not required to be inactive in the absence of the potentiating agent. Further, I do not think that the word says anything about what the potentiating agent does in the absence of the other drug. It could be active in some way in its own right, or it might not. I do not think the precise meaning of “potentiate” has a bearing on the outcome of the dispute however.

Other components

55. Mr Alexander submitted that the pharmaceutical composition claims (before amendment) were limited to a compound of formula (I) and a single blood pressure reducing agent. He sought to draw an analogy with the construction of the claim to an enantiomer (and a pharmaceutical composition containing it) adopted by Kitchin J in *Generics v Lundbeck* [2007] EWHC 1040 (Pat); [2007] RPC 32 at [60]. Seeking to draw analogies with decided cases about different claims in different patents is not a fruitful or legitimate use of authority. It is sufficient to say that in *Generics v Lundbeck* the whole point of the invention was the isolation of the enantiomer from its counterpart. In the present case the object of the invention is quite different: using the enantiomer to potentiate other agents, which expressly include the counterpart enantiomer. If SRRR is allowed to be present as a blood pressure reducing agent, why not other isomers or indeed anything else which fits the description “a blood pressure reducing agent”?
56. The analogy apart, Mr Alexander submitted that the Court should not, if it can help it, arrive at a construction of the claim which has the result that the claim will read on to prior art referred to in the patent. That is a valuable canon of construction which has been relied on in a number of cases: see *Beloit Technologies Inc v Valmet Paper Machinery* [1995] RPC 705 at 720 lines 30-33, and *Ultraframe v Eurocell Building Plastics* [2005] EWCA Civ 761; [2005] RPC 36 at [47], but it is not a rigid rule: see Lewison J’s discussion of the principles in the *Ultraframe* case at first instance [2004] EWHC 1785 at [72] to [73].
57. In the present case, Mr Alexander argues that 362, which is referred to in the Patent, would anticipate the composition claims unless they are construed as limited to mixtures of a compound of formula (I) and one (and only one) blood pressure reducing agent. 362 discloses a preferred compound which includes an RSSS isomer and multiple other isomers (i.e. compound 76 which must include RSSS as well as a number of isomers which have adrenergic activity). That mixture inevitably falls

within the claim (widely construed) once made into a pharmaceutical composition, which is something expressly taught by 362. Mr Alexander develops the argument by pointing out that in claim 4 the patentee has appreciated the need not to claim a given RSSS in combination with itself – how could he have overlooked the need to disclaim combinations of RSSS with more than one other blood pressure reducing drug?

58. Mr Alexander supplements this argument with the further point that claim 5 refers to “the blood pressure reducing agent of claim 4”: implying, he says, that there is only one of them. I do not think there is anything in this supplementary point: the implication is not a necessary one.
59. Mr Wyand submits that the word “comprising” in claim 4 is the term conventionally used to indicate the threshold requirements of the claim: the word “consisting” generally being used when a negative requirement is what is meant. So much is recognised by the application to amend. Thus, claim 4 requires a mixture which may have more than one of each of the following: a pharmaceutically acceptable carrier, a compound of formula (I) and a different blood pressure reducing agent.
60. I prefer Mr Wyand’s submissions. Whilst, when confronted with the effect of 326 on the composition claims, the patentee might wish his claims to be limited to a compound of formula (I) and a single blood pressure reducing agent (or at least to a single agent of same structural formula), I cannot see in general why he would wish his claims to be so circumscribed. The discovery on which the invention is based, that RSSS will potentiate a wide range of blood pressure reducing agents would apply as much to compositions with a single agent to compositions with multiple agents. I cannot see any way of writing into the claim a specific exclusion when the other agents are those which occur when 362 is carried out.
61. Mr Alexander argued rather more faintly for a similar limitation in claim 1, the use claim. Here, it seems to me, he is on weaker ground still. The use is:
- “for potentiating the effects of blood pressure reducing agents”.
62. The use of the plural is particularly ill-adapted to limit the claim to a singular blood pressure reducing agent. Moreover Mr Alexander cannot ask his forensic (*Beloit*) question about 326 here. In addition to acknowledging 326 as prior art, the Patent acknowledges that the preferred compound of 326 is old: see page 4 lines 15-17. The skilled person would therefore understand that the patentee thought that he was overcoming the effect of 326 on the novelty of claim 1 by claiming the invention in use form. He would see no reason to read limitations into the claim to create further distinctions with 326 based on what is (or rather is not) present in the medicine.

The proposed amendment

63. Janssen has applied to amend claim 4 to substitute the words “consisting of” for “comprising”. The amendment has a corresponding narrowing effect on claims 5, 6 and 7.
64. Actavis does not oppose the amendment. Moreover, it accepts that the amendment has an effect, as it no longer argues that claims 4, 6 and 7 lack novelty. Actavis contends that the claims as so amended remain obvious.

The validity attacks

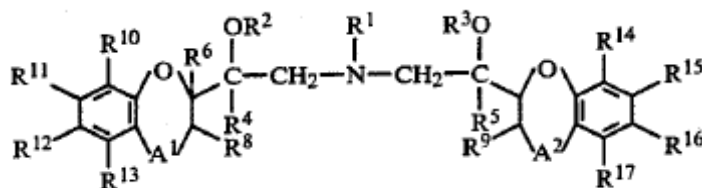
65. The grounds on which validity is attacked are lack of novelty and obviousness. There are two main starting points for these attacks. The first is an earlier Janssen patent in the field (“the 362 Patent” or “362”). The second is an alleged oral (or more precisely oral and visual) disclosure at a meeting in Guildford (“the Guildford Forum”). A further attack based on the disclosure of a written version of the oral and visual disclosure for the purposes of its inclusion in the conference proceedings, was not in the end pressed on me as an independent starting point.

The 362 Patent

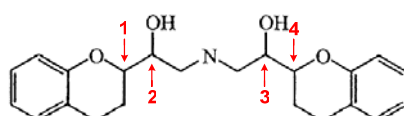
66. 362 discloses a class of derivatives of 2,2'-iminobisethanol. In column 1 it is pointed out that:

The compounds of the present invention differ from the said prior art compounds by the replacement of one oxygen atom in the benzodioxane ring by a direct bond or an optionally substituted methylene moiety and by their increased β -adrenergic blocking activity.

67. The general formula for the compounds is shown below:



68. All the compounds actually prepared in the examples have a core structure where the variables A^1 and A^2 simply close the ring structures with a direct bond. So the core structure is as shown in the formula below, in which the chiral centres are marked 1-4:



69. 362 points out (column 4 lines 34-39) that “it is evident” that the compounds of the invention may have several asymmetric carbon atoms. At lines 40-58 it continues:

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g., counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids.

Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

It is evident that the stereochemically isomeric forms may be further resolved into their optical isomers, (+) and (–) by the application of methodologies known to those skilled in the art. Stereochemically isomeric forms of the compounds of formula (I) are naturally intended to be embraced within the scope of the invention.

70. 362 does not go to the extent of determining the absolute stereochemical configurations of the compounds and their precursors. Instead, it uses its own nomenclature by identifying the first isolated material from a separation as “A” and the second as “B”. So a final compound put together from an A oxirane and B amine would be designated “AB”. Professor Newton considered that 362 would convey to the skilled reader that the AB configuration was favoured. I accept his evidence on this point.
71. At column 5, 362 elaborates on the properties of the compounds as follows:

The compounds of formula (I) and their pharmaceutically acceptable acid addition salts and stereochemically isomeric forms possess strong β -adrenergic receptor blocking activity and as such they can be used in the treatment and prevention of disorders of the coronary vascular system.

Due to their useful β -adrenergic receptor blocking activity and, more particularly, in view of their selective β_1 -adrenergic receptor blocking activity, combined with their vasodilating properties, resulting in a useful antihypertensive activity, the compounds of formula (I), the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof are useful agents in the treatment and the prevention of disorders of the coronary vascular system.

72. It is common ground that the reference to “disorders of the coronary vascular system” in the passage quoted above would be read as “disorders of the cardiovascular system”.
73. Thus the compounds of 362 are put forward as being strong β - blockers and importantly selective β_1 - blockers which combine with vasodilating properties to produce a useful antihypertensive activity. It is important to bear in mind that the

reader is not told anything about where, amongst the various enantiomers present, the activity lies.

74. The specification goes on to say that

In view of their useful properties in the treatment and the prevention of disorders caused by the coronary vascular system, the subject compositions may be formulated into various pharmaceutical forms.

75. Accordingly, there can be no doubt that the specification of 362 discloses the use in the manufacture of a medicine of the compounds which 362 specifically describes. It also describes pharmaceutical compositions which comprise the specific compounds.

76. 362 itself concentrates on a preferred compound, compound 76, in which all the substituents are hydrogen. 362 discloses that the individual enantiomers of that compound have been made and tested.

77. Actavis focuses attention on a different compound, compound 84. Compound 84 has the same structural formula as nebivolol. The isomeric form is listed as AB. It is common ground that the skilled person would understand from the disclosure of 362 that compound 84 was a mixture of two pairs of enantiomers. The two pairs are (1) SRRR and RSSS (in fact d- and l- nebivolol) and (2) two further isomers, namely RSRR and SRSS.

78. Table 1 in column 25 of the '362 Patent shows the biological activities of a selection of the final compounds, some of which are individual stereoisomers and others are mixtures. The data are based on the guinea pig atrium model which provides a measure of β_1 -receptor blockade and the guinea pig tracheal ring model which provides a measure of the effect on β_2 -receptors. The ED₅₀ ratio for β_2/β_1 -antagonism provides a measure of cardioselectivity – the higher the value the better. Compound 84 is one of the top 4. It has the favoured AB configuration. Compound 79, which is a single stereoisomer of the preferred compound, is not far behind.

79. Table 1 does not provide any information to back up the claim to vasodilating properties.

Lack of novelty over 362

80. The law of novelty has recently been reviewed by the House of Lords in *Synthon v SmithKline Beecham* [2006] RPC 10. Lord Hoffmann, having reviewed the authorities said:

If I may summarise the effect of these two well-known statements, the matter relied upon as prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent.

81. Does 362 disclose subject matter which, if performed, would necessarily infringe claim 1 of the Patent? Actavis rely exclusively on Compound 84. The manufacture of a pharmaceutical composition (a medicament) using compound 84 as active

ingredient is disclosed in 362. Compound 84 will contain the RSSS isomer, as well as the SRRR isomer and the other stereoisomeric pair of RSRR and SRSS. The composition will have adrenergic and/or vasodilating properties as required by claim 1 and as taught by 362.

82. There is clearly no express teaching in 362 that the RSSS isomer is potentiating the effect of any of the other isomers as blood pressure reducing agents. In the light of the way I have construed claim 1, a first question is whether, if compound 84 is used in the manufacture of a medicine, the RSSS isomer will **in fact** potentiate the effects of another blood pressure reducing isomer.
83. The starting point is that we know (now) that when a medicine is made from only RSSS and SRRR the former does potentiate the latter. So much is clear from the data in the Patent. There is no direct evidence as to what happens when all four isomers are present. Professor Caldwell was of the view that it was not possible to predict for certain, from the behaviour of one pair of enantiomers, what would happen if all four were tested together:

A. Yes, but the reason that I am being less than direct in answering, not answering your question directly, is that to me you are assuming that the other pair is completely inert of any activity at all. If I tested all four together, yes, I see beta-blockade. I have no evidence that if I tested, in the same way that we have here -- set aside semantics for the moment -- a potentiation, an interesting interaction between those two enantiomers, one looks like it does not do very much until you put it in with the other one. We must not assume that the other two enantiomers that to my knowledge have not been examined, we must not assume that they are silent and of no consequence. You are assuming that when you test compound 84 that you will get this nice division of activity and so on, and I just do not know anything at all about the other enantiomers that enables me to... You know, I can quite understand experimenters would hope that we would have the situation that you have got but we are talking here about testing a mixture of four compounds together. We have seen how mixtures of two can have interesting effects but teasing those things apart, and I am asked to predict the kind of answers I might expect to see, I just do not know. I have seen far too many instances of interactions of a whole variety of types between enantiomers to do anything other than raise it as an issue at this stage.

84. These remarks were made in the context of predicting whether compound 84 would have vasodilation characteristics: which is something that 326 claims that it would have. Of course one cannot be absolutely sure until one has tested it that a second pair of enantiomers will not prevent the potentiation effect from occurring. Professor Newton thought that antagonism between the pairs of isomers in a racemate was extremely unlikely, but neither he nor Professor Reid addressed directly the potential effect of the other pair. In my judgment it is overwhelmingly likely that the potentiating effect seen in the RSSS:SRRR racemate will also occur in the mixture of compound 84.

85. Is that finding good enough for an inevitable result? The legal requirement is that this feature of the claim be the inevitable result of carrying out the prior teaching. Does that mean that if there is some other possibility, even a fairly remote one, that some other result would follow, I should conclude the result is not inevitable? Or am I concerned to establish what, on the balance of probabilities would in fact occur? In my judgment, it is the latter approach which is correct. The inevitable result test does not require proof of individual facts to a quasi-criminal standard. It may be impossible to establish the relevant technical facts to that standard. It is another matter if the evidence establishes that sometimes one result will follow and sometimes another, depending on what conditions are used. But there is nothing of that kind suggested here. It is simply a question of what occurs in fact.
86. It follows that it is necessary for me to go on to consider the position in law on the basis that it is the inevitable result of the teaching of 362 that the RSSS isomer of compound 84 does potentiate another blood pressure reducing agent when the mixture of four isomers is used as a medicine. Mr Alexander argued that 362 would still not destroy the novelty of claim 1, because there is no disclosure in 362 that the RSSS isomer is potentiating the effect of the SRRR isomer.
87. Conventional patent law would hold that the absence of teaching as to how the properties of the prior art are achieved cannot possibly matter. In whatever way they are achieved, the properties are the inevitable result of carrying out the prior teaching. The fact that the person who carries out the prior teaching does not have complete knowledge of the underlying mechanism does not matter. It would not be a defence to infringement if he were to claim ignorance of the mechanism.
88. Mr Alexander argues that a claim can validly cover the use of a known compound so as to produce a hitherto undiscovered technical effect. He says that claim 1 is a claim of this character, and for claims of that kind it does not matter that the technical effect is inherent in the use of the compound to produce the known technical effect. That conclusion, he says, follows from the decision of the Enlarged Board of Appeal in G2/88 *MOBIL/Friction reducing additive* [1990] EPOR 73, a decision which both the House of Lords and the Court of Appeal have declined opportunities to hold wrongly decided: see *Merrell Dow v Norton* [1996] RPC 76 at 93 and *Bristol Myers Squibb v Baker Norton* [2001] RPC 1 at [49]. He relies in particular on the statement in *Mobil* at paragraph 10.3,

If that technical feature has not been previously made available to the public then the claimed invention is novel, even though such technical effect may have inherently taken place in the course of carrying out what has previously been made available to the public.

89. *Mobil* was a case about an additive for oil. The additive itself was known for the purpose of rust prevention in engines. Mobil had discovered it was useful for friction reduction. The case appears to proceed on the basis that this was a new and different technical effect, not one which underlay the previous use at all. Mobil could not claim the additive itself, because it was old. Moreover it would be added in similar amounts to the old additive, so no new method could be claimed. But Mobil were allowed to claim the use for the novel purpose, friction reduction. Novelty of purpose alone would not have been enough, as that was “in the mind” ... “subjective” and therefore

“not relevant”: see paragraph 7.1. But novelty of purpose coupled with an undisclosed technical effect was enough to confer novelty. And that was so even if the undisclosed technical effect would inherently have occurred alongside the known technical effect when using the additive for the known purpose.

90. If *Mobil* is correctly decided, then unadvertised technical effects which underlie new uses of known materials are an exception to the rule about inevitable results. The technical feature of the claim (actually achieving friction reduction) was inherent in the old use and an inevitable result of pouring the additive into the engine. Yet this technical feature was held not to have been made available to the public. Mr Alexander says this is no different from the new medical treatment cases. No doubt when an old medicine (known for disease X) is found to treat a new disease, Y, it could be said that it is inevitable that some of the patients treated to date with this medicine for X may have had disease Y, and inherently been treated for it. Yet the novelty of purpose, using it for making a medicine for Y is enough. That principle is now definitely part of our law: see *Eisai/Second Medical Indication* (G05/83) 1985 OJEP0 64 and *Wyeth and Schering* [1985] RPC 545.
91. *Mobil* concerned the fate of claims directed to the use of a known compound for a new purpose based on new, undisclosed (yet actually achieved) technical effects. The claimed new purpose, friction reduction, was undoubtedly a different purpose from rust prevention, made possible by the new and different technical effect. The present case is not easy to fit into that category. As Mr Wyand points out, at least so far as the compounds made in 362 are concerned, their purpose was use as β -blockers and vasodilators, which is the same ultimate purpose as that in claim 1. Someone who uses compound 84 to make a medicine having adrenergic or vasodilating properties is not using it for a new purpose. Moreover the undisclosed technical effect (that one component isomer of compound 84 assists another isomer in its β -blocking or vasodilation) does not and cannot be used as the basis for a new use of compound 84. It is what underlies the old use of compound 84. Of course patenting the component isomer for use outside the context of compound 84, would be novel on entirely conventional grounds.
92. I think there are signs that the courts in the EPO and this country are taking quite a limited view of what *Mobil* decided. In *BMS v Baker Norton* [1999] RPC 253, Jacob J (as he then was) was faced with a claim in Swiss form to the use of a compound for making a medicine to treat cancer according to a dosage regimen which was claimed to have reduced side effects. A prior disclosure (“the Winograd lecture”) disclosed everything (including the dosage regimen) with the exception of the reduced side effects. Jacob J was pressed with the argument that this undisclosed technical effect allowed BMS to patent the Winograd procedure. He distinguished *Mobil*. Having cited a passage from Laddie J’s judgment in *Evans Medical Limited’s Patent* [1998] RPC 517 at 586 which stated the inevitable result principle (subsequently confirmed in *Synthon*) Jacob J said at 253

It is implicit in what Laddie J said, I think, that *Mobil* has its limits. It should be remembered that *Mobil* was treated as a case where the new use was different from the old. Perhaps a clearer example is *BASF/triazole derivatives* (T231/85) [1989] OJEP0 74 of the discovery that a particular compound (previously used for influencing plant growth) also controlled

fungi. One can imagine cases where it was used for one purpose or the other. The purposes do not necessarily overlap. That is simply not the case here. All you have is more information about the old use. In due course no doubt more information about the exact mode of action of taxol will emerge. No-one could obtain a patent for its use simply by adding “for” at the end of the claim and then adding the newly discovered details of the exact mode of action.

93. Jacob J might have gone on to say that the technical effect which underlay the old use in *BASF* was quite different to the technical effect which underlay the new use. Both the purpose and the technical effect on which it was based were different. Jacob J also reviewed two EPO cases which showed that the EPO itself had come to appreciate the distinction between “true new uses” and cases of “mere more information about old uses”: *Dow Sequestering Agent* (T958/90) [1994] EPOR 1 and *American Cyanamid/Melamine Derivatives* (T279/93) [1999] EPOR 88. He therefore came to the conclusion that the reduction of neutropenia was merely new information about the old use.
94. In *Dow Sequestering Agent*, a prior document, when properly understood disclosed the use of two agents, NTA and IDA, in admixture as sequestering agents. The patentee contended, in reliance on *Mobil*, that a claim to the use of IDA to improve the sequestering ability of NTA gave rise to a valid claim. The Technical Board of Appeal held that the sequestering activity of the combination formed part of the state of the art. Hence the only new information provided by the patent was that the sequestering activity of the mixture was greater than that provided by NTA alone. The Board held that was not sufficient to give rise to novelty. One way in which the Board tested its conclusion was that the new information merely provided “an additional reason to use this known mixture in the known way for the known purpose”. The patent accordingly made no contribution to the art.
95. In *American Cyanamid/Melamine Derivatives* the patentee had discovered that certain compounds used in prior art processes for making melamine derivatives resulted in less impurities being formed. He put forward an amended claim in which he claimed the use of those compounds “in order to reduce the formation of impurities”. Again the Board held that there was no novelty. There was no new use, merely a reason for preferring one prior art product over others.
96. *BMS* went to the Court of Appeal where this part of the reasoning was upheld. Aldous LJ did so on the basis that the lecture contained clear and unmistakable directions to do acts which would have the inevitable consequence of reduced neutropenia, a conclusion which he held consistent with *Dow* and *American Cyanamid*: see [46]. Buxton LJ at [88] explicitly approved Jacob J’s conclusion that the reduction of neutropenia was a mere discovery about an old use.
97. The Court of Appeal has recently had cause to re-examine the judgment in *BMS*: see *Actavis v Merck* [2008] EWCA Civ 444. But on the question of whether clear and unmistakable directions in an item of prior art to do acts which fall within the later claim will anticipate, and more information will not save it, *BMS* was not doubted: see [57].

98. A glance at the Case Law of the Board of Appeal of the EPO, 5th Edition 2006 shows that *Dow* and *American Cyanamid* continue to be applied: see pages 117-118.
99. In my judgement, merely explaining the mechanism which underlies a use already described in the prior art cannot, without more, give rise to novelty. In *Mobil*, the technical effects which underlay the new and old uses were different and distinct. So also in Mr Alexander's example about disease X and disease Y. It is not the case that every discovery about the mode of action of a drug can be translated into a new purpose and claimed as such.
100. I think that all that is done here is to explain why the results that would be obtained with compound 84 are as good as they are. The same technical effect underlies both the old use and the new, and the new use is for the same purpose. So if, as I have held, the inevitable result of 362 is that the RSSS isomer potentiates one of the other isomers in compound 84, claim 1 is not saved by *Mobil*.
101. So far as claim 4 is concerned, on the view which I have taken of the unamended claim, it was anticipated by 362, which teaches a pharmaceutical composition having all the features of claim. The same applies to claims 6 and 7.
102. However, the amended claims are novel. They are novel on the conventional ground that there are no clear and unmistakable directions in 362 to make a pharmaceutical composition having *only* the RSSS and SRRR isomers of compound 84.

Obviousness over 362

103. The familiar structured approach first articulated by the Court of Appeal in *Windsurfing v Tabur Marine* [1985] RPC 59 (CA) has recently been explained and restated in the judgment of Jacob LJ in *Pozzoli v BDMO SA*, [2007] EWCA Civ 588; [2007] FSR 37 at [23].

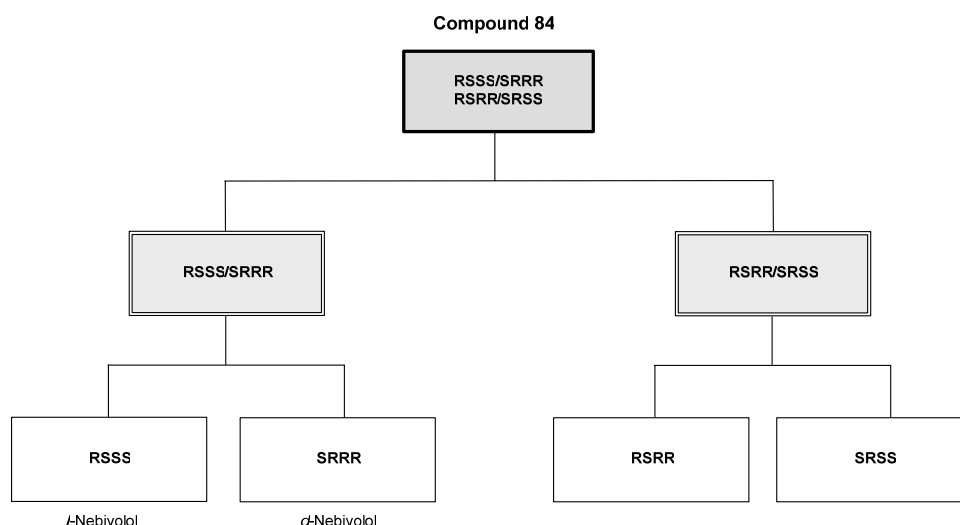
"In the result I would restate the Windsurfing questions thus:

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

104. I have identified the person skilled in the art and the relevant common general knowledge above.

105. Mr Alexander submitted that the central inventive concept of the Patent is summarised in the following sentences from the Patent:
- “In US Pat No. 4,654,362 there are described 2,2’-iminobisethanol derivatives having β -adrenergic blocking properties. It has now been found that a certain class of said bis-ethanol derivatives potentiate the activity of blood pressure reducing agents.”
106. I think a little care needs to be taken with use of that statement as the inventive concept. Insofar as the claims are wide enough to encompass the use of compound 84 itself, the statement is merely further information about something which is known. I think it is safer to concentrate on what is defined by the claims. It is particularly worth concentrating on claims 6 and 7 which define the commercial product Actavis wish to sell. Those claims require a pharmaceutical composition consisting of RSSS and SRRR nebivolol and a carrier, and no further blood pressure reducing agents in a 1:1 mixture.
107. The difference between those claims and the 362 is that, whilst 362 prepares a pharmaceutical preparation containing compound 84, and therefore a mixture of the RSSS and SRRR isomers and a carrier, the other isomeric pair are present as well, whilst in the claims they are absent.
108. Actavis’ obviousness case is along the following lines:
- i) Investigation of the Table 1 compounds in 362 would be undertaken because the claim to a combination of β -blocking and vasodilating would be of great interest at the date – just what the art was looking for;
 - ii) Compound 84 is one of the better ones in 362 and is accordingly worth including on the list;
 - iii) Investigation at the priority date would have involved testing the isomers;
 - iv) An obvious approach would have been to test compound 84 itself and then separate into the two pairs of stereoisomers;
 - v) Those pairs would then be tested. At this point the team would observe that the activity resided, or resided predominantly, in the RSSS and SRRR pair;
 - vi) The tests would have included tests for β -blockade and vasodilation;
 - vii) The active pair would then be resolved into their individual stereoisomers;
 - viii) These would be tested (for both activities), both alone and together and the potentiation effect would be discovered.
109. This is not an argument, therefore, that it would be possible to predict in advance the potentiating properties of the RSSS isomer. It is an argument that, following obvious lines of investigation, a skilled team would be bound to make the invention. It could be labelled “obviousness by inevitable result”.

110. There is no reason in principle why such arguments cannot succeed. But it is particularly important to ensure that the path or paths said to be followed by the notional team are not guided by hindsight.
111. One principal area of dispute is the way in which the skilled team would have gone about investigating the biological profile of the enantiomers: “top down” or “bottom up”. The dispute is important because the top down approach involves preparation of an RSSS/SRRR racemate from compound 84 as a first step, whilst the bottom up approach proceeds first via the synthesis of the individual enantiomers.
112. Professors Reid and Newton for Actavis contended for a “top down” approach. That approach is illustrated by the following diagram:



113. Starting from Compound 84 at the top, the two pairs of isomers are first separated and each pair tested. This would reveal that the main activity lay in the RSSS and SRRR. These two could then be resolved or synthesised and tested and the results compared with the results for the racemate (either those obtained at the earlier stage or in a fresh experiment).
114. Janssen challenge this approach. They argue that a “bottom up” approach would be adopted in which all four isomers of compound 84 would be synthesised. They say that this is what is taught by 362 itself, where the individual isomers of the preferred compound are all synthesised, and in which there is no evidence of a pairwise approach. Furthermore, a paper by Brittain in 1982 showed that when a Glaxo group had investigated the isomers of labetalol (by then already on the market), it had used a bottom up approach as well.
115. Both sides advanced perceived problems with the other’s approach. Until you had tried it, you would not know whether you were going to encounter problems with the top down approach in either stage. On the other hand, nothing in 362 told one whether the stereospecific synthesis of individual enantiomers (as would be required in the bottom up approach) would work equally well with the 6-fluoro carboxylic acid precursor required for nebivolol.

116. Professor Caldwell's view was that he would have been much more interested in the stereospecific synthesis. Once he saw how easily the alternative route, separation of the two pairs, had gone, he saw the attractiveness of that approach. But he maintained that without that knowledge, which it is correct that the skilled person does not have when deciding on his strategy, the skilled person would consider that a separation of compounds with four chiral centres would present more difficulty than would be the case if they had two. I am unable to place much weight on this assertion about the first stage, which was not put to Professor Newton, in the absence of any real explanation from Professor Caldwell as to why this should be so. But the second stage, the resolution into individual enantiomers might well prove to be difficult, as Professor Newton agreed.
117. In terms of this type of difficulty, I consider that the evidence shows the top down route to be potentially more risky, particularly at the second stage. The doubt about the viability of the synthesis with the nebivolol precursor was, it seemed to me from the evidence, somewhat remote.
118. The perceived difficulty of the respective routes is not the only consideration. Professor Newton explained it in this way:

Q..What I want to put to you is that if you have a mixture of four, the whole mixture shows interesting activity, it would be the natural next step to resolve into the individual enantiomers and test each of those to determine what was the source of the activity?

A. No, chemically what you have said makes no sense. Basically, if you have a mixture of a Labetalol-like compound, you have two diastereomers. Diastereomers will have totally different physical properties. If you want to get hold of those you can just put them down a column and you can separate them. If you are in the situation where you do not know any more than the fact that you have two diastereomers and biological activity that is the way you would go. Otherwise you are going to have to resolve twice. You do not want to resolve twice. There is no point in doing that. The quickest way to get the answer to the question is, "Right, test the diastereomers. If they are both active, right, now I know I have to resolve both of them. If only one of them is active, NFI, and the other one I resolve." That is the logical way you always do it.

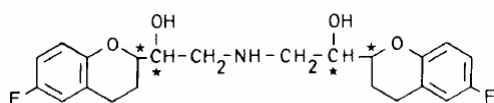
119. NFI means "no further interest". It seems to me that Professor Newton's first step makes sense, but it is by no means a necessary conclusion that the skilled person would follow it. The skilled person might be persuaded by the disclosure of 362 that making the individual enantiomers by stereospecific synthesis was a more assured route. It would be a decision that would be weighed up by the skilled team. Different teams might go different ways, as the evidence in this case shows.
120. If the skilled team were to take the first "top down" step, and separate the two pairs so as to create an RSSS/SRRR racemate of compound 84, there was no real dispute that one would test the racemate for activity. But I am not persuaded that would necessarily involve making a pharmaceutical composition within claims 4 and 6. The compound might be tested on a tissue preparation. The evidence does not enable me to say that the material that would be prepared for testing in this way could properly be regarded as a pharmaceutical composition.

121. In order to arrive at the conclusion that the pharmaceutical composition he should make is one consisting only of RSSS and SRRR of compound 84, the skilled person would have to go further. This would involve resolving the racemate into the individual enantiomers, observing that SRRR is not as effective on its own as the racemate, and that it is assisted by the RSSS.
122. Mr Wyand submits that if the skilled team encountered (or thought they might encounter) difficulties with the final resolution step, they could synthesise the two enantiomers stereospecifically. That may be so. But, even then, the team would have to compare the results of testing the individual enantiomers with the results for the racemate, or compound 84 itself (if they had tested it). There is no *a priori* reason why they should do so. It has to be remembered that the reason for going down this road in the first place is not because the team expected to find any potentiation effect, but to synthesise the enantiomers. The vital observations, that SRRR is not as effective on its own as the racemate, and that it is assisted by the RSSS, could easily be missed.
123. Of course if the skilled team were to adopt the bottom up approach the difficulties are greater still. As the Patent shows, l-nebivolol would be likely to produce results which the team would regard as NFL. The evidence does not enable me to say either that the team would necessarily test for vasodilation, or that l-nebivolol would in fact attract notice if tested for that property.
124. All the above is, in my judgment, too much for the skilled person. It involves, as Mr Alexander submitted, far too much in the way of research.
125. It follows that claims 4, 5, 6 and 7 are not obvious in the light of 362.

The Guildford Forum

126. Actavis contends that the chemical structure **and** stereochemistry of nebivolol were disclosed at a scientific conference in Guildford in September 1987 in a presentation given to the conference by one of Janssen's employees, Robert Woestenborghs.
127. The Guildford Forum was concerned with analytical techniques for measuring low levels of drugs, metabolites and other biological compounds. The conference proceedings were published around six months after the priority date in a book entitled "Bioanalysis of Drugs and Metabolites especially anti-inflammatory and cardiovascular". I shall refer to this as "the Bioanalytical Book".
128. Mr Woestenborghs gave two oral presentations, both of which are referred to in the Bioanalytical Book. The presentations were respectively entitled "The use of stable-isotope methodology in pharmacokinetic studies involving flunarizine" and "HPLC-fluorescence method for the determination of the new β -adrenoreceptor blocking agent nebivolol in human plasma". It is the latter which is said to have made the relevant disclosure. The former was a much more substantial piece of work than the latter.
129. Actavis' case is that during the course of the Presentation, Mr Woestenborghs presented a slide showing the chemical structure and stereochemistry of nebivolol in

the same (or very similar) format as appears in the write up of his presentation in the Bioanalytical Book:



(mixture of two isomers,
SRRR and *RSSS*; * denotes
a chiral centre)

130. It will be observed that the structure is annotated with information about the location of the chiral centres, which are denoted in the conventional way with asterisks, together with an indication that nebivolol is a mixture of two isomers, the *RSSS* and the *SRRR*.
131. Actavis adduced evidence from a Mr Barkworth, who attended the Forum. He made notes at Mr Woestenborgh's presentation on his own copy of the abstract booklet provided to attendees. The notes included the structural formula of nebivolol which he took at the presentation. Given that it was an oral presentation this must have been from a slide or similar display, as he would not have been able to deduce the structure in any other way. The notes say nothing about stereochemistry: no asterisks and nothing about the identity of the isomers. But he would not necessarily have recorded that information if it had been shown. Mr Barkworth was not cross examined on any of this evidence and I accept it.
132. Two witness statements of Mr Woestenborghs were relied on by Janssen, and Mr Woestenborghs was cross examined. It was clear that he had no independent recollection of the events at the Forum. His written evidence was that he believed he had not disclosed the stereochemical structure at the Forum. He gave three reasons for this belief:
- i) Janssen's policy about not releasing details of research until a patent application had been filed;
 - ii) The stereochemistry was not relevant to the presentation he was giving: he was not describing a chiral method;
 - iii) His group at the time did not focus on stereochemistry.
133. By the time of his second witness statement Mr Woestenborghs had read the witness statement of Mr Barkworth. Mr Woestenborghs then said that if he did disclose anything about the structure of nebivolol at the Forum it would have only been the general chemical structure of the molecule, not the stereochemistry. By the time he was called to give his evidence in chief Mr Woestenborghs was prepared to accept that he had indeed shown the formula of nebivolol, but believed it did not include the stereochemistry.
134. Included within the documents disclosed by Janssen was a series of eight slides numbered from N1 to N9. The missing number was N2. Also included in the documents was a draft of the article in the Bioanalytical book with handwritten notes and annotations made by Mr Woestenborghs. The annotations include the square-bracketed numerals linked to passages of text. So, for example, the reference [F1] appears adjacent the title of the article. Slide N1 from the series of slides shows just that, the title. Reference numeral [F3] appears adjacent a set of bullet points in the

article. Slide N3 is a slide appropriate to those bullet points. Slides N4, N5 and N6 are slides of chromatogram, two about column conditioning and a third about purified water. In the text of the article the reference numerals [N4], [N5] and [N6] appear adjacent a section of text concerned with purity of the solvents. Slides N7, N8 and N9 are also directly referenced at the appropriate point in the text, by the references [N7], [N8] and [N9].

135. The place in the text where the square-bracketed numeral [2] appears is adjacent the chemical name of nebivolol, and above a marginal note “[Fig 1]” in typescript. The text includes a reference to Figure 1. The last page of the text is the structural formula of nebivolol with asterisks at the chiral centres. The penultimate page is this:

Legend to figure

Fig.1. Chemical structure of nebivolol

(mixture of two isomers: SRRR and RSSS).

136. Mr Woestenborghs did not accept that this annotated document was his notes for his oral presentation. He suggested that it might have been for some other presentation or publication, which he could not identify. Plainly the combination of slides and text are notes for a presentation: it would make no sense to have slides such as [1] and [3] included in a publication. I think by far the most likely explanation is that these are the notes for the presentation at Guildford, and I so hold.
137. I am sure that Mr Woestenborghs did display a slide with the structure of nebivolol on it. The real question is whether that it is more likely than not that the slide contained the stereochemical information that subsequently appeared in the Bioanalytical Book and was in the annotated document. The annotated notes for the lecture are powerful evidence that the stereochemical information was disclosed.
138. I should deal with Mr Woestenborghs’ reasons:
- i) Janssen’s policy about patent applications. The problem with this reason is that the patent application was not filed until 23rd March 1988, by which time it is likely that Mr Woestenborghs had supplied a copy of the article to the publishers. Given the brevity of the article, I think it is much more likely that it was this article and not the longer one which was delivered late.
 - ii) The stereochemistry was not relevant. If this was the case it was just as irrelevant when the article came to be submitted: but on Mr Woestenborghs’ account he must have *added* the information to that which was shown at the Forum.
 - iii) His group did not focus at the time on stereochemistry. This is as much an explanation for why the structure might have been disclosed.
139. Janssen’s strongest point is that nobody who was there gives direct evidence on this narrow point. Insofar as anyone took notes of the structure (Mr Barkworth) there is no indication of any stereochemistry, but as Mr Barkworth explains, he would not necessarily have noted the stereochemistry at the time.

140. I have come to the conclusion that the slide did show the stereochemical structure of nebivolol and the fact that it was a mixture of RSSS and SRRR isomers. I have taken into account how difficult it is for Janssen to establish the facts after this very considerable period of time. It is a conclusion that I arrive at with regret, given the consequences which follow and my findings that some claims would have otherwise survived. But it seems to me to be improbable in the extreme that the information as to stereochemistry would have been added to the material for publication in the Bioanalytical Book if it were not part of the original presentation. That Book was, after all, supposed to be a record of the proceedings.

Lack of novelty/obviousness over the Guildford Forum

141. Claim 1 is clearly anticipated by the disclosure at the Guildford forum. *Mobil* does not save it, for the reasons I have already given in relation to the 362 novelty attack. Claims 4, 6 and 7 are in my judgment lacking in novelty as well, both before and after amendment. To the extent that there is no disclosure of a “carrier”, or of the express requirement only to include one blood pressure reducing agent, or of a 1:1 mixture, those claims are obvious.
142. Claim 5 is different. It was suggested on the basis of some manuscript notes on Mr Woestenborghs’ annotated document that he disclosed how the two enantiomers worked together. I reject that suggestion. Without that information it is not obvious to use one enantiomer to potentiate other blood pressure drugs. Claim 5 is not obvious in the light of the Guildford forum.
143. It is not necessary to consider the arguments about disclosure for the purposes of publication, which raise more difficult issues.

Conclusion

144. Claims 1, 4, 6 and 7 are all invalid for lack of novelty/obviousness over the disclosure at the Guildford forum, but claim 5 is not. The application to amend therefore fails. I will hear counsel as to the form of order.