Neutral Citation Number: [2005] EWHC 2142 (Pat)

Case No: HC 04 C02059
HC 04 C02167
HC 04 C03986

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 12 October 2005

Before :

THE HONOURABLE MR JUSTICE PUMFREY

Between :

Ranbaxy UK Limited	**Claimant in 2059 and 2167**
Arrow Generics Limited	**Claimant in 3986**
- and -	
Warner-Lambert Company	**Defendant**

Simon Thorley QC and Richard Meade (instructed by **Bird & Bird**) for **Warner-Lambert**
David Kitchin QC and Michael Tappin (instructed by **SJ Berwin**) for **Ranbaxy**
David Kitchin QC and Mark Chacksfield (instructed by **Forsyth Simpson**) for **Arrow**

Hearing dates: 18-22, 25 July 2005

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

MR JUSTICE PUMFREY

Mr Justice Pumfrey :

Introduction

1. This is the judgment in two actions brought by Ranbaxy (UK) Limited ('Ranbaxy') and an action by Arrow Generics Limited ('Arrow') respectively against Warner-Lambert Company, ('Warner-Lambert'). Warner-Lambert is the owner of European Patent (UK) 0247633 ('633) and of European Patent (UK) 0409281 ('281), which are concerned with atorvastatin, a cholesterol synthesis inhibitor of great commercial importance. The calcium salt is sold under the name Lipitor.

2. In action 2167 Ranbaxy seek a declaration of non-infringement in respect of '633. Both Ranbaxy (in action 2059) and Arrow (in action 3986) seek to revoke '281, which claims atorvastatin calcium. The issues in respect of '281 are common to the latter actions, and the same evidence was relied on both by Ranbaxy and by Arrow.

3. So far as '633 is concerned, the issue is one of construction and easily stated. Does the claim cover the single enantiomer which might be illustrated by formula (I) of the claim, or does it *only* cover racemic atorvastatin, that is the mixture of two enantiomers which Ranbaxy says is denoted by formula (I) on a proper interpretation of the formula in context. This issue is raised by Ranbaxy only. After the trial but before this judgment was complete, I heard and rejected an application by Arrow to be joined as a party to the action in respect of '633.

4. So far as '281, is concerned, the issues are (a) obviousness over the *application* for the '633 patent (the '633 Application) and (b) anticipation by Warner-Lambert's application under the PCT number WO 89/07598 (the '598 application).

5. I am only concerned with claim 1 of '633 and with claims 1 and 2 of '281. If claim 1 of '633 is not infringed I understand that none of the others will be. Independent validity is only alleged in respect of claims 1 and 2 of '281.

6. At the outset of the trial, I ruled that Ranbaxy could not rely upon certain documents, largely representations made to certain patent offices, in which persons acting for Warner-Lambert had made representations about the disclosure of '633 much the same as that for which Ranbaxy now contend. I excluded the documents because I considered that they were not admissible on the question of construction.

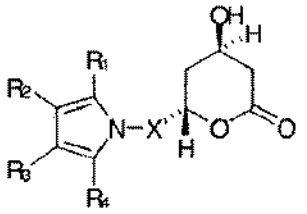
'633: legal principles

7. This is an application for a declaration of non-infringement, after an acknowledgment was refused by Warner-Lambert. The letter seeking the acknowledgment described the acts that Ranbaxy intended to do as follows:

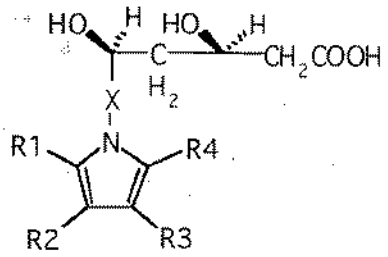
> 'Our client is considering whether to manufacture and/or import and/or sell atorvastatin calcium in the UK upon expiry of the data package exclusivity attaching to that pharmaceutical. The purpose of this letter is to ensure that our client's path is sufficiently cleared of patent issues prior to considering a launch and is sent pursuant to section 71 of the Patents Act 1977.

> Our client's atorvastatin calcium will comprise the single optically pure enantiomer [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt trihydrate.
>
> Our client requires acknowledgement from you that any acts including; manufacture, keeping, importing for disposal, sale and any other acts of the kind mentioned in Section 60 of the Patents Act 1977 and done in the United Kingdom would not constitute infringement of any of the claims of the '633 patent.'[1]

8. Claim 1 of the patent is as follows:

> "A compound of structural formula I
>
> 
>
>
> I
>
> wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$; R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms; either of R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl, cyclopentyl, cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms; R_4 is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl; or a hydroxy acid or pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I, and having the formula X

[1] This is not quite right. The material Ranbaxy plan to sell is not the trihydrate, and there is another immaterial error.



where X, R_1, R_2, R_3 and R_4 are as defined above."

9. The case is concerned with stereochemistry. The specialist terminology is explained by the experts, and I will only repeat it so far as necessary to make what follows comprehensible, and I state the problem here without explaining the terminology. I have underlined the parts of the claim that lead to the allegation of infringement. The reason there is said to be no infringement is that although the two structural formulae (I) and (X) appear to show the R-(R*,R*) compound, it is common in organic chemistry to use the structural formula of a single enantiomer to denote the racemate. How such a structural formula is being used must be determined by reference to context. This much appears to be common ground. Given that the racemate is to be considered as a distinct compound from either of the two enantiomers to be found in it, Ranbaxy says that the specification makes it clear that the compound with which it is concerned is the racemate, and that in its context formula I is being used to refer exclusively to the racemate. It follows that the claim is limited to the racemate and that accordingly the enantiomer of interest does not fall within it. That is a statement of the argument, but before I discuss it I must set out the applicable legal principles, identify the skilled person to whom this document is addressed and set out the relevant part of the common general knowledge.

Principles of construction

10. *Kirin Amgen v Hoechst Marion Roussel Limited* [2004] UKHL 46, [2005] RPC 9 (page 169) paragraphs [32] to [35] summarises the modern approach. Extracting short passages may tend to distort the overall meaning of this passage, but from it, and from the approval that it gives to the judgment of Jacob LJ in *Rockwater Ltd v Technip France SA* [2004] EWCA Civ 321, [2004] RPC 6 at [41] (and by inference also to the slightly different statement in *Mayne Pharma v Pharmacia* [2005] EWCA Civ 137 at [5]), I conclude that it is now clear that in deciding what the person skilled in the art would have understood the patentee to be using the language of the claim to mean, the court must approach the problem from the standpoint that the language chosen will be usually of critical importance. An over-meticulous analysis is one that is too willing to draw from a detailed analysis of the grammar, the punctuation and the particular words and phrases used inferences as to meaning that the words might support but which the skilled person would not draw, and it is the antithesis of giving to the words chosen in their context the meaning that the skilled person would give them. Carefulness is not to be equated with over-meticulousness.

11. This claim is couched in highly technical language. It uses the device of the chemical structural formula to convey its meaning. The structural formula does two things. It shows, in a highly schematic way, how the chemical bonds are located between different atoms of the molecule (or larger components, such as the benzene ring,

which may be depicted in many ways. For the benzene ring, this patent uses Ph or  .)

12. The problem in the present case is to interpret the formulae (I) and (X) in context. Quite apart from the myriad of different substitutions that are permitted by reference to the components X and R_{1-4}, the question is what possible 3-dimensional arrangements of the molecule are covered by the claim, that is, its stereochemical interpretation.

The skilled person

13. The title of the patent, together with the passage at page 1 lines 11-32 and the claims makes it clear that the patent is intended for those who will synthesise an active ingredient and formulate it for use in therapy as a hypolipidaemic or hypocholesterolaemic agent. The patent is therefore directed towards medicinal chemists with skills in organic synthesis. The evidence was that medicinal chemists often start their lives as organic chemists, and add the biological skills and knowledge to their degree-level skills in organic chemistry. Scrutiny of the document reveals that it is really only concerned with synthesis, and with describing the new class of compounds (page 4 line 3). Activity is described briefly (page 8 lines 20-34) and formulation is described in the most general and conventional terms (page 8 line 35 – page 9 line 14), as is dosage (page 9 lines 20-26). This is thus directed at the people employed by pharmaceutical companies to synthesise new active ingredients.

14. The principal expert called by Ranbaxy on this part of the case, Professor Clive, was an out-and-out synthetic organic chemist of wide experience. He was very careful in his answers. Dr Newton, who was called by Warner-Lambert, was a medicinal chemist of considerable eminence. There was an attempt, more by way of submission than on the basis of any evidence, to suggest that the perspective of a medicinal chemist and of a synthetic organic chemist on the disclosure of the '633 patent would be different. This suggestion was made because Prof Clive's approach, which was a very precise and painstaking approach to stereochemical descriptions, was unhelpful to the patentees and understandably they sought to diminish its significance by suggesting that it was in some way uncharacteristic of a medicinal chemist working in the pharmaceutical industry. I confess that to the extent that there was a difference between Prof Clive and Dr Newton, I considered it to be more a matter of personality than of substance. I shall deal with their respective positions as I deal with the various disputed points.

15. In any case, Dr Newton's evidence was that a medicinal chemist is a synthetic organic chemist who has got additional training and, in particular, additional training in the biological aspects of pharmaceutical action. This case is about notation and context, and so both Dr Newton and Prof Clive were in a position to give relevant evidence on the points that arose.

The common general knowledge as to notation

16. '633 claims a priority date of 30 May 1986, to which Ranbaxy accepts it is entitled. This is the date at which the common general knowledge is to be assessed.

17. The tetrahedral arrangement of the covalent chemical bonds that a carbon atom may make with four other atoms means that if there are four different units at the ends of

the four different bonds those units may be arranged in two different ways. When one says two different ways, it means that no amount of rotating will permit one arrangement to be superimposed on the other. They will be mirror images of each other, and are called enantiomers. This is shown in this diagram:

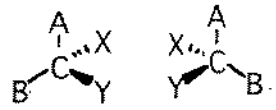


Figure 1. Enantiomers

18. This is an attempt to show a tetrahedral structure. Conventionally the bonds depicted by single lines are in the plane of the paper: the bonds denoted by a solid wedge (a heavy line may also be used) are out of the paper and the bonds denoted by a dotted wedge (or dotted line) are into the paper. The picture shows two imaginary molecules with an asymmetric carbon atom C. A, B, X and Y denote different atoms or groups positioned at the apexes of the tetrahedron. Because the molecules are handed, they are called chiral, and the asymmetric carbon atom(s) they contain are called chiral centres. A molecule is an enantiomer if it cannot be mapped to its mirror image by rotations and translations alone.

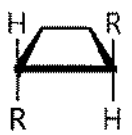
19. Enantiomers do not differ in any of their physical properties (melting point, boiling point and so on) but one, differing in their effect on plane polarised light. One enantiomer will rotate the plane of polarisation to the left or anticlockwise, and the other will rotate it to the right. A (+) or *d*- is conventionally used to denote the enantiomer which rotates the plane of polarisation to the right, and a (-) or *l*- is conventionally used to denote the enantiomer that rotates the plane of polarisation to the left.

20. Alternatively, the absolute configuration of the molecule can be worked out according to certain rules. The result of applying the rules is a decision either that the molecule is right-handed (denoted *R*) or left-handed (denoted *S*).

21. One enantiomer can only be synthesised in preference to the other if the stereochemistry is already present in the starting materials or if enantiomeric reagents are used. Unless the conditions for the reaction are stereospecific the result of the synthesis will inevitably be a 50/50 mixture of the two enantiomers of the chiral molecule. This is called a racemic mixture or racemate. There is no guarantee that the physical properties of the racemate will be the same as the physical properties of the individual enantiomers that go to make it up: for example the melting point may be higher, lower or the same. The racemate has no effect on plane polarised light, the mixture being precisely 50% (+) and 50% (-).

22. Where there are two asymmetric centres in a molecule, there are unsurprisingly four possible isomers. Looking just at the chiral atoms, both may be mirror images of each other, and the molecules form an enantiomeric pair. If one only is a mirror image of the other, then the molecules are called diastereoisomers. Thus each molecule of the four will have one corresponding enantiomer and two corresponding diastereoisomers. To distinguish the diastereoisomers terminology describing the relative position of significant groups may be used. If the significant groups are on the same side of a ring, it is called a *cis*- structure, and if on the opposite sides of a ring, it is called a *trans*- structure:

cis



trans

Diastereoisomers do not generally have the same properties. and may be separated in reliance on that fact.

23. The foregoing covers the terminology and the visual conventions in structural formulae used in the patent. I do not understand that any of the foregoing is said not to be part of the common general knowledge of the skilled person. It provides the notational framework for the specification's statements about the compounds of the invention.

The importance of chirality

24. Different enantiomers of a chiral molecule react differently with other chiral molecules. This is of particular importance in natural systems since enzymes, which are proteins responsible for all the chemical reactions carried out by the cell, are chiral molecules and are present only as a single enantiomer. I quote Dr Newton's report:

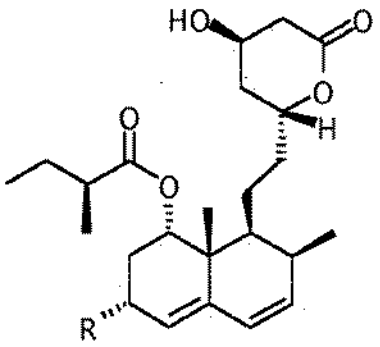
> '15. For many years it has been recognised that the vast majority of drugs exert their activity by binding to a protein receptor to form a drug-receptor complex. Although there are exceptions, this process is usually readily reversible and does not generally involve the formation of covalent bonds. The drug receptor complex is formed by a combination of hydrogen bonds, π-π stacking between aromatic rings, salt bridge formation between carboxylic acids and amines and hydrophobic binding. The particular parts of a drug that cause it to bind to its receptor are together termed the pharmacophore. Since the protein receptors are composed of a complex array of chiral amino acids it follows that the drug's binding site is in a chiral environment (although the drug itself may or may not be chiral).
>
> 16. However, in circumstances where the drug substance does have an asymmetric carbon atom or atoms, the binding efficiency to a given receptor and therefore the biological activity of the enantiomers or diastereoisomers will be different. Within a chiral environment the two enantiomers of a racemate are totally different compounds and very often the majority of the biological activity observed for a racemate resides within a single enantiomer. Sometimes both the enantiomers of a racemate are biologically active but act at different receptors and cause different effects.
>
> 17. One of the most unfortunate and best known examples of this was the mild sedative and anti-emetic Thalidomide. The drug has an asymmetric centre but was marketed as the

> racemate. The R-isomer is a non-mutagenic sedative, whilst the S-isomer is mutagenic and caused widespread deformities amongst those children whose mothers took the drug during pregnancy .... Although this is a specific example, the principle was well understood by the skilled person at the 30 May 1986 priority date of the '633 Patent.'

25. I understood the evidence to be that the skilled person at the priority date would expect that where a drug was a chiral molecule, it was highly likely that only one of the enantiomers and diastereoisomers (if any) would be responsible for its pharmaceutical activity. This did not mean, and does not mean, that chiral drugs had to be administered as single enantiomers but there is undoubtedly a modern tendency to prefer single enantiomers where resolution of the racemate is practicable.

The common general knowledge in relation to statins

26. The other aspect of the common general knowledge which it is necessary to consider is the common general knowledge in respect of statins generally. By 1986, statins were a well-known class of compounds recognised as having a potential application for cholesterol-lowering drugs. The first statins, mevinolin and compactin, were natural products that existed as single enantiomers. Much work had been done on these compounds, and it was recognised that they had a 4(R)-*trans*- structure:



In compactin, R= H, and in mevinolin R=CH_3.

It may be seen that the lactone ring in the top right of the structure is the same as the lactone ring of formula I of the patent. What is different is the substituent at the 6 position on that ring.

27. The document called Stokker ('3-Hydroxy-3-methylglutaryl coenzyme A Reductase Inhibitors' J Med Chem 1985 28, 347-358 also seems to have been accepted to be a document the skilled person would undoubtedly become aware of in doing any statin work, if not common general knowledge in the strict *Beloit v Valmet* sense, at the priority date. It reports a substantial statin study, and both Prof Clive and Dr Newton said that it disclosed that it was likely that all the activity lay in the 4(R)-*trans*-isomer.

28. It was also known that the active form of the molecule was the open-chain hydroxy acid formed by hydrolysing the lactone ring. This acid can readily form salts, for example the sodium salt.

The disclosure of the specification

29. After the acknowledgment of certain prior art, the patent starts its Description of the invention (page 2 line 11), with a statement of the invention. It is described as certain '*trans*-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl) alkyl]-4-hydroxypyran-2-ones'. There follows a remark about EP-A-179559, which is said not to disclose the 3- or 4-carboxamido substitutions in the pyrrole ring with which this invention is concerned. These are the substituents labelled R_2 and R_3 in formula I. Then formula I is set out. There is no dispute that the lactone ring is shown with the *trans*-substitution, as is repeated at page 2 line 34.

30. Page 3 of the patent sets out the method of preparing the compounds of formula I. This is a general description, and appears to be set out for all the compounds that formula I covers ('In another aspect of the present invention, there is provided a method of preparing the compounds of structural formula I above...'). The first stage (compound VIII to compound IX) results in a chiral compound. It is common ground that compound IX will be a racemate if synthesised according to this scheme.

31. The next stage in the synthesis (page 3 lines 34-53) is described as producing a compound of formula X. Formula X in fact depicts a single *trans* enantiomer, but again it is common ground that the result of the synthesis described will be a racemate consisting of the two *trans* enantiomers.

32. At page 4 line 3, the description returns to the inventive class of compounds, this time with reference to the bridging group X in formula I. The bridging group is an alkyl chain and the preferred one is ethylene (page 4 line 7). After this short discussion, the stereochemistry of the compounds is expressly discussed in a short but significant paragraph at page 4 lines 8 to 12:

> 'The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-*cis*- and S-*cis*-isomers and the other two of which are the R-*trans*- and S-*trans*-isomers. This invention contemplates only the *trans*- form of the compounds of formula I above.'

33. At page 4 line 21, the description of the preferred reaction sequence which 'is used to prepare compounds of the present invention' is described. The specification turns first to the synthesis of compound VIII. This is not chiral and need not be further considered. Reaction sequence II on page 7 sets out in detail the steps from compound VIII to compounds X and I. This sequence forms part of the invention (claim 8), and I have outlined it above. In talking of compound X, the specification states (page 7 line 51) that it contains 'a predominance of the desired R*, R* configuration at carbon atoms three and five which bear the hydroxy groups'. I have not discussed the R* notation under the heading of common general knowledge. The notation is used to describe pairs of atoms that are relatively R to each other. It is disambiguated by adding the appropriate absolute value, so that R(R*,R*) is the same as (R,R). The specification explains that it is the (R*,R*) configuration that gives the desired *trans*-configuration to the resulting lactone.

34. The results of comparing 'representative examples of compounds in accordance with the present invention' are set out in Table 1. The preparation of each of these compounds is described in Examples 1, 3 and 4 of the patent, and it is common ground that each of these Examples will produce a racemate.

35. Finally, and this is a small point, that may be neutral, when the draftsman comes to put a name to a compound rather than a structural formula, in claims 3, 4 and 5, only in claim 3 does he include the (±) symbol to denote the racemate.

36. Mr Kitchin QC submits that this reaction scheme, the only scheme given for reaching 'compounds of the present invention' having formula I and which undoubtedly yields the racemate, will stand for all intents and purposes as a definition of what the patent means by formula I. It means the racemate. This consideration is reinforced by the consideration that Dr Newton agreed that from a medicinal chemistry standpoint, racemates and their component enantiomers 'are totally different compounds'. The reason is that the biological response to one of two enantiomers of a racemate is completely different.

37. Against this, it is necessary to consider the common general knowledge:

    i) The skilled person knew that compactin and mevinolin were potent anti-cholesterolaemics, and were single (R, R) enantiomers;

    ii) He knew from Stokker that it was likely that all active compounds of this description would be single *trans*- enantiomers, the (R,R) enantiomers, the (S,S) enantiomers being likely to have no activity;

    iii) He knew from his common general knowledge that a racemic mixture can be resolved into its component enantiomers. Professor Clive under cross-examination described this as a standard procedure, but not mindless. He put it like this (transcript pages 329-330):

> 18 Q. … You have given evidence, and I am not going to go
> 19 through it again, as to the teaching of the 633 patent, the
> 20 specific examples of the 633 patent, which you say teach you
> 21 to make a racemate.
> 22 A. They do indeed.
> 23 Q. The skilled man would not need to be told how to resolve that
> 24 racemate if he wished to.
> 25 A. The skilled man would know how to go about the business of
> 2 resolving racemates.
> 3 Q. You accept, as I understand it, that the skilled man reading
> 4 the 633 patent would know that one enantiomer was likely to be
> 5 more active than the other.
> 6 A. That is correct.
> 7 Q. Can I suggest to you that that would be a reason for any
> 8 skilled addressee wanting to resolve the racemate that was
> 9 produced by carrying out the teaching of 633.
> 10 A. The way I put it on the other side of the Atlantic is that if
> 11 somebody were given the 633 and told to do something helpful
> 12 with it, they would immediately decide to do a resolution.
> 13 Q. They do not need to be told to do it or how to do it.
> 14 A. They would be motivated to do it and would have a high
> 15 expectation of success. They might need to consult the
> 16 literature on particular methods, but they would know the
> 17 general drift of things.

38. So we have a patent which describes formula I as the compound of the invention, and tells the skilled person to make the compound of the invention by a method which will only produce a racemate. When it comes to the admittedly thin description of the treatment of human beings, it says nothing about resolution, or about the near certainty that only one enantiomer composing the racemate will matter. When it compares compounds of the invention with the prior art compactin, what it compares are, in fact, racemates. In the claim it uses a formula which may also be used to denote the enantiomers of interest in accordance with an acknowledged convention that permits it to be used to denote racemates.

39. Against this background, it is not surprising that Mr Kitchin QC relied strongly upon Lord Hoffmann's remark that a specification is not a document *inter rusticos* for which allowances must be made. But this is an invention in a field that is well investigated. The skilled person's common general knowledge extends to the overall characteristics of the claimed compounds, which are analogous to existing compounds that also possess those characteristics. It is also a feature of communications between skilled persons that the writer will feel no need to set out material which he can safely assume the other is aware of. In the case of a patent, which is a document directed to a person skilled in the art, the writer can assume that the reader possesses the common general knowledge. In my view, a proper approach to construction of this claim to ask why the patentee, who has covered a two-element composition for use in a drug, would wish not to cover one element of that composition which any reader would know was the effective element and which could be isolated using routine techniques. Of course, clear words would be conclusive, but there are no clear words. I can see that to ask this question would not be justified if the skilled reader did not have a clear understanding that the claimed material would have a component that was new and useful, but there is every difference between on the one hand an omission that was surprising but for which the patentee might have reasons, and on the other an omission that is both surprising and would in the eye of the reader immediately deprive the patent of any commercial effect.

40. Professor Clive's view was that if one is going to use the name, or structure, of a single enantiomer in a document to denote a racemate, then you cannot use the same name or structure to denote the enantiomer as well. That seems to me to be obvious, although I imagine that it must be possible for context to change within a document and meanings to change accordingly. I have in mind a document divided into two parts, one headed 'Preparation of the racemate' and the other headed 'Properties of the enantiomer of interest' in which the same formula was used throughout. The change in context must, I think, be sufficient to change the meaning of the formula. The author of a document is obliged to explain what he is doing.

41. In the '633 patent, it is absolutely clear from context throughout that formula (I) is being used to denote a racemate. In my judgment, every time the skilled person sees formula I or formula X he will see it with eyes that tell him that in that racemate, there is a single enantiomer that is the effective compound, and that he can resolve the racemate using conventional techniques to extract that enantiomer. When one comes to claim 1, which echoes the purpose of the invention with its conventional reference to pharmaceutically acceptable salts, he will, in my judgment, continue to see the formulae in this light. In my view, the claim covers the racemate and the individual enantiomers.

42. In the result, therefore, I refuse the declaration sought.

The '281 patent

43. Claim 1 of the '281 patent is to the hemicalcium salt of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid. This can be conveniently referred to as atorvastatin calcium. It is the commercial material of interest.

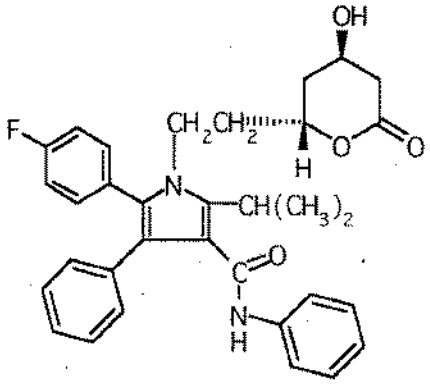
44. It is accepted that the invention of claim 1 is entitled to priority from 21 July 1989. Two grounds of invalidity are raised: anticipation by WO 89/07598 ('598) and obviousness in the light of the application for '633 ('633A).

45. On this part of the case, evidence was given by Dr Cunningham for Ranbaxy and Arrow. Dr Spargo gave evidence for Warner-Lambert. No criticism could be made of either. I can first deal with the allegation of anticipation.

46. '598 is a section 2(3) citation which means that it is not available to support an allegation of obviousness. These circumstances emphasise the importance of not drifting away from the strict principles of anticipation, which are set out in *General Tire v Firestone* [1972] RPC 457 at 485. For a claim to be anticipated by a prior disclosure, the prior disclosure must contain a clear description of, or clear instructions to do or make, something that would infringe the patentee's claim if carried out after the grant of the patentee's patent. If, on the other hand, the prior publication contains a direction which is capable of being carried out in a manner which would infringe the patentee's claim, but would be at least as likely to be carried out in a way which would not do so, the patentee's claim will not have been anticipated, although it may fail on the grounds of obviousness. A signpost, however clear, upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee. This formulation is sometimes glossed as requiring that the invention be the 'inevitable result' of carrying out the directions of the prior publication. This is the test applied in the European Patent Office as well:

> '7.5 In the case of a prior document, the lack of novelty may be apparent from what is explicitly stated in the document itself. Alternatively, it may be implicit in the sense that, in carrying out the teaching of the prior document, the skilled person would inevitably arrive at a result falling within the terms of the claim. An objection of lack of novelty of this kind should be raised by the examiner only where there can be no reasonable doubt as to the practical effect of the prior teaching...' (Guidelines for Examination Part C chapter IV)

47. '598 is an application for ways of making, particularly, formula I, which is the same as formula I of '633 save that group X is explicitly ethyl, $-CH_2CH_2-$. It is particularly interested in formula Ia:



Compound XII (see the reaction scheme on page 40 of the application) is the ring-opened hydroxy acid form of compound Ia. Then, at page 44, lines 33-5 '598 says that the preferred isomer of this invention is the 4R, 6R-isomer of the compounds of formulas I, Ia and XII. So far as compound Ia is concerned, this is atorvastatin in its lactone form, and so far as compound XII is concerned it is the carboxylic acid, which can either be made following the explicit reaction scheme, stopping before the lactone or, as the patent says, may be produced from the lactone compound of Formula Ia by conventional hydrolysis of the lactone compound of Formula Ia (page 43 line 11)

48. On page 43, the application continues (line 15):

> 'In the ring-opened dihydroxy acid form, compounds of the present invention react to form salts with pharmaceutically acceptable metal and amine cations formed from organic and inorganic bases. The term "pharmaceutically acceptable metal salt" contemplates salts formed with the sodium, potassium, calcium, magnesium, aluminum, iron and zinc ions.'

49. It follows that the material claimed in claim 1 is an expressly specified salt (calcium) of the preferred isomer of one of the three materials explicitly specified. If one is in any doubt, it is easy to compare the final structural formula on page 12 of '281 against formula XII on page 40 of '598. They are identical, save that in '281 the calcium salt, and in '598 the acid, are shown. In fact, the synthetic route described in '598 actually produces a racemate. But this time, the precise enantiomer (4R,6R) is specified. This notation means the same thing as the [R-(R*,R*]... used in respect of the acid in claim 1 of '281. The evidence (which I have already discussed) was that resolution to obtain the enantiomers was common general knowledge. It is no answer to an allegation of anticipation that the specification gives clear and unmistakable directions to use the common general knowledge to produce a specific material.

50. I conclude that this is a clear case of anticipation of claim 1 of '281. '598 gives specific directions to make the three preferred enantiomers, one of which falls within the claim.

51. So far as claim 2 is concerned, Warner-Lambert surprisingly suggest that'598 does not disclose pharmaceutical compositions of atorvastatin. This is incorrect. Claim 15, which claims a method of making compound Ia, concludes with this feature:

> (e) and if desired, converting the resulting compound of Formula I_a to a hydroxy acid

corresponding to the opened lactone ring of structural Formula I_a by conventional hydrolysis and further, if desired, converting the hydroxy acid to a corresponding pharmaceutically acceptable salt by conventional means, and if so desired, converting the hydroxy acid to a compound of Formula I_a by heating in an inert solvent.

52. It is occasionally said that there cannot be clear and unmistakable directions to do something which is described as optional. I do not agree: to describe the thing as optional is to describe the thing. It is rather like the disclosure of something as adjustable: it necessarily also discloses something that is not adjustable—see *Gillette v Anglo-American* (1913) 30 RPC 465. Claim 2 is also anticipated.

Obviousness

53. There is a dispute between the parties as to the right approach to obviousness in this case. Warner-Lambert take as their exemplar the decision of the Technical Board of Appeals 3.3.1 of the European Patent Office on the present patent. The Examining Division had rejected the application in the light of a document (US 4,681,893) whose disclosure is substantially identical to '633A upon which Ranbaxy and Arrow rely before me. This document discloses in Example 2 the *sodium* salt of the atorvastatin *racemate*. Warner-Lambert submitted new claims (the claims with which I am concerned) and submitted that the claim to the hemicalcium salt of the R-*trans* enantiomer was not obvious. This argument was successful, for reasons appearing clearly in the following extract from the decision of the Board:

> '4.1 Claim 1 of the present application is directed to the hemicalcium salt of a particular R-enantiomer of a 4-carboxamido substituted β,δ-dihydroxy-1H-pyrrole-1-heptanoic acid showing hypocholesterolemic activity. ['633A], which is the state of the art acknowledged in the application as filed on page 1, line 10, refers to similar compounds having the identical hypocholesterolemic activity (column 7, line 33), notably the sodium salt of the racemate of the claimed enantiomer.
>
> The Board considers, in agreement with the Appellant and the Examining Division, that this disclosure of ['633A] represents the closest state of the art and, hence, takes it as the starting point when assessing inventive step.
>
> 4.2 In view of this state of the art, the problem underlying the present application as submitted by the Appellant consists in providing a hypocholesterolemic compound having **improved** handling properties, in particular improved hygroscopicity and solubility.
>
> 4.3 As a solution to this problem the present application proposes the hemicalcium salt of the particular R-enantiomer as defined in claim 1.

> 4.4 To support his submission that the alleged improvement is achieved by the claimed invention, the Appellant referred to his experimental report filed on 20 June 2000. That test report comprises experimental data about the hygroscopicity and the solubility of the hemicalcium salt of the R-enantiomer according to the claimed invention, on the one hand, and of the sodium salt of the racemate of that enantiomer according to example 2 of ['633A], on the other....The Board is satisfied that the problem underlying the patent in suit as defined in point 4.2 above is successfully solved by the claimed subject-matter.
>
> 4.5 Finally, it remains to be decided whether or not the proposed solution to the problem underlying the patent in suit involves an inventive step.
>
> ['633A], i.e. the closest prior art document (see point 4.1 above) is directed *inter alia* to pharmaceutically acceptable salts of the racemates of 4-carboxamido substituted β,δ-dihydroxy-1H-pyrrole-1-heptanoic acids having hypocholesterolemic activity. However, that document does not address the problem underlying the present application of improving the handling properties, in particular hygroscopicity and solubility, of hypocholesterolemic compounds. Thus, ['633A] neither gives any hint on how to solve that problem nor any incentive to modify those salts of the racemates into the hemicalcium salt of the particular R-enantiomer as defined in claim 1 in order to improve the handling properties thereof. Thus,['633A] does not point to the claimed solution proposed for solving the problem underlying the present application."

54. Before me, the question was examined both on a problem-solution basis and on the approach set out in *Windsurfing* [1985] RPC 59. I shall set out the facts relating to the common general knowledge in the art, and then return to the rival analyses.

55. Much of the common general knowledge I have already considered. By 1989, resolution of racemates with pharmaceutical activity was well established. So far as this family of statins is concerned, the skilled addressee (the team to whom I have already referred) would have known that the activity would reside in the R,R enantiomer, and would also have known that the active form was not the lactone but the open chain acid and its salts.

56. It was also known that the salts would be likely to be more soluble, and so possibly more bioavailable, than the free acid. Dr Spargo accepted that the skilled person would investigate the salts as well as the free acid. The problem confronting the skilled addressee is to get the active ingredient into a pharmaceutical composition suitable for administration. A solid dosage form requires a solid active ingredient: the obvious choices are the salts.

57. To test salts for their properties, it is standard practice for the skilled person to carry out a 'salt screen'. In the case of an acid, this would include the standard sodium, potassium and calcium salts. These are the most commonly used salts. A review article by Berge & ors. from 1977 called 'Pharmaceutical Salts' in the Journal of Pharmaceutical Science showed that these three cations were the commonest by an order of magnitude, as Dr Spargo accepted, and they are all obviously 'pharmaceutically acceptable'. The screen would on Dr Cunningham's unchallenged evidence include a test for hygroscopicity, rate of dissolution and solubility. The hygroscopicity test is carried out in a controlled humidity chamber, or otherwise using the standard equipment of any formulation laboratory. The whole process is entirely routine.

58. Remembering that the foregoing is the knowledge that the skilled person will necessarily bring to bear on the disclosure of '633A, one can turn to compound 1 of Table 1, which is atorvastatin lactone racemate, and Example 2, which describes making atorvastatin racemate sodium. Atorvastatin lactone racemate is made according to Example 1. These are the two leading examples of the specification. Dr Cunningham's evidence was that compound 1 of Table 1 was of particular interest, a conclusion with which Dr Spargo agreed.

59. '633A also contains a general disclosure in respect of all the ring-opened compounds to the effect that they may be used as salts (page 7 line 54 to page 8 line 4):

> 'The ring-opened hydroxy acids of structural formula II[2] above are intermediates in the synthesis of the lactone compounds of formula I and may be used in their free acid form or in the form of a pharmaceutically acceptable metal or amine salt in the pharmaceutical method of the present invention. These acids react to form pharmaceutically acceptable metal and amine salts. The term "pharmaceutically acceptable metal salt" contemplates salts formed with the sodium, potassium, calcium, magnesium, aluminum, iron and zinc ions. The term "pharmaceutically acceptable amine salt" contemplates salts with ammonia and organic nitrogenous bases strong enough to form salts with carboxylic acids. Bases useful for the formation of pharmaceutically acceptable non-toxic base addition salts of the present invention form a class whose limits are readily understood by those skilled in the art.'

60. There is, in my view, a clear teaching that the lactone racemate may be hydrolysed to produce the acid racemate, and that the acid may be used to react to form metal salts, calcium being one of those expressly mentioned. Furthermore, it describes how to make the sodium salt by reacting the lactone directly with sodium hydroxide in a 1:2 mixture of tetrahydrofuran/water.

61. What, then, is the difference between this and the invention of the patent in suit? The first is that '633A discloses compound 1 as a racemate, and not as an enantiomer, and the second is (so far as the example is concerned) the salt is the calcium and not the

[2] This is an error for X. Formula II is an α-haloester and not an acid. This is plainly a reference to the acid produced by hydrolysis of the lactone, which is Formula X.

sodium salt, and (so far as the general teaching is concerned) calcium is chosen from a list of seven inorganic cations.

62. Is the difference obvious? In my judgment it most certainly is. The resolution of the racemate was common general knowledge at the date. It was becoming preferred in the industry generally, and this particular resolution did not, on the evidence, involve any work that was not common general knowledge. Seven salts are specifically described. How can it be inventive to use one?

63. The answer to this problem raises a difficulty which, in English law, has been more or less laid to rest. There is no doubt that where there is a disclosure of a class of compounds, it is possible to select from that class a subclass united by a common feature distinguishing it from the rest: these are so-called selection patents. A fortiori, it is possible to select a single compound having advantageous properties from a class— see *IG Farbenindustrie AG's Patents* (1930) 47 RPC 289. But underlying this principle is the necessity for the prior disclosure to be a disclosure of a class, rather than a disclosure of the individual members of that class as distinct entities. The difference is explained by Lord Wilberforce in *E I Du Pont de Nemours (Witsiepe's) Application* [1982] FSR 303. This was an opposition under section 14 of the Patents Act 1949, and the only issue was prior publication. Although a patent could be successfully opposed under the 1949 Act if the invention was '*clearly* obvious and lacking in inventive step' that question was not in issue in this case. Lord Wilberforce explains that a selection invention will not be prior published if (1) all the selected members of the class possess the advantage (2) the later specification discloses what that advantage is and (3) the prior publication of the wider class does not refer to that advantage. He says this:

> 'The present position was compendiously stated by Lord Diplock:
>
> > "The patents at any rate to the extent that they claim the products parahydroxy-penicillin and Amoxycillin respectively, are selection patents.
> >
> > "The inventive step in a selection patent lies in the discovery that one or more members of a previously known class of products possess some special advantage for a particular purpose, which could not be predicted before the discovery was made (*In re I. G. Farbenindustrie A.G.'s Patents* (1930) 47 R.P.C. 283 per Maugham J at pp. 322/3). The quid pro quo for the monopoly granted to the inventor is the public disclosure by him in his specification of the special advantages that the selected members of the class possess." (*Beecham Group Ltd. v Bristol Laboratories International S.A.* [1978] R.P.C. 521 AT 579.)"
>
> My own opinion contains observations to a similar effect—l.c. p. 568.
>
> That case was concerned not with any question as to validity, but with one arising under a contract, but it has been

> applied to a validity issue by the New Zealand Court of Appeal in a judgment dated 22nd December 1981. The general principle is now securely part of the law and needs no fresh discussion in the present case. I confine myself to such aspects as are necessary for our decision.
>
> In the first place, in order to leave open a field for selection by a subsequent inventor, it does not matter whether the original field is described by formula or by enumeration. A skilled chemist could, in most cases, quite easily transform the one into the other and the rights of the subsequent inventor cannot depend upon the notation used. In the present case, the I.C.I. specification uses both a formula, and, to some extent, an enumeration: it does not matter to which one directs attention.
>
> Secondly, the size of the initial group or class is not in itself decisive as to the question of prior publication of an invention related to a selected member or members. A selection patent might be claimed for one or several out of a class of 10 million (cf. *I.G. Farbenindustrie A.G.'s Patents* v.s. p. 321) or for one out of two (cf. the selection of one of two epimers of a synthetic penicillin combination). *The size of the class may be relevant to a question of obviousness, and that question in turn may depend, in part, upon whether the later invention relates to the same field as that occupied by the prior invention, or to a different field. If an ordinary uninventive man would not be likely to look for the advantages he desires to produce in the area occupied by the prior invention a decision to do so may well amount to the beginning of an inventive step..*.' [my emphasis].

64. In other words, the selected class may still be obvious, but the nature of the advantage will be one of the factors to be taken into account in assessing obviousness. *Witsiepe* was a case under the 1949 Act, but the same principles have been accepted by the Court of Appeal in a 1977 Act case, *Hallen v Brabantia* [1991] RPC 195, and it is too late to query that. In any event, it seems to me that the principle is a sound one. Unless the later patent states what the advantage possessed by the selected class is, it is merely an arbitrary selection among things already disclosed, and will lack novelty.

65. I think that the belief that the law of selection is concerned with obviousness to be a misconception. Obviousness only becomes relevant if the later patent is not anticipated, and the obviousness of the selected class will be decided according to the normal principles. It will no doubt help the patentee to repel an allegation of obviousness if he can point to a statement of the advantage possessed by the selected class, but I do not believe it to be essential, as I believe Lord Wilberforce makes clear.

66. The EPO view is stricter. As expressed in T198/84 *Hoechst/Thiochloroformates* [1985] OJEPO 209, it seems to be to the effect that a newly discovered effect can never add novelty to a narrower class if the class is otherwise old. The claim was to a method of making thiochloroformates using a particular catalyst in the range 0.02 to 0.2 mol%. The prior art was a disclosure of the process with the same catalyst present

in the range 0-100 mol%. The Board held that there was no anticipation: in [7] they say this:

> '...
>
> To prevent misunderstanding, it should be expressly emphasised that when examining so-called selection inventions as to novelty the Board adheres to the principle that the sub-range singled out of a larger range is new not by virtue of a newly discovered effect occurring within it, but must be new *per se* (cf. T12/81 *BAYER/Diatereoisomers* OJ EPO 8/1982 296 303). An effect of this kind is not therefore a prerequisite for novelty; in view of the technical disparity [sc. between the new class and the old] however, it permits the inference that what is involved is not an arbitrarily chosen specimen from the prior art, that is, not a mere embodiment of the prior description, but another invention (purposive selection)'

67. I read this as saying that so far as the EPO is concerned, there must be no disclosure of the selected class, either as to its individual members or as to the class as a whole if the invention is to be new. To give an example, if the disclosure of the seven inorganic cations was to be construed in context as a disclosure of the class but not of the individual members, the calcium salt would be new. If it were a disclosure of the individual salts made having those cations, the invention would be old. The advantage possessed by the selected class or individual over the prior art class merely confirms the conclusion to be drawn from considering the prior art disclosure as a whole.

68. As a matter of English law, '281 could not be a valid selection patent because no advantage other than that claimed by the disclosed materials is claimed for the invention of claim 1. But since for obvious reasons anticipation is not in issue, questions affecting selection do not need to detain us. The real difficulty is caused by certain aspects of the problem-solution approach. I start with the description of this approach from the Guidelines:

> 9.8 Problem-and-solution approach
>
> In practice, in order to assess inventive step in an objective and predictable manner, the examiner should normally apply the so-called "**problem-and-solution approach**".
>
> In the problem-and-solution approach, there are three main stages:
> (i) determining the "closest prior art",
> (ii) establishing the "objective technical problem" to be solved, and
> (iii) considering whether or not the claimed invention, starting from the closest prior art and the objective technical problem, would have been obvious to the skilled person.
>
> 9.8.1 Determination of the closest prior art
>
> The closest prior art is that combination of features, disclosed in one single reference, which constitutes the most promising starting point for an obvious development leading to the invention. In selecting the closest prior art, the first consideration is that it should be directed to a similar purpose or effect as the invention or at least belong to the same or a closely related technical field as the claimed invention. In practice, the closest prior art is generally that which corresponds to a similar use and requires the minimum of structural and functional modifications to arrive at the claimed invention (T 606/89, not published in OJ).

> The closest prior art must be assessed from the skilled person's point of view on the day before the filing or priority date valid for the claimed invention.
>
> In identifying the closest prior art, account should be taken of what the applicant himself acknowledges in his description and claims to be known. Any such acknowledgement of known art should be regarded by the examiner as being correct, unless the applicant states he has made a mistake (see VI, 8.5).
>
> 9.8.2 Formulation of the objective technical problem
>
> In the second stage, one establishes in an objective way the **technical problem** to be solved. To do this one studies the application (or the patent), the closest prior art and the difference (also called "the **distinguishing feature(s)**" of the invention) in terms of features (either structural or functional) between the invention and the closest prior art and then formulates the technical problem.
>
> Features which cannot be seen to make any contribution, either independently or in combination with other features, to the solution of a technical problem are not relevant for assessing inventive step (see T 37/82, OJ 2/1984, 71 and T 294/89, not published in OJ). Such a situation can occur for instance if a feature only contributes to the solution of a non-technical problem, for instance a problem in a field excluded from patentability (see T 931/95, OJ 10/2001, 441).
>
> In the context of the problem-and-solution approach, the technical problem means the aim and task of modifying or adapting the closest prior art to provide the technical effects that the invention provides over the closest prior art. The technical problem thus defined is often referred to as the "**objective technical problem**".
> The objective technical problem derived in this way may not be what the applicant presented as "the problem" in his application. The latter may require reformulation, since the objective technical problem is based on objectively established facts, in particular appearing in the prior art revealed in the course of the proceedings, which may be different from the prior art of which the applicant was actually aware at the time the application was filed. In particular, the prior art cited in the search report may put the invention in an entirely different perspective from that apparent from reading the application only.
>
> The extent to which such reformulation of the technical problem is possible has to be assessed on the merits of each particular case. As a matter of principle any effect provided by the invention may be used as a basis for the reformulation of the technical problem, as long as said effect is derivable from the application as filed (see T 386/89, not published in OJ). It is also possible to rely on new effects submitted subsequently during the proceedings by the applicant, provided that the skilled person would recognise these effects as implied by or related to the technical problem initially suggested (see IV, 9.11 and T 184/82, OJ 6/1984, 261).
>
> It is noted that the objective technical problem must be so formulated as not to contain pointers to the solution, since including part of a solution offered by an invention in the statement of the problem must, when the state of the art is assessed in terms of that problem, necessarily result in an ex post facto view being taken of inventive activity (T 229/85, OJ 6/1987, 237).
> The expression "technical problem" should be interpreted broadly; it does not necessarily imply that the solution is a technical improvement over the prior art. Thus the problem could be simply to seek an alternative to a known device or process providing the same or similar effects or which is more cost-effective.

69. There are two possible difficulties with this approach (there may be as many, or more, with *Windsurfing*, I do not know). The first is its concentration on the closest prior art, which must stem from a belief that if an invention is not obvious in the light of the

closest prior art it cannot be obvious in the light of anything further away. This runs the risk of offending against the principle that a skilled man must be permitted to do that which is obvious in the light of each individual item of prior art seen in the light of the common general knowledge. There is an illustration of this risk in the present case. The second is that the reformulation of the problem can obscure that which is objectively obvious. But as stated, I cannot see this approach producing a different result from that produced by a *Windsurfing* analysis in the vast majority of cases. Where results differ, I suspect that it is because of the importance that a judge following the *Windsurfing* approach will give to the common general knowledge.

70. I am not particularly concerned about the EPO result in the present case. This was an appeal in the course of prosecution, with all the risks that hearing only the patentee entails. I am, however, rather more concerned about the methodology. First, I do not see why Example 2 of '633A was taken to be the closest prior art. Why was a disclosure of the racemic hydroxy acid, together with the list of possible cations, not considered? Why does the patentee appear to have been allowed to pass over the greater part of the teaching of the document in relation to possible cations? Again, I suspect the answer to this question lies in the exigencies of in-prosecution appeals, and in the precise terms of the objection taken by the Examining Division.

71. Second, I do not understand the reformulation of the problem. There was, objectively, no problem with the sodium racemate until internal documents showing what may have been a tendency towards gel formation in the sodium salt were disclosed to the EPO. But this tendency was discovered at the same time as the calcium salt was tested. One of the documents in the case was the so-called 'Racemate Report'. This document recorded what was on Dr Spargo's evidence a preliminary salt selection study of the atorvastatin racemate, carried out before the priority date. It appears that the calcium and n-methylglutamine salts showed promise. Data contained in this report and in one other underlay a letter to the EPO from Warner-Lambert's representative stating that the sodium salt showed poor hygroscopicity and a tendency to become sticky which was not shared with the calcium salt. This led to the recharacterisation of the 'problem' recorded in the part of the decision I have quoted. But there was no objective problem: the calcium salt was being tested alongside the sodium salt. We find ourselves in the strange position that if the sodium salt had been satisfactory, there would have been no invention in going for the calcium instead, but since it was not, there was an invention. It seems to me that if redefinition of the problem is permitted on the basis of any advantage which was known to the patentee before the priority date but not referred to in the specification or which is discovered after the priority date then there is a substantial risk that the reformulation will result in a finding of non-obviousness: how can one solve an (objective) problem that one did not know existed?

72. It is for this reason that in this jurisdiction after-discovered advantages are highly unlikely to be capable of supporting inventiveness, for the reasons given by Jacob J in *Richardson-Vicks* [1995] RPC 568 and T867/95 *RICHARDSON-VICKS/Cough/cold mixtures* (TBA 3.3.4). The later decision emphasises in [14] that reformulation of the problem can be allowed "provided the skilled man could recognise the same as implied in or related to the problem initially suggested".

73. I do not detect in this case any real difference in the substantive law between the jurisdictions. It is true that the problem-solving techniques may be different, but I do

not see either in this case or in others differences that cannot be attributed to differences of appreciation, rather than principle. I return to the present case.

74. Having now been presented in '633 with a new lactone (formula I) and a new open-chain acid (formula X) what does the skilled person do? The answer is that he carries out preformulation testing for such things as absorption in vivo (which is why the lactone was rejected) and he will include a salt screen for his acid, to see which of the salts shows a potentially desirable combination of features. In my view, once the evidence establishes that this work will be done and involves no inventive endeavour, the various salts that are screened will be obvious. He is screening for pharmaceutical formulation. Claims 1 and 2 are obvious.

75. In the result, I refuse the declaration of non-infringement sought by Ranbaxy in respect of '633, and I find '281 invalid for anticipation and obviousness. I will hear counsel on the order if it cannot be agreed.