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Case No: HC06C03050

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

11th July 2007

Before :

THE HONOURABLE MR JUSTICE PUMFREY

- -

Between :

(1) LES LABORATOIRES SERVIER	
(2) SERVIER LABORATORIES LIMITED	**Claimants**
- and -	
(1) APOTEX INC	
(2) APOTEX PHARMACHEM INC	
(3) APOTEX EUROPE LIMITED	
(4) APOTEX UK LIMITED	**Defendants**

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Iain Purvis QC and **Andrew Lykiardopoulos** (instructed by **Bristows**) for the **Claimants**
Antony Watson QC and **Colin Birss** (instructed by **Taylor Wessing**) for the **Defendants**

Hearing dates: 13th March – 20th March 2007

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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.

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THE HONOURABLE MR JUSTICE PUMFREY

Mr Justice Pumfrey :

1. This is an action for infringement of EP (UK) 1 296 947. The claimants are, respectively, the proprietor and an exclusive licensee under the patent in suit. It is not necessary to distinguish between them and I shall refer to them together as "Servier". The defendants are members of a Canadian group of companies widely concerned in the manufacture of generic pharmaceuticals, and I shall refer to them collectively as "Apotex". Apotex challenges the validity of the patent in suit. Servier seeks to amend the specification and claims in a manner I shall describe in more detail below.

2. The language of the specification of the patent is French, and the filed translation was, by agreement, taken to be definitive. The invention is entitled a "New α crystalline form of perindopril tert-butylamine salt, a process for its preparation and pharmaceutical compositions containing it". Perindopril is an ACE inhibitor used in the treatment of hypertension. The patent in suit claims priority (which is not disputed) from a French application made on 6th July 2000. The original patent for the compound itself was filed with the EPO on 29th September 1981, claiming priority from 2nd October 1980. The first marketing authorisation was granted in France in June 1988 and the supplementary protection certificate for the UK was applied for on 30th June 1993 and expired on 21st June 2003.

3. The other relevant protection for this compound is EP 0 308 341 in respect of "the industrial synthesis of perindopril" which was filed with the EPO on 16th September 1988, claiming priority from a French application of 17th September 1987. This patent will (if still in force) expire on 16th September 2008.

4. The patent is a valuable one: Servier's turnover in the United Kingdom is about £70m, and Apotex sold perindopril having a value of £4m in the short period before Mann J granted an interlocutory injunction restraining further importation, which remains in force. A number of generic companies have interested themselves in perindopril, and two others, known in these proceedings as Krka and Lupin, have both settled with Servier.

The Patent

5. The patent is a very brief document. It opens with a statement that the present invention relates to a new α crystalline form of perindopril tert-butylamine salt, setting out the structural chemical formula upon which nothing turns. A brief passage (page 1 line 5ff of the translation) describes the valuable pharmacological properties of perindopril, as to which there is no dispute. Then at line 15, the following passage appears:

> "In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light, humidity or oxygen level.

> The patent specification EP 0 308 341 describes an industrial synthesis process for perindopril. However, that document does not specify the conditions for obtaining perindopril in a form that exhibits those characteristics in a reproducible manner.
>
> The Applicant has now found that a particular salt of perindopril, the tert-butylamine salt, can be obtained in a well defined, perfectly reproducible crystalline form that especially exhibits valuable characteristics of filtration, drying and ease of formulation."

6. Curiously, on the same day as the application in suit was filed, Servier filed two other patent applications: number EP 1 294 689 in respect of the β crystalline form of the tert-butylamine salt of perindopril, and number EP 1 296 948 in respect of the γ crystalline form of the tert-butylamine salt of perindopril. It is not, as I understand it, suggested that there are any other crystalline forms of this salt, and the same passage as that quoted above appears also in the other two patents.

7. More surprising still is that patent EP 0 308 341 is said to be in respect of a process for the industrial synthesis of the tert-butylamine salt of perindopril which is, as I understand it, the only salt of perindopril hitherto used. The principal point of interest about the synthesis described in 341 is that the crystalline form of perindopril is obtained in stage 3D of the process (the final step) as follows:

> "Place in a reactor approximately 140 litres of ethyl acetate and 10 kg of [material obtained previously]. Add gradually approximately 2.20 kg- of tert-butylamine, heat to reflux until all has dissolved; filter. Cool, filter off and dry. Yield: 95%."

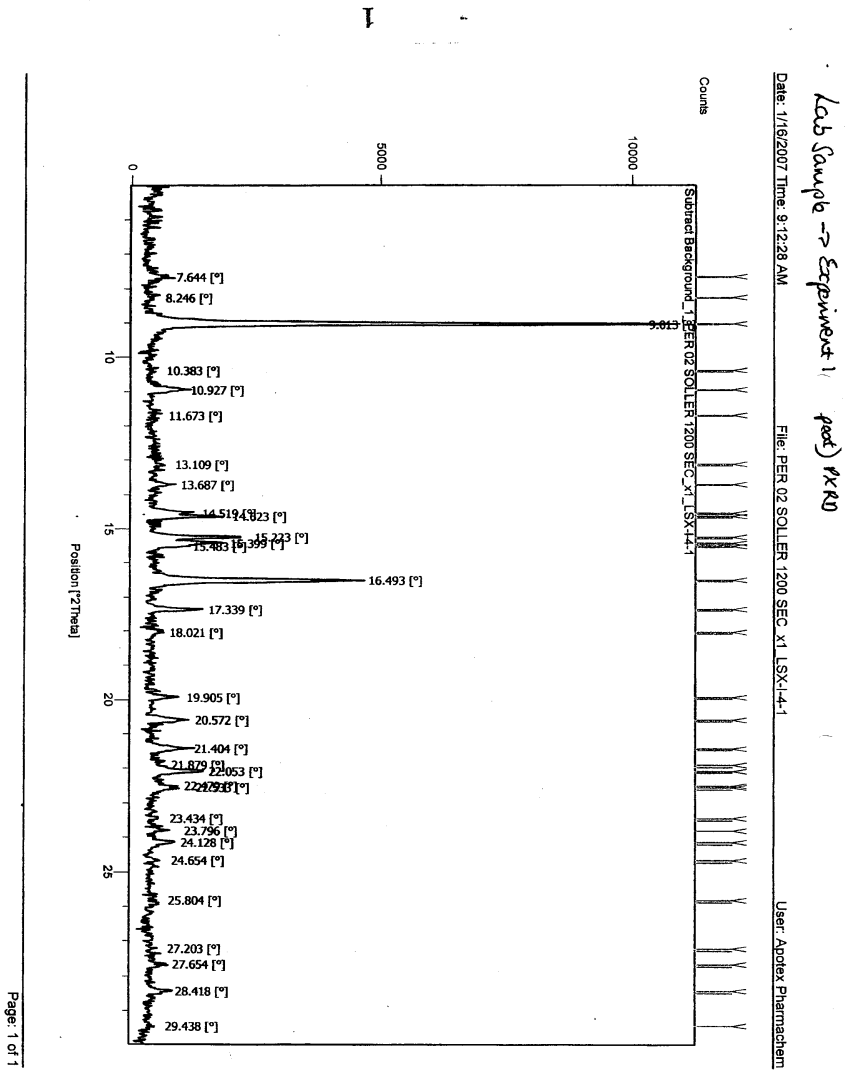
8. It is this passage to which the specification in suit is referring when it says that 341 does not specify the conditions for obtaining perindopril in a form that exhibits the characteristics set out in paragraph 5 in a reproducible manner, and, indeed, detailed conditions for the crystallisation of the salt are not stated.

9. The directions contained in the specification for obtaining the α crystalline form are described generally (page 3 lines 1-4) as heating the tert-butylamine salt in ethyl acetate at reflux and then "cool[ing] gradually until crystallisation is complete". A number of bullet points on page 3 of the translation give additional instruction as to concentrations and rates of cooling. Thus, at lines 9-10, it is suggested that the concentration of the tert-butylamine salt in ethyl acetate is preferably from 70-90 grams per litre – the concentration specified in 341 falls within this range (87 g/litre). Secondly, it is stated that it is advantageous to carry out the cooling in two stages, first from reflux to between 55°C and 65°C at a rate of from 5 to 10°C/hour, preferably from 6 to 8°C/hour, and then to ambient temperature. It is also suggested that it is advantageous to seed during the cooling step.

10. It is said that the resulting product is in the form of individual needles about 0.2mm long, permitting rapid and efficient filtration and drying.

11. The use of a terminology such as ‘α form’ is merely a matter of convenience. The only published characterising information relating to the α form of perindopril is this patent specification: at the priority date and at the publication date this was, on the evidence, just a new name for a crystalline form of perindopril. Such terminology is commonplace, but should not be taken in this context to refer to anything previously identified.

12. The manner in which the α crystalline form of perindopril tert-butylamine salt is characterised is by means of a powder X-ray diffraction profile. During the proceedings, this was referred to variously as the spectrum or pattern produced by XRPD or PXRD. In the body of the specification, the stated spectrum is described as having been obtained on a particular diffractometer, and full experimental details are given. Generally speaking, powder X-ray diffraction is a technique employed for the purpose of elucidating the different inter-planar distances between parallel planes in which the atoms of a crystalline material are located. There are many such planes even in a simple crystal, and the powder X-ray diffraction pattern provides a series of inter-planar distances which are determined by the actual structure of the crystal. The technique does not describe the actual crystal structure, for which a single crystal is required. The technique is extremely widely used, a database being maintained by international cooperation containing over half a million reference materials. The technique yields a spectrum which has two essential characteristics: a diffraction angle (conventionally expressed as 2θ) and the relative intensity of the peaks. If plotted out on a piece of paper, it shows peaks and troughs: here is an example:



13. Computer software is used to identify the position of the peaks and to compare the relative intensities of the diffracted beams. Such software identified the peaks in the example above and labelled each of them with their respective angle 2θ. This is not, as I understand it, a process reliably performed by computer alone. Dr Tarling, who gave evidence for Servier, said that when the computer program has done its work, the peaks that it selects must be reviewed by a technician to ensure that they accurately reflect the data. The technician will have in mind the conditions under which the analysis has been performed. Matters of particular concern are overlapping peaks, peaks entirely lost underneath others, and peaks that have been smoothed out by averaging routines within the computer program or which have been obscured by noise suppression techniques. So there is a degree of subjective assessment in any XRPD analysis.

14. The claim contains a tabulated version of the form α XRPD spectrum. No continuous spectrum is shown, and would, no doubt, give rise to difficulties of interpretation if included in the patent claim. Obviously, if two sets of data are to be compared, they must be normalised to the same X-ray wavelength, because the angles of diffraction will depend upon the wavelength of the incident X-rays. This is done in the claim by specifying a copper anti-cathode, and further wavelength information is given in the body of the specification to show which of the copper lines is employed.

15. So far as the claim is concerned, it could scarcely be supposed that any problem of interpretation is raised. But it is, or perhaps the problems are better viewed as a lack of specification. The first problem is caused by the column headed "Intensity" in the table which is said to characterise the α crystalline form of perindopril erbumine[1]. Dr Tarling does not, in his written reports, refer to the intensity figures. Under cross-examination (transcript 380) he expressed the view that "not a lot" could be done with the absolute intensities. Dr Tarling's evidence is therefore that the skilled reader would ignore the intensity column, but he was emphatic that the relative intensities of the final column, expressed as percentages of the highest peak, were important. In fact, both experts were agreed that relative intensities could be affected by a degree of orientation in the sample of crystals among other things, but it appears that Professor Cima was used to seeing variations of 20% and took the view that 30% was certainly possible. Indeed, I think Dr Tarling rather took the view (transcript 383) that preferred orientation in the sample might give rise to variations in relative intensity which would require elucidation by other techniques, such as a mathematical manipulation consisting of a Fourier transformation of the the crystal lattice, if the lattice geometry is known. Next, the angles 2θ are expressed to a very high degree of precision: 1/1,000 of a degree. These are plainly the result of a computer analysis by the EVA software (see page 5 line 2) and the apparent precision is spurious. In fact, Servier advanced the case that differences of about ±0.2° are ignored. The position of a peak, its 2θ value, is affected by the width of the peak if there are more than one unresolved peaks in fact present, or if the tail of an adjacent peak is of sufficient amplitude to affect it. I was not given any evidence tending to support a figure of ±0.2° for the precision of these measurements. Professor Cima did not deal with this subject in his witness statement and he was not cross-examined.

16. Dr Tarling had approached the comparison to be made between experimental results and the angles 2θ specified in the patent as follows. He had assumed that the patent specified absolute values rather than experimental results and had accordingly not attributed any error to them. So far as results to be compared with them were concerned, he had allowed a rule of thumb of ±0.2° precision. Since the angles 2θ set out in the claim are themselves stated in the specification to be experimental results, they must themselves have an intrinsic error in them, as I think Dr Tarling accepted. (See transcript 398 to 400.) It is preferable, as Dr Tarling acknowledged, that when comparing two experimental results subject to errors of ±0.2°, the root mean square error should be employed and, that means that a result within 0.2° of the stated value in the claim should be taken as being the same within experimental error[2]. Accordingly, if the skilled person reads the table in the claim as being a table of

[1] Erbumine is the accepted abbreviation for the tert-butylamine salt.

[2] I believe the transcript is in error at page 400, where at line 7 it says "±0.2° between the two", since the figure in question should be twice 0.14, the figure appearing at line 5, and thus 0.28º or 0.3º with the appropriate precision.

experimental results subject to the customary error identified by Servier of ±0.2°, then an experimental result must be taken to be the same if it is within ±0.3° of the stated value; if the results stated in the claim are absolute, then a result will not be materially different if it is within ±0.2° of that stated value.

17. It seems to me to be probable that the most likely interpretation of these figures is indeed as a set of experimental results. So far as the example in the patent is concerned, only one experiment is referred to. There is no question of repetition of measurements over and above that required for a single determination. And those figures are transposed directly into the claim.

18. Finally, I should refer to other processing that may have taken place. It is conventional for processing software to provide a cut-off to eliminate noise. There seemed to be no agreement as to what an appropriate cut-off for the processing of these results would be, and Professor Cima was of the view that the ultimate comparison must always be performed on the raw data.

19. In the result, it seems to me that the essential problem with this claim lies in the area of precision. I have attempted to deal with the question without indicating its significance, since both parties have on occasion been tempted to attempt to resolve individual problems of construction by reference to problems arising with the results of some of the experiments. In this case, this is not legitimate, since a uniform approach to the claim is required in order to arrive at a fair result.

The Witnesses

20. It is convenient at this point to state my assessment of the witnesses, although I have already referred to some comparatively uncontroversial evidence given by Dr Tarling and Professor Cima. Professor William Motherwell FRS, Alexander Williamson Professor of Chemistry at UCL, gave evidence on behalf of Servier relating to the manufacture and crystalline form of perindopril erbumine. His counterpart on behalf of Apotex was Dr Peter Spargo, now Managing Director of a consultancy called Scientific Update LLP, but until 2003 the Group Director, Head of Chemical Research and Development Europe, and Head of Worldwide Pharmaceutical Sciences Veterinary Medicine Portfolio with Pfizer Global Research and Development. Both witnesses were cross-examined, and both were most helpful. On the specifics of X-ray powder crystallography, Servier called Dr Tarling and Apotex called Professor Cima. Dr Tarling is employed at UCL in the Staff Development and Training Unit, having been a lecturer in crystallography from 1989 to 1992 at Birkbeck College and from 1992 to 1995 a Royal Society Industrial Research Fellowship Fellow, working part-time on X-ray powder diffraction and also as a self-employed patent consultant. Since 2001, after a spell at the School of Crystallography at Birkbeck part-time, he became a staff development adviser at Birkbeck and subsequently at UCL. Professor Cima is the Sumitomo Electric Industries Professor (that is, a professor with tenure) at the Department of Materials Science and Engineering at the Massachusetts Institute of Technology, where he is the Director of Ceramics Processing Research Laboratory and an investigator at the Materials Processing Centre and the Centre for Biomedical Engineering. He has had an interest in novel crystal forms of pharmaceuticals and, in particular, in development of a high throughput system for discovering them. As will become apparent, Dr Tarling and Professor Cima differed widely in their view of the proper interpretation of the experimental data in this case. Both were called for cross-

examination, and Dr Tarling was cross-examined by Mr Birss on his conclusions. Mr Purvis QC submits that he was unshaken in his conclusions by the cross-examination. Professor Cima was called for cross-examination, but in the event Mr Purvis did not put any questions to him. Accordingly, I did not have the opportunity to see whether Professor Cima also would be unshaken in his conclusions. Furthermore, I have not had an opportunity to compare the cogency of Dr Tarling's rejections of various points put to him with anything that Professor Cima had to say.

21. Obviously, it does not follow from Dr Tarling's refusal to accept what Professor Cima says that I should accept what Dr Tarling had to say. Professor Cima has submitted a report, and that report stands as his unchallenged evidence. Furthermore, I myself was somewhat concerned by one aspect of Dr Tarling's evidence, which I pursued in a series of questions at the end of his time in the witness box. I did not find his appeal to experience altogether satisfactory. Since Professor Cima had expressed a contrary view, at least in its conclusions, I should like to have been in a position to compare their respective approaches. As it is, I have to accept Professor Cima's conclusions as the untested, bona-fide, results arrived at after a proper consideration of the materials.

Infringement

22. The Apotex material was described in a Process and Product Description. Three powder X-ray diffraction analyses of three separate batches of product were performed and are shown in the product description. To a degree, this is overtaken by the results of experiment 3 of Apotex's experiments, in which a PXRD analysis (together with an infrared spectrum) was performed. This experiment was not repeated, and Dr Tarling and Professor Cima both say that there is no difference, as a matter of substance, between the results of experiment 3 and the claimed pattern. It follows that the claim is infringed. Notwithstanding this agreement, it is important that there are differences between the various spectra of the allegedly infringing material and that called for by the claim. Dr Cima, supported by Dr Spargo, says that all the spectra, both those relating to infringement and those relating to validity, would be recognised by the skilled man as the same. Dr Tarling draws a distinction between the differences in the infringement spectra and some of those relied on for invalidity. It is on this topic that the difficulty in the case turns.

Validity

23. The principal attack is anticipation by 341. It is said that a skilled person carrying 341 into effect would inevitably fall within the claim. The whole of the case on 341, apart from a short point on interpretation, was run in tandem with the case on infringement. In short, it is contended that the differences between the various PXRD patterns obtained in respect of the purported repeats of the 341 process are no more different from the claimed pattern than is the pattern obtained for Apotex's own perindopril erbumine, and no more different from the claimed pattern than is the result of recrystallising the product of 341 according to the teaching of the patent in suit as to cooling regimes. If the material resulting from the recrystallisation does not fall within the claims, then the patent is, obviously, alleged to be insufficient. Finally, it is contended that all of Servier's production since perindopril erbumine went on the market has been in form α, and that this too anticipates the patent in suit.

24. This patent, entitled "Method of industrial synthesis of perindopril and its principal intermediates", teaches a detailed scheme for a synthesis of perindopril starting from 2-carboxyindole. The disclosure of the specification is explicitly of an industrial synthesis. The threshold question is whether it is legitimate to perform a laboratory-scale repetition of this method and to take the crystal structure of the result as representative of the result in the case of an industrial process. In order to meet this problem to some extent, Apotex performed the synthesis at the laboratory scale and at the pilot plant scale. The laboratory-scale synthesis is Experiment 1, and the pilot-plant-scale synthesis is Experiment 2. The protocols for the respective syntheses were written by Dr Spargo without sight of the patent in suit. Dr Spargo was subjected to a lengthy cross-examination on the preparation of the protocols, but this came to nothing. Both Dr Spargo and Professor Motherwell (under cross-examination) were quite clear that any skilled person seeking to put the industrial process of 341 into practice would first conduct a run at laboratory scale. Professor Motherwell was quite clear that an initial run at pilot scale would not be the first step (transcript 211)

> Q. You are talking about experiment 4?
> A. I am talking about experiment 2, experiment 4, that narrow window of concentration. I totally accept that the normal process is in the lab and then on to the pilot and then on to the process.
> Q. I am sure we need not go to it but if you read 341 it makes it plain that it is a new synthesis route. It is not a tweak. It is a new synthesis route and, "Bring me the head of somebody in a pharmaceutical laboratory who said 'Let us try this new route straightaway on a pilot scale"?
> A. No, of course not, one would never do that.
> …
> MR. WATSON: Professor, it is our case that a reasonable pharmaceutical chemist, being given 341, would try it out at laboratory scale first, that is, carry out experiment 1 which you saw?
> A. I think that is a reasonable premise.
> Q. You have no criticism of experiment 1 as a fair and reasonable attempt to carry out on laboratory scale what is taught in 341?
> A. No, I think it was correctly performed.

25. I find, accordingly, that confronted with the instructions contained in 341 for an industrial process, the skilled person would inevitably first carry out the process described upon a laboratory scale, and that there was no criticism to be made of the protocol adopted by Dr Spargo in ignorance of the patent in suit with a view to emulating what the skilled person would in fact do in those circumstances.

26. Turning now to the pilot-scale experiment, Experiment 2, no criticism can be made of the protocol or its performance. Servier contend that Experiment 1 should be followed in any case in which anticipation is to be assessed by a performance of Experiment 2, to which Experiment 1 must always be taken to be a preliminary. Whether this is the case or not, if the skilled person will inevitably perform Experiment 1 – albeit by way of a work-up for pilot-scale production – then if the product of Experiment 1 inevitably falls within the claim, that claim is anticipated. The reason is that the teaching of 341 could not be carried into effect without infringement.

27. That takes me to Experiment 4, which is a repetition of the example of the patent in suit, 947. No criticism is made of the protocol of this experiment, which is accepted by Servier to be a reasonable implementation of the directions in that document.

The Results of Experiment 1

28. Experiment 1 in Apotex's notice was repeated. Servier accept that the product of the notice experiment and its repeat had the same crystalline form as that claimed in the patent. It is instructive to observe that this concession is made notwithstanding the differences between the various spectra identified in paragraphs 52, 53 and 54 of Dr Tarling's first report and also the barely consistent statement in paragraph 56 of that document that "the data for Experiment 1 and the repeat of Experiment 1 are not an exact match to the data set out in claim 1 of the patent within the experimental margin of error".

29. Given this acceptance, obviously the patent is anticipated, unless it can be convincingly demonstrated that the result on a laboratory scale of performing a reasonable laboratory-scale implementation of 341 will not inevitably result in a material having the PXRD spectrum set out in the claim. So far as this is concerned, Professor Motherwell accepted that it seems that form α is the stable form of perindopril and, absent special circumstances, it follows that any process for producing perindopril from ethyl acetate will produce this form in the absence of impurities. The β form, identified in the patent to which I have referred, is not stable and is created by special crystallisation techniques. Professor Motherwell said that eventually it reverts to the α form. The γ form is not produced by recrystallisation from ethyl acetate and is accordingly irrelevant. Dr Tarling referred in passing to an ε form, but this is undocumented and uncharacterised, and I disregard it. If, therefore, a convincing case is to be made that the production of α form from 341 is anything other than inevitable, either a plausible candidate for an alternative polymorphic form or an experiment demonstrating a repetition of 341 plainly not resulting in form α is required. In my view, the clear evidence of the production of form α in the notice experiment and in its repeat, taken with the lack of any plausible candidate for an alternative polymorph, places the evidential burden fairly and squarely on Servier to produce evidence which will demonstrate, on the balance of probabilities, that form α is not the inevitable consequence of what is accepted to be a reasonable experiment. This it has failed to do, and I conclude that on the evidence the production of form α in Experiment 1 is inevitable.

30. I should add a footnote to the foregoing discussion. Given that form α is the stable form, it is difficult to see how, if 341 fails to give form α, perhaps because of the presence of impurities, the patent in suit can help. In fact, I do not believe that there was any material at all from which one could fairly draw the inference that any fair repetition of 341 would not produce the α form.

31. Servier's position is that carrying out the process of 341 is "likely to lead to variability in the crystalline structure" although the nature of the variation is not described. They further contend that although the repetition of the pilot-scale experiment, Experiment 2, resulted in a product within the claims, the notice Experiment (i.e. the spectrum obtained by Apotex and included in the Notice of Experiments) did not do so and that, to that extent, the result was unpredictable.

These objections do not relate to the results of Experiment 1 or its repetition, and I shall deal with them below.

The Results of Experiment 2

32. Servier accepts that the product of Experiment 2 obtained at the repetition was a product satisfying the requirements of claim 1 of the patent. It does not accept that the product of the experiment forming the subject of the Notice of Experiment 2 fell within the claim. Accordingly, Mr Purvis QC submits that while the pilot-plant version of 341 is capable of producing the α form, it will not inevitably do so. The evidence said to underlie this contention may be summarised as follows. Taking the evidence from the crystallographers first, Professor Cima observed that the PXRD patterns produced by the product of Experiments 2 and 4, as set out in the notice, are "the same as each other but there are some variations to the peaks claimed in the patent". In paragraph 21 of his statement, he said:

> "The symmetries of the crystals from experiments 2 and 4 of the notice are very similar in form to that claimed in the patent and demonstrated by experiments 1 and 3 of the notice and experiments 1, 2 and 4 of the repeat. As a crystallographer, I would not say that they were a different form but that they are a distorted form of that produced in experiments 1, 2, and 4 of the repeats."

He then says that the only published polymorphs of perindopril erbumine are the α, β and γ crystalline forms and that these are plainly neither β nor γ.

33. Dr Tarling concluded:

> "The data for experiment 2 do not match the data set in claim 1 of the patent within the experimental margin of error and the data for the repeat of experiment 2 are not an exact match for the data set out in claim 1 of the patent within the experimental margin of error."

The chemists were asked about this, Dr Spargo being asked if he could adjudicate between the two crystallographers. He said yes, he could. He had seen the results of the other characterising experiments, in particular infrared spectra, and had compared the crystals, and he said that so far as infrared spectroscopy was concerned the crystals were indistinguishable. His preference appears to be for repeated experiments to get some appreciation of how much variation there might be. He concluded:

> "On the face of it, and in the context of my experience in the industry, this is the same polymorphic form and you would not have even got to a crystallographer."

Professor Motherwell was worried by the apparently low yield of Experiment 2 during the repeat (65%) and by the potential yield stated in 341 being much higher (95%). He therefore had doubts about the manner in which the repetition had been conducted. Dr Spargo was inclined to dismiss this, on the footing that there was no

doubt that the process was producing useful material in useful quantities. I append here a superimposed plot of the results to be considered for the repeats. It can be seen how similar they are. The notice experiments are undoubtedly less clear and I set them out afterwards. The superimposed plots are not as nice a fit as those obtained in the witnessed repeats. In these various plots "Lab" refers to Experiment 1, the laboratory-scale repeat of 341; "Pilot" refers to Experiment 2, the pilot-plant repeat of 341; "API" to the spectrum obtained for Apotex's active ingredient in Experiment 3,

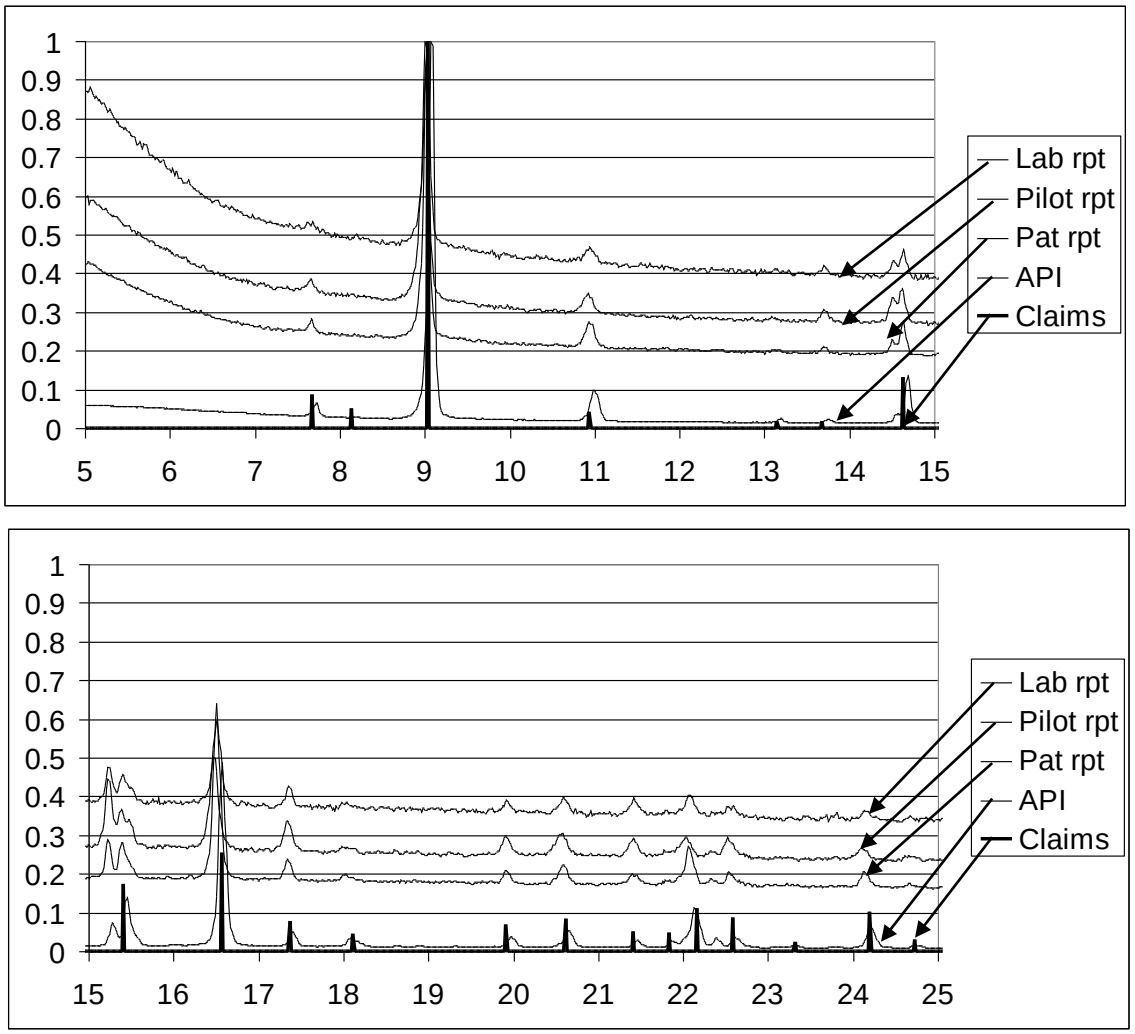


Figure 1 - Repeats

which was not repeated; and "Pat" to Experiment 4 which was an attempt to repeat the patent in suit.

34. Experiment 4 provides a useful touchstone for the dispute that is going on in this case, because Dr Tarling again formed the view that the repetition of experiment 4 was within the claim, whereas the notice Experiment 4 was not. Of course, the criteria for sufficiency of description on the one hand and the enablement of an inevitable result on the other are not the same. For the purpose of anticipation, the prior documents must enable something which *inevitably* falls within the claim. Where the prior art does not describe the end to be achieved, it is illegitimate to employ a refinement of technique or whatever to cause the desired result to be achieved. Where the sufficiency of a disclosure of a method is under discussion, of course the skilled

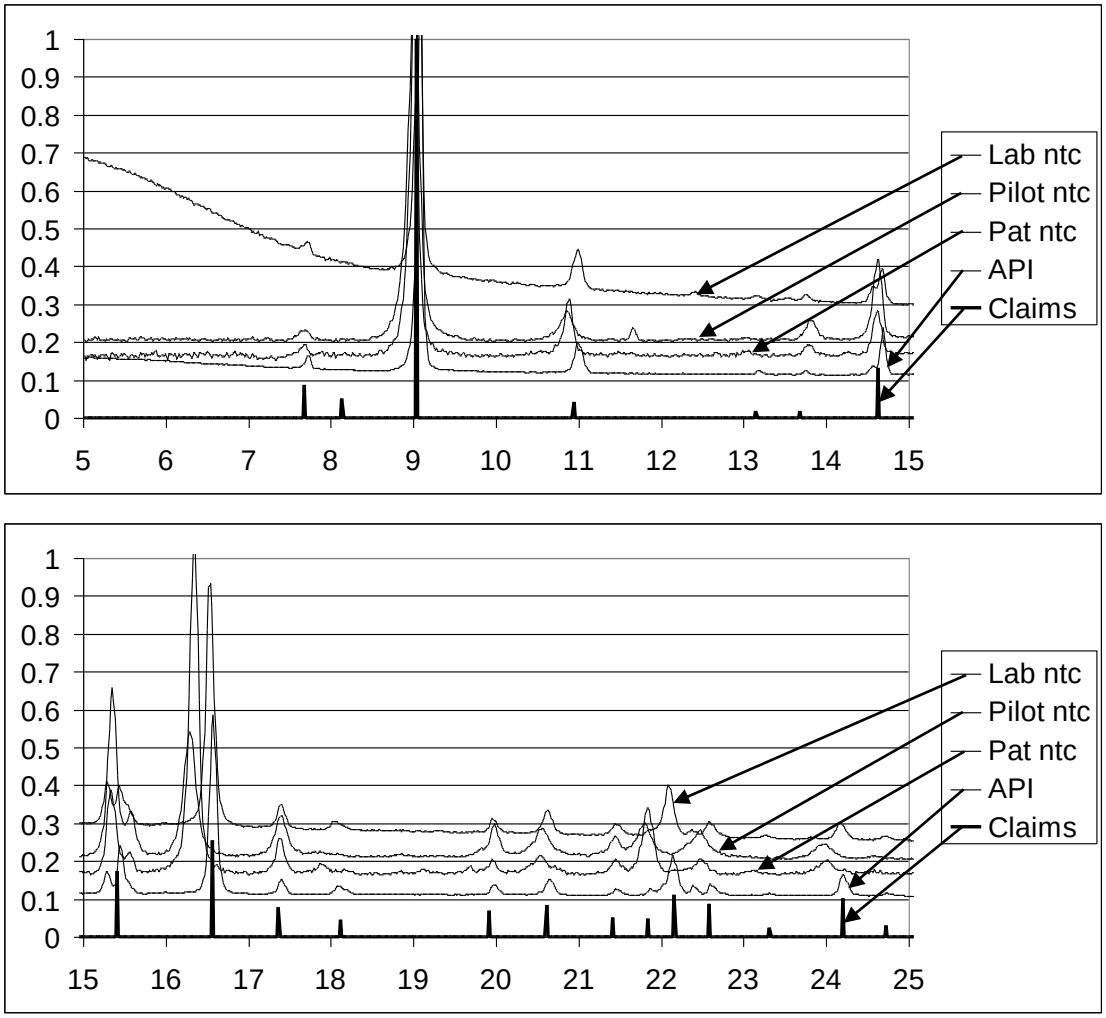


Figure 2: Notice experiments

person is entitled to do such preliminary work and carry out such uninventive refinements, without undue effort, with a view to producing a product falling within the claim. Rather oddly, in the present case, nobody criticised the method employed in the notice Experiment 4. Dr Spargo thought it fell within the claim. Professor Cima thought it was distorted, but did not correspond to any other known polymorph.

Conclusion on the Experimental Evidence

35. On the whole, I prefer the rather more robust approach adopted by Apotex's witnesses. The hole at the centre of Servier's case was a complete failure to demonstrate any plausible alternative reason for the results of any of the experiments which was said not to produce the α form in the shape of an identifiable alternative polymorph. While the detailed analysis of the results undoubtedly revealed differences, it was not convincingly demonstrated that the differences represented a different crystalline form. Indeed, no alternative crystalline forms could be pointed to. The analysis was not assisted by the fact that Professor Cima's evidence, adduced in support of Apotex's case, was unchallenged. He took the view that the results relied on by Dr Tarling as showing a different polymorph merely represented a distorted crystal. Since the onus lay upon Apotex so far as invalidity was concerned, I should, I think, be very cautious before not taking that unchallenged evidence at face value.

36. I have already referred to my worry about the categorical nature of Dr Tarling's evidence. Mr Watson QC produced a substantial document setting out what he contended were inconsistencies, or surprising propositions, advanced by Dr Tarling, particularly in the light of the advice for expert witnesses contained on the latter's professional website and in the light of the reasoned objections advanced by Professor Cima. One of these needs to be referred to. Dr Tarling relied on the presence of unresolved doublets and triplets (diffraction lines close together) to explain apparent errors in the position of the spectra in the product description and the Experiment 3 lines. He simultaneously found doublets in the patent spectrum unresolved in the experimental data and unresolved doublets in the experimental data (the product description, in this case) unresolved in the patent. The simultaneous failure of the equipment described in the patent to resolve some doublets resolved by the experimental apparatus, itself incapable of resolving other doublets resolved by the equipment described in the patent is odd. These manipulations were necessary for the fit to satisfy his requirements (see his exhibit SET3). This is, I think, obviously the employment of hindsight.

37. The same observation may be made in respect of his need to attribute additional peaks in the spectra of the experimental results to unresolved doublets. He only knew where to find the doublets by assuming the patent data was correct, and that the experimental data had to match it. Professor Cima did not accept that Dr Tarling's treatment of allegedly unresolved doublets in the patent data was legitimate although Dr Tarling was obliged to use it if there were not to be obvious peaks in Apotex's data to which nothing in the patent corresponded. I suspect that Dr Tarling was not entirely comfortable with the spectrum set out in the patent: he told me he would like to "run the patent again". This, of course, is what Experiments 2 and 4 did.

38. How, then, is it possible to reconcile Dr Tarling's contention that the Notice Experiments 2 and 4 produced products which do not fall within the claim with the contrary, but unchallenged, conclusions of Professor Cima? Mr Purvis QC submits that the operation undertaken by Professor Cima is illegitimate, having regard to the correct interpretation to be put upon the claim. He says that at the date of the application, there was no knowledge of any alternative polymorphic form of perindopril erbumine and that accordingly the non-existence of other characterised polymorphs can have no influence upon a determination that a particular polymorph falls within the claim. In my judgment, this is quite wrong. Mr Purvis is of course correct that the terms of the claim have to be construed as of their date. However, a finding that a material does not fall within this claim is an implicit finding that it is another polymorph: there is no doubt that the material is crystalline. If after-acquired knowledge shows either that there are no other polymorphs or that such other polymorphs as have been identified are nothing like the material under consideration, that fact is logically probative of the contention that the polymorph under consideration is the claimed polymorph. It is a striking feature of this case that on a number of occasions Dr Tarling said that he had no firm hold on what polymorph α in fact was. I suspect that in truth the claim is inadequate properly to characterise a polymorph at all and that the technical errors in it reveal a degree of ignorance of the manner in which a patent claim should approach a problem of this description. Professor Motherwell was very conscious of the difficulties in defining crystal polymorphs in a satisfactory manner. This was informative and, taken with Dr

Tarling's two assertions of a lack a clear definition of polymorph α, tends to suggest that the real problem with this patent is a want of a clear claim.

39. In my judgment, claim 1 of the patent is anticipated by 341.

Obviousness

40. Professor Motherwell accepted that Servier's cooling regime, at last so far as that is described in the evidence, is an obvious implementation of 341. On the assumption that the pilot-plant process described in Notice Experiment 2 does not inevitably fall within the claim, it certainly renders such processes obvious to carry out, and these processes include the crystallisation process used by Servier to crystallise the material from ethyl acetate. Assuming, therefore, that the process which Servier have been running since 2000 is obvious in the light of 341, and if that produces form α, then the product of that process is an obvious product to produce and it is in form α. It was an obvious product to produce at the publication date of 341. This renders the patent invalid. The process claims 2 to 7 are merely a recital of typical process conditions, and on the assumption that it is possible to repeat 341 in the manner described and either produce a material which does or does not fall within the claim, then it cannot be suggested that any of the conditions in these claims are conducive to success. They accordingly lack any inventive step and must be invalid.

Amendment

41. Because of the view that I have taken of the unamended claims, I have left this question till last. The amendment to the patent specification sought by Servier is to amend claim 2 by introducing into it the features of present claim 5. In other words, the requirement that the solution be "cooled gradually until crystallisation is complete" is replaced by a requirement that it be cooled "to a temperature of from 55 to 65°C at a rate of from 5 to 10°C per hour, and then to ambient temperature until crystallisation is complete". This claim covers the process of Experiment 4, which is accepted to repeat example 1 of the patent. Experiment 4, of course, does not inevitably result in a material falling within the claim, if Dr Tarling's analysis is correct. The significance of the conditions is accordingly quite obscure and they must be taken to be arbitrary and lacking in any inventive step. In any event, the claim as proposed to be amended remains invalid, and the patent must be revoked in its entirety.

Concluding Remarks

42. There are certain matters which have arisen in the course of this trial to which I have not found it necessary to make explicit reference. In particular, I have not referred either to the allegedly variant interpretations of the patent advanced by Servier against different defendants in the proceedings to which I have alluded, and I have not found it necessary to refer to the case advanced for arguable infringement before Mann J. Nor have I considered what is a difficult question, whether the sale of Servier's own material, which was in the α form, invalidates the claim, because I consider it unnecessary to do so in the light of the other conclusions. The application to amend fails and the patent must be revoked. The claim for infringement would otherwise have succeeded.