



BL O/346/07

21 November 2007

PATENTS ACT 1977

BETWEEN

Sandoz AG

Applicant

and

Mewburn Ellis LLP

Defendant

PROCEEDINGS

Request under section 74B of the Patents Act 1977 for
Review of an opinion issued on patent number EP(UK) 1343750

HEARING OFFICER

Peter Back

DECISION

- 1 This is a review of an opinion (“the Opinion”) under Section 74B of the Patents Act 1977 (“the Act”). Mewburn Ellis LLP requested an opinion under section 74A of the Act on the validity of patent number EP (UK) 1343750 (“the patent”) in the name of Ciba Specialty Chemical Holdings Inc. An opinion was issued as Opinion Number 03/06. The opinion concluded that claims 1-6, 11, 12, 17 and 19 do not involve an inventive step.
- 2 Ownership of the patent has transferred to Sandoz AG by an assignment dated 24 April 2006. Sandoz AG (the Applicant) filed a request for review of the opinion under section 74B of the Act. The Defendant in these proceedings is Mewburn Ellis LLP who submitted the original request for the Opinion. Statement and counterstatement have been submitted and both parties have agreed that I should decide the matter on the papers.
- 3 The purpose of a review under section 74B has been explained in previous reviews^{1 2}. Nevertheless, it is worth making the point here that opinions are not binding for any purpose nor will any part of the present Opinion, which might remain after this review, be binding for any purpose. Further, I am not

1 Roger Coloston Downs’ patent, BL O/015/07, 18 January 2007

2 Ms Penelope Mary Townsend’s patent BL O/078/07, 16 March 2007

providing a second opinion; I am reviewing whether the examiner was in error in reaching his conclusion.

- 4 The Applicant has requested a review of the Opinion under section 74B. Rule 77H(5)(a), made under section 74B, governs the making of applications for reviews, and provides as follows:

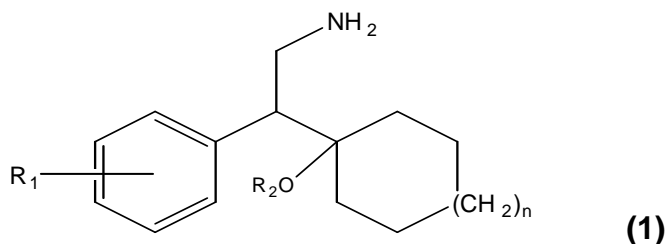
(5) The application may be made on the following grounds only—

(a) that the opinion wrongly concluded that the patent was invalid, or was invalid to a limited extent;

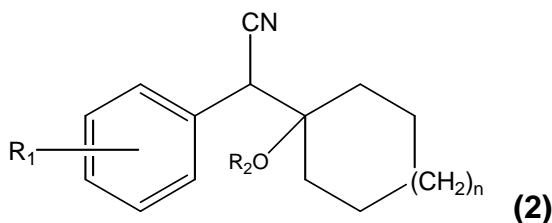
The Patent

- 5 The invention disclosed in EP 1343750 relates to a process for the preparation of phenethylamine derivatives by hydrogenation of phenylacetonitriles in the presence of a nickel or cobalt catalyst. It also relates to particular phenethylamine derivatives *per se*. The patent contains three independent claims, which read as follows:

Claim 1 *A process for the preparation of a compound of formula*

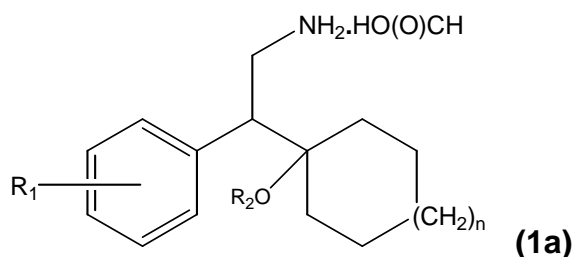


or salts thereof, wherein R_1 is hydrogen, hydroxyl, or unsubstituted or substituted alkyl or alkoxy, R_2 is hydrogen or a substituent which can be converted to hydrogen, and n is 0, 1 or 2 comprising hydrogenating a compound of formula



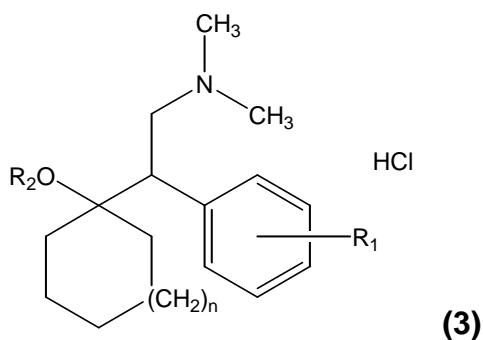
wherein R_1 , R_2 and n are as defined above, in the presence of a nickel or cobalt catalyst.

Claim 16 *A compound of formula*

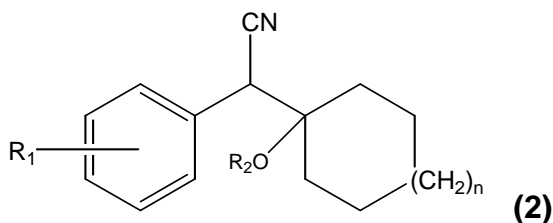


wherein R_1 , R_2 and n are as defined in claim 1.

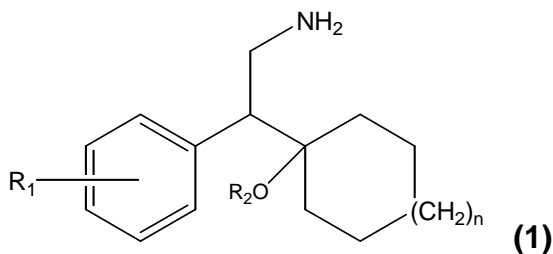
Claim 17 A process for the preparation of a compound of formula



wherein R_1 is hydrogen, hydroxyl, or unsubstituted or substituted alkyl or alkoxy, R_2 is hydrogen or a substituent which can be converted to hydrogen, and n is 0, 1 or 2 comprising hydrogenating a compound of formula



wherein R_1 , R_2 and n are as defined above, in the presence of a nickel or cobalt catalyst to give the compound of formula



wherein R_1 , R_2 and n are as defined above, and converting the compound of formula (1) to the compound of formula (3)

The Opinion

- 6 The Opinion seeks to establish whether the claims of the patent are obvious in view of a combination of disclosures contained in the following documents:

US 4535186 (HUSBANDS *et al*) (**D1**)

Yardley *et al*, *J Med Chem*, 1990, 33, 289-2905 (**D2**)

US 5266731 (AYERS *et al*) (**D3**)

Robinson *et al*, *Organic Syntheses*, Coll Vol 3, 720 (1955); Vol 23, 71 (1943) (**D4**)

US 3255248 (SUESSENGUTH *et al*) (**D5**)

March, *Advanced Organic Chemistry – Reactions, Mechanisms, and Structure*, Third Edition (1985) (**D6**)

Freidlin *et al*, *Russ Chem Rev*, 1964, 33, 319-330 (**D7**)

- 7 The Opinion examiner noted that the patent is derived from a PCT application published as WO 02/50017. **D1** and **D2** were listed under category 'A' (background art) on the corresponding International Search report and no other documents were identified. **D2** shares many of the authors of **D1** and discloses much of the same fundamental information, i.e. the use of rhodium to form a phenethylamine derivative through the catalytic hydrogenation of the corresponding nitrile. He established that at no stage were **D1** and **D2** elevated to novelty or inventive step citations prior to grant. Accordingly he concluded that as the possibility of obviousness was not formally raised during the pre-grant process, no objection arose under rule 77D(1)(b).
- 8 He further noted that there were proceedings before the United States Patent and Trademark Office in connection with a corresponding US application, 10/130196. The US examiner had raised an inventive step objection in a report (submitted as **D8** by the requester) against claims 1-15 and 17-19 on the basis of **D1**. In writing the opinion, he took into account the content of **D8** as well as the proprietor's written rebuttal to the US examiner's objection (submitted as **D9** by the requester), which contains similar arguments to those set out in the proprietor's observations. The version of US claims 1-19 accompanying **D9** are broadly equivalent to those in the EP patent.
- 9 The Opinion request referred only to an allegation of obviousness in respect of the claims as a whole rather than considering them on an individual basis. In general, a request for an opinion on validity or infringement should identify the specific claims that are alleged to be invalid or infringed. Nevertheless, the requester's comments were confined to the possibility that it would be obvious to use nickel or cobalt catalysts in the methods of **D1** and **D2**. The Opinion examiner assumed that the requester was therefore concerned only with those claims where these catalysts are used in a hydrogenation reaction. As

claim 16 relates to compounds having a particular general formula *per se*, he deduced that the requester did not take issue with that claim and hence, he did not consider it in his opinion.

- 10 The Opinion examiner noted that independent claim 17 discloses the features of claim 1 but also includes the further step of converting the primary amine derivative to a tertiary amine, which is obtained in the form of a hydrogen chloride salt. Accordingly, he concluded that if he found claim 1 to be inventive, it would follow that claim 17 must also be inventive.
- 11 There was no dispute that the disclosures **D1** to **D2** and **D10** were all published before the priority date of the patent and therefore form part of the state of the art by virtue of Section 2(2).

The Review

- 12 The Opinion examiner considered the issue of inventive step by following the well established steps set out in *Windsurfing International Inc v. Tabur Marine (Great Britain) Ltd*, [1985] RPC 59 (“*Windsurfing*”) and I will do the same although in doing so I will take account of the recent reformulation of those steps laid down by the Court of Appeal in *Pozzoli Spa v BDMO SA & Anor* [2007] EWCA Civ 588 (“*Pozzoli*”). In that judgment, Jacob LJ restated the *Windsurfing* questions thus:
 - (1) (a) Identify the notional “person skilled in the art”
 - (b) Identify the relevant common general knowledge of that person;
 - (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
 - (3) Identify what, if any, differences exist between the matter cited as forming part of the “state of the art” and the inventive concept of the claim or the claim as construed;
 - (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

The Person Skilled in the Art

- 13 The Opinion identifies the person skilled in the art as a competent but unimaginative chemist skilled in the field of organic synthesis. Neither party has disagreed with this assessment and I see no reason to question it further.

The Common General Knowledge

- 14 As stated in the Opinion, the patent acknowledges that it was known at the priority date to form intermediates of formula **(1)** by hydrogenation in the presence of a rhodium catalyst and reference is made in the patent to **D1**. The relevant disclosures of **D1** (e.g. Example 2) and **D2** (e.g. Method A for Compound 5) make clear that the product is obtained by hydrogenating the corresponding nitrile derivative, which coincides with formula **(2)** in the patent.
- 15 The Opinion examiner considered whether the skilled addressee working in the field of organic synthesis would be aware of nickel or cobalt compounds as hydrogenation catalysts. He noted that the patent admits as much in paragraph [0013] and there is additional support by way of **D3** to **D7**. He also noted that the use of these catalysts in the hydrogenation of nitriles to amines is clearly reported in each piece of this prior art. For instance, column 1, lines 19-52 of **D3** states that “Raney nickel is one of the most widely used catalysts for secular hydrogenations to produce amines from nitriles” and that it “has become a hydrogenation catalyst of choice”. He noted that the patent states that rhodium catalysts have economic drawbacks and implies that they are expensive. In order to reduce these costs, the patent states that the rhodium must be recycled, which introduces a further process step and potentially compromises the effectiveness of the catalyst.
- 16 He concluded that the skilled person would understand that nickel and cobalt catalysts are suitable for hydrogenating nitrile compounds to amines and would be aware of the disadvantages of using rhodium in the process of **D1** and **D2**. The parties to this review do not appear to take issue with this assessment and I am satisfied that it is correct.
- 17 A further issue which I think should be considered in the context of the common general knowledge at the priority date is the Applicant’s argument that “**D3** teaches that hydrogenation using metal catalysts such as Raney nickel tend to form undesirable by-products” and I will consider this further under the fourth *Windsurfing* question.

The Inventive Concept

- 18 The Opinion does not specifically state what the examiner considered to be the inventive concept in the patent. The claims and paragraph [0001] suggest that the inventive concept as far as the Opinion and this review is concerned is the preparation of phenethylamine derivatives by hydrogenation of phenylacetonitriles in the presence of a nickel or cobalt catalyst. It is noted that the patent also includes claims to certain phenethylamine derivatives *per se* but as noted in the Opinion, the requester’s comments were confined to the possibility that it would be obvious to use nickel or cobalt catalysts in the methods of **D1** and **D2**. The examiner assumed that the requester was therefore concerned only with those claims where these catalysts are used in a hydrogenation reaction and I think he was right to do so.
- 19 However there is an additional issue which I am not sure the Opinion examiner considered fully. At paragraph [0002] the patent states that the “compounds of

formula (1) are known for being particularly useful as synthesis intermediates for preparation of pharmaceutical active substances.” The Applicant has argued that “where the cited prior art uses nickel or cobalt, educts to be converted are much more simple ones, and the products are usually made for technical rather than pharmaceutical applications” and that “the person skilled in the art knows that the presence of by-products, especially those difficult to separate from the desired product, is a potential hazard in the synthesis of a pharmaceutical.” The implication of this argument seems to me to be that the Applicant was inviting the Opinion examiner to construe claim 1 of the patent as being limited to producing pharmaceutically pure compounds.

- 20 The support for this argument appears to be no more than a brief statement in the patent that “compounds of formula (1) are known for being particularly useful as synthesis intermediates for preparation of pharmaceutical active substances”. I consider this argument to be tenuous but for reasons which I will come to, I am not sure that it makes much difference to the outcome of this review.

The difference between the cited matter and the inventive concept

- 21 As I have already stated, it is acknowledged in the patent that it was known at the priority date to form intermediates of formula **(1)** by hydrogenation in the presence of a rhodium catalyst and reference is made in the patent to **D1** which describes such a process.
- 22 Whilst it is not stated explicitly in the Opinion, it is clear to me that the examiner took the view that the difference between the cited matter and the patent is that the patent employs a nickel or cobalt catalyst in place of the rhodium catalyst of the prior art. In my view that is correct and the parties would appear to agree since the main thrust of their arguments goes to that point.

Would that difference have been obvious to the skilled man?

- 23 This brings me to what is clearly the crux of this review: was the Opinion examiner right to conclude that viewed without any knowledge of the invention as claimed it would have been obvious to the person skilled in the art to use a nickel or cobalt catalyst instead of the rhodium catalyst of the prior art.
- 24 The Applicant has put forward several arguments as to why the allegation of obviousness is not justified in the light of the documents identified by the Defendant and I shall deal with each of these in turn. In doing so I will look at the Applicant’s arguments in the light of the Opinion examiner’s conclusions and the Defendant’s response in its counterstatement.
- 25 I will start by summarizing the Defendant’s arguments that the claims of the patent do not involve an inventive step and the Applicant’s response.
- 26 The Defendant maintains that it was known at the priority date of the patent that compounds of the formula (1) in the patent could be prepared by hydrogenation in the presence of a rhodium catalyst. Documents **D1** and **D2**

- disclose such a reaction and the patent itself refers to document **D1**. It observes that the patent states that the rhodium catalysts used in **D1** are expensive and that the use of cheaper catalysts would be advantageous. It maintains that the patent acknowledges that cobalt and nickel are well known and that it identifies no other advantages of these catalysts.
- 27 It further maintains that documents **D3** to **D7** and **D10** clearly show that a skilled person wishing to select an alternative to rhodium as the catalyst used in the reaction described in **D1** and **D2** would be guided towards a catalyst containing nickel or cobalt, and in particular Raney Nickel.
- 28 The Applicant has argued that **D1** and **D2** are completely silent on the use of metal catalysts other than rhodium, that where the prior art uses nickel or cobalt the educts to be converted are much simpler ones, and the products are usually made for technical rather than pharmaceutical applications. It argues that the skilled person knows that the presence of by-products, especially those difficult to separate from the desired product, is a potential hazard in the synthesis of a pharmaceutical, and thus would not combine the teachings of **D3 – D7** with those of **D1 – D2**. It reinforces this argument by stating that **D3** teaches that using metal catalysts such as Raney nickel tends to form “undesirable by-products removable only with great difficulty and expertise”.
- 29 The Applicant goes on to describe what it calls an “important side reaction” to be avoided which it describes as “retro aldol reaction”, the implication being, I think, that the skilled man would be directed away from the use of nickel or cobalt catalysts by the expectation that such a side reaction would be likely to occur using those catalysts.
- 30 The Defendant has argued that the only advantage set out in the patent is that it replaces an expensive rhodium catalyst by cheaper ones and that the patent makes no reference to side reactions, nor is any indication given that the problem of avoiding such reactions is solved by the invention of the patent.
- 31 Having set out in summary the arguments put forward by both parties I will now review the Opinion examiner’s conclusions and consider whether or not he was wrong when he concluded that viewed without any knowledge of the invention as claimed it would have been obvious to the person skilled in the art to use a nickel or cobalt catalyst instead of the rhodium catalyst of the prior art.
- 32 He stated that in essence, the core argument put forward by the Applicant against the allegation of obviousness is that the use of a nickel or cobalt catalyst would be expected to promote an undesirable retro aldol side reaction during the conversion of the nitrile to the amine and in the production of a pharmaceutical, it is especially important that this should be avoided. The Applicants say that **D3** teaches that using metal catalysts such as Raney nickel tends to form “undesirable by-products removable only with great difficulty and expertise”. I think this argument would carry some weight if it was established that it was common general knowledge at the priority date of the patent, however as stated by the Defendant and noted by the Opinion examiner, what **D3** actually says is that such by-products “*have been known*”. This suggests to me, as it did to the Opinion examiner, that these side reactions are by no

means certain and I note that **D3** refers to side reactions in a specific context involving reactants and by products which are quite different to the compounds of **D1** and **D2**.

- 33 On this same issue the Defendant has argued that reference to the side reaction represents an unallowable attempt to reformulate the problem solved by the invention as it was not previously mentioned in the patent. To support this position, the Defendant drew attention to *Ranbaxy and Arrow Generic v Warner-Lambert* [2005] EWHC 2142. Paragraph 72 of the judgment states that “after-discovered advantages are highly unlikely to be capable of supporting inventiveness” and that “reformulation of the problem can only be allowed provided the skilled man could recognise the same as implied in or related to the problem initially suggested”.
- 34 The Applicant countered this by saying that the patent describes the achievement of “high yields which meets economical demands” as the object of the invention and that is indeed stated in paragraph [0004] of the patent. It argues that any solution that meets this objective needs to avoid unfavourable side reactions to achieve those high yields. I think this argument only stands up if I construe claim 1 narrowly as being restricted to the production of pharmaceutically pure compounds.
- 35 The Opinion examiner was not convinced by this line of argument and took the view that “*the only problems outlined in the patent in connection with the prior art were that rhodium was expensive and had shortcomings when recycled*”. [my emphasis]. He continued to say that “*Problems associated with low yields or side reactions were not mentioned. I do not place significant importance on the correlation alleged by the proprietor that nickel and cobalt catalysts result in high yields, which inevitably involve the avoidance of the side reaction. Yields can be dependent on various factors like process conditions and the nature of the starting material. At any rate, I am not convinced that a high yield automatically means that the side reaction, if it exists, has been averted entirely. Accordingly, I do not think that there is any indication that the side reaction represented a problem addressed by the patent.*”
- 36 Although the Applicant in its submissions makes much of the need to avoid the so called retro aldol reaction, there is no mention of this problem in the patent. The Opinion examiner formed the view that the disclosure of **D3** was not particularly suggestive that there would be difficulties in the use of nickel or cobalt in this respect. I would add that there appears to be nothing in the submissions before me or the Opinion examiner to suggest that a tendency of cobalt and nickel catalysts to produce undesirable by-products formed part of the common general knowledge at the time.
- 37 Having considered the arguments and the Opinion examiner’s finding I take the view that the side reaction problem is one that is little more than hinted at in the prior art as things which “*have been known*” in the context of reactants and by-products which are rather different to those envisaged in **D1** and **D2**. Further, I find the Applicant’s argument that the side reaction problem is identified in the patent in its reference to the achievement of “high yields which

meets economical demands” as the object of the invention to be somewhat convoluted and unconvincing. In addition I can find no arguments that lead me to conclude that the possibility of such side reactions was common general knowledge. Accordingly I am satisfied that the Opinion examiner was correct in his view that the potential of a side reaction would not have deterred the skilled man from considering the use of nickel or cobalt catalysts in the reaction of **D1** and **D2**.

- 38 This brings me to the Defendant’s submission that the only advantage identified in the patent of using nickel and cobalt catalysts is in relation to their lower cost. The Opinion examiner disagreed and noted that paragraph [0034] of the patent clearly states that nickel and cobalt catalysts have the surprising advantage of being recyclable without further treatment and with no change in activity. Moreover, by comparing the patent with **D2** (see Method A for Compound 5), it would appear that the yields for equivalent hydrogenation reactions are higher using nickel than with rhodium. However I’m not convinced that this issue amounts to much. The clearly stated objective of the patent is to “provide a process for the preparation of phenethylamine derivatives in high yields which meets economical demands.

Summary

- 39 Having reviewed the *Windsurfing* questions as re-framed by *Pozzoli* I have found that the Opinion examiner rightly identified the skilled man as a competent but unimaginative chemist skilled in the field of organic synthesis and there appears to be no dispute about this. Further, in considering the common general knowledge, the Opinion examiner concluded that the skilled person would understand that nickel and cobalt catalysts are suitable for hydrogenating nitrile compounds to amines and would be aware of the disadvantages of using rhodium in the process of **D1** and **D2**. Again the parties to this review do not appear to take issue with this assessment and I am satisfied that it is correct. To that I would add that I can find nothing in the submissions before me or the Opinion examiner to show that the tendency for nickel and cobalt catalysts to generate undesirable by products envisaged in **D3** formed part of the common general knowledge at the relevant time.
- 40 Although the Opinion examiner did not specifically state what he considered the inventive concept to be, it is clear that he reached his conclusions on the basis that it is the preparation of phenethylamine derivatives by hydrogenation of phenylacetonitriles in the presence of a nickel or cobalt catalyst. I have considered whether the Opinion examiner should have construed claim 1 more narrowly as being restricted to the production of pharmaceutically pure compounds. As I have said, I do not find the Applicant’s arguments on this point convincing and I am satisfied that Opinion examiner was not wrong in his approach.
- 41 With regard to the differences between the cited matter and the inventive concept, it is clear from the parties submissions and the Opinion examiner’s conclusions that the difference between the cited matter and the patent is that the patent employs a nickel or cobalt catalyst in place of the rhodium catalyst of the prior art. In my view that is correct and the parties would appear to agree

since the main thrust of their arguments goes to that point.

- 42 On whether this difference would have been obvious to the skilled man the Opinion examiner concluded that the skilled man would have known at the priority date of the patent that nickel and cobalt catalysts are suitable for hydrogenating the nitrile compounds of **D1** and **D2** to the corresponding amines. He noted that such catalysts were well known and less expensive than rhodium. In his view, this advantage would have been self-evident to the skilled addressee and provide sufficient motivation for at least a trial having a reasonable probability of success. In the absence of any supporting evidence, he was unable to accept the Applicant's view that the retro aldol side reaction was a known problem or that there would be an expectation that the use of nickel or cobalt would promote this effect. As I have noted there appears to be no evidence that such side reactions were common general knowledge. As I have already indicated, I am satisfied that the Opinion examiner was correct in his view that the possibility of a side reaction would not have deterred the skilled man from considering the use of nickel or cobalt catalysts in the reaction of **D1** and **D2**. In any event, the side reaction argument is only relevant if claim 1 is construed as being limited to the production of pharmaceutically pure compounds and, as I have said, I am satisfied that the Opinion examiner was not wrong when he failed to adopt this construction.
- 43 On this basis the Opinion examiner concluded that claim 1 of the patent is obvious. I am satisfied that this is an entirely reasonable conclusion to have reached. With regard to independent Claim 17 he noted that it discloses the features of claim 1 but also includes the further step of converting the primary amine derivative to a tertiary amine, which is obtained in the form of a hydrogen chloride salt. He observed that this additional reaction is plainly disclosed in **D1** (e.g. Example 3) and **D2** (e.g. preparation of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol on page 2903) and is performed using a mixture of formic acid and formaldehyde. Since he had already found that claim 1 lacks an inventive step, he concluded that claim 17 must also be obvious. In my view he was correct to do. He then went on to consider the dependant claims 2 to 6, 11, 12, and 19. In each case he found that the subject matter of those claims was to be found in the cited prior art and concluded that these claims too are obvious. I am also satisfied that this finding is correct.

Conclusion

- 44 As I have already stated, the purpose of this review is to consider whether *the opinion wrongly concluded that the patent was invalid, or was invalid to a limited extent*. I have considered the Opinion examiner's reasoning in relation to each of the modified *Windsurfing* questions in the light of the submissions from both parties. In each case I have concluded that he was correct in his findings. I am satisfied therefore that the opinion was correct in its findings that Claims 1-6, 11, 12, 17 and 19 do not involve an inventive step. Accordingly I make no order to set aside the opinion.

Appeal

45 Under the practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

Peter Back

Divisional Director acting for the Comptroller