

PATENTS ACT 1977

APPLICANT Council of Scientific and Industrial
Research

ISSUE Whether patent application number GB
0512845.9 complies with section 1(1)(b)

HEARING OFFICER C L Davies

DECISION

Introduction

- 1 International patent application number PCT/IB2002/005724 entitled “Process for preparing taxol side chain using heterogeneous trifunctional catalyst” was filed in the name of Council of Scientific and Industrial Research on 23 December 2002. The international application was published by WIPO as WO 2004/056742 A1 on 8 July 2004 (with an international search report (ISR) dated 5 August 2003), entered the UK national phase as GB0512845.9 and was re-published as GB2411402 on 31 August 2005.
- 2 The international search report cited 8 category Y documents, against all original claims. An International Preliminary Examination Report dated 3 February 2005 and based on the original application, was very brief, asserting only that the invention as defined in at least some of the claims did not appear to be novel and/or to involve an inventive step.
- 3 The Examiner’s main objection, raised in the first Section 18(3) Report, was to a lack of inventive step against all original claims, based on two documents from the ISRF and common general knowledge of the skilled worker. In response, the Applicant maintained that their claims were inventive. Several rounds of argument between Examiner and Applicant followed, where the Examiner maintained the inventive step objection, with the Applicant, in each response, dismissing the objection. A hearing was offered on 20 August 2007.
- 4 The matter came before me to decide at a hearing on 11 October 2007. This was attended by Mr Christopher Hamer of Mathys and Squire (the “Attorney”,

representing the Applicant, Council of Scientific and Industrial Research), together with his colleague Mr John Fisher, and Dr Jason Bellia, Senior Patent Examiner.

- 5 Following the hearing and to aid in reaching my decision, the Applicant was invited to file further submissions regarding *Brugger and others v Medic-Aid Ltd* [1996] RPC 635 and Chemical Reviews, 1994, Vol.94(8), Kolb et al., pp.2483-2547 (cited on the ISR and referred to as D8 in the following paragraphs). The Applicant did so (in a letter dated 30th November 2007) and I have also taken these points into consideration.

The Application

- 6 The application relates to an improved synthetic process for the preparation of the C13 taxol side chain. The proposed route utilises heterogeneous catalysis to effect a Heck coupling followed by an asymmetric dihydroxylation (AD) reaction to prepare an enantiomerically enriched 1,2-diol, offering the advantage over the prior art that separation of the catalyst from the final product is more straightforward, whilst in addition precluding osmium traces (and hence eliminating osmium toxicity) from the final product.
- 7 Taxol itself is a drug which was originally isolated from the bark of the Pacific Yew (*Taxus brevifolia*) and found to be an extremely effective cancer therapeutic agent, in particular for the treatment of ovarian cancers. Ecological concerns over extraction of the drug from such trees led to the need to develop synthetic routes for producing taxol, of which, the current application forms part.

Abbreviations

- 8 A short list of abbreviations used in subsequent paragraphs of this decision can be found in Appendix 1.

The Claims

- 9 The latest set of claims on file were those filed on 26 April 2007 and this is the set upon which my decision is based. There are 14 claims in total, with claim 1 being the only independent claim and reading:

Claim 1:

1. A process for the synthesis of taxol side chain comprising (a) synthesizing (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate by in tandem or simultaneous Heck coupling of bromobenzene and methyl acrylate and N-oxidation of an amine in the presence of cinchona alkaloid and using a recyclable multifunctional catalyst of the formula IE-PdOsW, wherein IE is an ion-exchanger selected from the group consisting of LDH, or a quaternary ammonium salt anchored on silica, clay, alumina, magnesia or resin, (b) converting the diol obtained in step (a) without further crystallisation into bromoacetate, (c) reacting the bromoacetate with NaN₃ in an organic solvent followed by deacetylation with NaOAc in another organic solvent to obtain an azido alcohol (d) subjecting the azido alcohol to

benzoylation followed by hydrogenation to obtain the (2R,3S)-(N)-benzoyl-3-phenylisoserine methyl ester.

- 10 Claim 7 defines the cinchona alkaloid and reads:

Claim 7:

7. A process as claimed in claim 1 wherein the cinchona alkaloid comprises a chiral ligand selected from the group consisting of (DHQ)₂PHAL, (DHQD)₂PYR, (DHQD)₂AQN, DHQD-OAc, DHQD-CLB, DHQD-PHN, DHQD-MEQ, DHQD-IND, and pseudoenantiomeric forms thereof.

- 11 Claim 14 defines the multifunctional catalyst and reads:

Claim 14:

14. A process as claimed in claim 1 wherein the catalyst is selected from the group consisting of LDH-PdOsW, resin-PdOsW and SiO₂-PdOsW.

Issue to be decided

- 12 The issue to be decided at the hearing was whether the claims satisfy section 1(1)(b) of the Patents Act 1977 (the "Act"), i.e. whether they comprise an inventive step.

The Law

- 13 The law regarding inventive step is found in sections 1 and 3 of the Act. The relevant parts read as follows:

Patentable Inventions

1.-(1) A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –

- (a) ...
- (b) it involves an inventive step;
- (c) ...

and references in this Act to a patentable invention shall be construed accordingly.

- 14 The following part of section 3 is also relevant, since it defines what is meant above by 'inventive step'.

Inventive Step

3. An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above (and disregarding section 2(3) above).

Citations from the International Search Report:

- 15 For convenience, the documents referred to in subsequent paragraphs of this decision are summarised as follows. Note: the numbering corresponds to their appearance in the ISR:

D1: Angew. Chem. Int. Ed., 2001, Vol.40(24), Choudary et al., pp.4620-4623

D2: Tetrahedron Lett., 1998, Vol.39, Lee et al., pp.2163-2166

D4: J. Org. Chem., 1994, Vol.59(17), Wang et al., pp.5104-5105

D8: Chem. Rev., 1994, Vol.94(8), Kolb et al., pp.2483-2547

The Arguments

- 16 For convenience, in the following paragraphs, I have separately set out both the Examiner's and the Applicant's arguments, which I have then addressed in order to come to my final decision.

The Examiner's Arguments:

- 17 The Examiner was presented with an ISR which cited 8 documents under category Y. He also had sight of an IPER referring only in general terms to the fact that "*In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step ...*"
- 18 The Examiner therefore considered the claimed invention in the light of each document and reached a prima facie view that on the basis of two of the citations and with common general knowledge, the invention was obvious. The Examiner raised this objection in his first section 18(3) examination report (23 November 2005):

'The invention as defined in claims 1-15 is obvious in view of what has already been disclosed in the following documents:

Angew. Chem. Int. Ed., 2001, Vol.4(24), Choudary *et al.*, pp.4620-4623. See Table 1 entries 16 and 17 (D1).

Tetrahedron Letters, 1998, Vol.39, Lee *et al.*, pp.2163-2166. See scheme 1 (D2).

Choudary *et al.* discloses the preparation of (2*S*,3*R*)-methyl-2,3-dihydroxy-3-phenylpropionate by a Heck reaction followed by asymmetric dihydroxylation using a LDH-PdOsW catalyst. Lee *et al.* discloses the preparation of the taxol side chain (2*a*) by conversion of (2*R*,3*S*)-methyl-2,3-dihydroxy-3-phenylpropionate by reaction with HBr-AcOH, azide formation, ester hydrolysis, benzoylation and hydrogenation. Therefore, it would be obvious to the skilled worker to generate the methyl-2,3-dihydroxy-3-phenylpropionate required in Lee *et al.* using the methodology disclosed in Choudary *et al.* The ability to alter the enantiofacial selectivity of a dihydroxylation reaction by use of the appropriate (DHQ)₂PHAL rather than

(DHQD)₂PHAL catalyst to prepare the desired (2*R*,3*S*)-product is well known in the art. Therefore, claims 1-15 are not inventive.'

- 19 As the rounds of arguments and counter-arguments progressed, the nature of the original inventive step objection shifted somewhat, with the Examiner, in a report prior to the hearing presenting the following inventive step objection based on the test found in *Windsurfing*¹ (as modified by the Court of Appeal in *Pozzoli*²):

"[I]t is my preliminary view that:

(1)(a) The notional person skilled in the art is a preparative organic chemist with an interest in the synthesis of the taxol side chain.

(1)(b) The common general knowledge includes the knowledge that it is possible to update known preparative routes by substituting steps from a known synthesis with new preparative routes, particularly when motivated by improvements in factors such as yield, ease of isolating products, enantiomeric excess, and availability or cost of reagents. The skilled person would also know that a published synthesis using iodobenzene could be suitably modified to use bromobenzene with little consequent effect on the outcome of the synthesis as compared to the literature. It was also known that syn-1,2-diols were highly significant intermediates for taxol side chain synthesis.

(2) The inventive concept is clearly defined in claim 1.

(3) Both D1 and D2 (as indicated in previous reports) forming part of the state of the art it was known to provide a route to syn-1,2-diols in general and (2*S*,3*R*)-dihydroxy-3-phenyl-propanoate in particular starting from methyl acrylate and iodobenzene given in D1 (step 17). It was also known from D2 that the same (2*S*,3*R*)-dihydroxy-3-phenyl-propanoate compound could be used to prepare a taxol side chain as in the route of D2 (scheme I)

The difference between the state of the art and the present inventive concept lies in the skilled person recognising that bromobenzene could be substituted for iodobenzene in step 17 of D1, and that the step 17 synthesis could suitably replace the alternative or even apparently "most attractive" routes to syn diols indicated in D2 these routes being at least obvious to try having regard to the preferred stated yields and enantiomeric excess in step 17.

(4) I find the differences between the state of the art and the present inventive concept to be matters of common general knowledge and as such require no invention. Therefore I find claim 1 obvious. Furthermore

¹ *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59

² *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588

claims 2-15 are also considered non-inventive the inventive concepts of these claims being conventional in the art.”

20 In response, the Attorney highlighted the fact that D1 and D2 disclosed different isomers of methyl-2,3-dihydroxy-3-phenylpropionate. The Examiner responded by pointing out that:

“..... the skilled person’s knowledge of asymmetric dihydroxylation (AD) would mean they would be aware that in the Sharpless AD reaction the cinchona alkaloid (DHQD)₂-PHAL has a complementary partner (DHQ)₂-PHAL which gives the opposite sense of chiral induction. Thus given that D1 describes a tandem Heck-modified Sharpless AD procedure the availability of the other pseudoenantiomer (DHQ)₂-PHAL to try to prepare the 2R, 3S enantiomer would be obvious.”

21 It was this line of argument, consistent with that raised in the first section 18(3) examination report, which was considered at the hearing.

The Applicant’s Arguments:

22 The Applicant’s pertinent arguments were those raised by the Attorney at the hearing, together with those made in response to the invitation for further submissions, as indicated in paragraph 5 above.

23 At the hearing, the Attorney opened by dismissing the Examiner’s arguments as set out in the correspondence, arguing that the *Windsurfing/Pozzoli* analysis put forward was not valid and was constructed with the benefit of hindsight i.e. the Examiner had used *ex post facto* analysis. The Attorney subsequently asserted the following:

24 Firstly, that the Examiner had in his application of *Windsurfing* and the assessment of inventive step, started from the wrong prior art document. The Attorney asserted that the appropriate starting point was another of the documents cited on the ISR, namely D4 and argued that the skilled worker would start from D4 to produce (2R,3S)-2,3-dihydroxy-3-phenylpropionate and, in view of the poor yielding latter half of the disclosed C13-side chain synthesis, would look to improve conversion of (2R,3S)-2,3-dihydroxy-3-phenylpropionate to the taxol side chain. With this in mind, the Attorney argued that the skilled worker would then turn to D2, which clearly shows an improved method of converting this specific (2R,3S)-isomer into taxol side chain. The Attorney further argued that the use of the teachings of D4 and D2 by the skilled worker would be natural, given that these documents were published in 1994 and 1998 respectively.

25 Secondly, the Attorney asserted that the skilled worker would not be motivated to consider D1 for an improved synthesis of (2R,3S)-2,3-dihydroxy-3-phenylpropionate since D1 (a) does not disclose the correct isomer of 2,3-dihydroxy-3-phenylpropionate; (b) does not disclose or remotely suggest the use of (DHQ)₂-PHAL ligand; (c) teaches a lower enantiomeric excess (e.e.) for the (2S,3R)-isomer than is obtained for the (2R,3S)-isomer according to the method of D4; (d) uses an entirely different kind of catalyst system, i.e. heterogeneous rather than homogeneous catalysis; and e) the (DHQD)₂-PHAL and (DHQ)₂-

PHAL ligands are merely pseudoenantiomers and thus it should not be presumed that one may be substituted for the other.

26 Thirdly, the Attorney argued that common general knowledge “is what we have written down in front of us on paper” and used the High Court decision in *Percell Group Ltd v Instrumentation and Microelectronic Systems Ltd* to support this.

27 In response to the invitation for further submissions (note paragraph 5), the Attorney made reference to *Saint-Gobain PAM SA v Fusion Provida Limited and Electroshell Castings Limited* [2005] EWCA Civ 177, pointing out that in the “obvious to try” test, the words of Lord Justice Jacob should be considered:

‘The “obvious to try” test really only works where it is more-or-less self-evident that what is being tested ought to work.’

28 The Attorney made the point that when assessing the inventive step of the present claims, the pertinent question to ask is whether the skilled person would consider it more-or-less self-evident that the replacement of the (DHQD)₂-PHAL ligand with the (DHQ)₂-PHAL ligand in the IE-PdOsW catalysed tandem Heck reaction and asymmetric dihydroxylation would work, and with better e.e. than can already be obtained.

Analysis of the Arguments:

29 The approach to be taken in the UK to determine whether an invention is obvious is the *Windsurfing* test as modified in light of *Pozzoli*.

30 I note the Examiner adopted this test in formulating his inventive step objection but at the hearing, the Attorney asserted that the Examiner had used *ex post facto* analysis in determining a lack of inventive step, and in this respect, raised several points in an attempt to show why he considered the Examiner’s assessment to be incorrect.

31 I shall first cover those more general issues raised by the Attorney, together with some other matters that do not easily fit within the *Windsurfing/Pozzoli* test framework, before using my own application of the *Windsurfing/Pozzoli* test to come to a reasoned decision on inventive step for this application.

32 Clearly the Attorney’s assertion of *ex post facto* analysis can only be shown to be invalid if the points made in relation to the application of the *Windsurfing/Pozzoli* analysis are themselves not valid. I shall therefore consider each of these points in turn.

Starting point for assessing obviousness:

33 The Attorney stated that D4 (published 1994) would be the starting point for the skilled worker. He argued that the skilled worker would never even consider D1 (published 2001) given the efficacy (particularly high enantiomeric excess) of the method which might be arrived at by using the process of D2 (published 1998) to access the taxol side chain from the (2*R*,3*S*)-isomer prepared by the method of D4. Whilst I do not doubt that this would generate an attractive route to the taxol side chain, I am not persuaded by this argument.

34 Firstly, it is the state of the art at the priority date of the application (December 2002) that must be considered. The period between 1998 and the priority date of this application has seen a continuing evolution of the approaches to asymmetric synthesis in general, and asymmetric dihydroxylation in particular, with D1 being an example of the attempts to improve this type of methodology.

35 Secondly, the mere fact that the combination of D2 and D4 may result in an effective method of preparing the taxol side chain does not preclude the consideration of other approaches. This is consistent with *Brugger and others v Medic-Aid Ltd* [1996] RPC 655 in which Laddie J held that:

‘if a particular route is an obvious one to try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well. If a number of obvious routes exist it is more or less inevitable that a skilled worker will try some before others....There is no rule of law or logic which says that only the option which is likely to be tried first or second is to be treated as obvious for the purpose of patent legislation.’

36 There are two routes which might be considered obvious: the combination of D2 and D4 or the combination of D2 and D1 with common general knowledge. In their response to the invitation for further submissions, the Applicant highlighted the fact that *Brugger* was not the most recent case on the “obvious to try” test and referred to *Saint-Gobain PAM SA v Fusion Provida Limited and Electroshell Castings Limited* [2005] EWCA Civ 177. In my opinion, this appears to have no bearing on whether alternative routes might be chosen and thus I will only consider this precedent later in relation to the discussion of the appropriateness of the combination of D1 and D2 in the light of the common general knowledge. Similarly I do not consider the Attorney’s further comments about the merits of the combination of D2 and D4 as opposed to the combination of D1 and D2 as proposed by the Examiner (eg. higher enantiomeric excess in one compared with the other) pertinent in light of *Brugger*. Thus I can see no reason for me to consider any further the combination of D2 and D4.

The common general knowledge of a skilled worker:

37 The Attorney stated that the common general knowledge must be that which is written down and set forth in front of us and used the words of Aldous J in *Percell Group Ltd v Instrumentation and Microelectronic Systems Ltd* (SRIS C/47/93) to support this view:

‘In the present case the defendants contend that the invention was obvious having regard to common general knowledge, thus it is relevant to look at what was done by persons in the field and the thoughts they expressed at the time. That could provide the best indication of what was obvious at that priority date.’

38 Having considered *Percell Group*, it is clear to me that the state of the common general knowledge in that case was primarily established by the use of expert witnesses and such an approach is clearly not available to me here. In addition, the words of Aldous J do not appear to limit me to consideration only of

documents presented at the hearing, but merely point to consideration of the thoughts, actions and writings of those in the field at the priority date of the present application in order to establish what constitutes the common general knowledge. However, I do share some sympathy with the Applicant in that the lack of identification of documents during the course of correspondence on this case or indeed at the hearing, to demonstrate what constitutes the common general knowledge has made determination of its scope troublesome. In view of the importance of this issue, the Applicant was invited to file submissions on D8 (a review of catalytic asymmetric dihydroxylation reactions).

- 39 The courts have attempted to define the common general knowledge many times over and the widely accepted explanation by Laddie J in *Raychem Corp's Patents [1998] RPC 31* is particularly instructive in the present case:

“The common general knowledge is the technical background of the notional man in the art against which the prior art must be considered. This is not limited to material he has memorised and has at the front of his mind. It includes all that material in the field he is working in which he knows exists, which he would refer to as a matter of course if he cannot remember it and which he understands is generally regarded as sufficiently reliable to use as a foundation for further work or to help understand the pleaded prior art. This does not mean that everything on the shelf which is capable of being referred to without difficulty is common general knowledge nor does it mean that every word in a common text book is either. In the case of standard textbooks, it is likely that all or most of the main text will be common general knowledge. In many cases common general knowledge will include or be reflected in readily available trade literature which a man in the art would be expected to have at his elbow and regard as basic reliable information.”

- 40 This is therefore the definition of the common general knowledge that I shall use below, to inform my view of what constitutes the common general knowledge in this particular field at the priority date.

- 41 Having previously established that I can see no reason why the combination of D4 and D2 alone should be considered, I must consider whether the skilled worker would have been aware of the teaching of D1 at the priority date. At the hearing, the Attorney disputed this, arguing that the skilled worker would not find D1 because it related to the wrong isomer ie. the (2S,3R)-isomer as opposed to the (2R,3S)-isomer. He asserted that ‘it is well known that different isomers are novel and inventive in their own right’ and that when searching ‘you are very specific on which isomers you are looking at for novelty and inventive step considerations.’, The Examiner however, is of the opinion that the skilled worker, considering the teaching of D2 and noting the poor yield of the methyl-(2R,3S)-2,3-dihydroxy-3-phenylpropionate (1a), would search for alternative methods for its preparation. The Examiner subsequently asserted that D1 would indeed be found in a literature search for alternative methods for preparing the (2R,3S)-2,3-dihydroxy-3-phenylpropionate, since the skilled worker would not restrict a search to the specific isomer. Whilst I am in no doubt that different isomers may be patentable in their own right, I must consider what the skilled worker would do

when presented with the problem of developing an improved route to the taxol side chain. In this respect, I agree with the Examiner in that I do not think the skilled worker would restrict their search to the particular (2*R*,3*S*)-isomer in this instance and that the skilled worker would indeed be aware of D1 at the priority date.

- 42 The “Introduction and General Principles” section of D8 (published 1994) is instructive in placing the chemistry considered at the hearing into context:

‘During the last decade a number of powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. *Catalytic* asymmetric reactions provide an especially practical entry into the chiral world due to their economic use of asymmetry inducing agents. A number of processes have gained wide acceptance, and some of them are even used on an industrial scale.’ (pp 2483)

- 43 The subsequent fourteen or so years have seen a continuation of that trend. Thus the range of chiral small molecules (chiral building blocks) available for organic synthesis, and natural product synthesis in particular, has been greatly increased without the previous limitations of having to primarily use those compounds naturally available (chiral pool reagents).

- 44 The introduction to D2 also makes clear that:

“[h]omochiral 1,2-diols are useful as chiral building blocks in asymmetric synthesis.” (p 2163)

Methyl-(2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate is therefore just such a building block and in my view, the skilled worker in this instance would look at all possible approaches, particularly asymmetric approaches, to methyl 2,3-dihydroxy-3-phenylpropionate. Thus asymmetric approaches to the other isomer would be considered given that appropriate asymmetry inducing reagent choice would in many instances allow the desired isomer to be produced instead. In my view, it is also conceivable that, given the key role of 1,2-diols in natural product synthesis, the skilled worker would in any case have been aware of D1. By whichever route, I am satisfied that the skilled worker would have located D1.

Windsurfing/Pozzoli:

- 45 Having considered some of the more general, or at least background issues raised in relation to inventive step by both the Examiner and the Attorney, I shall now apply the *Windsurfing/Pozzoli* test:

Step 1a — Identify the notional “person skilled in the art”

- 46 I consider the scope of the definition of the skilled person stated by the Examiner to be too broad in that he was merely referred to as a preparative organic chemist with an interest in the synthesis of the taxol side chain. In my view, the skilled person would be a *natural product* synthetic organic chemist having a particular interest in the synthesis of the taxol side chain, who is fully aware of and up-to-

date with asymmetric synthesis in general and in particular the approaches to chiral 1,2-diols, given their key role in accessing natural product intermediates. In my view, it is important that he is chiefly interested in natural products, as the fact that such compounds generally display chirality makes their awareness of the development of asymmetric methodologies (as touched on in consideration of the likelihood of locating D1 above) all the keener given their need to prepare chiral small molecules as building blocks for natural product synthesis. Thus the skilled worker will seek improvements for making chiral 1,2-diols (or other potential precursors) and therefore improved production of the taxol side chain from such non-racemic compounds

Step 1(b) — Identify the relevant common general knowledge of that person;

- 47 The Examiner asserted that the common general knowledge included knowledge of the Sharpless catalytic asymmetric dihydroxylation reaction (not least because this work attracted, in 2001, the Nobel Prize for Chemistry), in particular that the skilled worker 'would be aware that in the Sharpless AD reaction the cinchona alkaloid (DHQD)₂-PHAL has a complementary partner (DHQ)₂-PHAL which gives the opposite sense of chiral induction' and that the skilled worker would therefore be minded to try the use of the (DHQ)₂PHAL ligand to prepare the desired (2R, 3S)-isomer using the method of D1. The Attorney argued this was mere supposition.
- 48 To help me decide on this particular issue, the Applicant was invited to file submissions on the review of osmium mediated asymmetric dihydroxylation reactions by Sharpless (D8) (see paragraph 5 above). In response, the Applicant was of the opinion that D8 did not add anything, but gave no clear view as to whether they believed D8 or indeed any part of D8 formed part of the common general knowledge.
- 49 Having reviewed the arguments, I believe the skilled worker would, as a matter of routine (eg. research work and keeping abreast of the literature, particularly in view of the half Nobel Prize for Chemistry awarded in 2001 for this work) be familiar with the production of chiral 1,2-diols produced via solution phase osmium catalysed asymmetric dihydroxylation reactions particularly as developed by Sharpless. I accept this because of the number of references to this work in the documents before me: both D1 (reference 3a) and D2 (reference 2) reference Sharpless' work in the form of the D8 review; D4 is a Sharpless paper featuring this chemistry, and D8 was published approximately 8 years before the priority date of this application. I also accept that common general knowledge of the skilled worker would include recognition that DHQD and DHQ ligands are pseudoenantiomers and that the enantiofacial selectivity of a dihydroxylation reaction may be determined by use of either the appropriate DHQ or complementary DHQD pseudoenantiomer (e.g. using (DHQ)₂-PHAL would result in the opposite prochiral face of an alkene being dihydroxylated compared with that dihydroxylated using (DHQD)₂-PHAL). This complementary nature is well established throughout D8, with many tables showing DHQ and DHQD derived ligands giving an opposite sense of induction with a variety of alkenes, with this being illustrated in the simple mnemonic of Figure 5 (D8, p 2488). Thus while I do not contend that the specifics of individual tables of reactions in D8 could be said to form part of the common general knowledge, I accept that this general

notion does. In addition, the fact that these reactions are for many classes of alkene precursors, high yielding and afford good to excellent enantiomeric excesses, would be appreciated by the skilled worker.

Step 2 — Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

- 50 The Examiner asserted that the inventive concept is clearly defined in claim 1, to which the Attorney made no challenge. I agree with the Examiner that the inventive concept is clearly defined in claim 1.

Step 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;

- 51 D1 uses iodobenzene as the aryl halide whereas the claimed invention uses bromobenzene.
- 52 D1 uses a solid catalyst system (namely LDH-PdOsW), iodobenzene, methyl acrylate and the (DHQD)₂PHAL cinchona alkaloid to produce (2*S*,3*R*)-2,3-dihydroxy-3-phenylpropionate (with an enantiomeric excess of 98%), whereas the claimed invention uses the same solid catalyst system, bromobenzene, methyl acrylate and a cinchona alkaloid such as (DHQ)₂PHAL to produce (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate.

Step 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?

- 53 In my view, the skilled worker would recognise that iodobenzene and bromobenzene are commonplace reagents and that either aryl halide would be capable of performing the same function in the Heck coupling. This replacement would therefore appear to be trivial and since it was not raised by the Attorney during the hearing, is not at issue.
- 54 The skilled worker would, in my opinion, be continually searching for improved routes of making chiral 1,2-diols and in the subsequent conversion of chiral 1,2-diols to the C13 taxol side chain.
- 55 In this respect, the skilled worker will be aware of D2 as it falls squarely within the field of taxol side chain preparation.
- 56 At the priority date of the current application and following from my previous discussion of D1, I am also satisfied that the skilled worker would have been aware of D1, which teaches an improved way of making chiral 1,2-diols, using a heterogeneous trifunctional catalyst system, including LDH-PdOsW. From this document also, the skilled worker will recognise that:

(i) the route provided by D1 results in high yields and good to excellent enantiomeric excesses of chiral 1,2-diols, via an essentially low-cost process, and without the problems associated with the removal of osmium

residues, which is problematic with 1,2-diols produced via solution phase osmium-catalysed chemistry.

(ii) chiral diols are valuable intermediates for drugs such as diltiazem and taxol.

(iii) D1 teaches an attractive route to chiral 1,2-diols due to its economy of starting material compared with enzymatic resolution approaches (as in D2) and is attractive for pharmaceutical manufacture because of the avoidance of traces of toxic osmium in the final products.

(iv) entry 17 in Table 1 (D1, p 4622) gives rise to the (2*S*,3*R*)- isomer (with an enantiomeric excess of 98%) through Method B, which utilises a LDH-PdOsW catalyst, using the cinchona alkaloid derived chiral ligand (DHQD)₂PHAL (D1, p 4623).

57 In order therefore to determine the answer to Step 4 of my Windsurfing/Pozzoli analysis, I need to consider whether the differences identified in Step 3 of the test are obvious or non-obvious to the skilled worker, in particular, I need to consider whether:

a) the skilled worker would appreciate that the (2*R*,3*S*)-diol could be obtained by an analogous method to that used in D1

b) the skilled worker would appreciate that the DHQD-derived ligand could be replaced with DHQ

c) the fact that the reaction features heterogeneous catalysis rather than homogeneous catalysis significant.

58 Considering a) and b) together, in earlier paragraphs, it has been acknowledged that part of the skilled worker's common general knowledge would be recognition that osmium catalysed asymmetric dihydroxylation reactions allow the chirality of the product to be determined by the choice of the appropriate ligand and in particular, that DHQD and DHQ ligands give an opposite sense of chiral induction in these reactions. D1 clearly relates to an asymmetric dihydroxylation reaction. The Attorney argued that no mention of the different isomer (ie (2*R*,3*S*)-isomer) or of the possibility of using DHQ in place of DHQD is given in this document. On reading D1 however, I believe the attention of the skilled worker would be drawn to the fact presented on p 4620 that 'Sharpless asymmetric dihydroxylation of olefins offers one of the most efficient methods for the preparation of chiral diols'. Thus, in view of the skilled worker's common general knowledge, I believe the skilled worker would read the remainder of this document with such reactions at the forefront of their mind. It is in this context that consideration must be given on whether, seeing that entry 17 of D1 allows preparation of the correct compound but wrong isomer, the skilled worker would realise that the desired (2*R*,3*S*)-isomer may be prepared by replacing (DHQD)₂PHAL with (DHQ)₂PHAL. The skilled worker is not required to summon up a completely unrelated ligand, but merely to, in effect, have in mind the mnemonic (discussed earlier and presented in Figure 5 of D8), suggesting that in this type of reaction, use of the equivalent pseudoenantiomer would be expected to afford the 1,2-diol resulting from attack

of the other prochiral face of the substrate alkene.

59 Considering c), at the hearing, the Attorney argued that in view of the fact that D8 relates only to homogeneous asymmetric dihydroxylation reactions using solution phase osmium tetroxide, it is inappropriate to use this teaching in relation to the more complicated heterogeneous system with an immobilised osmium source, in view of the significant differences between these systems. It is clear that the system taught in D1 is more complicated than that in solution phase osmium asymmetric dihydroxylation reactions. However, reading of the introductory paragraphs of D1 makes it clear in my view that the method outlined is intended to be an improved version of the Sharpless methodology. Comparison of the solid phase reaction and the solution phase reaction also demonstrates many similarities: both reactions are asymmetric dihydroxylation reactions; they utilise the same class of ligand; an oxidant frequently used to regenerate the osmium catalyst in the solution phase is used for the same function in the D1 reaction (NMO), and both reactions proceed via an osmate intermediate whether free in solution or fixed at the surface of a double hydroxide matrix. It is clear from D1 that only the osmium species (rather than any of the other metals in the matrix) plays a part in the dihydroxylation and that the presence of the ligand is still key to achieving the high enantiomeric excesses demonstrated. This latter point is made clear when it is stated that:

‘the higher e.e. values obtained using a bulky chiral ligand, (DHQD)₂PHAL suggest that the OsO₄²⁻ ion is only present on the surface...’.(D1, p 4622)

60 I believe therefore that the skilled worker reading this would note that the choice of ligand is significant in the e.e. afforded and must be significant in the sense of the chiral induction. Therefore, there would appear to be sufficient information to make the use of the common general knowledge as illustrated by D8 appropriate in this instance.

61 In light of the above, I would therefore expect a skilled worker considering D1 and entry 17 in Table 1, in combination with his own common general knowledge to make the link that the (2*R*,3*S*)-isomer may be prepared by Method B (utilising LDH-PdOsW as a catalyst) by simply replacing the (DHQD)₂PHAL ligand (used to prepare the (2*S*,3*R*)-isomer) with (DHQ)₂PHAL to arrive at the desired (2*R*,3*S*)-isomer. Therefore, in view of the differences identified in Step 3 and the consideration in Step 4 as to whether those differences would be obvious to a skilled worker, I am satisfied that the differences identified in Step 3 do not warrant inventive ingenuity on the part of the skilled worker to arrive at the invention of claim 1.

62 I believe the above reasoning is consistent with *Saint-Gobain PAM SA v Fusion Provida Limited and Electroshell Castings Limited* [2005] EWCA Civ 177. Consideration of the skilled worker’s common general knowledge (as identified above) clearly shows that application of this test leads to the invention being obvious. I note that the Applicant, in the reasoning of their argument presented in their response of 30th November 2007, omitted to identify and therefore consider in full the common general knowledge of the skilled worker.

63 To summarise, on the basis of the arguments and documentation available to

me, I find the invention of claim 1 to be lacking an inventive step. On the basis of common general knowledge, I find that the skilled worker would consider it obvious to attempt the production of the (2*R*,3*S*)-isomer of methyl 2,3-dihydroxy-3-phenylpropionate using the methodology of D1, by replacing (DHQD)₂PHAL with its complementary pseudoenantiomer (DHQ)₂PHAL in Method B disclosed therein, which utilises LDH-PdOsW as a catalyst), and then subsequently use the (2*R*,3*S*)-isomer of methyl 2,3-dihydroxy-3-phenylpropionate so produced, in the method of D2 to access the taxol side chain.

Consideration of amendments

- 64 The Attorney indicated in a letter of 30th November 2007 that the Applicant may be willing to amend further should it facilitate grant of the present application, for example, to recite that the “(2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate is produced in 99% e.e. or greater”. It would seem to me that this potential amendment is merely defining the invention in terms of the result to be achieved. I have found the invention of claim 1 to be obvious and this potential amendment, in my opinion, does nothing to change this finding.
- 65 Having carefully read the application, I have been unable to find any appendant claim which, if incorporated into claim 1 would, in my opinion, render the invention patentable. Claims 2-13 appear to amount to no more than routine laboratory modifications.

Conclusion

- 66 I find that claims 1-14 do not comply with section 1(1)(b) of the Act insofar as these claims do not involve an inventive step. I refuse the application under section 18(3).

Appeal

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

C L Davies

Deputy Director acting for the Comptroller

Appendix 1:

Abbreviations used in the Decision:

| | |
|------|-----------------------------|
| DHQ | Dihydroquinine |
| DHQD | Dihydroquinidine |
| PHAL | Phthalazine |
| e.e. | Enantiomeric excess |
| AD | Asymmetric dihydroxylation |
| LDH | Layered double hydroxide |
| NMO | N-methyl-morpholine-N-oxide |