

OPINION UNDER SECTION 74A

Patent	EP(UK) 0777477
Proprietor(s)	SmithKline Beecham plc
Exclusive Licensee	
Requester	A. A. Thornton & Co, on 26 October 2006
Observer(s)	GlaxoSmithKline
Date Opinion issued	30 January 2007

The request

1. This opinion relates to a request made as to whether the patent in question is valid because it does not involve an inventive step having regard to:

EP0456720 (Mallinckrodt Inc)
EP0535841 (Euroceltique SA)
EP0220805 (Euroceltique SA)
2. Four further patent documents are cited as examples of disclosures of codeine in combination with ibuprofen (EP0068838, EP159852, EP274845, EP388125). A paper by AT Florence entitled "*Materials Used in Pharmaceutical Formulation*" Critical Reports on Applied Chemistry, 1984 Vol. 6 Blackwell Scientific Publications is also cited.

Observations and observations in reply

3. Observations in response to the request were received as above from the patent proprietor. These merely assert the claims of EP0777477 are valid and inventive over the cited art and make no further comment.
4. No observations in reply were received.

The Patent

5. The patent in question, EP0777477, published on 11 June 1997, is in force (EP/UK) and is derived from an International patent application filed under the Patent Cooperation Treaty (application number PCT/GB95/01947, publication number WO96/005834). It was filed on 16 August 1995 and has two priority dates of 23 August 1994 and 04 October 1994. The notice of grant was published on 13 November 2002.
6. There are 16 claims. Claims 2-15 are dependant on claim 1 which reads:

*“A pharmaceutical formulation comprising ibuprofen or a pharmaceutically-acceptable salt thereof and codeine or a pharmaceutically-acceptable salt thereof in association with a pharmaceutically-acceptable carrier wherein said carrier comprises a lubricant, a disintegrant and a diluent **characterised in that the lubricant is substantially free from stearic acid and stearate ions, and is selected from hydrogenated vegetable oils**”*
7. Claim 16 is a method claim for making a formulation of claim 1.
8. Four documents were cited on the International Search report of WO96/005834 in the category “Y”. This means that when taken together with at least one of the other documents, each document was considered by the search examiner to render the claims obvious.
9. WO96/005834 has 26 claims. Claim 1 of EP0777477 is the broadest product claim in the patent and is identical to claim 1 of WO96/005834. In WO96/005834 the method claim is dependant on all the preceding claims whereas in EP0777477 it is dependant on claim 1. Otherwise the method claim of WO96/005834 has the same wording as in EP0777477.
10. Rule 77D (1)(b) (Patent Rules 1995, as amended 1 October 2005) dictates that an opinion shall be refused if it concerns matters which have been previously considered during pre-grant proceedings. EP0535841 was cited in the “Y” category on the international search report. EP0456720 and EP0220805 were not cited in connection with the patent. I am not aware that any objections on the grounds of obviousness were raised in pre-grant proceedings and on this basis I consider that the request is admissible.
11. The requester has provided a detailed and systematic explanation on a claim-by-claim basis of why he considers the patent is obvious.

Discussion

12. The cited documents were published before the priority date of the patent and therefore form part of the state of the art by virtue of section 2(2) of the Act.
13. I will determine the question of inventive step using the classic test established by the Court of Appeal in *Windsurfing International Inc. v Tabur Marine (Great Britain) Limited* [1985] RPC 59. This test sets out the steps to assess inventive step as follows:
 - (i) to identify the claimed inventive concept embodied in the patent in question;
 - (ii) to assume the mantle of the skilled but unimaginative addressee in the art at the priority date and impute to him what was, at that date, common general knowledge of the art in question;
 - (iii) to identify what, if any, differences exist between the matter cited as being “known or used” and the alleged invention; and
 - (iv) to decide without any knowledge of the alleged invention, whether these differences constitute steps which would have been obvious to the skilled addressee or whether they require any degree of invention.
14. Fundamental to determining obviousness is who the skilled addressee would be in this case and what knowledge he would have at the relevant time. This notional person is a generally unimaginative worker in the field but may be a team and would take a practical interest in the prior art that was within his knowledge. In my opinion, in the present case the skilled addressee is a pharmaceutical formulation chemist.
15. When it comes to the common general knowledge of the skilled addressee, I accept the requester’s point that ibuprofen and codeine combinations were common general knowledge in the field at the relevant time, as illustrated by the patent documents I have referred to in paragraph 2 above. I also note that the patent in question says that codeine and ibuprofen combinations had been suggested as far back as the 1980’s.
16. This leads me to consider the other components of claim 1; the lubricant, the disintegrant and the diluent. From my own knowledge, I believe it is true to say that disintegrants and diluents were entirely conventional at the priority date and thus part of the common general knowledge. Thus,

much of the significance of the question of inventive step which I must determine revolves on the nature of the lubricant.

17. The requester states that it was also common general knowledge to use hydrogenated vegetable oils as pharmaceutical lubricants by the mid 1980s. The requester cites the paper by A T Florence as an example of the prior art in relation to hydrogenated vegetable oils and submits this document shows that it was also known in the art that stearates could be substituted by hydrogenated vegetable oils and gives hydrogenated cotton seed oil as an example. The Florence paper says that 0.25% w/w magnesium stearate may be substituted by 4% w/w hydrogenated cotton seed oil. However, Florence also points out that at a concentration of 1% w/w the vegetable oil had a much reduced effect on tablet crushing strength. The passage in Florence reads:

“Lubricants which demonstrated the best lubricating properties assessed by ejection force (magnesium stearate, hydrogenated vegetable oils and glycerides) caused the largest reduction in tablet crushing strength. The hydrogenated vegetable oils and glycerides when used at the 1% w/w level gave similar reductions in ejection force as 0.5% w/w magnesium stearate, but their effect on tablet crushing strength during mixing was much reduced. Thus, alternatives to magnesium stearates, which may overcome to some extent its deleterious behavior on tablet properties, are available but, in general, need to be used at a higher concentration for equivalent lubricating capacity.”

18. In summary, it is my opinion that pharmaceutical compositions comprising ibuprofen and codeine and that use of hydrogenated vegetable oil as a lubricant in pharmaceutical compositions were common general knowledge at the priority date of the patent.
19. I will now consider what constitutes the inventive concept. Lord Hoffmann in the House of Lords provided definitive guidance on claim construction in the judgment of *Kirin Amgen Inc and others v Hoechst Marion Roussel Ltd and others* [2005] RPC 9. In essence, I must determine what the skilled addressee would have understood the language of the claims to mean.
20. The main claim in question in the present case is straightforward and relatively short. Seemingly it presents no problems. However, the requester makes the particular point that the claims of EP0777477 are not limited to monophasic compositions, even though provision of monophasic tablets appears to be at the heart of the invention. In this respect, I note that the patent acknowledges that previous disclosures of monophasic formulations of ibuprofen plus codeine teach that stearic

acid and/or stearate ions are necessary to provide satisfactory formulations. The patent goes on to suggest that it seemed in the art at the time as if the only way to avoid stearic acid/stearate ions in the formulation, which was believed to give rise to exacerbated storage problems, was to employ multiphasic formulations. The patent then sets out the basis of invention by stating that surprisingly it has been found that a formulation can be prepared without the use of stearic acid or stearate ions and which is monophasic by employing a hydrogenated vegetable oil as a lubricant.

21. The question I must answer is whether the skilled addressee reading the patent would regard the formulation claimed in claim 1 as being limited to a monophasic formulation even though this feature is not specified in the claim. In my view the skilled addressee would conclude that the objective was to avoid the use of stearic acid/stearate ions because of the believed impact on storage. Whilst this would enable the production of a monophasic formulation, it seems that this would also be applicable to a multiphasic formulation. Accordingly, in my opinion, the claimed invention embraces both. Moreover, if "monophasic" was fundamental to the invention I would have expected the patentee to have included it in the claims. They did not. It follows, in my view, the inventive concept is that as set out clearly and unambiguously by the words of claim 1.
22. I will now consider the third and fourth *Windsurfer* questions in light of the main submissions in relation to each of EP0456720 ('720), EP0535841 ('841) and EP0220805 ('805) made by the requester.
23. The third *Windsurfer* question requires that I determine the difference between the cited prior art and the inventive concept. The fourth *Windsurfer* question requires that I determine whether these differences are obvious or whether they involve a degree of inventive ingenuity. The requester submits that each of '720 and '805 when considered in light of the common general knowledge render claim 1, at least, obvious. The requester also submits that the disclosure of '841 alone renders claim 1, at least, obvious.
24. I shall approach the third and fourth *Windsurfer* questions together in light of the submissions presented by the requester.
25. The requester submits that the invention in question is obvious in light of '720 in combination with common general knowledge. In '720 the examples show a single pharmaceutical active, ibuprofen, in compositions comprising stearates as a lubricant, disintegrants in addition to lactoses and celluloses which the patent in question describes as diluents. The statement of invention on page 2 lines 32-33 of '720 relates only to ibuprofen. The description, although mainly

concerned with ibuprofen, says that other analgesics may be included. It also teaches that it is highly desirable to add lubricants to aid the production of tablets. It lists stearic acid, metal stearates, and hydrogenated vegetable oils among six candidate lubricants. Thus, the differences between the composition exemplified in '720 and the inventive concept in question are that '720 does not specify the use of codeine and does not detail hydrogenated vegetable oil as a lubricant. The question is whether it would be obvious to select codeine as an analgesic for combination with ibuprofen in formulations and to include hydrogenated vegetable oils instead of stearates as a lubricant in these formulations.

26. The case law developed by the UK courts provides a number of sub-tests on the determinative fourth *Windsurfer* question. For example, is the invention 'obvious to try'? I must bear in mind that when assessing inventive step it is important to avoid using *ex post facto* analysis. In hindsight many things seem obvious. In determining whether a particular action is obvious to try it can be helpful to consider if the skilled addressee would be led to try something because there was a reasonable expectation that it would produce a useful result. It is also well established that invention might lie in overcoming technical prejudice.
27. Firstly, I accept the requester's submission in relation to '720 that the advantages of using ibuprofen and codeine were common general knowledge. In this respect, I think the selection of codeine as a candidate additional analgesic in the formulation taught by '720 is an obvious thing to try.
28. Secondly, the requester says it would have been obvious to avoid using stearates in ibuprofen/codeine compositions because of the known problems associated with stearates. He submits on account of the common general knowledge that it would be obvious to substitute the stearate in '720 with hydrogenated vegetable oil. As I have said above, it was common general knowledge that stearates and hydrogenated vegetable oils can be used as lubricants. Both would be obvious choices of lubricant and hold a reasonable expectation of success; seemingly no technical prejudice has been overcome. Moreover, in my view the skilled addressee who decided to try hydrogenated vegetable oils would not also include stearates. Thus, a formulation which contained a hydrogenated vegetable oil lubricant as an alternative to a stearate lubricant would lack stearates. I should add that this would be my view even if the skilled addressee did not appreciate at the relevant time the problems associated with the use of stearates in ibuprofen/codeine formulations.

29. In my opinion, the teaching of '720 includes clear signposts to do something that would nullify the two differences between '720 and the claimed invention; namely to incorporate codeine in the formulation and to use hydrogenated vegetable oil as an alternative to stearate. Consequently, I believe that claim 1 of EP0777477 is rendered obvious on account of the disclosure of '720 when taken into account with the common general knowledge.
30. The requester submits that the patent in question is obvious on account of the disclosure of '841 alone. The '841 patent discloses an ibuprofen/codeine tablet comprising disintegrants and lactose and microcrystalline cellulose. As I have already said, the patent in question considers lactose and microcrystalline cellulose as diluents. While '841 mentions the use of stearates, these are not present in the exemplified formulations. The '841 patent also details hydrogenated vegetable oils in a long list of controlled release matrix substances but again these are not included in the exemplified formulations.
31. The nub of the requester's submissions is that it would be obvious to include hydrogenated vegetable oils in the composition of '841 or to use them in place of microcrystalline cellulose in those compositions. I note that the patent in question is directed at solving the problem of poor storage properties. The '841 patent is not directed to that. However, in my view it is not essential to show that the '841 patent is directed at the same problems as the patent in question. What is important is whether, for whatever reason, the '841 patent would lead the skilled addressee to produce the formulation claimed in the patent in question without the need for any inventive ingenuity. The '841 patent suggests hydrogenated vegetable oils in a list of compounds that could be included in the compositions it discloses. Would it be obvious to include hydrogenated vegetable oils in the composition detailed in '841? I think it would in light of the clear signpost in '841. In my view it is immaterial that the driver for including hydrogenated vegetable oil is not for the purpose of providing a lubricant and that for example, talc is included as lubricant. I would also add that nonetheless it seems that the hydrogenated vegetable oil would inherently act as a lubricant. Accordingly, I believe that claim 1 of EP0777477 is obvious in light of the disclosure of '841 alone, particularly because there is no apparent reason why the skilled addressee would be deterred from following the suggestion that hydrogenated vegetable oils could be added to the compositions specifically exemplified.
32. Next, the requester states that the patent in question is obvious on account of '805 in light of common general knowledge. The '805 patent exemplifies tablets comprising codeine/ibuprofen, disintegrants and diluents and which lack stearate acid and/or stearate salts. The lubricants disclosed are starch or microcrystalline cellulose. The

requester points out that the '805 patent teaches that excluding stearate is a factor in promoting the stability of ibuprofen/codeine tablets. The formulations in '805 are "multiphasic". However, for the reasons I have given above this is not germane to the inventive concept of the patent in question.

33. Thus, the patent in question differs from the disclosure of the '805 patent because it contains hydrogenated vegetable oil as a lubricant. Instead '805 teaches the inclusion of a self-lubricating compression aid and cites microcrystalline cellulose and starch as candidates. The '805 patent also illustrates formulations that include sodium lauryl sulphate.
34. The requester suggests that once the problem with stearates had been identified it follows from the teaching of '805 that it would be obvious to exclude stearate ions or stearic acid from compositions comprising codeine and ibuprofen. That I accept. The requester then opines that it would be obvious to use hydrogenated vegetable oil as an alternative lubricant to the self-lubricating compression aids because it was known that hydrogenated vegetable oils were lubricants. As I have mentioned before, I accept that it was common general knowledge that hydrogenated vegetable oils are lubricants.
35. The question I have to determine is whether the skilled addressee would have included hydrogenated vegetable oils in the formulations of the '805 patent in place of the self-lubricating compression aids mentioned in that patent. The answer depends on whether the common general knowledge at the relevant time recognized that hydrogenated vegetable oils would have been considered for this purpose. The requester makes no submissions in relation to this point. I note that the '805 patent states that examples of self-lubricating compression aids will be well known to those skilled in the art of tablet formulation but I have no information on whether hydrogenated vegetable oil would have been considered to have fit the bill. I am of the opinion therefore, on the basis of the information I have, that it would not have been obvious to replace the self-lubricating compression aids in '805 with a hydrogenated vegetable oil.
36. Next, the requester states that it would be obvious to replace the sodium lauryl sulphate which is present in some of the exemplified formulations in '805 with a hydrogenated vegetable oil. The requester states that sodium lauryl sulphate was a known lubricant that could be used interchangeably with hydrogenated vegetable oil. I note that the patent in question describes sodium lauryl sulphate as a wetting agent. Sodium lauryl sulphate was and is a well known surfactant. Thus, would one replace the sodium lauryl sulphate in '805 with hydrogenated vegetable oils? The '805 patent does not provide any discussion of why the

sodium lauryl sulphate was included in the exemplified formulations and I do not believe I can safely conclude that it is included as a lubricant. It follows that I cannot conclude it would be obvious to replace it with a lubricant, particularly a hydrogenated vegetable oil. Accordingly, I do not believe that when considered in the light of the common general knowledge that '805 renders claim 1 of the patent in question obvious.

37. I turn to the dependant claims. Claim 2 concerns different types of hydrogenated vegetable oils, hydrogenated soya bean oil and hydrogenated castor oils. Claims 3 and 4 concern glycerol esters of hydrogenated vegetable oils. These are conventional types and alternatives of hydrogenated vegetable oils that were well known in the art. They do not impart an inventive step on the obvious invention of claim 1.
38. Claims 5-9 concern the types of disintegrants and diluents used. In my opinion the substances detailed in these claims, as the requester points out, for example croscarmellose, cross-linked carboxymethyl cellulose, a starch glycolate, and cross-linked polyvinylpyrrolidone, were commonly found in pharmaceutical formulations before the priority date. Thus, once again these features do not provide an inventive step.
39. Claim 10 details a weight ratio of lactose to cellulose of 3:1. In the '841 patent Example 1 illustrates a composition comprising lactose, microcrystalline cellulose, hydroxyethylcellulose and hydroxypropylmethylcellulose. The microcrystalline cellulose: lactose ratio is 1:1. Taking the three types of cellulose together the cellulose:lactose ratio is 1.3:1. In '720 the cellulose:lactose ratio is 1:1. In examples 1 and 2 of EP0388125, lactose and cellulose are given in a ratio of approximately 6:1 and 16:1, respectively. Does the ratio of 3:1 lactose to cellulose in claim 10 impart an inventive step to the otherwise obvious claim 1? The requester merely states these substances are obvious. However, the claim goes further than mere iteration of the two substances and details a specific range. I do not think the requester has provided sufficient grounds to establish the obviousness of this ratio. I do not have any information of a lactose:cellulose ratio which is close to 3:1. In the absence of such grounds and information I consider that claim 10 is inventive.
40. I agree with the requester that the silica and silicon di-oxide recited in claim 11 were well known state of the art flow-aids and therefore there is no invention in incorporating these in the obvious invention of claim 1.
41. Claim 12 recites common pharmaceutical ingredients, caffeine, decongestants, antihistamines and antitussives, that were known to be present in analgesic tablets, for example in over-the-counter cough and

cold remedies before the priority date. In my opinion, these ingredients represent an obvious addition to the already obvious invention of claim 1.

42. As the requester states, the amounts of ibuprofen and codeine that fall within the range for each of these compounds detailed in claim 13 are found in '805 which the patent in question specifically refers to. Claim 14 details the amount of codeine as 13.57 mg. In the examples of the '805 patent it is 12.50mg. To my mind that difference is not significant. Accordingly, in my opinion, the amounts of ibuprofen and codeine referred to in claims 13 and 14 do not take the invention of claim 1 over the threshold required for an inventive step,
43. Claim 15 is characterized by the lack of metal ions but I do not believe this is a significant feature of pharmaceutical compositions. Accordingly, this claim is also obvious.
44. Claim 16 merely recites a method for making the formulation of claim 1 and in view of my conclusions on claim 1 does not possess an inventive step.

Opinion

45. I conclude that the invention as defined in claims 1-9 and 11-16 of the EP0777477 patent does not involve an inventive step having regard to EP0456720 and EP0535841. In my view, claim 10 possesses an inventive step over the prior art cited by the requester.

Application for review

46. Under section 74B and rule 77H, the proprietor may, within three months of the date of issue of this opinion, apply to the comptroller for a review of the opinion.

NOTE

This opinion is not based on the outcome of fully litigated proceedings. Rather, it is based on whatever material the persons requesting the opinion and filing observations have chosen to put before the Patent Office.

Jim Houlihan
Examiner