Patents Act 1977 **Opinion Number** **10/15**

OPINION UNDER SECTION 74A

Patent	EP 2124945 B1
Proprietor(s)	Intermune, Inc.
Exclusive Licensee	N/A
Requester	Elkington and Fife LLP
Observer(s)	Potter Clarkson LLP
Date Opinion issued	24 August 2015

The request

1. The Comptroller has been requested by Elkington and Fife LLP (the Requester) to issue an opinion as to whether EP (UK) 2 124 945 B1 (the patent) is valid in terms of inventiveness in light of the following documents:

D1: M Selman et al., Drugs 2004; (64); 405-430

D2: OJ Dempsey, Respiratory Medicine (2006) 100, 187101885

D3: "CAPACITY Results Conference Call"- post published data submitted by the then applicant

D4: S Nagai, Internal Medicine Vol 41, No 12 (202)

D5: TN Tozer and M Rowland, Introduction to Pharmacokinetics and Pharmacodymanics, Baltimore, Lippincott Williams & Wilkins, 2006

D6: D. Babovic-Vuksanovic et al., Neurology 2006; 67: 1860-1862

D7: A Gennaro, Ed., Remington: The Science and Practice of Pharmacy, 20th edition, Baltimore, Lippincott Williams &Wilkins, 2000

D8: G Downies, J Mackenzie and A Williams Eds, Pharmacology and Drug Management for Nurses, 2nd edition, Edinburgh, Churchill Livingstone, 1999

Observations

2. Observations were received from Potter Clarkson LLP (the Observer) on behalf of the patentee who disputed whether the opinion should be allowed as well as arguing that the patent was inventive, and observations in reply were then received from the Requester.

3. The Observer provided copies of an article cited in the patent, the academic article by Azuma *et al* and a further document, an academic article by Raghu *et al,* considered by the European Patent Office (EPO) during prosecution of the application. I have identified these as EPO(D2) and EPO(D5) respectively, given the numbering apparently used in prosecution at the EPO:

   EPO(D2): A Azuma et al, Am J Respir Crit Care Med 171: 1040

   EPO(D5): G Raghu et al, Am J Respir Crit Care Med 159, 1061

4. In their observations in reply the Requester presented a further document to support their arguments concerning the lack of inventiveness of the patent:

   D9: LM Shaw & TC Kwong, The Clinical Toxicology Laboratory....2001, page 243

Allowance of the request

5. The request for an opinion on the validity of the patent is allowable in part, as discussed below.

6. Rule 94 (1)(b) states that the comptroller shall not issue an opinion if the question upon which the opinion is sought appears to him to have been sufficiently considered in any relevant proceedings. In decision BLO/370/07 the hearing officer stated that:

> *"It is an intrinsic part of the substantive examination process to assess the novelty and obviousness of the claims, as properly construed, in the light of the prior art. In this context "prior art" means documents cited in the search report (at least under category "X" or "Y", which indicate possible relevance to novelty or inventive step) as well as material which has come to the examiner's attention in some other way. I think it reasonable to suppose in general that the examiner will have done his or her job properly in the absence of indication to the contrary, and I see no reason why this assumption should not apply even if the examiner has decided not to raise objection on the basis of any citations at substantive examination."*

7. As the Requester acknowledges D6 was considered by the EPO examiner as the document most relevant to the inventiveness of the application. The Requester however submits it is part of the common general knowledge along with documents D1, D2, D5, D7 and D8.

8. Document D3 was, as both the Requester and the Observer acknowledge, made available to the EPO examiner as post-published evidence about the plausibility of the invention, to demonstrate that the dosage regimen claimed does indeed have a technical significance. Both the Observer and the Requester in their submissions refer to UK case law concerning the admissibility of such post-published evidence about whether it can be relied upon to support the inventiveness of the patent.

9. However, from the above I consider it reasonable to assume that the EPO examiner has given due consideration to both D6 in respect of its relevance to the inventive step and D3 concerning the plausibility of the invention during the examination process, including whether D3 should be accepted as post published evidence as part of determining the sufficiency of the disclosures in the specification. I shall therefore not re-consider either D6 or D3, in so far as it relates to sufficiency, in this opinion. Similarly I see no reason to revisit either of the documents EPO(D2) or EPO(D5) which the EPO examiner has cited and should have been sufficiently considered during the substantive examination of the patent application.

10. The Observer noted that document D4 was referenced in the paper by Azuma *et al* EPO(D2) which is cited in the patent. While I take note of the Observer's comments that the patent has been the subject of substantive examination by the EPO and that the prior art landscape identified by the Requester is no different to that considered by the EPO, I am satisfied that D4 was not itself considered by the EPO examiner prior to grant of the patent and that it was published before the priority date of the patent. It also discloses matter about subsequent trials of pirfenidone to treat patients with idiopathic pulmonary fibrosis (IPF) that are different to those previously considered. Therefore I will consider the relevance of D4 to the inventive step of the patent.

11. The other documents D1, D2, D5, D7 and D8 are all representative of the state of the art and so will be considered as part of the common general knowledge. I will also take account of D6 in this respect.

The Patent

12. The patent, EP 2124945 B1, is titled "Method of providing Pirfenidone therapy to a patient". It was filed on 18th December 2007, published on 2nd December 2009 and granted on 20th April 2011. No opposition was filed at the EPO within the time limit and the patent remains in force.

13. The patent relates to methods for decreasing adverse effects associated with pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) therapy. According to the patent, pirfenidone is a non-peptide synthetic molecule that is being investigated for therapeutic benefits to patients suffering from fibrosis conditions including idiopathic pulmonary fibrosis (IPF). However, a number of adverse reactions or events are associated with pirfenidone therapy, including gastrointestinal upset, nausea, fatigue, somnolence, dizziness, headache and photosensitivity rash.

14. The patent suggests that adverse effects are alleviated by dose reduction or

discontinuation, referencing a recent study by Azuma *et al* in which the dosage was reduced in a stepwise manner, and where if the adverse reactions continued the study medication was discontinued. The patent also states that Azuma *et al* discloses a dose titration schedule wherein the patients received a 200 mg dose of pirfenidone three times a day for the first two days; a 400 mg dose three times a day for the following two days; and the maximum 600 mg dose three times a day for the remaining treatment. The patent suggests that this dose escalation regime does not optimally match the rate at which a patient develops tolerance to reduce adverse effects, and that the maximum dose obtained is only 1800 mg per day, such that there remains an unmet clinical need for a method to administer higher doses of pirfenidone to a patient that minimizes or eliminates adverse effects.

15. The patent has four claims

> *1. Pirfenidone, in an initial dose escalation regimen, for use in treating idiopathic pulmonary fibrosis (IPF), wherein the pirfenidone is for:*
> *administering to a patient a first oral daily dosage of 801 mg as one capsule comprising 267 mg of pirfenidone three times a day for days one to seven of the dose escalation regimen;*
> *administering to a patient a second oral daily dosage of 1602 mg pirfenidone as two capsules comprising 267 mg of pirfenidone three times a day for days eight to fourteen of the dose escalation regimen; and*
> *administering a third oral daily dosage of 2403 mg pirfenidone as three capsules comprising 267 mg of pirfenidone three times a day for at least day fifteen of the dose escalation regimen and*
> *wherein said dosages are for taking with food.*
>
> *2. Use of pirfenidone in the manufacture of a medicament for treating idiopathic pulmonary fibrosis (IPF), wherein the medicament is for:*
> *administering to a patient at a first oral daily dosage of 801 mg as one capsule comprising 267 mg of pirfenidone three times a day for days one to seven of the dose escalation regimen;*
> *administering a second oral daily dosage of 1602 mg as two capsules comprising 267 mg of pirfenidone three times a day for days eight to fourteen of the dose escalation regimen; and*
> *administering a third oral daily dosage of 2403 mg as three capsules comprising 267 mg of pirfenidone three times a day for at least day fifteen of the dose escalation regimen; and wherein said dosages are for taking with food.*
>
> *3. A starter pack comprising:*
> *a first set of compartments each having a first dosage amount of piffenidone that is 801 mg per day as one pill comprising 267 mg of pirfenidone three times a day; and*
> *a second set of compartments each having a second dosage amount of pirfenidone that is 1602 mg per day as two pills comprising 267 mg of pirfenidone three times a day;*
> *At least one additional set of compartments each having a third dosage amount of pirfenidone that is 2403 mg as three pills comprising 267 mg of*

pirfenidone three times a day,
wherein the first set of compartments are for administering the first dosage amount of pirfenidone for Days 1, 2, 3, 4, 5, 6 and 7, and wherein the second set of compartments are for administering a second dosage amount of pirfenidone for Days 8, 9, 10, 11, 12, 13 and 14, and wherein the additional set of compartments are for administering a third dosage amount of pirfenidone beginning on Day 15.

4. The pirfenidone or use of according to claim 1 or 2, wherein the initial dose escalation regimen reduces the incidence of an adverse event associated with the administration of pirfenidone.

16. I shall discuss the disclosures in the description of the patent that support the invention later on. However, it is relevant to note here that the patent contains no examples or results of any test that show or suggest the dosage regimen reduces the incidence of adverse effects.

Claim construction

17. Before considering document D4 I will need to construe the claims of the patent following the well known authority on claim construction which is *Kirin-Amgen and others v Hoechst Marion Roussel Limited and others* [2005] RPC 9. This requires that I put a purposive construction on the claims, interpret it in the light of the description and drawings as instructed by section 125(1) of the Patents Act, 1977 (The Act) and take account of the Protocol to Article 69 of the European Patent Convention (EPC). Simply put, I must decide what a person skilled in the art would have understood the patentee to have used the language of the claim to mean.

18. Section 125(1) of the Act states that:

> *For the purposes of this Act an invention for a patent for which an application has been made or for which a patent has been granted shall, unless the context otherwise requires, be taken to be that specified in a claim of the specification of the application or patent, as the case may be, as interpreted by the description and any drawings contained in that specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly.*

19. The Protocol on the Interpretation of Article 69 of the EPC (which corresponds to section 125(1)) states that:

> *Article 69 should not be interpreted in the sense that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the claims. Neither should it be interpreted in the sense that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and drawings by a person skilled in the art, the patentee has contemplated. On*

the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patentee with a reasonable degree of certainty for third parties.

20. The Requester has argued that the claim is clear and there is no need to devise a separate inventive concept. Claims 1 and 2 define the invention in terms of a second medical use format claim or Swiss type claim to the use of the synthetic molecule pirfenidone for the treatment of IPF, a specific medical use, wherein a specific, escalating dosage regimen is defined. I agree that there is no need to devise a separate inventive concept beyond what is set out in the claims as there is no issue with the construction of the claims.

Inventive step

21. In the UK the law to determine whether or not an invention defined in a particular claim is inventive over the prior art and that which I must follow is set out in *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588, in which the well known *Windsurfing* steps were reformulated:

> *(1)(a) Identify the notional "person skilled in the art";*
> *(1)(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, determine whether those differences constitute steps which would have been obvious to the person skilled in the art.*

22. The person skilled in the art is suggested by the Requester to be a team including a clinician specialising in the field of fibrosis and a pharmacokineticist. I consider that such a team including these experts is a fair representation of the skills expected to be present.

23. The common general knowledge would of necessity be divided between that of the clinician and that of the pharmacokineticist as well as other members of the team.

24. In that regard I consider the common general knowledge would include those documents suggested by the Requester as D1, D2, D5, D6, D7 and D8 in the original request, as well as the later filed D9. The Observer does not disagree that these documents would be known to the skilled person, but argues a different interpretation of their relevance.

25. I consider that these documents are representative of the common general knowledge of the skilled team. The clinician who is a specialist in fibrosis would be aware of the teaching of documents D1, D2 (and D6) concerning trials on the use of pirfenidone in the treatment of IPF. Further, to the skilled clinician involved in such trials, it would be routine to think about improving the quality of life by looking at how drugs were administered, by using a suitable dosage regimen given that adverse

reactions to pirfernidone were known in the prior art. The use of capsules as a dosage form is well established in the common general knowledge, as shown in D7. Similarly the pharmacokineticist would be aware of the teaching in both documents D5 and D9 that escalating dosage regimes are known in the art and have been used with a wide range of medicines especially when there is a need to avoid adverse reactions. These documents also make clear that such escalating dosage regimes may well require specific design to be suitable for the drug and patient.

26. Furthermore, I consider that the skilled team would be aware of the relevance of document D4, which discloses additional open label trials of pirfenidone for the treatment of IPF. This sets out a further different dosage escalation regimen, albeit as the Observer notes based upon that of Raghu *et al* (EPOD5) which was considered by the EPO at substantive examination. Thus both the substance and the disease condition to be treated are known, and it is clear that the use of this substance to treat this disease condition is also known.

27. What then is the difference between the prior art as identified in paragraphs 11 and 24 above and that disclosed in document D4? It lies in the actual dosage regimen that is defined in the claims which sets out a different rate of escalation of pirfenidone concentration and the final dosage being given to the patient. Both the Requester and the Observer have produced graphs which set out how the different regimes differ in these respects. I have considered both the graphs carefully. I include below as Figure 1 the graph provided by the Observer merely because it provides more detail about the regimens disclosed in those other documents that were either cited in the patent or considered during prosecution at the EPO and have been referred to by both the Observer and Requester. This Figure clearly sets out the difference between the dosage regimen of the patent and that in D4 and thus I believe neatly summarises this point (I take note of the Observer's point that this figure has been prepared using the assumption of an average body of 70 Kg as made by the Requester, but this does not affect the usefulness of Figure 1 in illustrating the different regimens). The regimen set out in the patent (which is labelled as "Invention" in Figure 1), whilst an escalating dosage regimen, can be seen to be different from those already known both in terms of the rate at which the maximum dosage is reached and the actual maximum final dosage achieved.

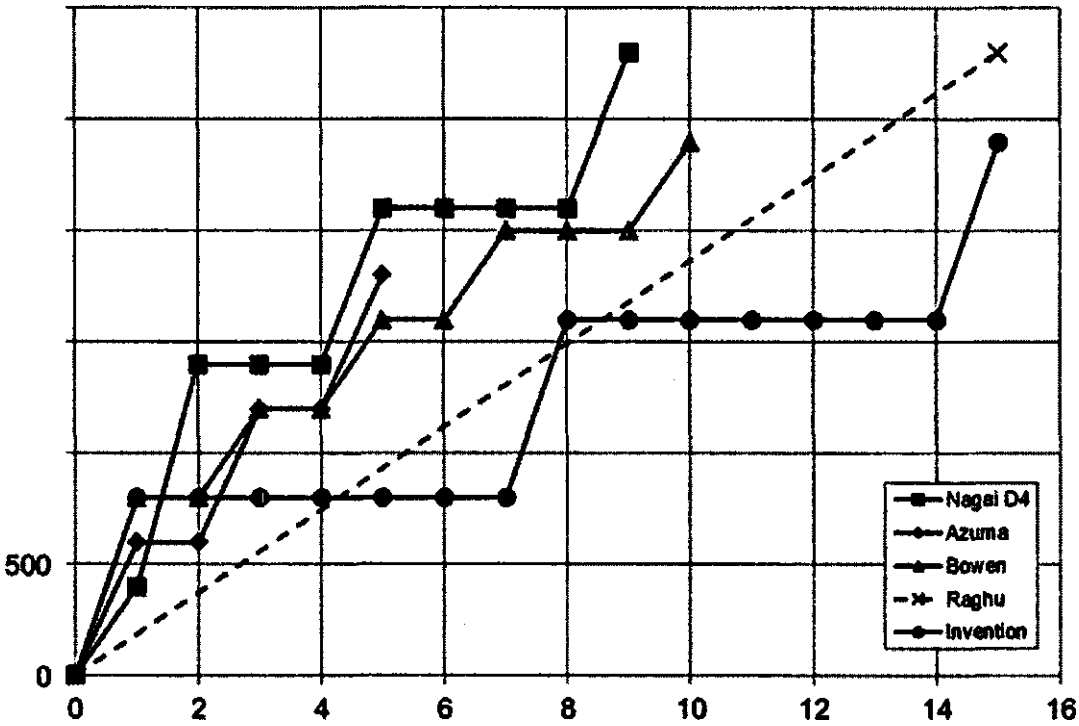

Figure 1: Graph representing the prior art dosage escalation regimens and the dosage escalation regimen of the patent EP 2124945 for pirfenidone.

28. Turning to the fourth *Pozzoli* question, I must start by taking account of the Court of Appeal's decision in *Actavis v Merck* [2008] RPC26 wherein the Court considered the allowability, or not, of second medical use claims which are defined in terms of a new dosage regime when both the substance and the disease condition to be treated are known in the prior art. The Court held that in principle, such second medical use claims are allowable:

> *29 ... Research into new and better dosage regimes is clearly desirable – and there is simply no policy reason why, if a novel non-obvious regime is invented, there should not be an appropriate patent reward. Such a reward cannot extend to covering the actual treatment but a Swiss form claim which specifies the new, inventive, regime is entirely in accordance with policy.*

29. However, the Court further made clear that there is a presumption that a new dosage regime will not be inventive unless there is a clear technical prejudice pointing away from the dosage regime:

> *32 So holding is far from saying that in general just specifying a new dosage regime in a Swiss form claim can give rise to a valid patent. On the contrary nearly always such dosage regimes will be obvious – it is standard practice to investigate appropriate dosage regimes. Only in an unusual case such as the present (where ... treatment for the condition with the substance had ceased to be worth investigating with any dosage regime) could specifying a dosage regime as part of the therapeutic use confer validity on an otherwise invalid claim.*

30. Both the Requester and Observer have commented on whether document D3, which was submitted to the EPO during substantive examination, shows that the patent is "plausible" from the information disclosed in the specification. Thus, the requirement for the patent to be sufficient is an issue that appears to have been considered by the EPO examiner. However, the Requester notes that the patent itself provides no examples or evidence to show that the escalating dosage regimen does in fact have the advantages and outcomes that are desirable; ie. not only that a higher dosage regimen is achievable but it also eliminates or minimizes the adverse events, which is the other reason for such a regimen and which would distinguish it from the prior art uses of pirfenidone to treat IPF.

31. The Observer in their response noted the following statement from paragraph 0009 of the application as filed (current paragraph 0008) :

> *"Indeed, it has been observed that even as the dosage escalates using the dosing escalation scheme described herein, adverse effects, such as somnolence, decrease."*

32. However, in the absence of any evidence to support this statement in the application as filed, such a statement is not proof of the desired effect, it is simply an assertion.

33. When I consider the disclosures in the basic patent there is no indication or discussion of any technical prejudice that points way from the claimed regimen or the provision of a higher final daily dosage amount. The discussion of the Azuma *et al* prior art citation, EPO(D2), suggests that the escalating dosage regimen it reaches is not optimal and only provides a maximum dose of 1,800 mg/day of pirfenidone. Whilst there may be a clinical need for further regimens to deliver a higher dose as the patent states at paragraph 0007, this does not suggest there is a technical prejudice against such a regimen. The detailed description is also silent on these issues. Instead it is directed to describing the presentation of pirfenidone in the form of blister packaged capsules as a starter pack. The description only briefly repeats the dosage regimen defined in the claims at paragraphs 0033-0035. It provides no further or additional information regarding the advantages and outcomes of the regimen that distinguish it from the prior art. Embodiments are described that relate to the nature of the pack, its presentation and format. The regimen and its advantages are not described in detail and at paragraph 0031 the description simply suggests that the regimen:

> *".... it is believed, better matches die* [sic] *development of tolerance to potentially adverse effects of the drug with increases in the dosage."*

34. A consideration of the Figures provided in the patent shows that they are all concerned with the nature and features of the starter pack, not with the actual dosage regimen when used on a patient with the IPF or the advantages or results that arise from using such a regimen.

35. Similarly the common general knowledge documents referred to above do not disclose any clear technical prejudice against a dosage regime such as that defined in the patent claims.

36. In fact, given the statement in the patent about there being an unmet clinical need for

further regimens, investigating other dosage regimens would be obvious standard practice for the skilled team seeking to address such a clinical need, as the Court of Appeal has identified. As I have set out in paragraph 11 above documents D1, D2, D5, D7 and D8 are all representative of the state of the art. From these it is clear that the team, in particular the pharmacokineticist, would be aware of the teaching of documents D5 and D9 that escalating dosage regimens are not only known, but can be adjusted as part of routine practice to achieve a desired dosage whilst minimising adverse effects. Similarly the team, especially the clinician, would be aware of the prior use and trials of pirfenidone to treat IPF, including the further document D4 identified by the Requester and that this document discloses further clinical trials using another dosage escalation regimen. None of these prior art documents about the use of pirfenidone suggest there is any technical prejudice pointing the skilled team away from investigating any further dosage regimens. I am satisfied that the skilled team would investigate escalating the dosage regimen to arrive at the desired final daily dosage using their general knowledge about such regimens and the drug pirfenidone in particular.

37. Therefore, I am of the opinion that claims 1 and 2 are not inventive because the dosage regimen they define is obvious, representing as the Court of Appeal has stated in *Actavis v Merck* the result of a standard practice to investigate appropriate regimens, without there being any technical or other prejudice to overcome. Consequently, I am also of the opinion that claims 3 and 4 lack an inventive step.

Conclusion

38. Taking account of all of the above, it is my opinion that the dosage regimen defined in claims 1 and 2 is not inventive over the prior art. Consequently, claim 3 to a starter pack of the medicine and the alleged advantages over the medicine as defined in claim 4 are also not inventive.

Application for review

39. Under section 74B and rule 98, the proprietor may, within three months of the date of issue of this opinion, apply to the comptroller for a review of the opinion.

Dr Patrick Purcell

Examiner

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 Office.