Patents Act 1977 **Opinion Number** **12/16**

OPINION UNDER SECTION 74A

Patent	EP 2018153
Proprietor(s)	Rosemont Pharmaceuticals Ltd
Exclusive Licensee	
Requester	Gill Jennings & Every LLP
Observer(s)	Rosemont Pharmaceuticals Ltd
Date Opinion issued	20 June 2016

The request

1. The comptroller has been requested by Gill Jennings & Every LLP ("the requester") to issue an opinion as to whether claims 1-21 of EP 2018153 are valid, in particular that the claims are not inventive, in light of the following eight documents D1-D8 supplied by the requester representing the prior art and the common general knowledge:

D1: CN1498612A

D1a: English Translation of CN1498612A

D2: US20040138295A1

D3: Zocor® product monograph August 2005;

D4: Remington, the Science and Practice of Pharmacy, 20th Edition, 2000, pages 240-241, 743-745 and 1294-1295;

D5: WO2003103640A1

D6: W01997016184A1

D7: The Merck Index; An Encyclopaedia of Chemicals, Drugs and Biologicals, Twelfth Edition, 1996, Entries 3883, 6182, 8782, 8805;

D8: J AOAC Int. 2005 Nov-Dec; 88(6):1631-6. Stability study of simvastatin under hydrolytic conditions assessed by liquid chromatography. Alvarez-Lueje et al.

Observations

2. Observations were received on 27 April 2016 from Haseltine Lake LLP on behalf of the patentee, Rosemont Pharmaceuticals Ltd ("the Proprietor"). The observations set out the view of the proprietor that the claims of the patent is inventive over the documents referred to by the requester. They asserted that little credibility could given to the disclosures of D1 because of the quality of the translation provided as D1a. In addition these observations included further evidence supplied to the European Patent Office ("EPO") in support of inventive step during prosecution of the application, which is referred to as D9.

   D9: Appendix A

Observations in reply

3. Observations in reply were received from the requester on 11 May 2016 in response those supplied the proprietor. These maintained the assertions that the invention was obvious and also discussed the further evidence supplied by the proprietor. These included a further verified translation of D1 to counter specific points raised in the observations:

   D1b: verified human translation of D1 (CN14968612A)

The patent

4. The patent entitled "Liquid Oral Compositions" was filed on 26 April 2007, claiming priority of 26 April 2006 and was granted by the EPO on 11 April 2012.

5. The patent relates to providing a liquid formulation of a statin, Simvastatin that is a lipid lowering agent. It can be used in preventing coronary diseases but the patent describes that the current brand leader is sold in solid tablet form, and that many patients, especially elderly ones, have difficulties in swallowing such tablets, etc. The invention defined in the claims relates to oral formulations of simvastatin as a liquid suspension and methods of preparing such formulations.

6. There are 21 claims, including two independent claims 1 and 21. The independent claims read:

> *1. An aqueous suspension which is suitable for oral administration, comprising simvastatin, at least one suspending agent, and at least one preservative, wherein the d_{90} of the simvastatin particles is less than about 100 μm.*
>
> *21. A method of making a simvastatin suspension which is suitable for oral administration, comprising the steps of:*
> *a. adding one or more suspending agents to purified water;*
> *b. adding one or more preservatives;*
> *c. adding simvastatin wherein the d_{90} of the simvastatin particles is less than about 100 μm and mixing until wetted out;*

d. adjusting the pH, if necessary, until the pH is less than or equal to 7.0; and
e. adding purified water to make up to the final volume.

Claim construction

7. Before considering the documents put forward in the request 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) and take account of the Protocol to Article 69 of the 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.

8. 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.*

9. And 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.*

10. Both the requester and observer agree that the patent relates to an aqueous suspension of simvastatin, methods of making such a suspension, and as such I see no need to construe the claims any further because their meaning would be clear to a person skilled in the art.

Inventive step – the law

11. The relevant provisions in relation to inventive step are Section 1(1)b and Section 3 of the Patents Act 1977.

12. The relevant Section 1(1) of the Act reads:

> *A patent may be granted only for an invention in respect of the following conditions are satisfied, that is to say –*
> *(a) the invention is new;*
> *(b) it involves an inventive step…*

13. Section 3 of the Patents Act 1977 states:

> *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).*

14. To determine whether or not an invention defined in a particular claim is inventive over the prior art, I will rely on the principles established 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.*

15. I will therefore use this approach to assess whether the claims involve an inventive step in light of documents D1-D8. I note that both the requester and the observer have referred to these principles in the request, observations and reply in their assessments of the documents they rely upon.

Inventive step

16. The requester sets out three alternative arguments as to why the invention of claim 1 lacks an inventive step:

    a. firstly, lack of inventive step over D1/D1a/D1b and D2, D4, D5

    b. secondly, lack of inventive step over D6 and,

    c. thirdly, lack of inventive step over common general knowledge

17. The requester makes a further fourth argument (d). that claim 21 lacks an inventive step over D1. Finally the requester argues (e). that the dependent claims 2-20 also lack an inventive step in light of the common general knowledge.

18. I will consider each of these arguments in turn. However, the application of the first two steps of *Pozzoli* are consistent to all these alternative arguments and so these

are set out below without being repeated.

(1)(a) Identify the notional "person skilled in the art";

19. The requester has identified the appropriate skilled person as "one skilled in the formulation or reformulation of pharmaceutical compositions." The observer has not disagreed with this assessment and I consider it to be accurate.

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

20. The requester has identified D4, Remington, as being part of the common general knowledge of the skilled person. They have also identified the existing formulations of the active ingredient simvastatin in medicinal products such as Zocor® as part of the common general knowledge. The requester and observer are some way apart on what constitutes the common general knowledge. The observer argues that because document D4 does not refer specifically to simvastatin or indeed statins in general, the skilled person would not consider this document to be part of the common general knowledge.

21. I do not accept the observer's interpretation of the relevance of D4 because whilst this is a general guide to pharmaceutical preparations and formulations, it is one that the skilled person would be fully aware of as part of the common general knowledge in this art. As the requester states in the observations in response it is a well-regarded text book in the field that the skilled person would be cognisant of. Consequentially the skilled person would be aware of the general principles of preparing pharmaceutical solutions, emulsions and suspensions this document sets out, irrespective of the specific active ingredient the skilled person was seeking to prepare or reformulate in a further medicinal product. For the same reasons I consider the skilled person would also be aware of D7, The Merck Index, as part of the common general knowledge about the nature and properties of compounds used in pharmaceutical preparations.

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

22. As I have set out above in construing the claim I believe the inventive concept of claim 1 can be identified as an aqueous suspension suitable for oral administration comprising simvastatin, at least one suspending agent, and at least one preservative, wherein the d_{90} of the simvastatin particles is less than about 100 μm. Claim 21 can similarly be identified as a method of preparing such a suspension. The patent sets out that such liquid forms are easier for oral administration in patients who experience difficulties in swallowing tablets or capsules, whilst maintaining the bioavailability of the active simvastatin.

23. Having established these first two steps I can now turn to the last two steps as applied in each of the alternative arguments made by the requester.

24. Firstly, (a). is the invention obvious over D1/D1a/D1b and D2, D4, D5?

(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

25. D1 discloses a dry formulation that is used to prepare a suspension of the statin simvastatin for oral use by a patient, which comprises a diluent or dispersing agent, a suspending agent, an antioxidant, a chelating agent, glidant and flavouring or colouring agents. Embodiments 2 and 5 in the description both relate specifically to the simvastatin statin and include examples of the other ingredients present in these formulations. The formulations aim to address the problems of prior art formulations by being easier to take orally whilst maintaining the stability and dissolution of the drug. Both D2 and D5 independently disclose different solid formulations comprising simvastatin, wherein the simvastatin particle size is 100 μm or less.

26. The difference however, between the formulations disclosed in D1 and those of the current invention as defined in claim 1, is that (a) the preparation is not an aqueous suspension, but rather that a powder that can be used to prepare a liquid suspension, and (b) no simvastatin particle size is disclosed or suggested in contrast to the specified 100 μm size set out in claim 1. Both D2 and D5 are different from the current invention as they disclose solid simvastatin formulations.

(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.

27. The requester asserts that claim 1 lacks an inventive step over the teachings of D1 in the light of the common general knowledge as represented in D4 and the disclosures in either one of documents D2 or D5 to come to a suspension with particles of a size of 100 μm or less. The observer, in contrast, disagrees and argues that nothing in the disclosures of these documents would result in the skilled person would teach the invention of claim 1. In particular the observer argues that D1a, the translation first supplied by the requester, is of such uncertain quality that the skilled person would not be able to clearly interpret the passages specifically referred to by the requester in support of their arguments. The observer suggests that references to "powdered dry suspension" is unclear and that this document does not clearly and unambiguously teach a liquid suspension. Further the observer argues that D1 does not teach any further advantages concerning the stability of the formulation. In contrast the observer also supplied a copy of data supplied to the EPO in support of their assertion that the formulation provides better simvastatin stability. Consequently, the observer asserts that the skilled person would not be motivated to combine the teaching of the various documents, D1/D1a, D4 and D2 or D5 to come at the invention claimed. In their observations in response, the requester referred to a further certified translation of D1, D1b, and made clear that, as D4 was considered to be part of the common general knowledge, the mosaic of documents they relied upon to demonstrate the lack of inventive step was D1 and either of documents D2 or D5.

28. Document D1/D1a/D1b does not directly disclose a liquid formulation of simvastatin particles of claim 1. However, it is my opinion that the skilled person, when considering this document and either of the translations provided would consider that it does disclose the preparation of a dry formulation which can be used to prepare a liquid simvastatin formulation for patient use. Paragraphs 2 and 3 of this document at page 2 of D1b, for example, make clear that the stability problems of statins such as simvastatin in terms of oxidation were recognised and that these, along with other issues such as convenience of administration, are addressed by the suspension. Further these paragraphs make clear that the suspension is prepared for use by the addition of water to form a suspension which can be taken orally by the patient. This document though, does not disclose the size of the simvastatin particles present in the suspension. It rather refers to the ingredients, when combined, being pulverisered and then sieved through a 65 mesh sieve.

29. The observer proposes that the skilled person would not consider either of documents D2 or D5 to be relevant in determining the size of the particle that would be present in such a formulation, both these documents being directed to the preparation of solid simvastatin formulations. The requester in contrast sets out that these documents show the skilled person would be aware that simvastatin particles of the appropriate size range, their preparation and properties, such as their solubility, would be known to the skilled person and that there are is nothing special about simvastatin compared to the general principles and properties for pharmaceutical formulations as taught in D4.

30. I consider that the arguments made by the requester about the whether the size of the particles is obvious to the skilled person are correct. The skilled person would be aware of the general texts used in formulation research, in particular D4. The general teachings in this text about the preparation of suspensions and the relevance of the particle sizes in determining the solubility, dispersability and bioavailability would form the background to their approach to arriving at a new formulation. Notwithstanding the fact that both documents D2 and D5 are primarily directed to preparing solid simvastatin formulations, the skilled person would be aware from both these documents that simvastatin had been prepared in a range of different sized particles. In D2 the size of the particles disclosed is 100 μm, whilst in D5 the particle size is only 2 μm. However, in both documents the size of the particles selected delivers the properties of bioavailability, solubility, etc, that the skilled person would recognise as being desirable in any suspension formulation. As such, especially given the broad size range up to 100 μm of the particles used in the prior art formulations, it appears to me that the invention, a liquid formulation of simvastatin particles of less than 100 μm, would be obvious to the skilled person to try with a reasonable expectation of success, as Jacob LJ set out in *Saint-Gobain PAM SA v Fusion Provida Ltd and Electrosteel Castings Ltd* [2005] EWCA Civ 177, [2005] IP & T 880. The fact that the formulation of D1 is apparently only made up into the liquid form at the point of use is of no significance for the skilled person given the ultimate use disclosed in D1.

31. As a result I am of the opinion that the invention as defined in claim 1 would be obvious to the skilled person when considering the disclosures of D1 or its translations D1a/D1b about preparing a dry suspension that can be used to prepare an aqueous formulation would, having considered the teachings in either D2 or D5,

and their common general knowledge of which D4 would form part.

32. I will now apply the same approach in assessing the last two steps when applied to the second line of argument made by the requester, (b). that the invention lacks an inventive step over D6.

(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

33. D6 discloses the use of statins, including simvastatin, in combination with another active ingredient, an ACAT inhibitor, in methods of regulating lipid concentrations in patients. The requester refers me to specific passages in the description that it says discloses liquid preparations of these active ingredients as finely divided particles with suspending agents, although no actual embodiments that comprise such liquid preparations are embodied. The requester then argues that in light of the common general knowledge demonstrated in D4 that the invention is obvious because of the disclosures in D6. The observer in reply contests that the particle sizes of claim 1 are not obvious from these documents.

34. Thus the differences between the inventive concept of claim 1 and the matter disclosed in D6 is that no actual suspension formulation is disclosed or exemplified in the description and there is no teaching about the specific particle size in such a formulation.

(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.

35. Whilst I believe the skilled worker considering the disclosures in D6 might be motivated to try a liquid formulation in preference to solid formulations such as tablets, I do not consider the skilled worker would arrive at a formulation with particles that are of a size less than 100 μm as required by claim 1. This document does not in my opinion disclose a liquid suspension; it suggests that this is an alternative, but does not go as far as disclosing any actual formulation. The common general knowledge represented by D4 would indicate to the skilled person that smaller particles have desirable properties at most, but does not in itself suggest or define that the particles should have a specific size. It appears to me to be hindsight to argue that when faced with this document a specific particle size can be arrived at out of all the possible options, notwithstanding the general knowledge of the skilled person. This does not appear to be a more or less self-evident choice as required for a lack of inventive step as set out by Jacob LJ in *Saint-Gobain* at para 35.

36. Consequently I am of the opinion that the invention of claim 1 is inventive over the disclosures in D6.

37. Finally, I turn to the third argument of the requester concerning claim 1, (c). that

claim 1 is not inventive over the common general knowledge.

(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

38. The requester states that starting from the Zocor® commercial product (D3), and that the preparation of crushed tablet preparations was known to overcome the problems of administering these, then the skilled person with knowledge of the common general knowledge such as in D4, would arrive at a formulation comprising 100 μm size particles.

39. The observer argues that the requester is with the benefit of hindsight combining these documents to arrive at a liquid formulation possessing an improved, or at least, acceptable shelf life.

(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.

40. The monograph for Zocor® D3 does not disclose an aqueous formulation of the active simvastatin as it is concerned with the commercial tablet preparations, and D4 does not disclose any specific particle sizes to be used in making simvastatin preparations.

41. The skilled worker would, as I have set out above, be aware of the teaching in D4 as part of the common general knowledge about the preparation of suspension formulations, and that in principle smaller sized particles are required for the effective preparation of these. However, I do not consider that the skilled worker would be minded to try any specific size particle without exercising some inventive skill. The common general knowledge in D4 would provide an indication that certain sizes of particles of simvastatin might work in a liquid formulation. Similarly, whilst crushing tablets to aid their use is known, this equally does not teach that any specific size of particle should be obtained. Again, as set out above, these disclosures do not meet the more or less self-evident choice suggested by Jacob LJ in *Saint-Gobain.*

42. Therefore, it is my opinion that the invention of claim 1 is inventive over the disclosures in the common general knowledge.

43. The requester has further argued that (d). claim 21 lacks an inventive step when the disclosure of D1 is considered in the light of the disclosures in D4 and also D8.

(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

44. D1 describes formulations for preparing a simvastatin suspension. The requester argues that D8 which makes clear that simvastatin stability is pH dependent, thus renders the further requirement of claim 21 that the pH of the suspension is less than or equal to 7.0 obvious in addition to the common general knowledge of D4 on the preparation of pharmaceutical suspensions. The observer, having argued that claim 1 is inventive, states that claim 21 is also inventive for similar reasons.

45. As stated above D1 does not itself define an aqueous formulation of simvastatin, rather a dry formulation that can be used to prepare such an aqueous formulation. The methods of preparation of these dry suspensions do not include a step analogous to step a. of claim 21 where one or more suspending agents are added to purified water. The closest the methods of preparation described in D1 come to such a step are where the methods use an oil or molten polyethylene glycol or polyvinylidene 6000 at the addition of the active ingredient. Further these methods are silent about the size of the particles used (step c. of claim 21), about adjusting the pH (step d. of claim 21) and the final step e. of adjusting the volume.

(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.

46. The requester suggests in their evidence that all the steps set out in claim 21 would be obvious to the skilled person given their common general knowledge as represented in D4. The steps of the preparation method are all routine steps that would be undertaken by any skilled person and that the adjustment of the pH of the suspension to pH 7.0 would further be obvious to the skilled person given the teaching of D8 that simvastatin stability is pH sensitive.

47. I consider that the skilled person would be fully aware of the standard steps used in making suspensions as set out in D4 as part of the common general knowledge. Thus, to the skilled person, these in general would all be obvious features of a method of making a simvastatin suspension, combining merely routine formulation steps

48. However, these documents are silent on the requirement set out in step c. that the simvastatin particles have a size of less than about 100 μm. The requester does not address this omission either in their request nor directly in their observations in reply. As I have set out above, I have considered that this requirement forms a key difference between the formulation and the prior art, and is a major point of disagreement between the requester and observer over the inventiveness of claim 1. Thus, it appears to me that this is not a feature that can be considered to be a routine or standard part of the preparation method of claim 21. Furthermore these documents are also silent about step d. where the pH of the formulation is adjusted to a pH of 7.0 or less. Thus, the skilled person seeking to make a simvastatin preparation could only be aware of about the pH stability requirements of simvastatin from the teaching of D8.

49. As set out above, I have found that claim 1 lacks an inventive step over the first argument (a). made by the requester, when the teaching of D1 is considered in the light of either of D2 or D5 and the common general knowledge of D4, but that it is inventive over the alternative arguments (b). or (c). made by the requester. D1

teaches preparing a dry formulation of simvastatin that can be made up into a suspension, and either one of D2 or D5 teach that particles of the appropriate size can be prepared. The particle size required can only be arrived at by the skilled person from the teaching in either one of D2 or D5. However, these documents do not teach that the formulation should be prepared with the specific pH range defined in claim 21. The skilled person seeking to make a liquid preparation would be aware of the common general knowledge of preparing aqueous suspensions represented in D4, but would not arrive at the specific pH claimed from the teaching of either of D2 or D5. Therefore, I find that the method of claim 21 is inventive when the teaching of these documents is considered. Alternatively, if as argued by the requester, the skilled person was aware of the teaching in D8, this document does not set out the specific particle size of step c. of claim 21 and so the skilled person would not arrive at these size particles without exercising some inventive skill. I do not consider that they would further consider either of D2 or D5 which are directed to solid formulations of simvastatin.

50. I therefore consider that the method of preparing a simvastatin preparation defined in claim 21 is inventive.

51. Finally, I turn to the final arguments in the request (e). that the dependent claims 2-20 lack an inventive step.

52. I will summarise these arguments for all the claims rather than repeat those made individually for each specific claim, because the requester asserts that since the features defined in each claim objected to set out well known examples or alternatives, then these are obvious over the common general knowledge or prior art. Thus, as claims 5-8 which define known buffering systems used in pharmaceutical formulations, or that the active ingredient simvastatin is present at concentrations that are routine, for example the amount of simvastatin defined in claim 18 is the same as pre-existing simvastatin preparations, then all these claims are obvious. The observer again asserts that because claim 1 is inventive, no objection exists concerning any of these claims.

53. Having accepted that the skilled person would be aware of D4 as part of the common general knowledge, and also that they would be aware of the prior art concerning simvastatin, its previous preparations and uses, I consider that these dependent claims are also obvious. Claims 2-17 define the nature of the formulation in more detail and appear merely to outline the use of known components such as buffers, preservatives, sweeteners, etc, at known ranges, whilst claims 18-20 define the active ingredient simvastatin at concentrations and for uses which are established in the prior art. As a result, all these dependent claims 2-20 are obvious as any one of these alternatives would be aspects of the formulation that the skilled person would try with a reasonable expectation of success, and without their having to exercise any inventive skill.

Conclusion

54. It is my opinion that, for the reasons set out above, independent claim 1 lacks an inventive step, and further that the dependent claims 2-20 also lack an inventive step. However, I find that claim 21 is inventive for the reasons set out above.

Application for review

55. 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.