Patents Act 1977 **Opinion Number** **04/19**

OPINION UNDER SECTION 74A

Patent	EP(UK) 2683361 B1
Proprietor(s)	Helm Swiss GmbH
Exclusive Licensee	
Requester	Helm Swiss GmbH
Observer(s)	Uni-Pharm Kleon Tsetis Pharmaceutical Laboratories S.A.
Date Opinion issued	04 June 2019

The Request

1. The comptroller has been requested by Helm Swiss GmbH ("the requester") to issue an opinion as to whether their patent EP(UK) 2683361 B1 ("the patent") would be infringed by a particular process for manufacturing an oral solution of levothyroxine (the "Anfarm Process") if carried out in the UK and, whether products obtained directly by means of the Anfarm Process would infringe if they were imported, disposed of, offered for disposal, used or kept in the UK.

2. The request was received from the requester's representative, Bristows LLP, on 15 March 2019. It was accompanied by a statement explaining the request as well as copies of the supporting documents below:

   Annex 1: EP(UK) 2683361 B1

   Annex 2: EPO Opposition Division Grounds for Decision dated 14 March 2018 upholding the validity of the patent

   Annex 3: Decision 6351/2017 of the Athens Court of First instance dated 31 August 2017 and a certified translation thereof

   Annex 4: Expert opinion of Professor Christos Kontogiannis dated 20 June 2017 and a certified translation thereof

   Annex 5: Patient Information leaflet and Summary of Product Characteristics for Oral Solutions of Levothyroxine manufactured by Anfarm Hellas S.A.

Observations

3. Observations were received from Uni-Pharm Kleon Tsetis Pharmaceutical Laboratories S.A. on 11 April 2019 which were accompanied by the following documents:

   Annex 1: EP 2932963 A1

   Annex 2: Patient Leaflet Information “Evotrox Oral Solution”

Observations in Reply

4. Observations in reply were submitted by the requester’s representative on 30 April 2019.

Matters to be considered by this opinion

5. The observer contends that the comptroller should refuse the request under Rule 96(2) of the Patents Rules 2007 due to unreliability of the expert evidence of Prof. Christos Kontogiannis submitted by the requester.

6. Section 74A(3) of the Patents Act 1977 (the “Act”) outlines the circumstances under which an opinion request may be refused:

   “The comptroller shall issue an opinion if requested to do so under subsection (1) above, but shall not do so –

   (a) In such circumstances as may be prescribed, or

   (b) If for any reason he considers it inappropriate in all the circumstances to do so”

7. Rule 94 of the Patents Rules 2007 states:

   “An opinion will not be issued if the request for an opinion appears to the comptroller to be frivolous or vexatious, or the question upon which an opinion is sought appears to have been sufficiently considered in any proceedings”

8. I do not consider that unreliability of evidence is a circumstance for refusal of an opinion. I will consider the evidence presented by both parties as part of this opinion.

9. Section 74A of the Act provides for the procedure where the comptroller can issue, on request, non-binding opinions on questions of validity relating to novelty, inventive step, added matter, sufficiency and excluded matter, amongst other things, and on questions of infringement. Any observations should be confined to the issues raised by the request and should not broaden the scope of the opinion by raising new issues. Consequently, if an observer wishes to explore validity issues not raised by the request then they must file a separate request.

10. The observer has alleged that the patent on which the request is based is invalid

however the issue of validity was not raised in the request. Therefore, the validity arguments and corresponding documents submitted by the observer will not be considered in this opinion.

The Patent

11. The patent entitled “Method for the preparation of a levothyroxine solution” was filed on 10 March 2011 and was granted on 25 November 2015. The patent remains in force in the United Kingdom.

12. The patent relates to a method for the preparation of an oral levothyroxine composition. Levothyroxine is a synthetic form of thyroxine, used as a hormone substitute for patients with thyroid conditions, such as hypothyroidism, as well as conditions in which the thyroid gland becomes enlarged causing swelling of the neck. The patent explains that oral solutions of levothyroxine are particularly suitable for use in children and in the elderly, who may have difficulty swallowing tablets, and has an added advantage over solid forms in terms of dose uniformity. However, solutions of levothyroxine are less stable compared with tablets during storage and are prone to decomposition. Furthermore, levothyroxine solutions may comprise relatively high amounts of liothyronine, which is believed to be the source of side effects in some patients.

13. The invention provides a faster process for the preparation of a stable levothyroxine solution that comprises less liothyronine. A key feature of the process is the dissolution of levothyroxine in a basic aqueous solvent having a pH of at least 8 to obtain a levothyroxine solution, after which the pH of the solution is lowered to a pH of between 5-6. The patent explains that dissolution of levothyroxine in a basic aqueous solvent is relatively fast compared to neutral or acidic water (pH<7) or similar aqueous solvents. Furthermore, an end pH of 5-6 is suitable for storage as well as for administering the levothyroxine to a patient.

14. The patent has fourteen claims. Claims 1-11 relate to a process for the preparation of an oral levothyroxine composition and claims 12-14 relate to a product obtained by the method.

15. Claim 1 reads as follows:

> *Method for the preparation of an oral levothyroxine composition, comprising the steps of:*
> *a) providing a salt of levothyroxine, preferably the sodium salt of levothyroxine,*
> *b) mixing levothyroxine with an aqueous solvent, the aqueous solvent being a mixture of water and a water-miscible organic solvent, the water-miscible organic solvent comprising glycerol,*
> *c) adjusting the pH to a pH of at least 8 to yield a basic aqueous solvent, and*
> *d) dissolving the levothyroxine in the basic aqueous solvent to yield a levothyroxine solution, and*
> *e) lowering the pH of the levothyroxine solution to between 5-6*

16. Claim 12 reads as follows:

> *Oral levothyroxine composition obtainable using the method according to any of the preceding claims*

Infringement

17. Section 60 of the Act governs what constitutes infringement of a patent:

> *(1) Subject to the provisions of this section, a person infringes a patent for an invention if, but only if, while the patent is in force he does any of the following things in the United Kingdom in relation to the invention without the consent of the proprietor of the patent, that is to say-*
>
> *(a) Where the invention is a product, he makes, disposes of, offers to dispose of, uses or imports the product or keeps it whether for disposal or otherwise;*
>
> *(b) Where the invention is a process, he uses the process, or he offers it for use in the United Kingdom when he knows, or it is obvious to a reasonable person in the circumstances, that its use there without the consent of the proprietor would be an infringement of the patent;*
>
> *(c) Where the invention is a process, he disposes of, offers to dispose of, uses or imports any product obtained directly by means of that process or keeps any such product whether for disposal or otherwise…*

18. In the Supreme Court in *Actavis v Eli Lilly*[1], Lord Neuberger states that the problem of infringement is best approached by addressing two issues, each of which is to be considered through the eyes of the notional addressee of the patent in suit, i.e. the person skilled in the relevant art. Those issues are:

> *(i) does the variant infringe any of the claims as a matter of normal interpretation; and, if not,*
>
> *(ii) does the variant nonetheless infringe because it varies from the invention in a way or ways which is or are immaterial?*

19. If the answer is “yes”, there is infringement; otherwise there is not.

Claim construction

20. Before I can determine whether there would be infringement of the claims of the patent I must first construe them. This means interpreting the claims in light of the description and drawings as instructed by section 125(1). In doing so, I must interpret the claims in context through the eyes of the person skilled in the art. Ultimately the question is what the person skilled in the art would have understood the patentee to be using the language of the claim to mean. This approach has been

[1] Actavis UK Limited and Others v Eli Lilly and Company [2017] UKSC 48

confirmed in the recent decisions of the High Court in *Mylan v Yeda*[2] and the Court of Appeal in *Actavis v ICOS*[3].

21. 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.

22. Neither the requester nor the observer has submitted a definition of the person skilled in the art.

23. In my view the person skilled in the art is a pharmaceutical formulation scientist working in the field of developing oral formulations of levothyroxine. I consider that such a person would be aware of the advantages of oral levothyroxine solutions including dose uniformity and ease of administration but would also be aware of the potential stability issues of levothyroxine solutions. In my opinion the person skilled in the art would also be aware of commonly used excipients and carriers used in orally administrable pharmaceutical solutions, including solvents, buffers, preservatives, flavourings etc.

24. Neither the requester nor the observer has made any comments in relation to the construction of the claims or how they should be interpreted. I consider that claim 1 is generally clear and straightforward to construe however there are some points that I believe are worthy of consideration.

25. Point c) of the process defines "*adjusting the pH to a pH of at least 8 to yield a basic aqueous solvent"*. I consider that the person skilled in the art would understand this wording to mean the addition of a component, which is inherently basic, to the aqueous solvent to raise the pH of the aqueous solvent to at least 8.

26. Point e) of the process defines *"lowering the pH of the levothyroxine solution to be 5-6"*. I consider that the person skilled in the art would understand this wording to mean the addition of a component, which is inherently acidic, to lower the pH of the levothyroxine solution to between 5-6.

Does the Anfarm Process and products directly obtained by that process infringe as a matter of normal interpretation?

27. I shall start by considering whether the Anfarm Process and products directly obtained by that process would infringe the patent if carried out in the United Kingdom as a matter or normal interpretation.

28. The requester has not presented any arguments in relation to whether the Anfarm Process and products directly obtained by that process infringe as a matter of normal

[2] Generics UK Ltd (t/a Mylan) v Yeda Research and Dev. Co. Ltd & Anor [2017] EWHC 2629 (Pat)
[3] Actavis Group & Ors v ICOS & Eli Lilly & Co. [2017] EWCA Civ 1671

interpretation.

29. The Anfarm Process as described in Annex 3 includes the steps: *"firstly, raising the pH of the water by adding the preservative sodium parahydroxybenzoate methylester to produce a basic solvent and then mixing this solution with an organic solvent comprising glycerol. Subsequently, the sodium salt of levothyroxine is delivered to this mixture of water and glycerol, levothyroxine is dissolved to yield a solution of levothyroxine, and finally the pH of the solution is reduced to between 5.3-5.7"*.

30. The process as defined in claim 1 of the patent differs from the Anfarm Process in that claim 1 requires mixing of a salt of levothyroxine with an aqueous solvent comprising water and glycerol and subsequently adjusting the pH to at least 8 to dissolve the levothyroxine, whereas the Anfarm Process requires first raising the pH of water by adding the preservative sodium parahydroxybenzoate methylester to produce a basic solvent, mixing the resulting aqueous solvent with glycerol and subsequently adding a salt of levothyroxine.

31. I am satisfied that as a matter of normal interpretation the Anfarm Process, as described in Annex 3, does not comprise the same sequence of steps as those defined in claim 1 of the patent. Therefore, in my opinion the Anfarm Process and products directly obtained by that process would not infringe the process of claim 1 as a matter or normal interpretation in accordance with section 60(1)(b) and 60(1)(c) of the Act.

Does the Anfarm Process and products directly obtained by that process infringe because it varies from the invention in a way or ways which is or are immaterial?

32. In *Actavis v Eli Lilly*[1], the Court provided a reformulation of the three questions in *Improver*[4] to provide assistance in determining whether a variant infringes. These reformulated questions are:

    (i) *Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, i.e. the inventive concept revealed by the patent?*

    (ii) *Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?*

    (iii) *Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?*

[4] Improver Corporation v Remington Consumer Products Ltd [1990] FSR 181

33. To establish infringement in a case where there is no literal infringement, a patentee would have to establish that the answer to the first two questions is “yes” and that the answer to the third question is “no”.

34. As I have discussed above I consider that the process as defined in claim 1 of the patent differs from the Anfarm Process in that claim 1 requires mixing of a salt of levothyroxine with an aqueous solvent comprising water and glycerol and subsequently adjusting the pH to at least 8 to dissolve the levothyroxine, whereas the Anfarm Process requires first raising the pH of water, by adding the preservative sodium parahydroxybenzoate methylester, to produce a basic solvent, mixing the resulting aqueous solvent with glycerol and subsequently adding a salt of levothyroxine. To ascertain whether the Anfarm Process would infringe the patent if used in the UK I must determine whether these differences (variations) are immaterial using the reformulated questions provided in *Actavis v Eli Lilly*[1] for guidance.

35. With respect to question (i) the requester submits that the Anfarm Process achieves substantially the same result as that of claim 1 of the patent in substantially the same way. The requester alleges that *“the “result” is the stable levothyroxine solution. The “way” is the dissolution of a salt of levothyroxine in a water/glycerol mix at high pH before lowering the pH to produce the final product”*.

36. The requester refers to the expert opinion of Prof Kontogiannis in which he reports:

> *“In both cases, the process is identical, i.e. the dissolution of levothyroxine in a mixture of water and glycerol having a pH of at least 8.*
> *Therefore, the order in which the active is added before or after the pH increase of the solvent is irrelevant since the critical step (innovation) is the increase in the pH and not the mode or time series of addition of the active substance.”*

37. The observer argues that *“there is no recognition of any main feature of the method as reported by Professor Christos Kontogiannis regarding the increase/decrease of the pH in the patent. This notion, anyway, stands in a stark contrast to the necessary presence of feature 3. in the claimed process. This process step appears to be important and a key feature of the claimed invention since in this process step already significant part of levothyroxine are dissolved. Thus, the forming of a dispersion is a necessary part of the inventive concept revealed by the patent which concept, however, is not practiced in the Anfarm Process. The key concept of the invention cannot be only the dissolution of levothyroxine in a solution having a pH of at least 8, since a significant part of a dissolution is carried out in a neutral solvent (feature 3.).”*.

38. The observer argues that a significant part of dissolution is carried out at a neutral pH from the dispersion of levothyroxine in the mixture of glycerol and water. However, I can find no teaching in the patent that indicates that both: dissolution of levothyroxine clearly occurs at a neutral pH, and that there is a technical advantage associated with this. Furthermore, I can find no teaching in the patent to direct the person skilled in the art that dissolution of levothyroxine at a neutral pH is an essential feature of the method. In addition, the dissolution of levothyroxine at a neutral pH is not a requirement of claim 1 and there is no suggestion in the patent

that this is an essential feature of the method as claimed. Claim 1 of the patent specifies that dissolution of levothyroxine occurs when the pH is adjusted to at least 8 at step (d), and there is no requirement or suggestion that dissolution should occur before this step.

39. Thus, in my view the inventive concept of the patent resides in the dissolution of levothyroxine in a mixture of glycerol and water at a pH of at least 8 followed by subsequent lowering of the pH to between 5-6.

40. No evidence has been presented to suggest that there is a substantial difference in the levothyroxine solution obtained following the method of the patent compared to that obtained following the method of the Anfarm Process. In the absence of any evidence to the contrary, whether the levothyroxine is added before or after the pH of the glycerol/water mixture is raised I do not believe would make a substantial difference to the result i.e. a basic solution of levothyroxine in glycerol and water. Furthermore, no evidence has been provided to suggest that forming an initial dispersion of levothyroxine in a glycerol and water mixture before adjusting the pH to at least 8 has a particular technical advantage over that of adding levothyroxine to a basic solution of glycerol and water.

41. In my opinion, the dissolution of levothyroxine in a basic glycerol and water solution, followed by lowering of the pH to between 5.3-5.7, as in accordance with the Anfarm Process, achieves substantially the same result in substantially the same way as the process of claim 1 of the patent. Therefore, my answer to question (i) above is “yes”.

42. With respect to question (ii) the requester argues that *“on being told that the Anfarm Process delivered a stable levothyroxine solution, the skilled person reading the Patent at the priority date would consider it to be obvious that it did so in the same way (i.e. dissolution at a high pH then lowering the pH)”*.

43. The observer alleges that *“there is no guidance or even remote suggestion in the patent that in order to adjust the pH one may use the antimicrobial agent/preservative as used in the Anfarm Process. In the Anfarm Process, contrary to the concept of the patent, first a solution of the preservative in water is produced. This step neither aims to adjust the pH nor to achieve the alleged result of the invention. To the contrary this step only serves to provide a solution of the preservative. Thus, the increase in the pH is a natural consequence of using sodium para-hydroxy benzoate, but otherwise the use of the solution comprising the preservative is completely unobvious as regards the achievement of particular results”*. However, I do not agree with the observer’s comments.

44. As I have discussed above the person skilled in the art would understand that *“adjusting the pH to a pH of at least 8 to yield a basic solvent”*, as defined in claim 1 of the patent, would require the addition of a component which is inherently basic. I consider that the person skilled in the art would be aware that whilst sodium parahydroxybenzoate methyl ester is used as a preservative it is also inherently basic as it is a conjugate base of a weak acid. Thus, I consider that the person skilled in the art would be aware that a basic solution would result following addition of sodium parahydroxybenzoate methyl ester to water. Indeed, I note that the observer states that *“the increase in the pH is the natural consequence of using sodium para-hydroxybenzoate”*. I therefore believe that the person skilled in the art

would be aware of the increase in pH resulting from the addition of sodium parahydroxybenzoate methyl ester and would appreciate that dissolution of levothyroxine in a solution containing sodium parahydroxybenzoate methyl ester, water and glycerol would take place at a basic pH.

45. It is my opinion that on being told that the Anfarm Process produces a stable levothyroxine solution, the person skilled in the art, reading the patent at the priority date, would consider it obvious that it does so in substantially the same way. Therefore, my answer to question (ii) above is yes.

46. With respect to question (iii) the requester submits that *"there is nothing in the specification which would make the skilled person conclude that the patentee intended strict compliance with the literal order of the steps in claim 1 was an essential requirement of the invention. The specification is silent as to whether the order of the steps must be followed slavishly, or whether some deviation is permitted"*.

47. The observer contends that *"the skilled reader would have to conclude that it is of significant importance to maintain the sequence of process steps and, in particular to implement the process steps in their literal meaning. This appears to be evident in light of paragraph [0029] of the patent. Here, the patent discloses that it is particularly the method of preparation which may be relevant to achieve a certain result. However, the only method disclosed in the patent as a whole includes the sequence of process steps b) to d) (features 3. to 5.). The final result of these steps is the complete dissolution of levothyroxine. In this regard, the patent explains that the dissolution of levothyroxine takes place in step b) (feature 3.)"*.

48. Step b) of claim 1 of the patent defines mixing of levothyroxine with the aqueous solvent [water and glycerol], however, it isn't until step d), i.e. after the pH is adjusted, that the dissolution of levothyroxine is claimed. Furthermore, the patent teaches at paragraph [0011] *"Also, the preparation is relatively fast; in particular the dissolving of levothyroxine in the basic aqueous solvent is relatively fast compared to dissolving in neutral or acidic water (pH<7)"*. I therefore do not accept the observer's argument that the patent teaches that dissolution of levothyroxine takes place in step b).

49. In my view the person skilled in the art would consider that the essential requirement of claim 1 of the patent is the dissolution of levothyroxine in a water and glycerol mixture at a pH of at least 8 and would also consider that the stage at which the levothyroxine is added to the glycerol and water mixture i.e. before or after the pH is increased, would be immaterial, as the end result would be the same i.e. the dissolution of levothyroxine in a water and glycerol mixture at a pH of least 8.

50. Based on the evidence presented I do not believe that the person skilled in the art would conclude that strict compliance with steps a) to d) of claim 1 is necessary. In my opinion the person skilled in the art would conclude that the essential element of steps a) to d) is the dissolution of levothyroxine in a basic solution having a pH of at least 8.

51. It is my opinion that the person skilled in the art would consider that the requirement of the *"pH being at least 8"* is an essential feature of the method and that the

patentee intended strict compliance with its literal meaning. The person skilled in the art would be aware that any solution having a pH of above 7 is basic. Therefore, I believe that the person skilled in the art would conclude that the requirement that the pH should be at least 8 is essential as this pH is deemed sufficiently basic to effect the required dissolution of levothyroxine in the water and glycerol mixture.

52. The requester refers to the judgement of the Athens First Instance Court (Annex 3) stating that the Anfarm Process comprises the step of *"1. Adding a preservative to water to produce a basic aqueous solvent with a pH greater than 8"*, however I can find no reference in the judgement that the pH of the solution is greater than 8. Indeed, the only reference to the pH is *"Firstly, raising the pH of the water by adding the preservative sodium parahydroxybenzoate methylester to produce a basic solvent"*.

53. I note that the requester, Prof. Kontogiannis and the observer seem to suggest that the pH of the basic solution described in the Anfarm Process is greater than 8. Whilst I have not been presented with any evidence to indicate that this is the case, I equally have not been present with any evidence to suggest that it isn't. Therefore, based on the comments made by the requester, Prof. Kontogiannis and the observer I consider that it is likely that the pH of the basic solution would be greater than 8 and thus I consider that the Anfarm Process varies in a way that is immaterial and therefore my answer to question (iii) is "no".

54. I therefore conclude that the Anfarm Process would infringe claim 1 of the patent if performed in the UK under sections 60(1)(b) and 60(1)(c) of the Act.

55. However, if it is shown that the solution does not have a pH greater than 8 then the Anfarm Process would vary in way that is material, and my answer to question (iii) would be "yes".

Opinion

56. In my opinion the Anfarm Process and products directly obtained by that process do not fall within the scope of the claims as a matter of normal interpretation.

57. However, I believe that the Anfarm Process varies in way which is immaterial and thus would infringe claim 1 of the patent if performed in the UK under sections 60(1)(b) and 60(1)(c) of the Act.

Natalie Cole
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.