Patents Act 1977 **Opinion Number** **05/19**

OPINION UNDER SECTION 74A

Patent	EP 2696884 B1
Proprietor(s)	Board of Trustees of the Leland Stanford Junior University
Exclusive Licensee	
Requester	HGF Limited
Observer(s)	Mewburn Ellis LLP (on behalf of the patent proprietor)
Date Opinion issued	05 July 2019

The request

1. The comptroller has been requested by HGF Limited ("the Requester") to issue an opinion as to whether EP 2696884 ("the patent") is valid, in particular, whether the claims are entitled to their priority, whether they lack either novelty and/or inventive step, and whether they lack sufficiency.

2. The request was received on the 10th April 2019 and was accompanied by a statement explaining the request as well as copies of the seven documents relied on.

3. The Patent entitled 'Long-acting peptide analogs' was filed on 05 April 2001 under the provisions of the Patent Cooperation Treaty (PCT) with an international application number PCT/US2012/032333. The application claimed an earliest priority date of 07 April 2011, and two later priorities of 11 April 2011 and was initially published as WO 2012/138867. After entering the European regional phase, the Patent was granted on 3 April 2019 and is in force in the UK.

4. The documents supplied by the Requester representing the prior art were all published before the filing and priority dates of the patent, and so may be considered as prior art for the purposes of novelty or inventive step. These documents are listed below, using the same numbering as used by the Requester:

(D1) US 2002/0068814

(D2) US 2008/0020978

*(*D3) *Werle M. et al., Amino Acids, vol. 30, pages 351 to 367 (2006)*

(D4) *Chapter M. C. et al., Pharmacol. Ther., vol. 125, issue. 1, pages 39 to 54 (2010)*

(D5) *Lee S-H. et al., Bioconjugate Chem., vol. 16, pages 377 to 382 (2005)*

(D6) *Dennis M. S. et al., J. Biol. Chem., vol. 277, pages 35035-35043 (2002)*

(D7) *WO 02/098446*

5. Observations were filed by Mewburn Ellis LLP ("the Observer") on behalf of the patent proprietor The Board of Trustees of the Leland Stanford Junior University ("the Proprietor") on the 8th May 2019. These were accompanied by three documents and a declaration in support of their observations. I have listed these below, extending the numbering being used by the Requester for convenience:

(D11) *Maletinska et al, (1997), J Mde Chem, 40: 3271-3279 (abstract)*

(D12) *Labudda et al, (2007) Acta Biochim Pol, 2007, 54(1): 193-8*

(D13) *Longo Et al (2014) Int'l J Pharm, 472, 156-164*

(D14) *Hsu Declaration, Aug 2015*

6. Observations in reply were filed by the Requester on 24th May 2019 in which the Requester cited three further documents not originally relied upon and a sequence search in Genome Quest (presented as Annex A). The three further documents, which were all published before the filing and priority dates of the patent, are set out below again using the same numbering as the Requester:

*(*D8*) WO 2006/082184*

(D9) *Gault V. A. et al., Biochem. J., 367, pages 913 to 920 (2002)*

(D10) *US 2008/026995*

Whether all parts of the request are allowable

7. The comptroller will only issue an opinion in relation to a prescribed matter. This is by virtue of section 74A(1) of the Patents Act 1977 (the Act). The matters for which an opinion may be sought are prescribed in rule 93(6) of the Patents Rules 2007, as amended, (the Rules). These matters do not include whether the patent is entitled to an earlier priority date, hence I am not able to give an opinion on that aspect of the request in isolation however it can be considered if it is necessary to determine the questions of novelty or inventive step

8. In this instance the relevance of all the documents that the Requester relies on in respect of its novelty or inventive step attack does not depend on the priority date of the patent. I will therefore not need to consider whether the patent is entitled to an earlier priority date. I will therefore consider the relevance of the documents the

Requester has provided to the novelty and inventiveness of the invention as defined in the granted claims, as requested by the Proprietor in their Observations.

9. The request also seeks an opinion on various matters relating to whether the Patent discloses the invention clearly enough and completely enough for it to be performed by a person skilled in the art (sufficiency).

10. In their observations in response the Proprietor argues that the patent has been assessed for sufficiency during examination at the European Patent Office, asserting that this indicates the examiner was satisfied that the application is sufficient. Therefore, the Proprietor requested that that sufficiency is not considered. The approach however taken by the IPO when a request has referred to these grounds is to provide an opinion unless the issue has been explicitly considered during examination, and so I will consider this in this opinion.

11. In their observations in reply, the Requester has provided three further documents, D8-D10, which they put forward as additional documents which can be mosaiced together to demonstrate that the invention lacks an inventive step. However, I do not believe that these documents simply illustrate any flaws in the observations and so the Proprietor has not had any opportunity to respond to these further inventive step arguments and therefore has not been able to comment on the entire argument. Therefore, I shall not consider them. The Requester also raises a further argument that claim 2 has no antecedent basis. Again, as this argument is new the proprietor has not had any chance to respond to it and so I will not consider it in this opinion.

The patent

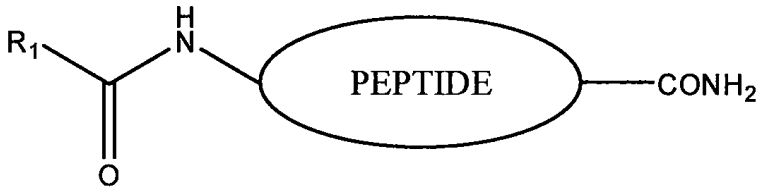
12. The Patent relates to polypeptide analogs of adrenomedullin, which is a member of calcitonin peptide hormone family. These analogs are modified at the N-terminal region by conjugation of an alkyl compound, such as a fatty acid which includes palmitic acid so that the in vivo serum half-life of these peptide analogs is increased when compared to the native polypeptide, thereby increasing their in vivo activity and effectiveness. They act as agnostic analogs for CLR/RAMP receptors and thus may have a limited effect on heart rate whilst affecting blood pressure significantly in patients and reducing peak and trough effects.

13. The patent contains claims 1-9 of which claim 1 defines the invention as set out below and for convenience the labelling of the four features (i)-(iv) of claim 1 applied by the Requester has been included:

(i) A biologically active adrenomedullin peptide having a serum half-life of greater than 1.5 hours,

(ii) wherein the peptide is modified at the amino terminus of the peptide

(iii) and has the structure:



(iv) where R1 is a linear or branched C3-C100 alkyl; preferably a C4-C30 alkyl optionally substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, sulfate, or phosphate, and which maybe saturated, or mono- or di-unsaturated.

14. Claims 2-4 are dependent upon claim 1 and define aspects of the peptide including the peptide sequence and the Markush formula represented by R1 in further detail. Claim 5 is a first medical use format claim of the peptide for use as a pharmaceutical, claim 6 defines a pharmaceutical composition comprising the peptide of claims 1-4. Claim 7 defines the peptide according to any one of claims 1-4 or the composition according to claim 6 for use in a method of delivering a long acting agonist for CLR/RAMP receptors activity to a host animal. Claim 8 and dependent claim 9 are second medical use claims for use of the peptide of claims 1-4 or the pharmaceutical composition according to claim 6 in reducing peripheral blood pressure. It will only be necessary for me to consider these dependent claims or the medical use claims that the Requestor argues also lack novelty or inventive step if I find that claim 1 lacks novelty.

Novelty and Inventive step- the law

15. 16. Section 1(1)(a) of the Act reads:

> *1(1) A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –*
> *(a) the invention is new;*

16. The relevant provisions in relation to novelty are found in section 2(1) and section 2(2) which read:

> *2(1) An invention shall be taken to be new if it does not form part of the state of the art.*
> *2(2) The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, process or information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way.*

17. When considering validity of the claims of the patent I will first need to construe them. This means interpreting them in light of the description and drawings as instructed by section 125(1) and take account of the Protocol to Article 69 of the EPC. 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 claims to mean. This approach has been confirmed in the recent decisions of the High Court in Mylan

v Yeda[1] and the Court of Appeal in Actavis v ICOS[2].

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 protection conferred by a patent or application for a patent shall be determined accordingly.*

19. 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).*

20. 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.*

Construction of claim 1

21. When considering the validity of the claims of the Patent I will first need to construe them. I must interpret them in the 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 claims to mean.

22. The Requester has identified the person skilled in the art in relation to inventive step as *"a scientist (who may have a degree or simply practical experience). Said scientist would have the common general knowledge and understanding of peptides, and the necessary skill to modify peptides"*. The proprietor has not commented on

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

this statement regarding the skilled worker and I do not believe is contentious.

23. Therefore in my view the person skilled in the art is a scientist working in the field of peptide modification. I consider that they would be aware that peptides can be translated initially as pro-peptides that are post-translationally modified to active forms and would have the knowledge that peptides can be modified by various methods to alter their properties, including increasing their activity and their half-life, especially when used in vivo.

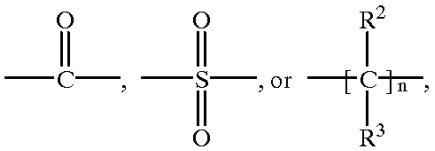
24. Although the Requester has discussed claim 1 in relation to whether it is sufficient or not, neither the Requester nor the Proprietor has made any comments in relation to the construction of claim 1 or how this claim should be interpreted. However, I consider that claim 1 is generally clear and straightforward to construe. The key features are that it is an active adrenomedullin peptide fragment that has an N terminal modification comprising a linear or branched C_3-C_{100} alkyl and which has a serum half-life of greater than 1.5 hours.

Novelty- claim 1

25. The requester submits that claim 1 is not novel in light of the prior art documents D1 or D2. To justify a finding that claim 1 of the patent lacks novelty I must find that the prior art disclosure clearly and unambiguously discloses all of the features of claim 1.

26. D1 discloses antagonists of calcitonin gene related peptide that are amino terminal modified to improve their binding ability to member of the CGRP-receptor superfamily. The requester argues that this document discloses all the features of the claimed invention.

27. Claim 1 defines the vasoactive peptide that is the subject of D1 thus:

> 1. A vasoactive peptide having the general formula:
>
> R^1—X—Z
>
> wherein Z is a vasoactive peptide, R1 is an organic group
>
> 
>
> and wherein R2 and R3 are independently H or an organic group and n is a whole integer between 1 and 10.

28. The Requester states that D1 further discloses that the vasoactive peptide may be adrenomedullin, and that a sequence that encompasses the adrenomedullin of the patent is disclosed as SEQ ID NO; 14, and that the modifications at R1 may be a C1 to C16 alkyl group. Further the Requester asserts that the CGRP exemplified retains

activity for more than 1 hour and thus has a serum half-life of greater than 1 hour.

29. The Proprietor contends that CGRP is a different peptide from adrenomedullin and D1 provides no evidence for extended half-life, rather it sets out “a prophetic example”.

30. In their observations in reply the Requester disagreed with the Proprietor’s contentions. They further argued that D1 disclosed that using adrenomedullin is a clear embodiment of the invention, as the sequence of SEQ ID NO:14 completely comprises the adrenomedullin peptide sequence listed as SEQ ID NO: 6 in the patent and further that experimental evidence of relaxation experiments on tissue rings incubated in Krebs-Henseleit solution, a known physiological buffer, with a modified peptide of the invention were still active after 90 minutes incubation and so the half-life extension is anticipated.

31. I consider that as the Requester has argued, D1 does disclose a modified adrenomedullin peptide that is active and has an N-terminus modification. Although such a peptide is not exemplified in the specification of D1, it is a clear alternative that is disclosed in D1 and is further claimed in dependent claim 6, which lists adrenomedullin, the sequence of which is disclosed, as one of the possible alternative vasoactive peptides.

32. The Requester also directs me to a single paragraph [0022] in D1 that R1 can be a C1 to C16 alkyl group as demonstrating that the alkyl modification of feature (vi) requirement is also met. However, I note that the claims of D1, when specifically defining the nature of the R1 group are restricted to a C1-C4 alkyl group- for example see claim 10, and such claims are dependent upon claim 1 of D1, but not claim 6, which defines that the vasoactive peptide can be adrenomedullin.

33. Furthermore, I am not convinced that the examples in D1 clearly and unambiguously discloses that a vasoactive peptide of D1 would have the necessary serum half-life of greater than 1.5 hours as the Requester asserts. Whilst the ring segment assays were incubated for 90 minutes before beginning concentration-response curve measurements, these were undertaken to determine antagonist affinity values and are in vitro tissue assays. As such I do not consider that these experiments clearly and unambiguously disclose or teach any serum half-life value. Moreover, these experiments were undertaken with CGRP analogues which comprise a fragment spanning residues 8-37 of CGRP and not a fragment of Adrenomedullin. Whilst both are members of the same superfamily and thus related, the skilled person would understand that these are not the same protein and do not, as the Requester suggests fall within the scope of the peptide of claim 1. The Requester further states in their request that Example 3 of D1 also supports their analysis. The Requester refers to results present in the paper of Fisher et al published in 1983 disclosed in Example 3 of D1 as demonstrating that CGRP peptides have a serum half-life of over 1 hour. However, the Requester has not supplied a copy of this paper nor is it listed in the cited documents. Therefore, as the Proprietor has observed, it appears to me that this example has not been performed with the modified peptides of D1 and no actual results are provided, and so I cannot agree with the analysis made by the Requester.

34. Thus, I agree with the Proprietor that D1 does not disclose each and every feature of

the adrenomedullin peptide of claim 1 clearly and unambiguously.

35. The Requester further asserts that the claimed invention lacks novelty over D2. This document, as with D1, defines inventions which relate to modified CGRP peptide antagonists. Claim 1 of this document reads thus:

> **1**. A composition of matter comprising:
>
> (a) a CGRP peptide antagonist, being a CGRP peptide comprising from its C-terminal end to its N-terminal end:
>
> (i) the C-terminal carboxy moiety is replaced with a moiety selected from
>
> (A) —C(=O)NRR, where R is independently hydrogen, (C_1-C_8)alkyl, haloalkyl, aryl or heteroaryl; and
>
> (B) —CH_2OR where R is H, (C_1-C_8)alkyl, aryl or heteroaryl;
>
> (ii) a first $CGRP_1$ receptor binding region; and
>
> wherein the CGRP peptide lacks a functional $CGRP_1$ receptor activation region; and
>
> (b) a pharmaceutically acceptable vehicle, wherein the pharmaceutically acceptable vehicle is conjugated to the CGRP peptide at a site other than at the peptide's C-terminal amino acid residue.

36. The Requester asserts that because the peptide of claim 1 of the patent that is the subject of the opinion is not clearly defined and that the CGRP protein is a member of the same superfamily as Adrenomedullin, the CGRP would fall under the broad scope of claim 1 of the patent. The Requester further asserts that the "vehicle" defined in claim 1 of D2 may be an alkyl group and that these examples use a polyalkylene glycol compound and so also fall within the scope of claim 1 of the patent. The Requester finally asserts in their observations in reply that these peptides have a serum half-life of greater than 1.5 hours as exemplified in Table 1B of D2.

37. The Proprietor contends that adrenomedullin is a different peptide from CGRP and that the modifications in D2 are to prevent side reactions during conjugation of the peptide to a vehicle and that the document says nothing about improving serum half-life.

38. Although the requester has asserted that a CGRP peptide would fall within the scope of the peptide defined by claim 1 of the patent, as I have set out above when considering D1 I do not believe that this is the case. I accept the point made by the Proprietor that although CGRP is a member of the same superfamily as Adrenomedullin, this is a different peptide and so does not fall within the scope of

claim 1 of the patent. Further, although the Requester has directed me to Table 1B as evidence that these peptides when conjugated with PEG have an extended serum half-life I note that these are both CGRP peptides that are actually PEGylated at the Lys 25 residue, rather than being N-terminal modified as defined in claim 1 of the patent. This is established by the sequences of both SEQ ID Nos: 172 and 173 as listed in Table 2B at page 23 of D2.

39. Consequently, it is my opinion that D2 does not clearly and unambiguously disclose the peptide of claim 1 of the patent, which is an active adrenomedullin peptide that is modified at the N-terminus with a C3-C100 alkyl and which has a serum half-life of 1.5 hours.

40. I therefore consider that claim 1 is novel over both the documents presented.

Inventive step

41. The Requester has also asserted that claim 1 lacks an inventive step in light of the disclosures in documents D3-D7 supplied with the request. They argue that having considered the differences between the matter disclosed in any one of these documents and the inventive concept of the claim as construed, these differences constitute steps which would have been obvious to the person skilled in the art.

42. The Proprietor in their observations submit that these differences and the effects of acylation are not so predictable, and so it would not be obvious to the skilled person that acylation would necessarily result in an adrenomedullin peptide with an increased serum half-life. In support of this position they supply three documents, D11-D13 which they assert demonstrate that N-terminal acylation would not necessarily affect adrenomedullin stability and serum half-life positively. They further provide some experimental data in D14 that whilst N-terminal palmitoylation of adrenomedullin does not negatively affect it's activity, palmitoylation at other residues does reduce the activity.

43. D3 supplied by the Requester is a review of strategies to improve plasma half-life of peptide drugs. The Requester highlights paragraph 3.1 which relates specifically to the role of N- and C-terminus modifications and discloses prior art in which a different protein RC-160, a somatostatin analogue, was conjugated with various fatty acids from C4 to C18, with improved resistance towards trypsin and serum degradation. The requester asserts that the only difference between D3 and the claimed invention is that it is an adrenomedullin peptide that is being modified and that this would be obvious to the skilled person.

44. I agree with the Requester that given the disclosure in this document the skilled person would consider that applying N-terminal modifications, which comprise fatty acids of chain lengths from C4 to C18, to adrenomedullin rather than RC-160 to be obvious when seeking to improve the serum half-life, given it has been successful with another peptide in this prior art.

45. D4 is a further review supplied by the Requester of different modification strategies applied to Class II G-protein coupled receptor ligands to enhance their therapeutic activity. The Requester asserts that at paragraph 3.2 this document discloses that

the modification of glucagon-like peptide-1 (GLP-1) either at the N-terminus or a lysine residue with fatty acids results in peptides with increased serum half-life. The Requester further highlights paragraph 9.2 as disclosing the modification of calcitonin ligands, including an adrenomedullin, to produce a ring structure variant without an N-terminus, with improved properties such as activity and recovery half-time. The Requester asserts that the only difference that exists between D4 and the claimed invention is the modification of an adrenomedullin peptide at the N-terminal with fatty acids, but that it would be obvious to the skilled person to apply the GLP-1 modifications disclosed to adrenomedullin.

46. However, I note that the prior art work referenced in paragraph 3.2 of D4 is the document supplied by the Requester as D5. The Requester again asserts that this document discloses the N-terminus modification of GLP-1 and so the only difference between this document and the claimed invention is the modification of adrenomedullin rather than GLP-1. It therefore would be obvious to the skilled person to apply these teachings to adrenomedullin to arrive at the claimed invention.

47. However, reading D5 in detail it is apparent that whilst GLP-1 has been modified at both the N-terminus and at an internal Lysine residue, it is the Lys modified variant that demonstrated increased potency over the N-terminus modified variant, and was also demonstrated to have increased serum half-life (see figures 4, 5 and 7 for example). I therefore believe that the skilled person considering the teaching of either of documents D4 or D5 would not consider it obvious to arrive at the invention claimed from either of these documents, as the N-terminus modification described does not appear to have the desired properties.

48. D6 discloses the use of albumin to improve small molecule drug pharmacokinetics. The Requester asserts that there are several references to the use of acylation to increasing the effect of proteins, although the Requester does recognise that the actual research is directed to the use of a recombinant fusion protein to bind albumin and therefore prolong the half-life of an immunoglobulin fragment, comparable to a PEG conjugated Fab fragment. These references are made to reports of modification of factor VIIa at the amino terminal although the modifications are simply described as with aromatic groups and acylation of insulin, but no details of these modifications are provided. The Requester states the difference that exists between D6 and the invention is the modification of an adrenomedullin peptide at the N-terminal with fatty acids, but argues that it would be obvious to the skilled person to arrive at the invention claimed starting from this document.

49. However, I am not convinced by this assessment of the disclosures in this document for the skilled person. I agree with the Proprietor that this represents a "*stretch of the imagination*" and I consider the skilled person would not find it obvious from the disclosures in this document that an acylation modification, specifically of a C3-C100 chain length at the N-terminus of adrenomedullin would necessarily generate a peptide with the desired serum half-life. I therefore consider the invention claimed does involve an inventive step over D6.

50. D7 discloses producing mixtures of non-polydispersed mixtures of conjugates comprising a drug coupled to oligomers that include polyalkylene glycol. The drug is a peptide and adrenomedullin is amongst many possible peptides listed and is exemplified as Example 43. D7 discloses that the modification may be at an N-

terminus but this is not specifically exemplified. Whilst the document describes these conjugates as having greater activity, it does not teach that the serum half-life is increased, although other advantages are disclosed. The Requester asserts that the only difference between D7 is the modification of an adrenomedullin peptide at the N terminus, but that it would be obvious to the skilled person to apply this feature which is known in the prior art, and is disclosed in D7.

51. However, whilst the Requester has directed me to page 39, lines 8-9 as an example of conjugation at the N-terminus, further lines 12-25 in this paragraph make clear that not all N-terminus peptides demonstrate a higher activity. As such it is not obvious to me from the disclosures in D7 that the skilled person would arrive at the claimed invention without an inventive step.

52. I therefore conclude that the invention of claim 1 lacks an inventive step given the disclosures in D3.

53. The Requester has also asserted that the dependent claims lack an inventive step over D2 at least, but has only presented detailed arguments in respect of D2. As I have already found that D2 does not anticipate the invention defined in claim 1 of the patent I shall not consider the arguments presented concerning these claims by the Requester.

Sufficiency

54. The Requester submits that the specification does not disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. Section 14(3) of the Act reads:

> *The specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by the person skilled in the art.*

55. It has been established that the reasoning used to assess whether an application satisfies section 14(3) is that as set out in the relevant principles of Eli Lilly v Human Genome Sciences[3], that is:

> *The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are those:*
> *(i) The first step is to identify the invention and that is to be done by reading and construing the claims;*
> *(ii) In the case of a product claim that means making or otherwise obtaining the product;*
> *(iii) In the case of a process claim, it means working the process;*
> *(iv) The sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and claims;*

[3] Eli Lilly v Human Genome Sciences [2008] RPC 29

(v) The disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;
(vi) The specification must be sufficient to allow the invention to be performed over the whole scope of the claim;
(vii) The specification must be sufficient to allow the invention to be so performed without undue burden

56. The Manual of Patent Practice explains at paragraph 14.60 that:

> *The purpose of the requirements imposed by s. 14(3) and s. 72(1)(c) is to prevent a patentee laying claim to products or processes which the teaching of the patent does not enable the skilled addressee to perform (Zipher Ltd v Markem Systems Ltd [2009] FSR 1). Thus, all consideration of sufficiency in essence deals with the extent to which the applicant has provided an enabling disclosure for their invention (see also 2.10 and 72.03).*

57. In Zipher Ltd v Markem Systems[4], the objection to classical sufficiency is summed up as follows:

> C*lassical insufficiency arises where the express teaching of the patent does not enable the skilled addressee to perform the invention. This type of insufficiency requires an assessment…of the steps to which it would be necessary for the skilled reader or team to take in following the teaching of the specification and in order to arrive within the claim. Plainly the steps should not include inventive ones. But a patent can also be found insufficient if the steps can be characterised as prolonged research, enquiry or experiment.*

58. The Requester has submitted arguments asserting that the specification does not provide support for the invention as defined in claim 1 and so argues that "*the claimed invention is not disclosed as a person skilled in the art would not be able to perform the invention over the whole area claimed, without undue burden and without needing inventive skill due to excess claim breadth"*. I will consider both of the arguments regarding claim 1 presented by the Requester.

59. Firstly, the Requester submits that the use of the umbrella term "peptide" without specifically providing the protein structure results in the skilled person having an undue burden placed on them to establish what is "a biologically active adrenomedullin peptide. This is in feature (i) of the claim as the requester had annotated it. They argue that because it is not plausible that all the other proteins that could be encompassed by this term would work and the specification provides only one example of an active peptide, SEQ ID NO: 6, the claim lacks sufficiency, as adrenomedullin is part of a large superfamily of related proteins (a superfamily is a grouping of proteins for which common ancestry can be inferred, often based on structural alignment even though no sequence similarity is evident).

[4] Zipher Lid v Markem Systems Ltd [2009] FSR1

60. Furthermore, the Requester secondly argues that the term "*where R1 is a linear or branched C3-C100 alkyl*." (feature (iv) in the annotation they have applied) is also "*extremely broad, and as such, it would not be possible for the skilled person to carry out the invention without undue burden*." because only one modification of a peptide is provided in the description, a linear C16 alkyl modification.

61. Thus, in summary, the Requester has asserted that neither the peptide feature and the alkyl modification feature of the invention are supported across their entire breadth and it would not be plausible to work across the whole scope of claim 1.

62. The Requester further contends that claims 3 and 7 also lack sufficiency because "*provides in vivo effectiveness*" and "*extended period of time*" it is not clear what is meant or encompassed (claim 3), nor is sufficient information provided to put the claimed invention into practice (claim 7).

63. The Proprietor did not make any observations on sufficiency, having requested that this matter was not subject of the opinion.

64. In their observations in reply the Requester further maintains their assertion that both that the peptide sequences and the acylation modification are broadly claimed. The requester provides some sequence analysis in Annex A in support of this argument, where a sequence search using the program GenomeQuest of sequences published in patents identified 2,275 hits with more than 65% sequence identity to the adrenomedullin sequence the Requester used in the search, but no evidence that these are from biologically active adrenomedullin peptides is provided.

65. As set out above it is a requirement under section 14(3) that the specification must provide sufficient disclosure of the invention to allow the person skilled in the art to obtain the product claimed. I therefore consider that the specification must provide enough information to enable the skilled worker to produce the amino terminal modified biologically active adrenomedullin peptide, without undue burden, i.e. without prolonged research, enquiry or experimentation, and without exercising any inventive ingenuity.

66. I consider that the skilled worker would be aware that adrenomedullin is encoded by the ADM gene initially as preprohormone, which is post-translationally modified to generate 2 biologically active peptides, adrenomedullin and a proadrenomedullin N-terminal 20 peptide (PAMP), as highlighted in paragraph [0017] of the patent. As such the skilled person would understand the subsequent paragraph [0018] which defines the term "adrenomedullin peptide" as encompassing "*any active peptide derived from the adrenomedullin precursor peptide*" from the teaching of the patent and the common general knowledge of this peptide as being the active peptides disclosed above and known in the prior art. They would also be aware from the common general knowledge that peptide sequences can be modified by, for example, conservative modifications of amino acids in a sequence that would not affect the function of the peptide, or for example by some deletions or extensions of the peptide length. This is demonstrated in Example 2 of the patent where a lysine residue is incorporated at the N terminus of SEQ ID NO: 6, which is the sequence of the active modified adrenomedullin peptide exemplified, and the further information about the possible modifications encompassed is given in the patent at paragraphs [0022-0026]. The patent further teaches the skilled person at paragraph [0021-0022]

what effectiveness and activity of the modified adrenomedullin peptide constitutes, as well as the biological activities measured in vitro and in vivo in the assays undertaken in Example 2. The skilled person would also be aware that whilst adrenomedullin is, as the Requester suggests, a member of a superfamily it is a distinct protein that is different from the other members of the family.

67. I therefore consider that the peptide is not broadly defined in the claims and so I disagree with the Requester in this respect about the sufficiency of claim 1.

68. However, as set above the Requester has also argued that the acylation (feature (iv) of claim 1) is broadly claimed and lacks sufficiency. The skilled person would be aware that the alternative structures represented by the R_1 group would be both wide ranging and very different in their structure. These could thus have many different properties, not all of which may result in an increased serum half-life, as asserted by the Requester. The skilled person would therefore look to the teaching of the patent in order to determine what acylation modifications would give rise to such an increase in serum half-life. However, I can find no further information in relation to what other modifications apart from the single palmitic acid acylation disclosed in Example 2 has any such effect. Furthermore, even with the benefit of their common general knowledge, I do not believe that the person skilled in the art would be able to determine any other specific modifications that would give rise to an adrenomedullin polypeptide with an extended half-life.

69. I note that although the Proprietor has not specifically commented on the question of sufficiency, in their response to the inventive step argument made by the Requester they have observed that "*Acylation cannot be generally extended to any peptide with a reasonable expectation of success in maintain activity and extending serum half-life*." They submitted documents D11-D13 to demonstrate that acylation may not necessarily have predictable results whilst the declaration in D14 demonstrates that palmitoylation of adrenomedullin at residues other than the N terminus reduced activity when assayed. The Observer thus observed that *"Acylation at the N-terminus can have unpredictable effects, and require systematic analysis*." This analysis indicates that a broad claim to acylation as a modification would not appear to be supported.

70. I am therefore in agreement with the Requester that the specification does not provide adequate information regarding the nature of the acylation represented by group R_1 to enable the skilled person to perform the invention as defined in claim 1. The single example of acylation provide in the specification, palmitoylation, is not sufficient for the skilled person to establish what other acyl modifications would actually work and give the desired increase in serum half-life of adrenomedullin, nor does the specification provide any detailed teaching that the skilled person even with the benefit of their common general knowledge could arrive at the claimed invention without significant experimentation and trial and error.

71. Furthermore, as I consider that as claim 1 is insufficient, the peptide as further defined in dependent claims 3 and 7 is also insufficient as the person skilled in the art would not be able to produce the product claimed.

72. In light of the above, I do not consider that the patent discloses the invention clearly and completely enough for it to be performed by a person skilled in the art and thus

claims 1, 3 and 7 do not meet the requirements of section 14(3) of the Act.

Opinion

73. On the basis of the evidence submitted and arguments put forward I am of the opinion that the invention as defined in claim 1 is novel.

74. On the basis of the evidence submitted and arguments put forward I am of the opinion that the invention as defined in claim 1 lacks an inventive step given the disclosure in D3.

75. It is also my opinion that, based on the arguments made, the patent does not disclose the invention clearly and completely enough for it to be performed by a person skilled in the art and thus does not meet the requirements of section 14(3) of the Act, consequently claims 1, 3 and 7 lack sufficiency.

Application for review

76. Under 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.

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.