Intellectual Property Office

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PATENTS ACT 1977

APPLICANT	Nymox Corporation
ISSUE	Whether patent application GB1713738.1 complies with the requirements of sections 14(3) and 1(1)(b)
HEARING OFFICER	Dr L Cullen

DECISION

1 This decision concerns whether the invention defined by the claims of patent application GB1713738.1 entitled "*Method of treating disorders requiring destruction or removal of cells using a Neural Thread Protein derived peptide*" ("the application") is disclosed by the specification in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art, as required by section 14(3) of the Patents Act 1977 ("the Act") and whether the invention involves an inventive step, as required by section 1(1)(b) of the Act.

Background

2 The application was filed on 27 January 2016 in the name of Nymox Pharmaceutical Corporation claiming an earliest priority date of 27 January 2015. It was published as international application WO 2016/120807 A1 on 4 August 2016 and republished as GB 2550804 A on 29 November 2017, following its entry into the UK national phase.

3 The compliance period, the period for putting this application in order under section 20, has been extended as-of-right under rule 108(2) of the Patents Rules 2007, as amended (hereafter 'the Rules') and further extended in successive two-month periods under rule 108(3) of the Rules to 8 June 2021.

4 Objections to sufficiency and a lack of an inventive step were maintained through various rounds of correspondence between the applicant and the examiner. As they were unable to reach agreement, the applicant requested a hearing on the matters outstanding.

5 The examiner set out the matters to be addressed in the pre-hearing report dated 28 September 2020.

6 The matter came before me at a hearing via video conference on 25 November 2020. The applicant was represented at the hearing by Ms Deborah Hart of Beck Greener LLP. I would like to record my gratitude to Ms Hart for providing her arguments in skeleton form in advance of the hearing. There was also one observer attending the hearing for training purposes.

The Invention

7 As set down in the section of the application as filed, entitled 'Field of the Embodiments', the invention relates to a method for treating conditions in humans that require the removal of what are termed, "*unwanted cellular elements*" using compounds based on small peptides. Examples of such unwanted cellular elements are benign tumours or malignant tumours.

8 The description refers to peptides derived from Neural Thread Protein (NTP) as being suitable as the active agent and lists 116 such peptides. Four NTP peptides are identified as preferred and are referred to as SEQ ID NO. 66, 111, 115 & 116.

9 The description incorporates a number of examples which record the results of treating human patients with the condition Benign Prostate Hyperplasia (BPH) with, what the application identifies as 'DRUG' in a clinical trial under double-blind conditions. However, no information is given on what type of ingredient DRUG is in these examples. BPH is a condition that affects males only so references in the claims and the specification and in the discussion below to humans and patients relate to human male patients.

The Claims

10 The set of claims currently on file (dated 13 August 2020) consists of four claims of which claim 1, as amended, is the only independent claim. Claim 1 reads as follows:

> *"An isolated peptide consisting the amino acid sequence in SEQ ID NO. 66 (Ile-Asp-Gln-Gln-Val-Leu-Ser-Arg-Ile-Lys-Leu-Glu-Ile-Lys-Arg-Cys-Leu) for use in a method of treating benign prostatic hyperplasia (BPH) in a treatment naïve human patient with no previous history of drug treatment for BPH comprising:*
>
> *administering intraprostatically to the treatment naïve human patient a therapeutically effective amount of the isolated peptide;*
>
> *wherein the method provides symptomatic improvement in the treatment naïve human patient compared to a control, as measured by a Mean International Prostate Symptom Score (IPSS), of from about 15% to about 95%; and*
>
> *wherein the method provides an improvement in treatment naïve human patients, when compared to the improvement found by treating*

treatment failure patients, of an amount within the range of from about 1,500% to about 2,500%."

Issues to be decided

11 There are two issues to be decided in this case:

i) Firstly, does the specification disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art, as required by section 14(3) of the Act? Related to this first issue is whether or not there is evidence in the application as filed that that active compound claimed is likely to be effective for the claimed therapeutic use. As noted above, independent claim 1 relates to a new therapeutic use for a specific peptide. However, the examples in the description do not identify this peptide.

ii) Secondly, does the invention as claimed involve an inventive step over the cited prior art, as required by section 1(1)(b) of the Act?

Sufficiency under Section 14(3)

The Relevant Law

12 Overall, section 14 of the Act, entitled "Making an application", is concerned with the manner of making an application for a patent, the form and content of an application, the requirements which must be fulfilled by the contents, and provides for withdrawal of the application.

13 Section 14(2) sets down what makes up an application and how the specification relates to that as follows:

*(2) Every **application** for a patent shall contain –*

(a) a request for the grant of a patent;

*(b) a **specification** containing a description of the invention, a claim or claims and any drawing referred to in the description or any claim; and*

(c) an abstract;

……

14 Section 14(3) relates to the specification and reads as follows:

……

(3) 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 a person skilled in the art.

.....

Thus, the specification must provide sufficient detail for the person skilled in the art to be able to perform the invention as claimed.

15 As set down in section 130(7) of the Act, section 14(3) is intended to have, as nearly as practicable, the same effect as the corresponding provisions of the European Patent Convention (EPC) and the Patent Cooperation Treaty (PCT). Article 83 EPC and Article 5 PCT require the invention to be disclosed "*in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*". An objection under this section of the Act is often referred to as “sufficiency of disclosure” or “sufficiency”. This pre-grant provision concerning the patent application accords directly with section 72(1)(c) of the Act which sets out the same requirement for the validity of the granted patent. Thus, while much of the case law relating to sufficiency derives from proceedings concerning granted patents under section 72, the principles set out in these cases are pertinent to section 14(3).

16 It is the responsibility of the applicant to ensure that, at the time of filing the application, the disclosure is clear enough and complete enough in respect of the invention defined in each of the claims. If it is not, then the application shall be refused or, if it is possible to do so, the claims must be restricted or amended to that matter which has been adequately disclosed, i.e., that for which there is an enabling disclosure. Deficiencies in the disclosure cannot be corrected subsequently by adding matter because of the prohibition under section 76(2) of the Act.

17 The overall purpose of section 14(3) is to prevent the patent applicant from claiming products or processes which the teaching of the specification does not enable the skilled person to perform. In effect, one is being asked to determine if there is enough information in the specification as filed by the applicant to allow the skilled person who has a reasonable knowledge and understanding of the technical area described to carry out the invention as defined in the claims.

18 Kitchin J provided a summary of the relevant principles to be applied when assessing sufficiency (at paragraph 239) in *Eli Lilly v Human Genome Sciences*, [2008] RPC 29 (hereafter *Eli Lilly*):

"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 these:

(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 the claims;

(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."

19 The claims are interpreted in the light of the description and the drawings as set out in section 125 of the Act. They are construed in a purposive manner following the established principles of UK patent law.

20 For the purposes of section 14(3), the skilled person is seeking to make the patent work and does so with the common general knowledge at the time the patent was filed. In contrast to the situation for inventive step purposes, the skilled worker has the patent in front of them, and thus is "*trying to carry out the invention and achieve success, ... not searching for a solution in ignorance of it.*" (see *Zipher Ltd v Markem Systems Ltd.*, [2009] FSR 1 at page 50, hereafter *Zipher*).

21 As noted by Lord Hoffman in the House of Lords decision in *Kirin-Amgen Inc v Hoechst Marion Roussel* [2005] RPC 9:

> "*Whether the specification is sufficient or not is highly sensitive to the nature of the invention. The first step is to identify the invention and decide what it claims to enable the skilled man to do. Then one can ask whether the specification enables him to do it."*

22 Whilst there is only one provision under the Act, it is well established in UK law that the understanding of what sufficiency is - in terms of the disclosure being clear and complete enough for the invention to be performed by the person skilled in the art - can be approached in three different ways, i.e.:

1) Classical insufficiency
2) Insufficiency by uncertainty/ambiguity
3) Insufficiency by excessive claim breadth

A summary of what should be understood by each of these approaches to sufficiency was provided by Floyd J (as he then was) in *Zipher* (see paragraphs 361 to 454, but especially paras 367-375 & 438-454).

Claim Construction

23 Sections 125(1) and 125(3) of the Act concern claim construction. They read as follows (my emphasis added in bold):

> "*(1) 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.

….

(3) The Protocol on the Interpretation of Article 69 of the European Patent Convention (which Article contains a provision corresponding to subsection (1) above) shall, as for the time being in force, apply for the purposes of subsection (1) above as it applies for the purposes of that Article."

Second Medical Use claims

24 In the present case we are concerned with a claim to a new therapeutic use, often referred to as a second medical use claim.

25 The question of what is necessary to render an application or patent relating to a second medical use sufficient was discussed by the Supreme Court in *Warner-Lambert Company LLC v Generics (UK) Ltd (t.a. Mylan) & Anor. [2018] UKSC 56,* (hereafter *Warner-Lambert*). In its decision, the court considered a number of principles that can be used to assess the sufficiency of medical use claims. The claims of interest were in the Swiss format, but the principles outlined apply equally to the new form of medical use claims which have replaced Swiss claims following the amendments to the European Patent Convention (EPC) in 2000 (given effect in section 4A of the Act). In the present case we are dealing with a claim in the new form, i.e. the post-EPC 2000 format.

26 As part of its judgment, the court in *Warner-Lambert* outlined, in paragraphs 36 and 37, how the concept of plausibility applies to the statutory requirement for sufficiency. Considering the earlier Court of Appeal judgment in this case, the Supreme Court found that there is a general principle for determining if a claim to a medical use is plausible which it set down as follows (my emphasis added in bold):

"36. The Court of Appeal's statement of the effect of the plausibility test has already been quoted (para 20 above). They considered that the threshold was not only low, but that the test could be satisfied by a "prediction … based on the slimmest of evidence" or one based on material which was "manifestly incomplete". Consistently with that approach, they considered (paras 40, 130) that the Board's observations in SALK laid down no general principle. I respectfully disagree. The principle is that the specification must disclose some reason for supposing that the implied assertion of efficacy in the claim is true. ***Plausibility is not a distinct condition of validity with a life of its own, but a standard against which that must be demonstrated. Its adoption is a mitigation of the principle in favour of patentability. It reflects the practical difficulty of demonstrating therapeutic efficacy to any higher standard at the stage when the patent application must in practice be made. The test is relatively undemanding.*** *But it cannot be deprived of all meaning or reduced, as Floyd LJ's statement does, to little more than a test of good faith. Indeed, if the threshold were as low as he suggests, it would be unlikely to serve even the limited purpose that he assigns to it of barring speculative or armchair claims.*

27 The following paragraph of this judgment sets out seven principles concerning the requirement for plausibility in medical use claims. These principles are discussed and

listed in para 4A.29.5 of the IPO's Manual of Patent Practice.[1] I find this list a helpful reminder when considering the plausibility of a claim to a medical use, i.e.

> *i) The proposition that a product is effective for the treatment of a given condition must be plausible.*
>
> *ii) It is not made plausible by a bare assertion to that effect, and the disclosure of a mere possibility that it will work is no better than a bare assertion.*
>
> *iii) The claimed therapeutic effect may be rendered plausible by a specification showing that something is worth trying for a reason; i.e. not just because there is an abstract possibility that it would work but because reasonable scientific grounds are disclosed for expecting that it might well work. The disclosure of those grounds marks the difference between a speculation and a contribution to the art.*
>
> *iv) Although the disclosure need not definitively prove the assertion that the product works for the designated purpose, there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true.*
>
> *v) That reasonable prospect must be based on a direct effect on a mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se.*
>
> *vi) This effect on the disease process need not necessarily be demonstrated by experimental data. It can also be demonstrated by a priori reasoning.*
>
> *vii) This evidence or reasoning must appear in the patent. The disclosure may be supplemented or explained by the common general knowledge of the skilled person. However, it is not enough that the patentee can prove that the product can reasonably be expected to work in the designated use, if the skilled person would not derive this from the teaching of the patent.*

28 The *Warner-Lambert* judgment also makes clear that the specification **as filed** must make the claimed use plausible; data filed after the filing date of the patent can only be used to confirm an effect made plausible in the specification or to refute a contention that the treatment does not actually work; it cannot be a substitute for sufficient disclosure in the specification.

29 Taking all the above into account, I consider that the law requires me to determine, based on the information in the application and taking account of the views of the examiner and applicant during the examination process, whether the application provides enough detail to enable the invention as claimed.

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[1] The Manual of Patent Practice explains the IPO's practice under the Act and Rules and makes helpful references to relevant case law. The Manual can be viewed online at the IPO's website: https://www.gov.uk/guidance/manual-of-patent-practice-mopp. For the present case, paragraphs 4A.29 and 4A29.2 - 4A.29.5 of the Manual are relevant

Analysis

The Invention as claimed

30 Independent claim 1 in the application in suit is quite specific (see above) and relates to one specific peptide and its use to treat human patients suffering from the condition, benign prostatic hyperplasia (BPH). In contrast to the usual situation when considering questions of sufficiency under section 14(3), we are not dealing with a broad claim and it is thus straightforward to identify the monopoly that is being claimed.

31 Treatment naïve patients are different to those patients who have BPH and have undergone a treatment for this condition already but this treatment has not been successful, so-called treatment failure patients. The claim gives the details of the two ways that the improvement of the treatment naïve patient is measured, firstly, there is an improvement relative to the control of between 15-95% and secondly, there is an improvement in the range 1500-2500% when compared to that seen in patients who have failed BPH treatment. I am satisfied that the person skilled in the art reading this claim with the view to working the invention would be satisfied that the effectiveness of the treatment could be measured using this approach. Thus, for the invention defined by this claim to be enabled, the application must make it plausible to the skilled person that the peptide of SEQ ID NO 66 has a positive therapeutic effect on treatment of naïve human patients with BPH

The Specification

32 Let us now turn to consider the specification as a whole and consider if it enables the skilled man to carry out the invention as claimed.

33 Looking at the specification as filed in the present case, the description has 79 pages and there are no drawings. The claims are listed on page 80 and, as noted above, they have been amended. When the application entered into the GB national phase, the applicant provided replacement pages for the description which, as was acknowledged in the skeleton argument, resulted in some paragraph numbers being repeated and some paragraphs not being numbered at all. In the discussion below, I will use page numbers from the description as filed in the national phase (on 25 August 2017) to refer to the relevant parts of the specification.

34 The description initially sets out the background or context in which the invention that is the subject of this application has been developed (see pages 1-6), it then uses a lot of what was referred to in the hearing as ‘boiler-plate’ or ‘standard language’ to provide as wide as possible a definition of the terms being used in the specification to identify the active ingredient (see pages 7-29 paras, [0003]-[0054]), how such active ingredients are derived (see pages 31-54, paras [0059]-[0112]); the meaning of the term “*conditions requiring removal or destruction of cellular elements, such as benign or malignant tumour*s (see pages 55-58, paras [0118]-[0125]), the forms in which the active ingredient may be obtained and administered (see paras [0126]-[0146], pages 58-66). Taking this into account and looking at the specification with the eyes of the skilled person seeking to make the patent work, I note the following:

a) In the section of the description entitled ‘*Summary of the Embodiments*’ (see pages 7 & 8, paras [0003]-[0007], it is stated that this invention is based on the

"*discovery that certain NTP peptides, <u>including</u> a specific peptide described by the amino acid sequence Ile-Asp-Gln-Gln-Val-Leu-Ser-Arg-Ile-Lys-Leu-Glu-Ile-Lys-Arg-Cys-Leu is capable of treating and/or killing unwanted cellular proliferations in mammals who have not received prior treatments".* It also goes on to state that "*these unwanted cellular proliferations include, inter alia, benign and malignant tumors, glandular (e.g., prostate) hyperplasia, unwanted facial hair, warts and unwanted fatty tissue"*

b) In the section entitled '*Detailed Description of Preferred Embodiments*' which contains much of the above mentioned boiler-plate type language, a definition is provided for the term "*NTP peptide*" (see pages 11-19 (para [0035], but especially final 2 lines on page 19 of the application as filed). The term NTP peptide is defined in this part of the specification as "*also preferably includes (but is not limited to) the amino acid sequences of SEQ ID NO 1 to 116*".

c) At the end of page 30, paragraph [0057], the specification states "*Preferred NTP peptides include one or more of the following*" and identifies four of the previously listed 116 NTP peptides, namely SEQ ID NO. 66, 11, 115 and 116. Table 1 below sets out the amino acid sequences of these four NTP peptides and shows how they all relate to SEQ ID NO. 66, the sequence identified in claim 1. SEQ ID NO. 111 has an amino acid sequence that is approximately half of the length of that of SEQ ID NO. 66; while SEQ ID NO. 115 or SEQ ID NO. 116 have an amino acid sequence that is approximately two-thirds of the length of that of SEQ ID NO. 66.

d) Immediately after this description of "*preferred NTP Peptides*" in para [0057] (page 30), the description refers in [0058] to "*a method of treating a mammal suffering from a condition requiring the removal or destruction of unwanted cellular proliferations, comprising administering an NTP peptide to the mammal, wherein the method removes or destroys unwanted cellular proliferations, and reduces the recurrence of such unwanted cellular proliferations over time*". This is developed further in para [0059] which is a very long paragraph that covers pages 31-35 of the description and is made of a number of separate parts. This paragraph opens with "*the embodiments described herein are premised in part on the surprising and unexpected discovery that certain NTP peptides have an increased efficacy in removing unwanted cellular proliferations from naive mammals, when compared to patients who have previously received treatment*". It then specifically refers to the use of the NTP peptide in treating BPH in a treatment naive patient (see para [0059], page 31). This is immediately followed by a discussion of the studies on this condition carried out in humans which are described in the examples and indicates the range of outcomes that would be considered positive outcomes.

e) The final part of para [0059] states:

> "*The embodiments described herein also are premised in part on the surprising and unexpected discovery that certain NTP peptides including a specific peptide described by the amino acid sequence lle-Asp-Gln-Gln-Val-Leu-Ser-Arg-lle-Lys-Leu-Glu-lle-Lys-Arg-Cys-Leu*
> (i.e., SEQ ID NO. 66)*, have an increased efficacy in removing unwanted cellular proliferations from mammals who have been*

symptomatic for less than 10 years, when compared to mammals that were symptomatic for more than 10 years."

f) Examples 1-7 on pages 67-79 describes the use of the active agent referred to as DRUG. DRUG is not identified explicitly in any of the examples and it also not identified in the description prior to its first mention in the examples. The examples describe the use of DRUG to treat human patients with BPH. Patients with this condition were given an injection into the prostate of (a) 'DRUG' in phosphate-buffered saline (PBS) or (b) PBS alone. The examples show how the changes in symptoms of BPH can be evaluated using the International Prostate Symptom Score (see Example 1, page 68 and Example 2, page 70).

g) The effect of DRUG was considered in relation to different types of human patients. Examples 1-7 provide the results from a double-blind study in human patients with various patient groups tested with and without DRUG (see Tables 1-10). These were identified as (i) "treatment naive" i.e. those with no previous history of conventional drug treatment for BPH; (ii) those who had symptoms of BPH for less than 10 years (iii) "treatment failure" i.e. those who had failed on other conventional approved drugs such as alpha blockers or 5-alpha reductase inhibitors and (iv) those who had symptoms of BPH for 10 years or more. Although, DRUG is identified in the examples as the active ingredient administered to the patients, the discussion of the results from these examples refers to "*use of the NTP peptide*" and "*uses of the NTP peptides*" – see example 1, page 69; example 2, page 71; example 3, page 72; example 4, page 74; example 6, pages 76 & 77 and example 6, pages 77 & 79.

Table 1: The four preferred peptides identified in the application as filed showing the common fragments between each sequence

Sequence ID	Amino Acid Sequence	Amino Acid Code
SEQ ID No. 66	Ile-Asp-Gln-Gln-Val-Leu-Ser-Arg-Ile-Lys-Leu-Glu-Ile-Lys-Arg-Cys-Leu	**IDQQVLSRIKLEIKRCL**
SEQ ID NO. 111	Ile-Asp-Gln-Gln-Val-Leu-Ser-Arg-Ile	**IDQQVLSRI**
SEQ ID NO. 115	Val-Leu-Ser-Arg-Ile-Lys-Leu-Glu-Ile-Lys-Arg-Cys-Leu	**VLSRIKLEIKRCL**
SEQ ID NO. 116	Ile-Asp-Gln-Gln-Val-Leu-Ser-Arg-Ile-Lys-Leu-Glu-Ile	**IDQQVLSRIKLEI**

35 In this instance, and given the points highlighted above, the skilled person seeking to work the patent would thus be aware from reading the description that this application concerns the use of NTP peptides to treat conditions involving unwanted cell growth. They would be aware that the applicant considers that there are 116 specific peptide sequences listed in the application which meet the definition of the term 'NTP peptide' used throughout this specification. While these are listed in the description, they would

also be aware that the specification says this term is not limited to just these 116 peptides. The skilled person would be aware that the specification refers to the 116 identified amino acid sequences as "*suitable NTP peptides*" and they would also be aware that, of these, 4 have been identified as being "*preferred NTP peptides*". They would be aware that closely related fragments of a peptide sequence will be likely to have similar properties. Thus, I can accept the point made by the agent Ms Hart in this regard in relation to SEQ ID NO. 66, 11, 115 and 116. These four sequences are closely related to each other and can all be considered to be derived from SEQ ID NO. 66 (as shown in Table 1 above). The skilled person would be aware that there are a number of conditions discussed which show such unwanted cell growth and that BPH is identified as one of these conditions. From the examples, they would recognise that an active substance is being used to treat BPH in human patients and that useful results have been achieved in relation to improving the symptoms of patients with BPH and that those who have had no treatment for BPH before had the best response. They would I think be confused by the use of the term DRUG in the examples and would be seeking to decipher and understand its meaning. They would note that the examples do refer to the use of "*the NTP peptide*" or "*NTP peptides*" and so would, on balance be satisfied that the term DRUG represents an NTP peptide.

36 Equally the skilled person reading this specification would be aware that the applicant has attempted to define NTP peptide very broadly and to indicate that the condition treated i.e. unwanted cellular proliferation, can include a number of conditions. BPH is not identified as a preferred condition and the specific peptide sequence identified as SEQ ID NO. 66 is never identified as being a preferred peptide for use in the treatment of BPH.

37 Given their interest in working this patent, I think it is reasonable to accept the agent's argument that the skilled person would also be aware that the applicant for the patent, Nymox, is a company based in the US and that they are a pharmaceutical company involved in conducting clinical trials in human patients. In these clinical trials in USA and in Europe, a candidate drug identified as NX-1207 is being used to treat BPH. It was known at the priority date of this application that NX-1207 is a peptide of some kind - it is referred to as a proapoptotic peptide[2]. The skilled person would also be aware that a company such as Nymox which is involved in clinical trials is not likely to have more than one candidate in clinical trials for the same medical condition given the cost and resources required for such a trial. Thus, I am satisfied that the person skilled in the art would realise that the drug candidate known as NX-1207 which Nymox has in clinical trials for BPH is likely to be an NTP peptide such as those discussed in the present application

38 In their skeleton argument and again at the hearing, the agent argued that the skilled person would also know that the candidate peptide drug undergoing clinical trials denoted as NX-1207 is Fexapotide, a peptide with an amino acid sequence correspondingly exactly to that of SEQ ID No. 66. The applicant argued that this information was available and accessible at the priority date from the PubChem

[2] This is discussed on page 810 of "*Future Directions for peptide therapeutics development*" by AA.Kasper & JM Reichert, *Drug Discovery Today*, 2013, Vol 18, No. 17/18, p 807-817 – see Annex D and para 1.21 of the skeleton argument (dated 18 November 2020) provided by the agent. Proapoptotic peptide = peptide that promotes programmed cell destruction (apoptosis).

database[3]. However, I do not agree with the agent on this point – while it is true that there may have been reference to the substance involved in these trails (i.e., NX-1207) before the priority date, the exact structure of the chemical compound involved in these studies would not have been known until after the standardisation process that PubChem carries out on substances in the PubChem Substance database to verify and identify unique chemical structures and then place these standardised structures in the PubChem Compound Database[4]. This is because, for example, the same chemical structure can have more than one substance name and each substance name from the Substance database will be linked and listed as synonyms for this unique chemical structure in the Compound database. This standardisation process had not been carried out for NX-1207 at the priority date of the application in suit as far as I can establish. Although NX-1207 was first deposited in the PubChem Substance database on 03 March 2012, the structure of this substance was not subject to standardisation by PubChem and entered into the PubChem Compound Database until 15 August 2015[5] so far as I am aware. The priority date of the application-in-suit is 27 January 2015. Thus, at the priority date of the application, the person skilled in the art, in my view, would have been aware that the candidate drug NX-1207 was a peptide, that it played a role in apoptosis, but not what the exact structure or sequence of this peptide was.

39 Thus, the question to answer is whether the skilled person, reading the specification and aware of the points highlighted above and that the clinical trials being conducted by Nymox into BPH involved a peptide identified as NX-1207, would conclude that the term DRUG used in the examples can be read, not just as an NTP peptide (i.e., 1 of the 116 identified sequences in para [0035] on pages 11-19 of the specification as filed) but more specifically as one of the four peptides closely related to SEQ ID NO. 66 or as SEQ ID NO. 66 alone and so provide the necessary enablement for the therapeutic use claimed in claim 1.

40 It is well established in UK law that the evidence in support of a medical use claim must be found in the application as filed. Post-filed evidence can be used to further

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[3] PubChem is an open chemistry database coordinated by the National Institutes of Health (NIH) in the USA. As an 'open' database, anyone can deposit their scientific data in PubChem and others may use it. Since its launch in 2004, PubChem has provided a resource for scientists, students, and the general public relating to chemical structures, database identifiers, chemical properties, physical properties, biological activities, related patents, and health, safety, and/or toxicity data. While it relates mostly to small molecules, it does increasingly include larger molecules such as nucleotides, carbohydrates, lipids, peptides, and chemically-modified macromolecules.

[4] See article entitled "*PubChem Substance and Compound databases",* by S Kim at al., *Nucleic Acids Research*, 2016, Volume 44, Issue D1, Pages D1202-13. This provides an overview of the PubChem Compound and Substance databases and how they are complied, organised and interact with each other – see especially Figures 1 and 2. This article is also available via the PubChem home page at PubChem Explained | PubChem Blog (nih.gov).

[5] See substance record entry 1215219-81-0 for PubChem Substance SID 135322613 for NX-1207 on PubChem database, showing that earliest deposit date for NX-1207 in the Substance database from the source (i.e. the depositor) was 31 March 2012. This substance name was subsequently associated with compound Fexapotide from 15 August 2015 – see Substance Record 9L8TV1O7E0 entry on PubChem database for Fexapotide (PubChem Compound CID 16207730, Substance SID 252163516) .

elaborate or explain this therapeutic use but only if there is a basis for doing so disclosed in the application as filed.

41 I agree with the view expressed by the examiner that it is not explicit from either the description or the Examples that DRUG represents SEQ ID NO.66. The skilled person reading the specification would not know which of the peptides of SEQ ID Nos. 1-116 (or even variants and derivatives thereof) is used in the examples in the treatment of BPH and represented by the term "DRUG". In the examiner's view this means that there is an undue burden on the skilled person in testing all of the possible NTP peptides to determine which one has the efficacy claimed and hence the application is considered insufficient.

42 However, I do not think that the situation is as clear cut as the examiner suggests. There are a number of points that the person skilled in the art seeking to work the invention based on their common general knowledge would take into account from the disclosure in the application that I think suggest that the active ingredient referred to as DRUG in the examples is likely to be the same active ingredient as claimed in claim 1. The person skilled in the art would be aware that the application is concerned with the use of NTP peptides; that 116 such NTPs are identified in the specification as being suitable (but not limited to these, see para [0035], end of page 19); that 4 of these 116 NTP peptides are identified as "*preferred*" and that these 4 peptides are closely related to each other. While, it is certainly the case that my task would have been easier had the specification been more explicit about what the term 'DRUG' actually refers to in examples 1-7, it is clear that this term refers to the active ingredient used in a double-blind clinical trial in male patients with BPH. The examples in the application go on to discuss how NTP peptides behave when reviewing the outcome of these examples, further indicating that "DRUG" is one such peptide. Although the claim requires a specific NTP peptide, this peptide does clearly fall within the definition of NTP peptide discussed in the specification and it is also one of the four peptides identified as preferred. On balance, I consider that the skilled person would consider that "DRUG" is likely (although not certain) to be either SEQ ID NO. 66 or one of the other 3 related "preferred" peptides, and so would consider that the application makes it plausible that the peptide defined in claim 1 does in fact have the claimed therapeutic activity. Definite proof is not necessary but there must be something in the specification to suggest that there is a reasonable prospect that the claimed product will be effective in the treatment of BPH - as set down in *Warner-Lambert* (see above). This is helped by the fact that the claim is a very narrow one in so far as it is specifically to a peptide of SEQ ID NO. 66 and that the 4 preferred NTP peptides identified are closely related to this peptide. If on the balance of probabilities, the skilled person considered that it is plausible that the peptide of SEQ ID NO. 66 has the claimed therapeutic effect, they would be able to establish quite quickly that it is in fact effective in treatment of BPH in humans. There is therefore no undue burden of research; the skilled person would start with SEQ ID NO. 66 as claimed.

43 Thus, I consider that there is enough in the specification as filed to take this beyond speculation. I consider that the claimed therapeutic effect is rendered plausible by the specification as there is enough to suggest that it is worth trying the single peptide identified as SEQ ID NO. 66 as a treatment for BPH, given the evidence relating to "DRUG" in the specification and the skilled person's assessment of what this evidence shows and the likely identity of the active agent.

Inventive Step under Section 1(1)(b)

The Relevant Law

44 Section 1(1)(b) and section 3 of the Act are concerned with whether the invention involves an inventive step.

45 Section 1 of the Act reads as follows:

> *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) …;*
>
> *(b) It involves an inventive step;*
>
> *(c) …;*
>
> *(d) ….*

46 Section 3 of the Act, entitled 'Inventive Step' reads:

> *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).*

47 Section 2(2) of the Act, which refers to the state of the art, reads:

> *The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, 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.*

48 The approach to assessing inventive step favoured by the UK courts is the structured approach found in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*[6] (Windsurfing) as modified by Jacobs LJ in *Pozzoli SPA v BDMO SA*[7] (Pozzoli), hereafter referred to as *Windsurfing/Pozzoli*. This approach involves the following steps:

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

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[6] *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59
[7] *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588

(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, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

Analysis

49 Taking the steps of the approach set down in *Windsurfing/Pozzoli* in turn:

Step (1) (a) Identify the notional "person skilled in the art"
(b) Identify the relevant common general knowledge of that person;

50 As confirmed in the correspondence between the examiner and the agent and again at the hearing, there was agreement between the applicant and the examiner in relation to person skilled in the art and their common general knowledge. In the pre-hearing report dated 28 September 2020 the examiner identified the relevant skilled person as being a team of scientists with an interest in the treatment of benign cellular proliferations. This team will have the knowledge and understanding of the molecular biology of various benign cellular proliferations including hyperplasia and the various ways in which they may be treated. This team would also have knowledge of the use of small peptides as drug candidates. I accept this characterisation of the person skilled in the art and their common general knowledge

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

51 The examiner went on in his prehearing report to state that the inventive concept of the claim is the use of peptide of SEQ ID NO. 66 in treating BPH in humans who have not been treated for BPH before ('treatment naïve patents') invention. The applicant agreed on this point also.

Step (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;

52 Turning now to consider the matter cited in prior art document US2013/0040900 A1, hereafter US'900, which I note includes the name of the sole inventor for the present application, P Averback, as one of its two inventors. The use of the peptide of present claim 1 (denoted as 'SEQ ID NO. 8' and 'NTP[122] peptide #1' in US'900) to treat conditions requiring removal or destruction of cellular elements in humans is discussed in this document (see para [0003] which describes the field of the invention). Such conditions include prostatic hyperplasia, including benign prostatic hyperplasia, which

are not always treatable by surgery (see paras [0005], [0010] and [0025]). In para [0036]-[0037], it is noted that NTP peptides have proven to be effective in causing cell death in both *in vitro* and *in vivo* models, such as in rats, and also in tumours of human origin. In the summary of invention and again in para [0158] of US'900, it is stated that NTP peptides can be used to treat unwanted cellular proliferations in mammals, such as benign or malignant tumours and glandular hyperplasia e.g. prostate. Such tumours encompass human ones (see para [0160]). It is noted in para [0161] that a method for removing benign tumours in surgically hazardous areas such as deep locations in the body (e.g., the organs) is "*particularly needed*". In para [0166], it is indicated that prostatic hyperplasia is one of the conditions that can be treated "*in particular*". Thus, I consider that there is a disclosure that NTP peptides can be used to treat prostatic hyperplasia in humans. Furthermore, in addition to these general statements, the examples in US'900 demonstrate that NTP[122]peptide#1 can reduce the volume of the prostrate in rats and so cause cell death and atrophy. Examples 1-3 show that intraprostatic injection of the NTP peptide equivalent to SEQ ID NO. 66 into male rats leads to a reduction in volume of the prostrate. Intraprostatic infusion of NTP[122]peptide#1 is described followed by volume calculation: in example 1, the reduction in prostate volume in NTP[122]peptide#1 treated rats was found to be on average 45% compared to controls. Example 2 shows a similar loss in volume as Example 1 and that injection of the NTP peptide into the prostate of rats resulted in significant cell loss and atrophy in this organ compared to controls. Example 3 shows that a number of different NTP peptides had the same imp[act as NTP[122] peptide #1 in terms of causing cell loss and atrophy at the site of injection. This loss was not seen in the controls and so was attributed to the NTP peptide.

53 The examiner considered that the difference between US'900 and inventive concept of present claim 1 is that there is no disclosure of the treatment of BPH with NTP peptide in human patients which have not received treatment for BPH before, i.e. treatment naïve patients. The applicant characterised the difference between US'900 and the present claim 1 was broader than that identified by the examiner. As stated in their skeleton argument, they consider that this document "*fails to disclose intraprostatic administration of an isolated peptide consisting of the amino acid sequence in SEQ ID NO. 66 to human patients*"; i.e., there is no disclosure of the treatment of BPH with NTP peptide in human patients yet alone treatment naïve human patients. I find that I agree with the view of the examiner. I consider that the difference between US'900 and inventive concept of present claim 1 is that there is no disclosure of the treatment of BPH in treatment naïve human patients.

54 The examiner argues that the whole point of testing treatments in animal models, such as rats, is to demonstrate their potential for treating humans. As a general proposition this seems reasonable and, in any event, there are several references in US'900 to humans, not least paragraph [0003] setting out the field of the invention which says "*The present invention is directed to methods of treating conditions requiring removal or destruction of cellular elements, such as benign or malignant tumors in humans,…*".

55 In contrast, the applicant argues that the skilled person would not automatically consider applying the teaching of the prior art document to humans. They point out that the anatomy of the prostate in rats and humans is different and that spontaneous Benign Prostate Hyperplasia (BPH) is absent in the mouse prostate and presumably by extension in the rat prostate.

56 It is argued by the applicant that it would not be possible to extrapolate results from studies on rodent models to the study of human prostate disease owing to species differences. However, US'900 is silent on the asserted differences between the species such that this document does not give the skilled person any reason not to try the treatment exemplified in rats, in humans. The applicant provided a paper reviewing models for studying BPH ("*Models for studying benign prostate hyperplasia"*, Mahapokai, W. *et al*. Prostate Cancer Prostatic Dis., 2000, Vol.3, pp.28-33, hereafter *Mahapokai*) to represent the common general knowledge to the relevant skilled person. It discusses the relevance of certain animal models as models for BPH in humans, and while it points out that rats may not be as useful as canines or monkeys in such models, it recognises that the latter species are expensive and not as easy to work with and so studies in rodents will likely continue as models. I do not believe that the skilled team would consider this document to represent a technical prejudice against trying the peptide that showed potential in the rat model in humans. At most, I think the skilled team would be aware that there is some debate about how appropriate the model studies in rats may be as a model of prostate disease, but that this is not enough to cause them to think that it is not a plausible or reasonable step to take based on rodent studies. Afterall, it is well established that drug design is almost always geared towards treating humans, not rodents but that the latter provide a useful indication of potential – if the studies in rats show a positive effect, then studies in humans would be a logical next step. The *Mahapokai* review document describes various rodent models of prostatic hyperplasia and their use in testing anti-BPH drugs. It does not indicate that these models should not be used to test treatments for BPH, just that there are some differences between species used in model studies to be aware of. This is not enough in my view for the relevant skilled person to consider that there is not a reasonable expectation of success from taking the teaching of US'900 and using the NTP [122] peptide#1 in humans.

57 Also, while I do not doubt the truth of the point that the applicant made regarding differences between species in model studies, this seems to me to be beside the point. Whilst the results disclosed in the US'900 are certainly from treating rats, the context in which this was done was clearly as part of a process for developing a treatment for use in humans, as the field of the invention explains. It does not seem to me that there is anything in this prior art document that teaches away from the fact that studies in rodent species are to demonstrate the likelihood that these compounds will prove useful in humans. Indeed, it is very well established that studies in rodent species such as rats and mice provide a reasonable basis for supporting a claim for treatment in humans. Thus, I agree with the examiner on this point. The skilled team considering US'900 would in my view consider the use of NTP [122] peptide#1 (i.e. peptide of SEQ ID 66 from application in suit) to treat BPH in humans. Given that the examples show that the NTP peptide can actually reduce the size of the prostate in rats, and the disclosure referred to above that BPH is a condition that can be treated using NTP peptides, the person skilled in the art will thus consider it plausible that this specific peptide is suitable to treat humans with BPH.

58 Consequently, I consider that the only difference between US'900 and inventive concept of present claim 1 is that there is no disclosure of the treatment of BPH in treatment naïve human patients.

Step (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

59 The applicant argues that there is nothing in US'900 to indicate that administering the peptide to treatment naïve patients would be particularly effective. They argue that a second medical use claim may rely for its inventive step on the patient group to be treated and refer to European Patent Office Technical Board of Appeal decision T 0108/09 (AstraZeneca/Teva)[8]. In that decision the Board discussed a series of earlier decisions all relating to groups of subjects and whether they establish novelty and/or inventive step. Citing this decision, the agent referred to the fact that pre-treatment and post-treatment cancer patients can be considered as separate patient groups. Such groups can be distinguished based on differences in physiology and in pathology, and it was argued that the same distinction could be made between treatment naïve and treatment failure BPH patients. Furthermore, it would not be obvious that treatment with peptide SEQ ID NO. 66 would be more effective in those who had not undergone treatment compared to those who had already had some treatment for BPH. I am satisfied that it has been established that patient groups can characterise valid patent claims, and that treatment naïve BPH patients may be different from treatment failure patients. I would also accept that the skilled person would not be able to predict the difference in efficacy between these patient groups, However, in this case, I consider that it is likely that the person skilled in the art will start with human patients who have not received treatment for BPH before.

60 Upon reading the prior art document, it is my view that the skilled reader, aware of the relevance of rodent studies as a way to demonstrate potential in humans, would understand that there was likely to be therapeutic benefit from administering the peptides to human patients. There is nothing to suggest that they should not be used to treat humans or that there is a particular group that present specific problems that need to be overcome. Thus, I consider that, in the terms identified by the court in *ICOS*[9], the skilled person would consider that there was a reasonable expectation of success in that this peptide could be used to treat humans with BPH. Although the work involved in terms of carrying out the investigations would be non-trivial, it would be obvious to investigate this peptide for treatment of BPH in humans. Furthermore, I consider that the most straightforward starting point to determine if this peptide is effective against BPH in humans would be those who had not been treated for this condition before, so that any effects could more clearly be attributed to the product being tested.

61 The examiner suggested that the tests in rats reported in the prior art may have been treatment naïve patients and argues that there is nothing to indicate that the treatment would not be considered for such a patient group. Although the prior art document is silent on the point, the whole point of the studies in rats was to determine the impact of NTP on prostate tissue. Thus, it seems to me very unlikely that prior to the administration of the NTP peptides the rats would have received any other treatment likely to have an effect upon the prostate, thus they were treatment naive. I say this because, had they received any such treatment then the results reported could not

[8] https://www.epo.org/law-practice/case-law-appeals/recent/t090108eu1.html
[9] Actavis Group PTC EHF & Ors v ICOS Corporation & Anor [2019] UKSC 15

have been reliably attributed to the NTP peptides. Strictly speaking therefore, the rats in those examples were likely to be treatment naïve.

62 I consider that the nature of the condition is also relevant here, the skilled person would be aware that BPH is a condition that occurs commonly in older men, and that trials in naive patients will be useful in that this is the most straightforward way to see if the active ingredient can have a positive effect on BPH. Also, this is not a condition where failure of other treatments and related likelihood of life-threatening outcomes makes treatment failure patients a more likely starting point.

63 The fact that once the skilled person has started to use this peptide in human patients, they would discover that it works better in treatment naive patients rather than treatment failure patients is a surprising and unexpected effect that could not be predicted from the prior art. However, if the prior art leads directly to the claimed invention (as I have argued above) a surprising "bonus" effect or advantage does not overcome an objection of obviousness. It is information that is in effect "lying in the road" and would emerge when taking the obvious step of testing the peptide in human patients. This is not a situation where there are a number of different possibilities to choose from and a choice or selection has to be made to decide which possibility to pursue, in such a situation an unexpected effect or advantage may overcome an objection to obviousness as the agent has argued. However, in the present case, there are not a number of possibilities to select or choose from; it is a situation where the person skilled in the art is likely to start with the most straightforward option, namely treatment naive patients. Thus, they are already on the route that leads to this additional information.

64 Consequently, I do not think that the selection of human patients who were specifically treatment naïve represents an inventive step over the cited prior.

Conclusion

65 Taking all of the above into account, based on the correspondence on file and the arguments presented to me at the hearing, I consider that the invention as claimed in claim 1 of patent application GB1713738.1 is disclosed in a manner which is clear enough and complete enough for the it to be performed by a person skilled in the art. Hence the application complies with section 14(3) of the Patents Act 1977

66 Further, I consider that the invention as claimed in claim 1 does not, however, involve an inventive step over the disclosure in US2013/0040900 A1 and so it does not meet the requirement of section 1(1)(b) of the Act.

67 As the application does not comply with the requirements of the Act, I refuse this application under section 18(3) of the Act.

Appeal

68 Any appeal must be lodged within 28 days after the date of this decision.

Dr L Cullen

Deputy Director, acting for the Comptroller