PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2023/050281	08.02.2023	09.02.2022

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61P37/06 A61P29/00

Applicant
PETMEDIX LTD

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Stein, Annette Telephone No. -0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2023/050281

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed.

   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),

      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-25(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-25(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).

☒ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-25(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25(partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25(partially)
Industrial applicability (IA)	Yes:	Claims	1-25(partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

1 **Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 Present claims 1-8 (as well as claims 9-25 dependent thereon) relate to an extremely large number of possible antibodies. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the antibodies claimed, see the antibodies defined by at least all of their six specific CDR sequences in the right order and according to a clear definition disclosed and supported by the present application in table 2 on pages 90-188. In this regard it is noted that the characterization of an antibody by at least all of its six CDR sequences is essential to its definition for the reason that antibodies functional properties depend (at least) on these sequences. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of these claims (PCT Guidelines 9.19 and 9.23).The search of claims 1-8 (as well as claims 9-25 dependent thereon) was restricted to those claimed antibodies which appear to be supported (see sequences of CDRs, VH/VL in table 2 on pages 90-188) taking also into consideration the lack of unity of invention.

2 **Re Item IV**

Lack of unity of invention

2.1 This Authority considers that the application does not meet the requirements of unity of invention and that there are 15 inventions covered by the claims indicated as follows:

Invention 1: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX097, PMX063, PMX086, PMX087, PMX094, PMX095, PMX096, PMX098, PMX099, PMX100, PMX101, PMX102, PMX103, PMX104, PMX105, PMX107, PMX108, PMX109, PMX110 or PMX111, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 2: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX154, PMX054, PMX084, PMX293 or PMX294, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 3: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX051 or PMX088, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 4: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX025, PMX026, PMX027, PMX089, PMX090, PMX091, PMX092 or PMX093, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 5: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX028, PMX029, PMX032, PMX033, PMX034, PMX035, PMX036, PMX038, PMX042, PMX045, PMX064, PMX082 or PMX083, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 6: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX030 or PMX031, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 7: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX035, PMX037, PMX040, PMX048, PMX049 or PMX065, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 8: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX039, PMX041, PMX043, PMX044, PMX046, PMX050, PMX055, PMX056, PMX057, PMX058, PMX059, PMX062 or PMX085, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 9: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX047 or PMX053, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 10: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is the antibody designated PMX052, which is characterized by at least all of its six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 11: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX060 or PMX061, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 12: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is the following antibody designated PMX106, which is characterized by at least all of its six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 13: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX054, PMX084, PMX293 or PMX294, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 14: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX155 or PMX156, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

Invention 15: claims 1-25(partially)

An antibody or fragment thereof that specifically binds to companion animal OX40L, wherein the antibody is selected from one of the following antibodies designated PMX291 or PMX292, which are characterized by at least all of their six CDR sequences as disclosed in table 2; and related subject-matter.

2.2 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:
According to Rule 13 PCT an application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept, i.e. having at least one common technical feature defining a contribution over the known prior art.
Present alternatives of claims 1-8 (see above for incomplete search) are linked by the common matter of an antibody that binds to companion animal OX40L, in particular to canine OX40L and further to an antagonistic antibody.
This common matter is, however, obvious (or even not novel) due to the following:
The provision of antibodies against a known antigen does not involve an inventive step since it amounts to work of a routine nature for the skilled person. Canine OXL40 was known in the art as evident from, e.g. D3 (see below). Furthermore, the transgenic mice platform used for antibody generation was also known in the art (see, e.g. D4, D5 below). Moreover, the functional property to bind to companion animal OX40L does not allow a clear distinction to be made over the state of the art. Whilst raised against a different species such as human, such antibodies could equally cross-react to other species including companion animals. For example, the antibodies disclosed in D1 and D2 are considered suitable for treatment of companion animals which require their binding to companion animal OXL40 (see D1, D2 below).
The antibodies of claims 1-8 are defined by their sequences (see above for the objection for lack of support and sufficiency of disclosure). These sequences, with the exception of the same VH and VL gene usage as disclosed in table 3, lack, however, a common significant structural element (Guidelines 10.17 PCT). Thus, the antibodies (antibody families) claimed are not linked by a single general inventive concept based on special technical features. Therefore, the

various antibodies claimed represent alternative solutions to the underlying technical problem of providing antibodies binding companion animal OX40L. As the claims do not comprise the same or corresponding special technical features, they lack the technical relationship between their subject-matter required by Rule 13.2 PCT and are not so linked as to form a single general inventive concept.

The application therefore does not fulfil the requirement for unity of invention within the meaning of Rule 13 PCT.

Since the Applicant did not pay additional search fees for the other inventions, an opinion will only be formulated for the subject-matter of the invention searched, i.e. invention 1 as specified above, i.e. subject-matter related to antibodies identified as family 10 identified in table 3 in combination with the claimed structural features in the claims and table 2.

3 **Re Item V**

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3.1 *Cited documents*

Reference is made to the following documents. As far as not otherwise indicated, reference is made to the passages cited in the search report:

D1	WO 2007/133290 A2 (GENENTECH INC [US]; MARTIN FLAVIUS [US]) 22 November 2007 (2007-11-22)
D2	WO 2005/094879 A2 (AMGEN INC [US]; ABGENIX INC [US] ET AL.) 13 October 2005 (2005-10-13)
D3	US 2013/209511 A1 (MEBATSION TESHOME [US] ET AL) 15 August 2013 (2013-08-15)
D4	WO 2020/074874 A1 (GENOME RES LTD [GB]) 16 April 2020 (2020-04-16)cited in the application
D5	WO 2018/189520 A1 (GENOME RES LTD [GB]) 18 October 2018 (2018-10-18)cited in the application
D6	WO 2022/029447 A1 (PETMEDIX LTD [GB]) 10 February 2022 (2022-02-10)

3.2 *Disclosure of the cited documents*

D1 discloses the generation, characterization and use of antagonist anti-OX40L antibodies (including fragments thereof) for treatment (autoimmune, inflammatory diseases) and diagnosis. Further encompassed are immunoconjugate thereof, combination treatments (e.g. steroids, cytokines, growth inhibitory agents), pharmaceutical compositions and kits. The treatment encompasses treatment of pet animals such as dogs, cats, horses. The exemplified antibodies are designated 8E12 and 13G5 which are shown to bind to and block human OX40L.

D2 discloses the generation of antagonist anti-OX40L antibodies for therapy including treatment of non-human animals such as dogs, cats suffering form OX40/OX40L inflammatory or arthritic condition including, e.g. atopic dermatitis, psoriasis. Further encompassed are combination treatment (e.g. cyclosporin, steroids, IL-4 inhibitor, IL-1 inhibitors, IL-6 inhibitors), antibody conjugates (e.g. prodrug, cytotoxic drug). Exemplified is the generation and characterization of antagonist human monoclonal antibodies.

D3 discloses the generation of rabies vaccine for companion animals comprising poxviral vector co-expressing rabies G polypeptide and canine OX40L, wherein canine OX40L has the sequence of SEQ ID NO: 12 which is identical to SEQ ID NO: 1 of the application. D3 also encompasses combinations of other antigens and canine OX40L.

D4 and D5 disclose the generation of canine, feline or equine antibodies for prevention/treatment of diseases in dog, cat, horse, respectively. The antibodies are obtained and selected based on a general platform for antibody generation, i.e. the Ky9^{TM} transgenic mouse used in the present application.

D6 (see also item VI below) discloses the same subject-matter as the present application but differs in the particular antibodies obtained.

3.3 *Novelty*

The present application meets the criteria of Article 33(1) PCT, because the prior art does not disclose the antibodies designated PMX097, PMX063, PMX086, PMX087, PMX094, PMX095, PMX096, PMX098, PMX099, PMX100, PMX101, PMX102, PMX103, PMX104, PMX105, PMX107, PMX108, PMX109, PMX110 or PMX111 characterized by at least all of their six CDR sequences as disclosed in table 2. Thus, these antibodies are new in the sense of Article 33(2) PCT.

3.4 *Inventive step*

The present application does claims 1-25 does not involve an inventive step in the sense of Article 33(3) PCT.

Given the fact that methods to obtain antibodies, including companion animal antibodies, directed against every well known and defined antigens, and to screen said antibodies in order to select those presenting specific characteristics are considered routine in the art, the subject-matter of the present application cannot be considered as inventive. An inventive step could only be acknowledged if the antibodies would show unexpected properties, which does not appear to be the case in view of antagonistic anti-OX40L antibodies known in the art such as disclosed in, e.g. D1 or D2, or if it had been unexpected that such antibodies could be produced at all, which also does not seem to be the case for the antibodies claimed. Thus, present claims 1-8 are not inventive.

The same holds true for the subject-matter of claims 9-25 in view of the disclosures of D1 or D2 already disclosing such subject-matter in the context of antagonistic alternative anti-OX40L antibodies.

3.5 *Further remark*

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 12 and 14-20 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

4 **Re Item VI**

Certain documents cited

As the priority documents for the present application are not available at the moment, said priorities are considered to be valid. Therefore the published document (Rule 70.10 PCT)) D6 is considered as not being part of the prior art (Rule 64.1 PCT). However, this document may be of importance regarding inventive step in a subsequent national/regional phase in case the first priority cannot be validly claimed.