

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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. PCT/US2022/074574	International filing date (day/month/year) 05.08.2022	Priority date (day/month/year) 06.08.2021
International Patent Classification (IPC) or both national classification and IPC INV. A61K39/08 A61K39/02		
Applicant ZOETIS SERVICES LLC		

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 43bis.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 notified the International Bureau under Rule 66.1bis(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:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Noë, Veerle Telephone No. +31 70 340-0	
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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 43bis.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 13ter.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. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>3, 4, 7-25</u>
	No: Claims	<u>1, 2, 5, 6, 26, 27</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-27</u>
Industrial applicability (IA)	Yes: Claims	<u>1-27</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 **Re Item V**

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

1.1 CITATIONS

Reference is made to the following documents:

- D1 WO 2020/102717 A2 (MATRIVAX INC [US]; KILLEEN KEVIN [US]; GRIFFIN THOMAS [US]) 22 May 2020 (2020-05-22)
- D2 WO 2010/086353 A1 (INTERVET INT BV [NL]; UNIV BERN [CH] ET AL.) 5 August 2010 (2010-08-05)
- D3 FREY JOACHIM ET AL: "Cytotoxin CctA, a major virulence factor of Clostridium chauvoei conferring protective immunity against myonecrosis", VACCINE, vol. 30, no. 37, pages 5500-5505, XP028931054, ISSN: 0264-410X, DOI: 10.1016/J.VACCINE.2012.06.050
- D4 ABDOLMOHAMMADI KHIAB LIDA ET AL: "Vaccination against pathogenic clostridia in animals: a review", TROPICAL ANIMAL HEALTH AND PRODUCTION, SPRINGER NETHERLANDS, DORDRECHT, vol. 1-2753, no. 2, 23 April 2021 (2021-04-23), XP037558933, ISSN: 0049-4747, DOI: 10.1007/S11250-021-02728-W [retrieved on 2021-04-23]

- 1.2 Claims 26-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/Rule 67.1(iv) PCT. 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 a first or further medical treatment.

- 1.3 NOVELTY (Art. 33(2) PCT)

- 1.3.1 D2 discloses a vaccine composition comprising cctA and a further antigen of *Clostridium chauvoei*, namely hyaluronidase or sialidase (see claim 11 and page 4, paragraph 1). Since the additional antigens hyaluronidase or sialidase are also *Clostridium chauvoei* components. D2 is novelty destroying for claims 1,2,5,6,26,27 is not novel.
- 1.3.2 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1,2,5,6,26,27 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).
- 1.4 INVENTIVE STEP (Art. 33(3) PCT)
- 1.4.1 For inventive step analysis of claim 1 (wherein the term component is limited to a formalin inactivated bacterium - see Art. 6 PCT) , Document D1 is considered to represent the most relevant state of the art and discloses a *Clostridium difficile* vaccine composition comprising (a) inactivated *C-difficile* whole cells or cell extracts and (b) one or more polypeptides comprising a toxoid or a non-toxic immunogenic polypeptide of *Clostridium difficile* Toxin A. The subject-matter of claim 1 differs in that a vaccine against *Clostridium chauvoei* is claimed.
- 1.4.2 The problem to be solved by the subject matter of claim 1 may therefore be regarded as the provision of a vaccine composition against an alternative *Clostridium* bacterium. The solution would be a vaccine against *Clostridium chauvoei*.
- 1.4.3 This solution cannot however be considered as involving an inventive step since it would be obvious for the person skilled in the art to apply the teachings of D1 to another *Clostridium* bacterium and arrive at the claimed vaccine. It would be obvious for the person skilled in the art to use the cctA antigen of *Clostridium chauvoei* as antigen to be combined with the *Clostridium chauvoei* whole cell extract the since cctA is known to be a major virulence factor and since it has been used in a vaccine composition which provides partial protection against *Clostridium chauvoei* (see D2 and D3).
- 1.4.4 Claim 19, related to a product defined in terms of a process of manufacture, and claim 26 related to the method of treatment comprising administering the vaccine, are for the same reasons not considered to involve an inventive step.

- 1.4.5 Dependent claims 20-25 and 27 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step because the features are obvious modifications for the person skilled in the art or have been disclosed in D1, D2 or D3 or in the review article on vaccination against clostridium in animals, D4
- 1.4.6 Also the method of preparing the vaccine composition of claim 10 is not considered to involve an inventive step in view of the cited documents. The skilled person knows how to culture bacteria and to concentrate the bacteria from the culture medium. From D2 and D3, it is known that cctA is secreted by the Clostridium chauvoei and has a molecular weight of 33kDa. It would therefore be obvious for the person skilled in the art that this protein can be concentrated from the medium. Also the method steps of claims 11,13-18 are considered to be obvious steps for the person skilled in the art. Culturing Clostridium chauvoei for producing formalin inactivated vaccines in a medium comprising a peptone is described in D4 and therefore claim 12 is not inventive.
- 1.4.7 The present application does therefore not satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims 1-27 does not involve an inventive step (Rule 65(1)(2) PCT).

2 Re Item VII

Certain defects in the international application

- 2.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1, D2, D3 and D4 is not mentioned in the description, nor are these documents identified therein.
- 2.2 If amendments are filed, it should be by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate. Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.
- 2.3 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based

(see also Rule 66.8(a) PCT). If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

- 2.4 The applicant is requested to note that in accordance with Rule 66.4 (a) PCT the issuance of an additional Written Opinion (WO) is facultative. Moreover, as the final action in the PCT procedure is an International **Preliminary** Examination Report (IPER) and not a decision, a violation of the right to be heard cannot exist. The applicant can not therefore rely on obtaining a second WO before the IPER is issued and is requested to answer this first WO in a complete manner.

3 **Re Item VIII**

Certain observations on the international application

- 3.1 The application does not meet the requirements of Article 6 PCT because the claims are not supported for the following reasons:
- 3.2 Present claims relate to any vaccine against *Clostridium chauvoei* comprising any *Clostridium chauvoei* component and cctA protein and to the use thereof. Support within the meaning of Article 6PCT is to be found, however, for only a very small proportion of these vaccines and uses claimed. The present application has demonstrated that a vaccine composition comprising whole cell formalin inactivated *Clostridium chauvoei* and comprising a bacterial cell culture permeate from this inactivated culture that is concentrated using a 10kDa molecular weight cut-off membrane is and comprising aluminium hydroxide as vaccine adjuvant is inducing a protective immune response. This cannot provide support for any vaccine covered by the claims. It is not plausible that any *Clostridium chauvoei* combined with cctA will be suitable for inducing a protective immune response and in the absence of any guidance in the present application on which components will achieve this effect, it is considered to be undue burden for the person skilled in the art to test all the vaccines claimed. Also claim 8 is not considered to be supported over its whole scope since the present application does not provide evidence that a whole cell extract or a partial extract, comprising less antigenic molecules compared to a bacterin, are sufficient for inducing a protective immune response.
- 3.3 The application does not meet the requirements of Article 6 PCT because claims are not clear for the following reasons:

- 3.4 The expression "a *Clostridium chauvoei* component" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim/s unclear, Article 6 PCT.
- 3.5 The parameter "RU of flagella" used in claims 3,4 and 19,20,22 is considered to be an unusual parameter to measure which makes it difficult to compare the amount with the prior art vaccines. Therefore claims 3, 4, 19, 20 and 22 are not clear.
- 3.6 The method of claim 10 appears to lack essential technical features and is therefore not clear. Example 1 (for the growth and inactivation of the bacteria) and 2 describe the method for preparing the vaccine and it is considered that all the steps of this process including the filter and membranes used are essential (see the features of the dependent claims). For these reasons claim 10 lacks clarity according to Art. 6 PCT taken in combination with Rule 6.3 (b) PCT (see also PCT Preliminary Examination Guidelines III.4.3).
- 3.7 It is also considered to be essential that *cctA* is inactivated by formalin treatment (as in example 1) in order to eliminate its toxicity.
- 3.8 The specification for an international application should be capable of being understood without reference to any other document (cf PCT Guidelines Ch. II 4.17). The expression "hereby incorporated by reference" found in the description in paragraph 96 is therefore not according to the PCT requirements.
- 3.9 The vague and imprecise statement in the description on page 22, paragraph 97 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, PCT/GL/3 III, 4.3a).