

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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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/US2016/042882	International filing date (day/month/year) 19.07.2016	Priority date (day/month/year) 20.07.2015
International Patent Classification (IPC) or both national classification and IPC INV. A61K47/18 A61K47/24 A61K47/28 A61K9/127		
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 González Ferreiro, M 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:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
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>3-5, 11-21, 23</u>
	No: Claims	<u>1, 2, 6-10, 22</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-23</u>
Industrial applicability (IA)	Yes: Claims	<u>1-23</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

Re Item V

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

Cited documents

Reference is made to the following documents:

D1 AU 750 379 B2 (MERIEUX ORAVAX) 18 July 2002

D2 US 2006/008519 A1 (DAVIDSEN ET AL) 12 January 2006

Patentability

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 of the human or animal body, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. This observation relates to claims 14, 15 and 18.

Novelty

Document D1 discloses a pharmaceutical composition which comprises an immunogenic agent derived from Helicobacter and at least one compound capable of promoting the induction of a T helper 1 (Th1) type immune response against Helicobacter selected from: (i) saponins purified from an extract of Quillaja saponaria; (ii) cationic lipids or a salt of the latter; the said lipids being weak inhibitors of protein kinase C and having a structure which includes a lipophilic group derived from cholesterol, a bonding group selected from carboxyamides and carbamoyls, a spacer arm consisting of a branched or unbranched linear alkyl chain of 1 to 20 carbon atoms, and a cationic amine group selected from primary, secondary, tertiary and quaternary amines, on condition that these lipids are not provided in the form of liposomes when the said composition contains no saponin or glycolipopeptide of formula (I); and (iii) glycolipopeptides of formula (I) (cf. page 4 line 27 - page 5 line 31). Liposomes containing cationic lipids recognized for their fusiogenic properties, such as 3-beta-(N-(N',N'-dimethylaminoethane)carbamoyl)cholesterol (DC-chol), dimethyldioctadecylammonium bromide (DDAB) and the BAY compounds described in EP 91645 and EP 206 037, for example Bay R1005 (N-(2deoxy-2-L-leucylamino-

beta-D-glucopyranosyl)-N-octadecyldodecanoylamide acetate are particularly useful liposomes for adding as adjuvant to all the immunogenic agents cited in D1 (cf. page 12 lines 6-22). Liposomes in D1 are made by combining cationic lipids with a neutral phospholipid, e.g. phosphatidylcholine or phosphatidylethanolamine (cf. page 10 lines 7-10). Useful glycolipopeptides for the purposes of D1 are of general formula (I) in which a sugar residue is a 2-amino-2-deoxy-D-glucose or 2-amino-2-deoxy-D-galactose residue; the 2-amino group of the amino sugar may be linked to glycine, sarcosine, hippuric acid, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, ornithine, citrulline, arginine, aspartic acid, asparagine, glutamic acid, glutamine, phenylalanine, tyrosine, proline, tryptophan or histidine (cf. page 10 lines 11-22). The glycolipopeptide N- (2-L-leucinamido-2-deoxy -D-glucopyranosyl)-N-octadecyldodecanoylamide (Bay R1005) is particularly mentioned in D1 (cf. page 11 lines 7, 8). The steps for the preparation of liposomes regarding the dissolving in an organic solvent, the removing of the organic solvent, the rehydrating in aqueous solvent and the microfluidizing belong to the common general knowledge in the formulation of liposomes. The subject-matter of claims 1, 2, 6-10 and 22 of the present application is therefore not new over D1.

The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1, 2, 6-10 and 22 is not new.

Inventive step

The subject-matter of **claims 1, 2, 6-10 and 22** is not novel, then it is also not inventive (Article 33(3) PCT).

Document D1, which is considered as the closest prior art to the subject-matter of the present application, deals with a vaccine preparation intended to induce, in a mammal, a protective immune response against a pathogenic organism infecting the mucous membranes (cf. page 1 lines 5-8).

The subject-matter of **claims 3, 4, 5, 11-21 and 23** of the present application differs from D1 in:

- the specific selection of the quaternary ammonium compound and the sterol (claim 3),
- the presence of an immunostimulatory oligonucleotide (claims 4, 5, 12, 23),
- the selection of the antigenic component (claims 11, 13-21).

Alike the present application, D1 addresses the preparation of vaccines with adjuvants. The technical effect of these differences is not apparent from the present application.

Therefore, in view of D1, the objective technical problem underlying the present application can be considered as to provide an alternative adjuvant comprising a glycolipid of formula (I).

It is known from D1 that other immunogenic agents, such as a polynucleotide molecule, are capable of being used in the vaccination procedure and compositions of D1 (cf. page 18 line 36 - page 19 line 4). The polynucleotide may be combined with agents which promote entry into the cell (cf. page 20 lines 4, 5). Anionic or neutral lipids have been known for a long time to be capable of serving as transporting agents, for example in the form of liposomes, for a large number of compounds including polynucleotides; a detailed description of these liposomes, of their constituents and of the processes for their manufacture is for example provided by the handbook *Liposomes: A Practical Approach*, RPC New Ed. , IRL press (1990) and belongs to the common general knowledge of the field (cf. page 20 lines 16-24). Cationic lipids are commonly used as transporting agents for polynucleotides, for example LipofectinTM also known by the name DOTMA (N-[1-(2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride), DOTAP (1,2-bis(oleyloxy)-3-(trimethylammonio)propane) and DDAB (dimethyldioctadecylammonium bromide) (cf. page 20 lines 25-32). The selection of different antigens for developing different vaccinations is as well an obvious possibility for the skilled person. For these reasons, the subject-matter of claims **3, 4, 5, 11-21 and 23** does not involve an inventive step (Article 33(3) PCT).

Documents D2 could also be used as the closest prior art to the subject-matter of the present application, arriving to the same conclusion when applying the problem-solution approach.

Document D2 relates to liposome formulations that are physically stable; in particular it relates to steric stabilization of cationic liposomes by an unique film method whereby glycolipids are incorporated into the liposomes; the stabilized liposomes in D2 can be used as an adjuvant for antigenic components in vaccines for immunization, where the final product is stable in aqueous media (cf. paragraph 0002). The cationic liposomes of D2 are stabilized by incorporating glycolipids into the liposome membranes (cf. paragraph 0055). Glycolipids have immunostimulatory properties themselves and can act in a synergistic way with the quaternary ammonium compounds to enhance the immune response; furthermore,

macromolecules e.g. oligonucleotide, peptide or protein antigens can be entrapped within the aqueous phase of both unilamellar and multilamellar liposomes (cf. paragraph 0075).

Industrial Applicability

The subject-matter of claims 1-23 is considered to meet the requirements of industrial applicability, therefore the present application meets the criteria of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

Documents D1 and D2 have not been identified in the description and the relevant background art disclosed therein has not been briefly discussed according to the requirements of Rule 5.1(a)(ii) PCT.

Re Item VIII

Certain observations on the international application

The terms: "DDA" employed in claim 3, "CpG" employed in claims 4, 12 and 19, "IBR, BVDV-1, and BVDV-2" employed in claims 13 and 14, have no precise meaning in absence of the non-abbreviated terms as they are not internationally accepted as standard descriptive terms, thereby rendering the definition of the subject-matter of these claims unclear (Article 6 PCT).

In the present application, the wording of claim 12 relates to "the vaccine composition of any one of claims 8-11, wherein the immunostimulatory oligonucleotide comprises CpG oligodeoxyribonucleotide" although the feature "immunostimulatory oligonucleotide" has not been directly included in the wording of said claims 8-11, which renders the definition of claim 12 unclear (Article 6 PCT).

In the present application, claim 18 refers to claim 18, which is an obvious error.