

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 <i>bis</i> .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/IB2016/054217	International filing date (day/month/year) 14.07.2016	Priority date (day/month/year) 21.07.2015	
International Patent Classification (IPC) or both national classification and IPC INV. A61K39/09 A61K39/385 A61K39/00			
Applicant PFIZER INC.			

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 notified 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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Irion, Andrea Telephone No. +49 89 2399-0	
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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. 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 43bis.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 43bis.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. 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>1-27</u>
	No: Claims	
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. VI Certain documents cited

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

and / or

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

see form 210

Item V

V.1 Reference is made to the following documents:

- D1 WO 2010/125480 A1 (COLEY PHARM GROUP INC [US]; DAVIS HEATHER LYNN [CA]; KRIEG ARTHUR MERT) 4 November 2010 (2010-11-04)
- D2 US 2011/195086 A1 (CAULFIELD MICHAEL J [US] ET AL) 11 August 2011 (2011-08-11)
- D3 WO 2012/119972 A1 (GLAXOSMITHKLINE BIOLOG SA [BE]; BIEMANS RALPH LEON [BE]; DUVIVIER PIER) 13 September 2012 (2012-09-13)
- D4 WO 2014/097099 A2 (PFIZER [US]) 26 June 2014 (2014-06-26)
- D5 WO 2014/092378 A1 (SK CHEMICALS CO LTD [KR]) 19 June 2014 (2014-06-19); & EP 2 932 980 A1 (SK CHEMICALS CO LTD [KR]) 21 October 2015 (2015-10-21)
- D6 CN 103 656 631 A (SINOVAC RES & DEV CO LTD) 26 March 2014 (2014-03-26) (see machine translation attached)
- D7 HICKS L A ET AL: "Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998-2004", JOURNAL OF INFECTIOUS DISEASES, vol. 196, no. 9, 1 November 2007 (2007-11-01), pages 1346-1354, XP002757890
- D8 SKINNER J M ET AL: "Pre-clinical evaluation of a 15-valent pneumococcal conjugate vaccine (PCV15-CRM197) in an infant-rhesus monkey immunogenicity model", VACCINE, vol. 29, no. 48, 20 September 2011 (2011-09-20), pages 8870-8876, XP028326015
- D9 R DAGAN ET AL: "Glycoconjugate vaccines and immune interference: A review", VACCINE, vol. 28, no. 34, 1 August 2010 (2010-08-01), pages 5513-5523, XP55117016
- D10 WO 2015/110940 A2 (PFIZER [US]) 30 July 2015 (2015-07-30) **(P-doc)**
- D11 WO 2015/110941 A2 (PFIZER [US]) 30 July 2015 (2015-07-30) **(P-doc)**
- D12 WO 2015/110942 A2 (PFIZER [US]) 30 July 2015 (2015-07-30) **(P-doc)**

V.2 Novelty (Article 33(2) PCT)

V.2.1 Prior art documents

Document D1 describes a polyvalent pneumococcal vaccine comprising conjugated and unconjugated *S. pneumoniae* saccharides (comprises between 7 and 23 different *S. pneumoniae* serotypes) (p. 15 l. 38-41). Said vaccine should contain 8, 9, ... or 16 conjugated saccharides and 15, 14, ... or 7 unconjugated saccharides (p. 13 l. 14-20). D1 describes a vaccine comprising conjugated Pn saccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15, 18C, 19A, 19F, 22F, 23F and 33F (p. 13 l. 22 - p. 14 l. 18). It is preferred that the capsular saccharide antigens are conjugated to CRM197 (p. 15 l. 20-21, p. 16 l. 6-7, p. 17 l. 34-35). Serotype 18C may be conjugated to TT and 19F may be conjugated to DT (p. 17 l. 38-39). Said vaccine comprises a TLR-9 agonist adjuvant. Experimental data are provided for vaccination with PCV-7 (conjugated antigens) in combination with PPV-23 (unconjugated antigens) (Example 2, p. 35-39).

Document D2 describes a multivalent immunogenic composition having 15 distinct PS-protein conjugates (serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F), preferably conjugated to CRM197 (abstract, paragraph [7]). It appears that the vaccine described in D2 is equivalent to Prevnar13 additionally including PS of serotype 22F and 33F conjugated to CRM197 (Table 5). Furthermore, aluminum adjuvant is present in the vaccine (paragraph [119]-[121]).

Document D3 describes a process for conjugation of capsular polysaccharides derived from at least 7 to 20 *S. pneumoniae* serotypes selected from 1, 2, 3, 4, 5, 6A ... 22F, 23F, and 33F (p. 16 l. 13-19).

Document D4 describes glycoconjugates of capsular polysaccharide (CPS) derived from *S. pneumoniae* serotypes 3, 10A, 12F, 33F (claim 24) and selected from 1, 4, 5, 6A, 6B, 7F, 8, 9V, 11A, 14, 15B, 18C, 19A, 19F, 22F and 23F (claims 67 and 82). Said CPS are preferably conjugated to CRM197 (p. 20 1st paragraph).

Document D5 describes an immunogenic composition comprising 13 different polysaccharide-protein conjugates selected from 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F and serotype 22F or 33F (abstract, paragraph [6], claim 1 of EP2932980). The carrier protein may be CRM197 (paragraph [7], claim 2 of EP2932980). EP2932980 is a family member of D5.

Document D6 (see the machine translation of D6) describes a 24-valent vaccine comprising capsular polysaccharides (24vPnC) derived from *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6A, 6B, 7f, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 33F, 23F, and 33F (abstract, paragraph [1], [11]-[12]). The carrier protein may be DT (CRM197) or TT (claims 3 and 4).

Document D7 describes that the incidence of pneumococcal disease caused by serotypes which are not included in the vaccine is increasing. D7 concludes that

Ongoing surveillance is needed to monitor the magnitude of disease caused by nonvaccine serotypes, to ensure that future vaccines target the appropriate serotypes (abstract).

Document D8 describes 15-valent pneumococcal conjugate vaccine (PCV) comprising PS from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F conjugated to CRM197 (abstract). D8 states that

the emergence of additional pneumococcal serotypes not contained in the vaccine Prevnar, including antibiotic resistant strains, has led to a renewed effort by vaccine manufacturers to develop vaccines with broader strain coverage [...] At this time, it is not known when, or whether, additional serotypes will replace those contained in these enhanced vaccines and therefore create a need for vaccines with broader coverage, however, based on changing epidemiology following the introduction of Prevnar, some increases in non-vaccine type disease following introduction of the new vaccines seems likely. (p. 8870 right-hand col. 2nd paragraph - p. 8871 left-hand col. 1st paragraph)

Document D9 describes mechanisms of interference on responses to conjugate vaccines, e.g. carrier-specific enhancement of T cell help, carrier-induced-epitopic suppression or bystander interference (p. 5514 left-hand col. 1st paragraph - p. 5517 left-hand col. 1st paragraph). D9 states that

when PCV-CRM197 was mixed with Hib-CRM197 (total of 45 microg CRM197 administered), the anti-pneumococcal antibody GMCs were reduced [83]. Similarly, PCV9-CRM197 mixed with MenC-CRM197 (total of 38.5 microg CRM197 administered) elicited reduced MenC GMCs [54]. Thus, immune interference with CRM197 may occur in formulations that go beyond a certain number of conjugates and/or CRM197 dosage. (p. 5519 right-hand col. 5th paragraph)

D9 suggests a relationship between the overall dosage of carrier administered and the level of interference observed (p. 5519 right-hand col. 8th paragraph, p. 5520 right-hand col. 3rd paragraph).

V.2.2 With respect to claims 1-27

None of the cited prior art documents D1-D9 describes a kit comprising a first immunogenic composition and a second immunogenic composition defined in claims 1-27. Therefore, the subject-matter of claims 1-27 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 1-27

The subject-matter of claims 1-27 differs from each of the closest prior art documents D1-D6, each describing a pneumococcal conjugate vaccine (PCV) comprising PS derived from at least 7 serotypes, in that said PCV is combined in a kit with a further vaccine (i.e. the first immunogenic composition) comprising at least one glycoconjugate selected from serotypes 15B, 22F, 33F, 12F, 10A, 11A, and 8 (preferably all seven).

The technical effect of this difference is not apparent from the application as originally filed, since the application is silent about any possible effect based on said combination (going beyond the prior art).

The technical problem to be solved may be regarded as providing an alternative pneumococcal conjugate vaccine.

On the one hand the skilled person knows from D7 and D8 that the incidence of pneumococcal serotypes changes over time (also due to the use of the pneumococcal vaccines) and that further serotypes has to be included in the PCV. Some of these serotypes are already part of the multivalent vaccines (see e.g. D2, D4 or D5). On the other hand the skilled person knows from D9 that overall dosage of carrier influences the elicited immune response against the antigens. Therefore, starting from the PCV used in the field (i.e. Prevnar® 7, Prevnar® 13, 10-valent Synflorix®) the skilled person would add further epidemiological important serotypes in the vaccination schedule. In order to minimize possible drawbacks discussed in D9, the skilled person would develop a separate immunogenic composition comprising the additional polysaccharide conjugates. Furthermore, the choice of various carrier proteins (i.e. CRM197, PD, DT or TT) falls under the routine work of the skilled person. Therefore, the solution provided in claims 1-27 is considered to be obvious for the skilled person, since no surprising technical effect is shown in the application. Hence the subject-matter of claims 1-27 is not inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability

V.4.1 With respect to claims 1-27

The subject-matter of claims 1-27 appears to be susceptible of industrial application.

V.5 Further remarks

5.1 With respect to claims 19-27

The subject-matter of claims 19-27 refers to the kit of any of claims 1-18 suitable for simultaneous administration or for use in a method of concomitant, concurrent or sequential administration. None of claims 19-27 is considered as a medical treatment, since no medical application is mentioned.

Item VI

VI.1 With respect to documents D10-D12

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited documents D10-D12 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the document D10-D12 could be relevant to the question of novelty.