**FORM 7**

**THE PATENTS ACT, 1970**

**and**

**THE PATENT RULES, 2003**

**NOTICE OF OPPOSITION**

We, Médecins Sans Frontières (India) through Leena Menghaney hereby give notice of opposition to Patent No. 286321 granted on application no. 8081/DELNP/2007 dated 19.10.2007 and published on 18.08.2017 by Wyeth LLC, USA, on the following grounds:

1. Section 25(2)(b)- That the invention claimed in the complete specification has been published before the priority date of the claim
2. Section 25(2)(e)-That the invention claimed is obvious and clearly does not involve any inventive step;
3. Section 25(2)(f)-That the subject of the claims of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act ;
4. Section 25(2)(g)- That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed

Our address for service in India is:

**A-13, First Floor,**
**Nizamuddin West,**
**Delhi 110013**

Dated this 17th day of August 2018
Opponent

**To**
**The Controller,**
**The Patent Office**
**DELHI**

**BEFORE THE CONTROLLER OF PATENTS,**

**THE PATENT OFFICE, DELHI**

**THE PATENTS ACT, 1970 AND THE PATENTS RULES, 2003**

IN THE MATTER OF A POST- GRANT OPPOSITION UNDER SECTION 25 (2)

AND RULE 55A OF THE PATENTS ACT, 1970

And

IN THE MATTER OF **PATENT NO. 286321** TITLED "MULTIVALENT PNEUMOCOCCAL POLYSACCHARIDE-PROTEIN CONJUGATE COMPOSITION", GRANTED ON APPLICATION NO. 8081/DELNP/2007 DATED 19.10.2007, AND THE GRANT PUBLISHED ON 18.08.2018 IN THE NAME OF WYETH LLC .....PATENTEE

And

IN THE MATTER OF NOTICE OF OPPOSITION FILED BY BEHALF OF MÉDECINS SANS FRONTIÈRES (INDIA) THROUGH LEENA MENGHANEY .....OPPONENT

**REPRESENTATION BY WAY OF OPPOSITION U/S 25(2)**

1. A notice of opposition under Section 25(2) of the Patents Act, 1970, is being submitted by the Opponent against Indian Patent No. **286321** (hereinafter referred to as the "Present Patent") in the name of Wyeth LLC (hereinafter referred to as the "Patentee").

## I. OPPONENT'S LOCUS STANDI

2. The Opponent herein, is a representative of Médecins Sans Frontières (India) (MSF India) a medical humanitarian organization. The Opponent is a humanitarian medical non-governmental organization that delivers

medical aid to persons affected by armed conflict, epidemics, natural disasters and exclusion from healthcare.

3. The Opponent's teams across the world *inter alia* vaccinate millions of people, both as outbreak response to diseases such as measles, meningitis, yellow fever and cholera, as well as routine immunisation activities providing health care to mothers and children. In 2014 alone, the Opponent delivered more than 3.9 million doses of vaccines and immunological products.

4. The Opponent's medical teams often see the deadly effects of pneumonia – a vaccine-preventable disease – in the vulnerable children treated in its health facilities. It has therefore purchased the pneumococcal conjugate vaccine (PCV) in the past to vaccinate babies against pneumococcus to prevent and reduce under-five pneumonia deaths in its emergency operations in regions such as Central African Republic, Ethiopia, South Sudan, Uganda and Greece among others.

5. Therefore, the Opponent is an entity which is closely associated with promoting research in the field of PCV, and hence is a person interested eligible to file a post-grant opposition under Section 25(2) of the Patents Act, 1970.

## II. BACKGROUND OF PCV

6. Pneumococcal conjugate vaccine, which protects children against severe forms of pneumococcal disease, such as pneumonia is included in the WHO's Model List of Essential Medicines and in the WHO's Recommended List of Routine Immunizations for Children. Pneumonia is the leading cause of child mortality worldwide, killing nearly one million children every year and in India is responsible for 20 per cent of all pneumonia deaths. In 2015, the National Technical Advisory Group on Immunisation recommended that PCV13 is preferable over PCV10 for the phased introduction of the vaccine in the Universal Immunisation Programme. In May 2017, the Government of India decided to do a phased

introduction of the 13-valent pneumococcal conjugate vaccine in its Universal Immunisation Programme (UIP) in three states, which will be gradually expanded to the rest of the country. However, the vaccine is significantly more expensive than others included in India's Universal Immunisation Programme. India needs to vaccinate over 25 million new-born babies against pneumococcus to prevent and reduce under-five pneumonia deaths.

7. Studies also show that Pneumococcal vaccine lowers antimicrobial resistance (AMR) by bringing down infection in the community and reducing antibiotic use in children, which is of significant public health importance in India.
8. The PCV accounts for almost half the price of the entire vaccination package for a child in the poorest countries. In India, besides being one of the most expensive vaccines to be included in the UIP, Pfizer sells Prevnar 13 (PCV13) at an unaffordable price of Rs. 3,800 (54USD) dose in the private market.
9. The Opponent emphasises on the public health significance of the vaccine and the negative impact of the wrongfully granted secondary patent restricting early introduction of PCV13 from Indian manufacturers that could significantly reduce the price of this life saving vaccine not just in India but globally. Vaccines produced in India for the prevention of other diseases have stimulated competition in what is otherwise a small field of global producers, resulting in lower and more sustainable prices for UNICEF, international agencies and Ministries of Health.
10. Therefore, there is all the more need to critically analyse any form of patent monopoly that may be granted to the essential vaccine that may hamper access to this life-saving vaccine in the private market and Immunization Programmes.

## III. PRESENT PATENT

11. The Present Patent no. 286321 stems from application no. 8081/DELNP/2007 filed at the Delhi Patent Office on 19.10.2007. The Present Patent titled, "*Multivalent Pneumococcal Polysaccharide-Protein Conjugate Composition*", was filed for in India by Wyeth LLC, USA.
12. The PCT Application No. PCT/US2006/012354 relating to the Present Patent was filed on 31.03.2006. The Present Patent claims priority from a US Application No. 60/669,605 filed on 08.04.2005.

## IV. ALLEGED INVENTION

13. The Applicant claims that the invention in the Present Patent relates to multivalent pneumococcal polysaccharide-protein conjugate composition. In particular, it relates to a 13-valent pneumococcal vaccine composition comprising the seven serotypes in the 7vPnC vaccine (4, 6B, 9V, 14, 18C, 19F and 23F) plus six additional serotypes (1, 3, 5, 6A, 7F and 19A). (Present Patent at internal page 3, lines 18-20).
14. The Applicant has admitted in the complete specification that preparation of capsular polysaccharides are well known and could be prepares by standard techniques known to those skilled in the art. (Complete specification of the Present Patent at internal page 12, lines 10-19).
15. It has been admitted in the complete specification that activation of the polysaccharides and the subsequent conjugation to the carrier protein could be achieved by means known in the art (Complete specification of the Present Patent at internal page 12, lines 24-26).
16. The Applicant in the complete specification also admits that carrier protein such as $CRM_{197}$ was known and well established in prior art (complete specification of Present Patent at internal page 13, lines 3-9).

## V. THE CLAIMS

17. 6 claims were granted under the Present Patent. The 6 claims as granted are reproduced below:

**Claim 1:** A multivalent immunogenic composition, comprising: 13 distinct polysachharide- protein conjugates, together with a physiologically acceptable vehicle, wherein each of the conjugate comprises a capsular polysaccharide from a different serotype of *streptococcus pneumonia* conjugated to a carrier protein $CRM_{197}$ the capsular polysaccharides are prepared from serotypes 1,3,4,5,6A,6B,7F,9V,14, 18C, 19A, 19F and 23F.

**Claim 2**: The immunogenic composition as claimed in claim 1, optionally comprising an adjuvant.

**Claim 3**: The immunogenic composition as claimed in claim 2, wherein the adjuvant is an aluminium-based adjuvant.

**Claim 4**: The immunogenic composition as claimed in claim 3, wherein the adjuvant is selected from the group consisting of aluminium phosphate, aluminium sulphate and aluminium hydroxide.

**Claim 5**: The immunogenic composition as claimed in claim 4, wherein the adjuvant is aluminium phosphate.

**Claim 6**: An immunogenic composition as claimed in claim 1 wherein said immunogenic composition is a single 0.5 mL dose formulated to contain: 2µg of each saccharide, except for 6B at 4µg; approximately 29µg $CRM_{197}$ carrier protein; 0.125 mg of elemental aluminium (0.5mg aluminium phosphate) adjuvant; and sodium chloride and sodium succinate buffer as excipients.

## VI. SUMMARY OF GROUNDS CONSIDERED FOR OPPOSITION

18. The Opponent brings this opposition under the following grounds, amongst others, each of which are without prejudice to one another: -

i. Claims 1-6 of the Present Patent are not novel as the alleged invention claimed in these claims have been published before

the priority date in any of the documents. Therefore, the Opponent brings this Opposition under **Section 25(2)(b)(ii)**- that the invention as claimed in the complete specification has been published before the priority date of the claim in India or elsewhere, in any other document;

ii. Claims 1-6 the Present Patent lack inventive step, and therefore fail under Sections 2(1)(j) and 2(1)(ja) of the Patents Act. Therefore, the Opponent brings this opposition under **Section 25(2)(e)**-that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published before the priority date in India or elsewhere in any document.

iii. Claims 1-6 of the Present Patent do not satisfy the test of Section 3(e) of the Patents Act as the subject matter does not exhibit any synergistic effect. Therefore, the Opponent brings this opposition under **Section 25(2)(f)** -that the subject of any claim of the complete specification is not an invention within the meaning of this Act.

iv. Claims 1-6 of the Present Patent do not satisfy the test of Section 3(d) of the Patents Act as the subject matter does not exhibit any synergistic effect. Therefore, the Opponent brings this opposition under **Section 25(2)(f)** -that the subject of any claim of the complete specification is not an invention within the meaning of this Act.

v. The method to arrive at claims 1-6 of the Present Patent has not been clearly described in the Present Patent. Therefore, the Opponent brings this Opposition under **Section 25(2)(g)-** That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

## VII. CLAIMS 1 TO 6 ARE NOT NOVEL, AND THEREFORE HAVE TO BE REJECTED UNDER SECTION 64(1)(e) OF THE PATENTS ACT

19. It is the Opponent's claim that document published before the date of priority of the Present Patent discloses the compounds of claims 1-6. Therefore, claims 1-10 should be rejected for lack of novelty.

**WO 03/051392 A2** (Published: 26.06.2003)

20. The Opponent relies on patent application publication no. WO 03/051392 A2 (hereinafter "WO '392" and annexed hereto as **Exhibit A**) titled, "*Vaccine*" published on 26.06.2003. Given that this document has been published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent. The publication discloses *Streptococcus pneumonia* vaccine comprising 11 or more polysaccharides from different *S.pneumonia* serotypes (see WO '392 at internal page, lines 6-10).
21. WO '392 notes that the number of *S. pneumonia* polysaccharides can range from 11 to 23 different serotypes. In particular it states that 11, 13 or 16 different serotypes would be preferred (See WO '392 at internal page 5, lines 4-6).
22. WO '392 notes, "*Preferably the multivalent pneumococcal vaccine of the invention will be selected from the following serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F, although it is appreciated that one or two other serotypes could be substituted depending on the age of the recipient receiving the vaccine and the geographical location where the vaccine will be administered. For example, an 11-valent vaccine may comprise polysaccharides from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. A 13-valent pediatric (infant) vaccine may also include serotypes 6A and 19A, whereas a 13-valent elderly vaccine may include serotypes 8 and 12F.*" (emphasis supplied) (See WO '392 at internal page 5, lines 11-19).

23. Thus, WO ’392 disclosed a 13 valent paediatric pneumococcal vaccine that would include serotypes 6A and 19A in addition to the serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
24. Further, WO ’392 identifies that the primary carrier protein to which the polysachharides are conjugates needn’t be limited to a specific embodiment. It states that the carriers, “*may include proteins or fragments thereof of DT (Diphtheria toxoid), TT (Tetanus toxoid), DT crml97 (a DT mutant), other DT point mutants, (e.g.at position Glu-148, see, e.g., U.S. 4,709,017, WO93/25210, WO95/33481), FragC (fragment of TT), Ply (pneumolysin and mutants thereof), PhtA, PhtB, PhtD, PhtE, (Pht A-E are described in more detail below) OmpC (from N. meningitidis), PorB (from N. meningitidis), etc. Preferably it is DT, TT or crml97. More preferably it is DT.*” (emphasis supplied) (See WO ’392 at internal page 4, lines 25-30).
25. WO ’392 also indicates that, “*The vaccines of the present invention are preferably adjuvanted. Suitable adjuvants include an aluminum salt such as aluminum hydroxide gel (alum) or aluminum phosphate, but may also be a salt of calcium, magnesium, iron or zinc, or may be an insoluble suspension of acylated tyrosine, or acylated sugars, cationically or anionically derivatized polysaccharides, or polyphosphazene*” (See WO ’392 at internal page 11, lines 33-34 and page 12 at lines 1-3).
26. Further, WO ’392 notes that, “*Vaccine preparation is generally described in Vaccine Design ("The subunit and adjuvant approach" (eds Powell M.F. & Newman M.J.) (1995) Plenum Press New York). Encapsulation within liposomes is described by Fullerton, US Patent 4,235,877. The vaccines of the present invention may be stored in solution or lyophilized. As a liquid, the vaccine of the invention is typically stored in 0.5ml solution/dose. Preferably the vaccine is adsorbed onto an aluminum salt. If the solution is lyophilized, it is preferably in the presence of a sugar such as sucrose or lactose or trehalose. It is still further preferable that they are lyophilized and extemporaneously reconstituted prior to use.*

*Lyophilizing of Streptococcus polysaccharides may result in a more stable composition (vaccine)*" (See WO '392 at internal page 14, lines 8-17).

27. Hence, on reading WO '392 one would come to know that the following has been disclosed
    *a.* A multivalent vaccine including one with 13 serotypes;
    *b.* The 13 valent formulation may have the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F;
    *c.* That the above identified serotypes may be conjugated to a carrier protein such as $CRM_{197}$;
    *d.* Lyophilizing of *Streptococcus* polysaccharides;
    *e.* Adjuvants what may be used included aluminium hydroxide or aluminium phosphate
28. Therefore, claims 1-6 of the Present Patent are not new and must be rejected for lack of novelty.
29. A tabular comparison of the disclosure in WO '392 and the claims of the Present Patent are made below:

| **Present Patent** | **WO '392** |
|---|---|
| Claim 1: Multivalent immunogenic composition with a physiologically acceptable vehicle, wherein each of the conjugate comprises a capsular polysaccharide form a different serotype…conjugated to a carrier protein $CRM_{197}$, the capsular polysaccharides are prepared from serotypes 1,3,5,6A,7F, 9V, 14, 18, 19A, 19F and 23F. | multivalent pneumococcal vaccine selected from the following serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. A 13-valent pediatric (infant) vaccine may also include serotypes 6A and 19A, whereas a 13-valent elderly vaccine may include serotypes 8 and 12F, in addition to the following serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. (See WO '392 at internal page 5, lines 11-19). |

| | |
|---|---|
| | Carriers, "*may include proteins or fragments thereof of DT (Diphtheria toxoid), TT (Tetanus toxoid), DT crml97 (a DT mutant), other DT point mutants…Preferably it is DT, TT or crml97...*" (See WO '392 at internal page 4, lines 25-30)<br>The vaccines of the present invention may be stored in solution or lyophilized. Lyophilizing of Streptococcus polysaccharides may result in a more stable composition (vaccine) (See WO '392 at internal page 14, lines 8-17). |
| Claim 2:The composition of claim 1, optionally comprising an adjuvant | The vaccines of the present invention are preferably adjuvanted. See WO '392 at internal page 11, lines 33-34 and page 12 at lines 1-3 |
| Claim 3: a composition claimed in claim 2, wherein the adjuvant is an aluminium based adjuvant | Suitable adjuvants include an aluminum salt<br>WO '392 at internal page 11, lines 33-34 and page 12 at lines 1-3 |
| Claim 4: The composition as claimed in claim 3, where the adjuvant is selected from group of aluminium phosphate, aluminium sulphate and aluminium hydroxide | Suitable adjuvants include an aluminium salt such as aluminium hydroxide gel (alum) or aluminium phosphate. (WO '392 at internal page 11, lines 33-34 and page 12 at lines 1-3). |

| | |
|---|---|
| Claim 5: the composition as claimed in claim 4, wherein the adjuvant is aluminium phosphate | Suitable adjuvants include an aluminium salt such as aluminium hydroxide gel (alum) or aluminium phosphate. (WO '392 at internal page 11, lines 33-34 and page 12 at lines 1-3). |
| Claim 6: composition as claimed in claim 1 wherein the said immunogenic composition is a single 0.5 mL dose formulated to contain 29µg $CRM_{197}$ carrier protein; 0.125 mg of elemental aluminium (0.5 mg aluminium phosphate) adjuvant; sodium chloride and sodium succinate buffer as exepients. | |

30. Claim 6 is dependent on claim 1. Given that claim 1 is not novel, claim 6 also lack novelty.
31. Therefore, it is submitted that the composition claimed in the Present Patent has been directly disclosed and unambiguously clear from a reading of WO '392.

## VIII. CLAIMS 1 TO 6 ARE OBVIOUS, DO NOT INVOLVE A TECHNICAL ADVANCE, AND LACK INVENTIVE STEP AS DEFINED UNDER SECTION 2(1)(ja) AND

**THEREFORE HAVE TO BE REJECTED UNDER SECTION 25(2)(e) OF THE PATENTS ACT**

32. Section 2(1) (j) defines an "invention" as "*a new product or process involving an inventive step and capable of industrial application*." For an alleged invention to qualify for a patent, it must satisfy the criteria of inventive step. Section 2(1)(ja) of the Patents Act defines an inventive step as "*a feature of an invention that involves technical advance as compared to the existing knowledge ... and that makes the invention not obvious to a person skilled in the art*".

33. Sub-sections (j) and (ja) of Section 2(1) of the Patents Act thus require a Patent Applicant to show that the feature of the alleged invention involves a technical advance and that it is not obvious to a person skilled in the art. These requirements are laid down to ensure that patents, which result in a monopoly, are granted only to genuine inventions.

34. Section 25(2)(e) of the Patents Act provides a ground for opposition if the alleged invention is obvious and does not involve any inventive step having regard to matter published, as described in section 25(2)(b) of the Patents Act. The published matter to be considered under this provision includes matter published in India or elsewhere in any document before the priority date of the alleged invention.

35. The Opponent submits that claims 1-6 of the Present Patent lack an inventive step and therefore should be rejected.

36. At the priority date of the alleged invention, as will be explained below, the following were well known to persons skilled in the art:

    a. Multivalent vaccines including 7-valent, 9-valent, 11-valent and 13-valent vaccines;

    b. Use of $CRM_{197}$ as carrier protein in conjugated pneumococcal vaccine;

    c. Use of Aluminium base as immunologic adjuvant with vaccines.

**a. Multivalent vaccines including 7-valent, 9-valent, 11-valent and 13-valent vaccines and use of $CRM_{197}$ as carrier protein in conjugated pneumococcal vaccine was known**

**WO 03/051392 A2** (Published: 26.06.2003)

37. Without prejudice to the above ground raised on lack of novelty, the Opponent relies on patent application publication WO '392 (annexed hereto as **Exhibit A**) titled, "*Vaccine*" published on 26.06.2003. Given that this document has been published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent. The publication discloses *Streptococcus pneumonia* vaccine comprising 11 or more polysaccharides from different *S.pneumonia* serotypes (see WO '392 at internal page, lines 6-10).

38. WO '392 notes that the number of *S. pneumonia* polysaccharides can range from 11 to 23 different serotypes. In particular it states that 11, 13 or 16 different serotypes would be preferred (See WO '392 at internal page 5, lines 4-6).

39. WO '392 notes, "*Preferably the multivalent pneumococcal vaccine of the invention will be selected from the following serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F, although it is appreciated that one or two other serotypes could be substituted depending on the age of the recipient receiving the vaccine and the geographical location where the vaccine will be administered. For example, an 11-valent vaccine may comprise polysaccharides from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. A 13-valent pediatric (infant) vaccine may also include serotypes 6A and 19A, whereas a 13-valent elderly vaccine may include serotypes 8 and 12F.*" (See WO '392 at internal page 5, lines 11-19).

40. Further, WO '392 identifies that the primary carrier protein to which the polysachharides are conjugates needn't be limited to a specific embodiment. It states that the carriers, "*may include proteins or fragments thereof of DT (Diphtheria toxoid), TT (Tetanus toxoid), DT crml97 (a DT mutant), other DT point mutants, (e.g.at position Glu-148, see, e.g., U.S. 4,709,017, WO93/25210, WO95/33481), FragC (fragment of TT), Ply (pneumolysin and mutants thereof), PhtA, PhtB, PhtD, PhtE, (Pht A-E are described in more detail below) OmpC (from N. meningitidis), PorB (from N. meningitidis), etc.* ***Preferably it is DT, TT or crml97****. More preferably it is DT.*" (emphasis supplied) (See WO '392 at internal page 4, lines 25-30).

41. WO '392 also indicates that, "*The vaccines of the present invention are preferably adjuvanted. Suitable adjuvants include an aluminum salt such as aluminum hydroxide gel (alum) or aluminum phosphate, but may also be a salt of calcium, magnesium, iron or zinc, or may be an insoluble suspension of acylated tyrosine, or acylated sugars, cationically or anionically derivatized polysaccharides, or polyphosphazene*" (See WO '392 at internal page 11, lines 33-34 and page 12 at lines 1-3).

42. Hence, a POSITA on reading WO '392 one would come to know that a 13 valent pneumococcal vaccine may contain the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. The POSITA would also be taught that these serotypes may be conjugated to a carrier protein such as $CRM_{197.}$ Further, WO '392 also teaches that aluminium hydroxide or aluminium phosphate may be used as adjuvants.

**US 5,623,057** (Granted 22.04.1997)

43. The Opponent relies on US patent no. US5,623,057 titled "Pneumococcal Polysaccharide Conjugate Vaccine" (hereinafter "US '057" and annexed hereto as **Exhibit B**) granted in 1997. Given that this document has been

published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent.

44. US ’057 discloses a conjugate vaccine comprising capsular polysaccharide from *Streptococcus pneumonia* bacteria linked to an immunogenic carrier protein. The conjugate vaccine disclosed therein is a mixture of 1-10 different pneumococcal polysaccharide immunogenic protein.

45. US ’057 also discloses a process of making polysaccharide immunogenic protein conjugates with a variety of pneumococcal subtypes, including 1,2,3,4,5,6B,7F,8,9N,9V,10A,11A,12F,14,15B,17F,18C,19F and 23F (See US ’057 at column 4, lines 35-40).

46. Hence, a POSITA working on a multi-valent vaccine, on reading US ’057 would be motivated to work on the disclosed serotypes and use it in different combinations.

**US 4,902,506** (Granted: 20.02.1990)

47. The Opponent relies on a US Patent No. 4,902,506 titled “*Immunogenic Conjugates*” granted on 20.02.1990 (hereinafter “US ’506” and annexed hereto as **Exhibit C**). Given that this document has been published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent.

48. US ’506 discloses an immunogenic conjugate comprising capsular polymer derived from *Streptococcus pneumoniae* which is conjugated to a bacterial toxin or toxoid being CRM197.

49. US ’506 discloses that no biohazard exist in working with $CRM_{197}$ as a carrier protein. Further it states that “*In case of $CRM_{197}$, which is immunologically identical to native toxin, treatment with formalin (though there is no need to detoxify) greatly enhances the immunological response.*” (See US ’506 at column 6, lines 21-25 and claim 5 at column 24)

50. Further, US '506 claims various serotypes as a part of an immunogenic conjugate. These serotypes include serotype 3, 6, 12, 14, 19, 23 and 51. (See US '506 at claims 1, and claims 13-19).

51. Hence, a POSITA working on a multivalent vaccine would take note of the serotypes disclosed in US '506 and will also recognise that $CRM_{197}$ can be used as a carrier protein.

**Mbelle *et al*** (Published: 08.09.199)

52. The Opponent relies on the publication titled, " *Immunogenicity and Impact on Nasophrayngeal Carriage of a Nonvalent Pnemococcal Conjugate Vaccine*" authored by Nontombi Mbelle *et al* (hereinafter referred to as "Mbelle *et al*" and annexed hereto as **Exhibit D**) published in Journal of Infectious Diseases 1999:180:1171-6. Mbelle studied the safety, immunogenicity, and impact on carriage of a 9-valent pneumococcal conjugate vaccine.

53. Mbelle *et al* studied 9-valent pneumococcal conjugate vaccine containing, " *2µg of the carbohydrate of serotypes 1,4,5, 9V, 14, 18C, 19F, and 23F carbohydrate and 4 µg of serotype 6B conjugated to mutant diphtheria toxin* $CRM_{197}$*."* (See Mbelle *et* al at internal page 1171, RHS column, para 2)

54. Hence, a POSITA working on a multi-valent pneumococcal conjugate vaccine, on reading Mbelle *et al* would not only be acquainted with the serotypes used in the 9-V vaccine but will also be taught the amount of serotypes that may be used. Futher, Mbelle *et al* also teaches the serotypes in 9-V conjugate vaccine could be conjugated to $CRM_{197}$.

**Hausdorff *et al*** (Published: 2000)

55. The Opponent relies on publication titled "*Which Pneumococcal Serogroups Cause the Most Invasive Disease: Implications for Conjugate Vaccine Formulations and Use, Part I*" authored by William P. Hausdorff *et al*(hereinafter "Hausdorff *et al*" and annexed hereto as

**Exhibit E**) published on 2000 in Clinical Infectious Diseases 2000;30:100-21. Given that this document has been published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent.

56. The authors of this publication analysed more than 70 data sets to compare the serogroups causing invasive pneumococcal diseases with those represented in conjugate vaccine (See abstract).

57. Hausdorff *et al* recognises that, "*To improve upon the current pneumococcal polysaccharide vaccines, most efforts have focused on the development of conjugate vaccines in which polysaccharides (or their derivatives) are covalently linked to carrier proteins.* " (See Hausdorff *et al* at internal page 100, RHS column 31-33 and internal page 101, LHS column at lines 5-7).

58. Further, Hausdorff notes that, " *The 7-valent (7-V) formulations of 3 major manufacturers include conjugates derived from polysaccharides or oligosachharides from types 4,6B,9V, 14, 18C, 19F, and 23F. The 9-valent (9-V) formulation is 7-V serotypes plus serotypes 1 and 5. The 11 valent (11-V) formulation is 9-V plus serotypes 3 and 7F.*" (See Hausdorff *et al* at internal page 101, RHS column, lines 44-48).

59. Hausdorff *et al* also noted that, "*For young children serogroups 6 and 14 are first and second in the region except Asia(where they are third and fifth, respectively), and serogroup 19 is among the 4 most common in all region except Latin America (fifth). The 7-V vaccine formulation contains the 7 most common serogroups in the United States and Canada and Oceania, 6 of the 7 most common in Europe, 5 of the 7 most common in Latin America, and 4 of the 7 most common in Africa and Asia. The 7 most common serogroups in each region are represented in the 9-V vaccine formulation, with exception of serogroup 15(seventh in Africa) and serogroup 7 (sixth in Asia).* (See Hausdorff *et al* at internal page 103, lines 27-27).

60. Hausdorff *et al* also notes the serotypes that need to be analysed when it notes that, "*In general, these potentially cross-reactive serotypes (mostly 6A and 19A) are responsible for 8-15% of the IPD burden."* It also discusses that "*To maximise coverage of IPD in younger children, for example, future vaccines may need to include serotypes 6A and 19A, depending on the degree of cross-protection seen in ongoing efficacy trials with the current vaccine formulations (containing 6B and 19F).*"(See Husdorff *et al* at internal page 117, RHS column, lines 42-46)

61. Therefore, a person skilled in the art, who is working on developing multivalent vaccine, on reading Hausdorff *et al* would not only come to know that different 7-V formulation with serotype *4, 6B, 9V, 14, 18C, 19F, and 23F, 9-V formulation with 7-V serotypes plus serotypes 1 and 5, and 11-V formulation with 9-V plus serotypes 3 and 7F* exist. Further, the POSITA would also be motivated to test the effect of adding serotype 6B and 19F to existing formualtions.

**b. Use of Aluminium base as immunologic adjuvant with vaccines was known**

**WO 00/56359** (Published: 28.09.2000)

62. The Opponent relies on the Patent publication no. WO 00/56359 (hereinafter referred to as "WO '359" and hereto annexed as **Exhibit F**) titled, "Vaccine" published on 28.09.2000. Given that this document has been published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent. The publication relates to vaccines comprising a pneumococcal polysaccharide conjugate antigen, formulate with a protein antigen from *Streptococcus pneumonia* and optionally a Th1 inducing adjuvant; pneumococcal polysaccharide conjugates adjuvanted with a Th1 adjuvant; and bacterial polysaccharide conjugates in general conjugated to protein D from *H.influenzae*.

63. WO ’359 notes that, “*Polysaccharide antigen based vaccines are well known in the art. Four that have been licensed for human use include the Vi polysaccharide of Salmonella typhi, the PRP polysaccharide from Haemophilus influenzae, the tetravalent meningococcal vaccine composed of serotypes A, C, W135 and Y, and the 23-Valent pneumococcal vaccine composed of the polysaccharides corresponding to serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33 (accounting for at least 90% of pneumococcal blood isolates).*” (See WO ’359 at internal page 2, lines 4-9). That is, as on the date of priority of the Present Patent, 23 valent vaccines were known.

64. Particularly, WO ’359 discloses a 13 valent combination when it states, “*Typically the Streptococcus pneumoniae vaccine of the present invention will comprise polysaccharide antigens (preferably conjugated), wherein the polysaccharides are derived from at least four serotypes of pneumococcus. Preferably the four serotypes include 6B, 14, 19F and 23F. More preferably, at least 7 serotypes are included in the composition, for example those derived from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. More preferably still, at least 11 serotypes are included in the composition, for example the composition in one embodiment includes capsular polysaccharides derived from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (preferably conjugated). In a preferred embodiment of the invention at least 13 polysaccharide antigens (preferably conjugated) are included…*

*…whereas for infants or toddlers (where otitis media is of more concern) serotypes 6A and 19A are advantageously included to form a 13 valent vaccine*.” (See WO ’359 at internal page 11 at lines 21-30 and internal page 12 at lines 7-8).

65. That is, WO ’359 discloses a 13 valent combination of capsular polysaccharides derived from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

66. Further, WO ’359 recognizes that polysaccharides *per se* are poor immunogens and therefore need to be conjugated to protein carriers, which provide bystander T-cell help. WO ’359 discloses that, “*…Examples of such carriers which are currently commonly used for the production of polysaccharide immunogens include the Diphtheria and Tetanus toxoids (DT, DT* ***CRM197*** *and TT respectively)…*” (emphasis supplied) (See WO ’359 at internal page 14 at lines 12-20). In fact, claim 6 of WO ’359 claims a immunogenic composition comprising at least one *Streptococcus pneumonia* polysaccharide antigen and at least one *Streptococcus pneumonia* protein antigen or immunologically functional equivalent thereof wherein the carrier protein is selected from a group which includes CRM197 (See WO ’359 claims 1-6, in particular claim 6).

67. It also discloses that, “*Aluminium-based adjuvants (such as alum, aluminium hydroxide or aluminium phosphate), first described in 1926, remain the only immunologic adjuvants used in human vaccines licensed in the United States.*” (See WO ’359 at internal page 3, lines 29 to page 4 at lines 1-2). Further, it notes that, “*The vaccines of the present invention are preferably adjuvanted. Suitable adjuvants include an aluminium salt such as aluminium hydroxide gel (alum) or aluminium phosphate…*” (See WO ’359 at internal page 15, lines 4-8). Further, claim 8 of WO ’359 claims an immunogenic composition wherein the adjuvant comprises an aluminium salt (See WO ’359 at internal page 74, claim 9).

68. Hence, a POSITA working on developing a pneumococcal conjugate vaccine, on reading WO ’359 would be taught the the combination of capsular polysaccharides derived from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F conjugated to protein carriers such as $CRM_{197}$ with aluminium based adjuvants.

**S K Obaro** (Published: 2002)

69. The Opponent relies on publication titled "*The New Pneumococcal Vaccine*" authored by S K Obaro (hereinafter "Obaro" and annexed hereto as **Exhibit F**) published in Clinical Microbiology and Infections 2002; 8, 623-633. Given that this document has been published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent.

70. Obaro disclosed that, " *The 23-valent capsular polysaccharide vaccine is not effective in children less than 2 years old, the most vulnerable age group for invasive pneumococcal disease."* (See Obaro at internal page 625, RHS, paragraph 3).

71. Further, Obaro notes that, "*Different proteins have been selected for conjugation, and these include diphtheria and tetanus toxoids, the meningococcal outer-membrane complex, and diphtheria protein* $CRM_{197}$*...The immune response to the pneumococcal polysaccharide vaccines have varied considerably, depending on the carrier protein used*" (See Obaro at internal page 626 at LHS column, para 3). That is, coupling the polysaccharide serotype certain protein carrier to form a polysaccharide-protein conjugate enhanced the immune response.

72. Obaro also discloses that, "*The seven-valent pneumococcal conjugate vaccine (Prevnar) includes seven purified capsular polysaccharides of S. pneumonia, each coupled to a non-toxic diphtheria protein analog (cross-reactive material, CRM). The vaccine contains approximately 2µg each of the capsular polysaccharide from serotypes 4, 9V, 14, 19F and 23F, and oligosachharide from 18C, 4µg of serotype 6B, 20µg of the carrier protein* $CRM_{197}$*, and 0.125mg of aluminium in each 0.5mL dose as an aluminium phosphate adjuvant.*" (See Obaro at internal page 626, LHS column, para 4)

73. Hence, a POSITA working on developing a pneumococcal conjugate vaccine, on reading Obaro would be taught the basic serotypes used in the 7-valent conjugate vaccine, as well as the amount of serotype, carrier

protein and adjuvant to be used. The POSITA would also be taught that $CRM_{197}$ is used as a carrier protein. Obaro also teaches that aluminium phosphate can be used as an adjuvant.

**La Pena *et al*** (Published: 2004)

74. The Opponent relies on the translated copy of the publication titled " *Present and Future of the pneumonia vaccine*" authored by C. D. La Pena and others published in Pediatrika 2004; 24(4): 147-155 (hereinafter referred to as "*La Pena et al*" and annexed hereto as **Exhibit F**). Given that this document has been published before the date of priority, viz. 08.04.2005, this publication can be relied on as prior art for the Present Patent. The publication discloses that 7-valent and 23-valent vaccines were available in the market and that 9, 11 and 13-valent vaccines were being developed. It states that, "*Currently, there are two available vaccines to prevent invasive pneumococcal illness in Spain:23-valent polysaccharides (VNP-23v) and 7-valent conjugated (VNC-7v).*
*Other conjugated vaccines, 9, 11 and 13-valent, are being developed, although they have not yet been marketed*" (See La Pena *et al* at internal page 1, para 4 and 5)
75. La Pena *et al* discloses that, "*The 23-valent pneumococcal capsular polysaccharide vaccine (23 serotypes) causes a response in the body that is independent of T lymphocytes and therefore is not immunogenic in those less than 2 years of age, when the incidence of pneumococcal disease is highest. However, conjugation with an appropriate protein improves the immunogenicity of the capsular polysaccharide antigens…*". It further notes that, "*With this knowledge, a new 7-valent pneumococcal conjugate vaccine (7 serotypes) has been studied and subsequently marketed, which may make it possible to prevent pneumococcal disease.*" (See La Pena *et al* at internal page 3 paras 2 and 3)

76. La Pena *et al* point out that the 7-valent pneumococcal conjugate vaccine contains seven serotypes of *Streptococcus pneumonia* 4, 6B, 9V, 14, 18C, 19F and 23F, conjugated individually with a protein, a nontoxic mutant of the diphtheria toxin, $CRM_{197}$.

77. La Pena *et al* notes that the 23-valent polysaccharide pneumococcal vaccine contains the serotypes 1,2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17E, 18C, 19A, 19F, 20, 22F, 23F and 33F. It also discloses that this "*vaccine has certain drawbacks in that it induces poor immune response in children less than 2 years of age, precisely the age with the greatest incidence of pneumococcal disease*." (See La Pena *et al* at intetnal page 9 penultimate para)

78. La Pena *et al* also discloses that new serotypes are being incorporated to the 7-valent conjugate vaccine, *with 9-valent (which incorporates the serotypes 1 and 5), 11-valent (Adding 3 and 7F) and 13-valent (6A and 19a) vaccines in various stages of research, which could broaden the spectrum of ages and countries…*" (See La Pena *et al* at internal page 12, penultimate para)

79. Hence, a POSITA reading La Pena *et al* would be taught that new pneumococcal vaccines which are 9-valent, 11-valent and 13 valent are being developed. POSITA would also be motivated to use the serotypes 1,5 for 9-valent, 3 and 7F for 11 valent and 6A and 19a for 13 valent vaccines.

**Summary**

80. Hence, a POSITA reading US '057 would be taught that a pneumococcal polysaccharide vaccine may include serotypes such as 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F and 23F. Further, on reading US '506, WO '392 with US '057, a POSITA would be motivated on work on the disclosed serotypes serotype including 3, 6, 12, 14, 19, 23 and 51, and also conjugate $CRM_{197}$. Further, on reading these prior art documents with Mbelle *et al* and Hausdorff *et al* would try to

work around known serotypes in the 7-V and 9-V. The POSITA would also take note of the teaching in Hausdorf *et al* that future vaccines may need to include serotypes 6A and 19A, depending on the degree of cross-protection seen in ongoing efficacy trials with the current vaccine formulations (containing 6B and 19F). Further, on reading WO '359, the POSITA would be motivated to work on the disclosed 7-V, 11-V and in particular 13-V pneumococcal vaccine using the 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. In light of the other prior art documents, the POSITA would be motivated to conjugate the serotypes with $CRM_{197}$. On reading these prior art documents with Obaro, the POSITA would be taught the quantity of serotypes, carrier protein $CRM_{197}$ and aluminium adjuvant to be used in a multivalent pneumococcal vaccine. Further, on reading these prior art documents along with La Pena *et al*, a POSITA would be motivated to explore 11-valent vaccines by adding 3 and 7F and 13-valent vaccines by adding 6A and 19a to the known serotypes of 4, 6B, 9V, 14, 18C, 19F and 23F.

81. Hence, on reading on the above discussed prior art documents together, a POSITA can arrive at a 13-valent pneumococcal vaccine with the known serotypes, including a combination of 1,3,4,5,6A,6B,7F,9V,14, 18C, 19A, 19F and 23F, with $CRM_{197}$ as carrier protein and aluminium as adjuvant. In this regard, the Opponent also relies on an opinion shared by Dr. Warren Kaplan on the prior art documents identified here (annexed hereto as **Annexure K**).

## IX. That claims 1-6 of the Present Patent ought to be rejected under Section 25(2)(f), as they are not an invention within the meaning of the Patents Act

82. Section 25(2)(f) of the Patents Act allows opposition to grant of patent on the ground of the claimed invention not being an invention within the meaning of the Patents Act, 1970. Section 25(2)(f) reads as follows:

"(2) *At any time after the grant of patent but before the expiry of a period of one year from the date of publication of grant of a patent, any person interested may give notice of opposition to the Controller in the prescribed manner on any of the following grounds, namely:—*

*(f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.*"

**That claims 1-6 of the Present Patent fail under Section 3(e) of the Patents Act, 1970**

83. It is submitted that claims 1-6 of the Present Patent should be rejected on the basis of Section 3(e), as the claimed compounds are mere admixtures resulting in mere aggregation of properties.

84. Section 3(e) of the Patents Act, 1970 provides that, a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof does not qualify as an invention. An applicant claiming a combination of compounds is required to show and enhanced additive effect or synergism in the complete specification itself. It is a settled principle that, "*The question of efficacy and or synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification.*" (See order of the Asst. Controller of Patents & Designs in patent application no. 314/MUM/2008, at lines 3-5 at internal page 7 annexed hereto as **Ex I**).

85. Further merely providing the composition of each of the ingredients in terms of weight does not discharge the burden on the Applicant to show synergism. The Asst. Controller of Patents & Designs, while rejecting application no. 3725/CHENP/2006 on grounds of Section 3(e) noted, "*Applicant doesn't provide any supportive experimental data or comparative examples highlighting the surprising and or synergistic effect of the claimed formulation over the prior art compositions. Instead examples 1, 2 and 3 provide only the amount of individual components in grams.*" (See the order of the Controller in 3725/CHENP/2006, hereto annexed as **Exhibit J** at internal page 4. Para 8)

86. It is shown above (in the ground relating to inventive step) that various serotypes were known in the prior art, that could be used in a pneumococcal vaccine. In the Present Patent, the Patentee has failed to show the synergistic effect of the claimed combination of identified serotypes, as on the date of filing the application for the Present Patent. Therefore claims 1-6 fail the muster of Section 3(e) of the Patents Act and must be revoked.

**That claims 1-6 of the Present Patent do not satisfy the test of section 3(d) and therefore are objected to under section 25(1) (f)**

87. Without prejudice to other grounds raised herein, it is submitted that claims 1-3 fail under section 3(d) of the Patents Act.

88. Section 3(d) of the Patents Act states:

> "*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

*Explanation-For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy*."

89. Section 3(d) of the Patents Act was amended in 2005 to prevent patents on modification of known substances. The statute requires product claim relating to a known substance, to satisfy the requirement of S. 3(d). It is an established position of law that S. 3(d) has to be satisfied independently of Section 2(1)(j) and S. 2(1)(ja) [see *Novartis AG versus Union of India and Others* (2013) 6 SCC 1]. This requirement under S. 3(d) is to be satisfied by the Applicant by showing efficacy (see *Novartis AG versus Union of India and Others* 2007 4 MLJ 1153, para 13). In case of pharmaceutical products this efficacy would have to be shown in terms of therapeutic efficacy. Further, such data has to be provided by the Applicant in the complete specification (see the order of the Hon'ble IPAB, Novartis AG versus Union of India, MIPR 2009 (2) 0345, para 9(xvii)).

90. That WO '392 discloses a multivalent pneumococcal vaccine with 23 serotypes. It also discloses a multivalent vaccine with 11 serotypes. Assuming without admitting that this 11 valent (and not the identical 13 valent combination disclosed therein) forms the closest combination to the combination claimed in the Present Patent, the Patentee has failed show any enhanced therapeutic efficacy of the claimed combination over the known 11 valent combination. It is reiterated that such data of enhanced efficacy had to be shown in the complete specification.

**X. That claims 1- 6 of the Present Patent must be rejected as the complete specification does not sufficiently and clearly describe the working the invention**

91. It is submitted that the Present Patent does not sufficiently and clearly describe the invention claimed. Further the claims are not appropriately supported by the specification of the Present Patent. Hence, without prejudice to the grounds raised in this representation, the Opponent invokes Section 25(2)(g).
92. It is submitted the complete specification of the Present Patent does not set out the problem to be solved or the novel feature of the claimed invention of the 13 valent vaccines.
93. Further, the claims 1-6 are vague as they do not set out the amount of $CRM_{197}$ to be used.
94. The optional use of an adjuvant in claims 2-5, is not supported by any rationale. The complete specification of the Present Patent does not cite instances where the adjuvant is to be used, and those where the adjuvant may not be used.

**PRAYER FOR RELIEF**

In view of the above said references Opponent prays as follows:

a) To be heard and be allowed to lead evidence (documentary and oral) before any order is passed;
b) To revoke Patent no. 286321 by rejecting claims 1-6 of the Patent;
c) To allow the Opponent to file further documents as evidence if necessary to support the averments;
d) To allow amendment of the opposition as and when the need may arise;

e) To allow the Opponent to make further submissions in case the Applicant amends the claims;

f) For costs in this matter;

g) For any further and other relief in the facts and circumstances that may be granted in favour of the Opponent in the interest of justice.

Dated this 17th day of AUGUST 2018.

[OPPONENT]

**To**

**The Controller,**

**The Patent Office Branch**

**DELHI**