389267

FORM 7A

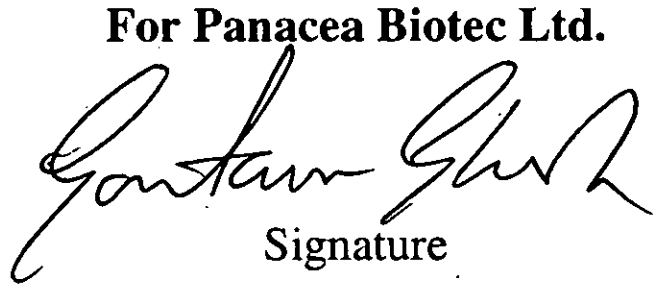
THE PATENTS ACT, 1970 (39 OF 1970)

AND

THE PATENT RULES, 2003

REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT

(see rule 55)

1. State names, address and nationality	I, We **Panacea Biotec Limited** hereby give representation by way of opposition to the grant of patent in respect of application no. **10072/DELNP/2012** dated **20/11/2012** made by **WYETH LLC** and published on **07/11/2014**
2. State the grounds taken one after another	On the grounds as given in the Statement of representation enclosed herewith
3. Complete postal index number / code and state along with telephone and fax number	**Panacea Biotec Limited** **B-1 Extn./A-27, Mohan Co-operative Ind. Estate, Mathura Road, New Delhi – 110 044** **Tel: +91 11 41679076** **Fax: +91 11 41679068**
4. To be signed by the opponent or by his /her authorized registered patent agent	**For Panacea Biotec Ltd.**  Signature
5. Name and designation of the natural person who has signed	**Dr. Goutam Ghosh** **Senior Vice President** **Panacea Biotec Ltd.**

To,
The Controller of Patents,
The Patent Office,
Delhi

BEFORE THE CONTROLLER OF PATENTS

DELHI

In the matter of Pre grant Opposition under section 25(1) of The Patents Act, 1970 *as amended by* Patents (Amendment) Act 2005,

And

In the matter of Patents Rules, 2003 as amended by Patents (Amendment) Rules 2006

And

IN THE MATTER of Patent Application No. 10072/DELNP/2012 filed on 20/11/2012 made by **Wyeth**, Five Giralda Farms, Madison, New Jersey, 07940, Unites States

.....Applicant

And

IN THE MATTER of representation by way opposition of the grant of a patent thereto by Panacea Biotec Ltd. B-1 Ext. /A-27, Mohan Co-op. Indl. Estate, Mathura Road, New Delhi, 110 044, INDIA

.....Opponent

REPRESENTATION UNDER SECTION 25(1)

We, Panacea Biotec Ltd, (hereinafter called 'opponent') make the following representation under Section 25(1) of the Act in opposing the grant of Patents on the application indicated in the cause title.

IMPUGNED APPLICATION

The impugned application no. 10072/DELNP/2012 entitled "Streptococcua Pneumoniae Vaccine Formulations" nationalized on 20/11/2012 arises out of International application No. PCT/IB2011/052275 filed on 25/05/2011 For the purpose of priority date the date considered is 04/06/2010.

The impugned application to the best of the information of the opponent is not granted and therefore the present opposition is within time and ought to be taken on record. The Opponent believes that the Application is still under examination and has not matured into a granted patent. The Opponent further states that in its search of the Patent Office Gazettes [for Gazette published through June 2015], no patent was advertised as granted for this Application. Hence the current pre-grant opposition is covered within the framework envisaged in the Act and the Rules made there under.

1. THE OPPONENT'S BUSINESS AND ACTIVITIES

The opponent, Panacea Biotec Ltd, is a Company incorporated under laws of India and having its principal office at B-1 Ext./A-27, Mohan Co-op Indl. Estate, Mathura Road, New Delhi, 110 044, INDIA .The opponent is a leading manufacturer of medicines and vaccines in this country and the opponent's products are sold under different brands and enjoy considerable goodwill and reputation. The opponent is very well known and has been operating in this country for several decades. The opponent is also engaged in the research and development of vaccines, biopharmaceuticals, medicines and pharmaceutical products and preparations.

2. LOCUS STANDI

Locus standi is not a condition precedent for an opposition under Section 25(1). In any event it is stated that the application under opposition relates to an alleged invention in the field of medicinal products. The opponent being engaged in the research and development as well as in the manufacture of drugs/medicinal compositions for many years and is thus a person interested.

3. GROUNDS OF OPPOSITION

The application is opposed on the following grounds of Section 25 (1) (Opposition to the Patents) which reads as under:

a. 25(1): Where an application for a Patent has been published but a Patent has not been granted, any person may in writing represent by way of opposition to the Controller against the grant of Patents on the ground -

b. That the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim

(i) In any specification filed in pursuance of an application for a Patent made in India on or after the 1st day of January, 1912; or

(ii) In India or elsewhere, in any other document.

Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29.

c. That the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a Patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;

d. That the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim;

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 as mentioned in clause (a) or having regard to what was used in India before the priority date of the applicant's claim;

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;

g. That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

h. The applicant has failed to disclose to the Controller the information required by Section 8 or has furnished the information which in any material particular was false to his knowledge.

The opponent reserves the right to alter, modify, add or delete some of the grounds during the course of the present proceedings.

The present Opposition is based on the below claims as available on the IPAIR web-site. The Opponent opposes present claims 1 to 29. Should the Applicant amend his claims from the below version, the Opponent reserves his/her right to file a fresh pre-grant opposition or amend the present pre-grant opposition.

4. CLAIMS

The claims currently pending before the IPO, are as given below:

1. A multivalent immunogenic composition comprising a plurality of capsular polysaccharides from Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F conjugated to a carrier protein, and further comprising 2-phenoxyethanol (2-PE).

2. The multivalent immunogenic composition of claim 1, wherein said composition comprises seven or more capsular polysaccharides from Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

3. The multivalent immunogenic composition of any one of claim 1 -2, wherein said composition comprises 2-PE at a concentration of between 7 mg/mL and 15 mg/mL.

4. The multivalent immunogenic composition of claim 3, wherein said composition comprises 2-PE at a concentration of about 10 mg/mL.

5. The multivalent immunogenic composition of any one of claims 1-4, wherein said composition comprises not less than 7 mg/mL of 2-PE.

6. The multivalent immunogenic composition of any one of claims 1-4, wherein said composition comprises not less than 10 mg/mL of 2-PE.

7. The multivalent immunogenic composition of any one of claims 1-4, wherein said composition comprises not less than 15 mg/mL of 2-PE.

8. The multivalent immunogenic composition of any one of claims 1-7, wherein said composition further comprises and adjuvant, and wherein said adjuvant is aluminum phosphate.

9. The multivalent immunogenic composition of any one of claims 1 -8, wherein the antigenicity of the immunogenic composition is stable for not less than 1 year, 1.5 years, 2 years or 2.5 years.

10. The multivalent immunogenic composition of any one of claims 1-9, wherein, following inoculation with one or more micro-organisms, the concentration of said micro-organisms is reduced over time.

11. The multivalent immunogenic composition of claim 10, wherein, following inoculation with one or more bacteria strains, the composition presents at least 1.0 log reduction from the initial micro-organism count at 24 hours, at least 3.0 log reduction at 7 days from the previous value measured and not more than 0.5 log increase at 28 days from the previous value measured.

12. The multivalent immunogenic composition of claim 10, wherein, following inoculation with one or more bacteria strains, the composition presents at least 2.0 log reduction from the initial calculated count at 6 hours after inoculation, at least 3.0 log reduction at 24 hours from the previous value measured and no recovery at 28 days.

13. The multivalent immunogenic composition of any one of claims 10-12, wherein the micro-organism strains are one or more strains selected from P. aeruginosa, S. aureus, E. coli and B. subtilis.

14. The multivalent immunogenic composition of any one of claims 10-13, wherein the composition is inoculated multiple times.

15. The multivalent immunogenic composition of claim 13 or 14, wherein a second inoculation occurs at 6 hours following the initial inoculation, a third inoculation occurs at 24 hours following the initial inoculation, a third inoculation occurs at 7 days following the initial inoculation and a fourth inoculation occurs at 14 days following the initial inoculation.

16. The multivalent immunogenic composition of any one of claims 1-15, wherein said composition further comprises one or more of a buffer, a cryoprotectant, a salt, a divalent cation, a non-ionic detergent, and an inhibitor of free radical oxidation.

17. A multivalent immunogenic composition formulation of pneumococcal capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, individually conjugated to CRM197, wherein the multivalent immunogenic composition is formulated in a sterile liquid to comprise: about 4.4 μg/mL of each polysaccharide, except for 6B at about 8.8 μg/mL; about 58 μg/mL CRM197 carrier protein; about 0.25 mg/mL of elemental aluminum in the form of aluminum phosphate; about 0.85% sodium chloride; about 0.02% polysorbate 80; about 5 mM sodium succinate buffer at a pH of 5.8; and about 10 mg/mL of 2-phenoxyethanol.

18. A vial containing a multivalent immunogenic composition of any one of claims 1-17.

19. The vial of claim 18, wherein said vial contains more than one dose of the immunogenic composition.

20. A pre-filled vaccine delivery device comprising a multivalent immunogenic composition of any one of claims 1-19.

21. The pre-filled vaccine delivery device of claim 20, wherein said device is or comprises a syringe.

22. The pre-filled vaccine delivery device of claim 19, wherein said device is or comprises a dual or multiple chamber syringe or vials or combinations thereof.

23. The pre-filled vaccine of claims 20-22, wherein said multivalent immunogenic composition is formulated for intramuscular or subcutaneous injection.

24. A kit for preparing the multivalent immunogenic composition of any one of claimsl-17, wherein the kit comprises (i) said plurality of capsular polysaccharides in a lyophilized form of the composition of any one of the above claims, and (ii) aqueous material for reconstituting component (i) in order to provide the aqueous composition.

25. A multi-dose vaccine comprising 4 doses of a vaccine in a vial, each dose comprising from 4 to 20 mg/mL, preferably 10 mg/mL of 2- phenoxyethanol, wherein a dose is 0.5 mL of vaccine.

26. A container comprising two doses or more, at 0.1 to 2 mL per dose, of the multivalent immunogenic composition of any one of claims 1-17.

27. The container of claim 26 wherein the dose is a 0.5 mL dose.

28. The container of claim 26-27 comprising 2 to 10 doses.

29. A method for measuring the efficacy of a vaccine formulation comprising one or more select preservative agents in the presence of some or all of the immunogenic and non-immunogenic components of the vaccine composition, wherein the test comprises at least two steps of inoculating the test composition with a select micro-organism population and comparing the log reduction of inoculated micro -organism(s) over time and under particular environmental conditions (e.g., temperature) to the log reduction in a control composition lacking the test preservative(s).

5. DOCUMENTS RELIED UPON BY THE OPPONENT

Sr. No.	Description of Documents
D1	WO2000056360, SKB, published on Sept 28, 2000
D2	WO2000062801, SKB, published on October 26, 2000
D3	CPMP report, on Points to consider on the reduction elimination or substitution of thiomersal. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003929.pdf
D4	WHO meeting report- Thiomersal in vaccines: a regulatory perspective, dated 15-16 April 2002 http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Thiomersal_WHO_Consult%20April%2015_16_April2002.pdf
D5	Vaccine Excipient & Media Summary, Part 2, Excipients Included in U.S. Vaccines, by Vaccine- 2007
D6	J Pharm Sci 2007 Dec;96(12):3155-67, Meyer et al
D7	Lett Appl Microbiol. 1994 Feb;18(2):115-6. Lowe et al
D8	INFANRIX-EMEA Scientific Discussion- Dated 2004 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000295/WC500032649.pdf
D9	TWINRIX- http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5037a4.htm Dated September 2001
D10	WO1998034594A1 (Merck) published on 03/02/1998
D11	Sharma et al, Biologicals 36 (2008) , 61-63
D12	US20070065469 published on March 22, 2007
D13	June 2010- DEVELOPMENT OF A MULTI-DOSE FORMULATION FOR PREVNAR 13™-http://dc.engconfintl.org/vaccine_iii/35/
D14	EMEA assessment report for PREVNAR 13 -2009

	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001104/WC500057250.pdf
D15	Prevnar 13™ [Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)]- Review of manufacturing process- USFDA- Feb 2009
D16	US pharmacopeia- Chapter on Antimicrobial Effectiveness http://www.pharmacopeia.cn/v29240/usp29nf24s0_c51.html
D17	Sutton et al, PDA Journal of Pharmaceutical Science and Technology, Vol. 56, No. 6, November/December 2002 http://www.microbiologynetwork.com/content/file/PDA_2002_6_Development-of-the-Antimicrobial-Effectiveness-Test-as-USP-Chapter-51.pdf
D18	Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems, Chapter 18- Excipients used in Vaccines- 2006 https://adiyugatama.files.wordpress.com/2012/03/excipient-development-for-pharmaceutical-dosage-forms.pdf
D19	Pneumococcal Conjugate Vaccine – Target Product Profile – WHO- Published 31/10/2007 http://www.who.int/immunization/sage/Parts1and2_TPP_Master_Table_final_draft.pdf
D20	Divya Parmar, Elaine M Baruwa, Patrick Zuber & Souleymane Kone (1st March 2010) Impact of wastage on single and multi-dose vaccine vials: Implications for introducing pneumococcal vaccines in developing countries, Human Vaccines, 6:3, 270-278, DOI: 10.4161/hv.6.3.10397 http://www.tandfonline.com/doi/pdf/10.4161/hv.6.3.10397
D21	Pneumococcal disease: Global burden, epidemiology, scope for vaccine prevention- CDC-August 2007 http://www.sabin.org/sites/sabin.org/files/20_9_0900_stephanie_schrag.pdf
D22	WHO- Target Product Profile and technical requirements Pre-tender Meeting Pneumococcal Vaccines under the AMC *Unicef Supply Division, Copenhagen 26 August 2009*
D23	WO2007026249

6. GENERAL DISCUSSIONS OF THE ART RELATING TO THE ALLEGED INVENTION OF THE APPLICATION UNDER OPPOSITION

Preservatives in general may be defined as compounds that kill or prevent the growth of microorganisms, particularly bacteria and fungi. They are used in vaccines to prevent microbial growth in the event that the vaccine is accidentally contaminated, as might occur with repeated puncture of multi-dose vials. In some cases, preservatives are added during manufacture to prevent microbial growth.

The United States Code of Federal Regulations (the CFR) requires, in general, the addition of a preservative to multi-dose vials of vaccines; indeed, worldwide, preservatives are routinely added to multi-dose vials of vaccine. Tragic consequences have followed the use of multi-dose vials that did not contain a preservative and have served as the impetus for this requirement. One particularly telling incident from Australia is described by Sir Graham S. Wilson in his classic book, *The Hazards of Immunization*

> *In January 1928, in the early stages of an immunization campaign against diphtheria, Dr. Ewing George Thomson, Medical Officer of Health of Bundaberg, began the injection of children with toxin-antitoxin mixture. The material was taken from an India-rubber-capped bottle containing 10 mL of TAM. On the 17th, 20th, 21, and 24th January, Dr. Thomson injected subcutaneously a total of 21 children without ill effect. On the 27th a further 21 children were injected. Of these children eleven died on the 28th and one on the 29th. (Wilson 1967)*

This disaster was investigated by a Royal Commission and the final sentence in the summary of their findings reads as follows:

> *The consideration of all possible evidence concerning the deaths at Bundeberg points to the injection of living staphylococci as the cause of the fatalities.*

From this experience, the Royal Commission recommended that biological products in which the growth of a pathogenic organism is possible should not be issued in containers for repeated use unless there is a sufficient concentration of antiseptic (preservative) to inhibit bacterial growth.

The U.S. requirement for preservatives in multi-dose vaccines was incorporated into the CFR in January 1968, although many biological products had contained preservatives, including

thimerosal, prior to this date. Specifically, the CFR states: Products in multi-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Polio-virus Vaccine, Live Oral; viral vaccine labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume (v/v) glycerin. [21 CFR 610.15(a)]

The CFR also requires that the preservative used...[s]hall be sufficiently non-toxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in combination used it shall not denature the specific substance in the product to result in a decrease below the minimal acceptable potency within the dating period when stored at the recommended temperature. [21 CFR 610.15(a)]

Preservatives cannot completely eliminate the risk of contamination of vaccines. The literature contains several reports of bacterial contamination of vaccines despite the presence of a preservative, emphasizing the need for meticulous attention to technique in withdrawing vaccines from multi-dose vials. The need for preservatives in multi-dose vials of vaccines is nonetheless clear.

Thimerosal is a mercury-containing organic compound (an organomercurial). Since the 1930s, it has been widely used as a preservative in a number of biological and drug products, including many vaccines, to help prevent potentially life threatening contamination with harmful microbes. Over the past several years, because of an increasing awareness of the theoretical potential for neurotoxicity of even low levels of organomercurials and because of the increased number of thimerosal containing vaccines that had been added to the infant immunization schedule, concerns about the use of thimerosal in vaccines and other products have been raised. Indeed, because of these concerns, the Food and Drug Administration has worked with, and continues to work with, vaccine manufacturers to reduce or eliminate thimerosal from vaccines and is also encouraging alternatives to Thimerosal. In 1999, The U.S. Public Health Service and the American Academy of Pediatrics jointly called for Thimerosal to be removed from vaccines as soon as possible.

Based on a survey of U.S.-FDA-approved preserved vaccines, other viable alternatives to Thimerosal as a preservative in commercial vaccines packaged in multidose vials are

- **phenol** [used in the Typhoid Vi Polysaccharide (Typhim Vi; Sanofi Pasteur, SA) and the Pneumococcal Polysaccharide (Pneumovax 23; Merck & Co, Inc) vaccines], and
- **2-phenoxyethanol** [used in the DTaP (Infanrix®; GSK)- D6, Hepatitis A (Havrix ®; GSK)-D7, Hepatitis A/Hepatitis B (Twinrix ®; GSK)- D8 and IPV (IPOL®; Sanofi Pasteur, SA) vaccines- D9]

The ingredient 2-phenoxyethanol (phenoxyethanol) is well-known for its antimicrobial efficacy against a range of microorganisms, and it is particularly effective against Gram-negative microorganisms such as Pseudomonas species. It is used as a preservative in many cosmetic and pharmaceutical products including vaccines. Introduced in the 1950s, it has had a long history of safe use as a cosmetic preservative. In recent years, the use of phenoxyethanol has expanded due to its low sensitization potential and global approval. Although the phenoxyethanol used in formulations is typically synthetic, it does occur naturally in green tea and has a proven record of safety even at high dosages.

7. THE INVENTION AS CLAIMED IN CLAIMS 1 TO 16 AND DEPENDENT CLAIMS 17 TO 29 ARE NOT NOVEL UNDER SECTION 25(1)(b)(ii) OF THE PATENT ACT

D1 discloses conjugated pneumococcal vaccines with 2-PE as preservative. Although the carrier protein is PD, the concept of using 2-PE for multivalent pneumococcal vaccines is known in this prior publication. According to the formulation of this art, 2-phenoxyethanol was added to a concentration of 5 mg/mL

D2 discloses a combined RSV + 23-valent pneumococcal vaccine wherein phenoxyethanol (5mg/ml) was added to the formulations as preservative. D2 specifically provides a vaccine composition comprising: (a) one or more Streptococcus pneumoniae polysaccharides either conjugated to a protein or peptide, or non-conjugated; and (b) an RSV antigen in conjunction with an adjuvant which is a preferential stimulator of a Thl type response

D23 discloses a kit, comprising a first immunogenic component and a second immunogenic component, wherein: (a) the first immunogenic component comprises an aqueous formulation of a conjugated capsular saccharide from Streptococcus pneumoniae; and (b) the second immunogenic component comprises a conjugated capsular saccharide from Neisseria meningitidis serogroup C (see claim 4). Further D23 provides that the kit comprises 2-phenoxyethanol (see claim 25). D23 also teaches that "Where antigens are adsorbed, a composition may be a suspension with a cloudy appearance. This appearance means that microbial contamination is not readily visible, and so the vaccine preferably contains a preservative. This is particularly important when the vaccine is packaged in multidose containers. Preferred preservatives for inclusion are 2-phenoxyethanol and thimerosal. It is recommended, however, not to use mercurial preservatives {e.g. thimerosal) where possible". D23 also teaches that pneumococcal polysaccharides are conjugated to CRM-197. Compositions of the invention preferably include saccharide antigens for at least serotypes 6B, 14, 19F and 23F. Further serotypes are preferably selected from: 1, 3, 4, 5, 7F, 9V and 18C. 7-valent (as in PREVNAR™), 9-valent (e.g. the 7 serotypes from PREVNAR, plus 1 & 5), 10-valent (e.g. the 7 serotypes from PREVNAR, plus 1, 5 & 7F) and 11-valent (e.g. the 7 serotypes from PREVNAR, plus 1, 3, 5 & 7F) coverage of pneumococcal serotypes is particularly useful.

8. THE CLAIMED INVENTION, AS CLAIMED IN CLAIMS 1-29 IS UNPATENTABLE AS OBVIOUS UNDER SECTION 25 (1) (e) OF THE PATENT ACT.

The invention currently claimed combines two well-known prior art elements viz., 13 valent conjugated vaccine and a well-known preservative 2- phenoxyethanol. Prevnar-13 was already marketed before the effective priority date of the instant application viz 04/06/2010. During the meeting on 21-24 September 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorization to Prevnar 13® on 24 September 2009. Also Prevnar 13® was approved by the U.S. Food and Drug Administration on February 24, 2010. 2- Phenoxyethanol is a widely used preservative in cosmetic, pharma and vaccine industry and has a proven track record of safety even at high concentrations.

In the same month that the instant application was filed Wyeth/Pfizer had already disclosed in D13 that "*Multiple preservatives which include phenol, 2-phenoxyethanol (2-PE), meta-cresol, methylparaben and propyl paraben and thimerosal (as a control) were evaluated as potential candidates for a multi-dose formulation of Prevnar 13 based on preservative effectiveness and product stability. 2-PE showed superior antimicrobial effectiveness in Prevnar 13 formulations as per European Pharmacopoeia (EP) requirements and in multiple challenge studies with various organisms, as per WHO Open Vial Policy, to mimic worst case inadvertent microbial contamination that might occur during immunization of subjects when the formulation is presented in multi-dose vials. Prevnar 13 in the presence of 5mg dose of 2-PE is stable for over two years and meets the preservative effectiveness standards based on the EP 5.1.3 as well as WHO multi-organism challenge test. The data support the use of 2-PE as a more effective preservative with the potential to replace thimerosal, the most commonly used preservative in multi-dose vaccine formulations*".

A patent may not be obtained if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Under an obviousness determination, the scope and content of the prior art are to be determined and differences between the prior art and the claims at issue are to be ascertained.

D3 on page 5 indicates that with respect to safety and efficacy data indirect evidence of the immunogenicity of the vaccine antigen in the presence of an alternative preservative for example 2- phenoxyethanol can be obtained from clinical trials where the vaccine antigen was combined with other vaccine antigens in a combined vaccine containing 2-phenoxyethanol.

Similarly D4 on page 5, states that the current approach of industry to new vaccines is to develop thiomersal-free products in mono-dose presentations. If a preservative is needed, an alternative to thiomersal such as 2-phenoxy-ethanol (2-PE) is preferred. More specifically from an Indian perspective D4 recites on page 13, section 3.3 that "in India, thiomersal is present in most of the vaccines. Licensed vaccines on the Indian market can be either manufactured locally or imported. Most, but not all, of these vaccines contain thiomersal as a preservative at a concentration of 0.01%. Some contain other preservatives, like phenol and 2-phenoxyethanol.

The majority of these vaccines is being filled in multi-dose vials, and therefore need to contain a preservative.

D5 provides an account of presence of 2-phenoxyethanol in various approved vaccines in US, including Daptacel, Infanrix, Pediarix, Havrix, Twinrix, Ipol, Decavac and Adacel. D6 to D9 further establishes the safe inclusion of 2-phenoxyethanol as a preservative.

D10 states that for multidose vaccine formulations, preservatives are required to prevent contamination of and to stabilize the composition of subsequent doses after the first dose is used. The preservative must enable the vaccine formulation to pass efficacy tests or antimicrobial challenge tests according to the United States Pharmacopeia (USP) in the U.S., British Pharmacopeia (BP), and European Pharmacopeia (EP) in Europe. Thimerosal is a commonly-used preservative in vaccines. Thimerosal is a mercurial compound that is potentially toxic, and causes allergic reaction in about sixteen percent of the population. Thimerosal is also toxic to the environment. It would be advantageous to find new and safer preservatives for vaccines to replace thimerosal. In this application, we report on new combinations of preservatives for vaccines: methyl and propyl parabens, benzyl alcohol, and 2-phenoxy-ethanol. These combination preservatives are non-toxic, yet effective. D10 further elaborates that toxicity of 2-phenoxyethanol is low. It has been in commercial use for several decades. The presence of 2-phenoxyethanol is known in volatile naturally occurring substances, such as green tea. The acute oral LD50 in rats is 1.26-2.33 mL/kg. The acute dermal LD50 in rabbits is 2.0 mL/kg.

D11 states that "As now the vaccine formulations contain 2- phenoxyethanol as a preservative, its reliable determination is one of the important quality control parameters". DTwP vaccine produced by Panacea Biotec Ltd., containing formalin-treated pertussis components, diphtheria toxoid and tetanus toxoid was used for testing and this formulation contained 2-phenoxyethanol at a concentration of 5mg/ml.

D12 recites that the preservative present in the pharmaceutical formulation of the present invention can be any pharmaceutically acceptable preservative. Preferably, the preservative is selected from the group consisting of benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, phenol, benzalkonium chloride, benzethonium chloride, chlorobutanol, 2-phenoxyethanol, phenyl mercuric nitrate and thimerosal. The concentration of the preservative

will be readily available to those skilled in the art in agreement with requirements of health authorities regarding the safety of multi-dosage formulations. Accordingly, the concentration of the preservative can be, for example, from about 1 mg/ml to about 30 mg/ml, depending on the preservative actually used. More preferably, the preservative is benzyl alcohol. In a preferred embodiment thereof, the pharmaceutical formulation according to the present invention comprises benzyl alcohol as preservative being present at a concentration of from about 7 mg/ml to 12 mg/ml, most preferably at a concentration of about 9 mg/ml.

Where "the problem is known, the possible approaches to solving the problem are known and finite, and the solution is predictable through use of a known option," a solution that is obvious to try may indeed be obvious. In the present case

- A 13- valent conjugated pneumococcal vaccine was approved and available in the market before the priority date of the current application
- Mercury containing preservatives like Thimerosal were objected to and a possible alternative was clearly 2-Phenoxyethanol
- There are many vaccines with 2- Phenoxyethanol available before the effective filing date of the instant application
- Conjugated Pneumococcal vaccines with 2- Phenoxyethanol as a preservative have been reported in prior arts D1 and D2
- Dose optimization is well within the skill of a person of ordinary skill in art and further D12 taught the broad range of 1-30 mg/ml

The subject matter of all of the claims of the instant application would have been arrived at by following the teachings and suggestions of the prior art which would have motivated a person of ordinarily skilled in the art to develop a pneumococcal vaccine by choosing common pharmaceutical excipients, specifically preservatives and optimizing the prospective formulation by selecting a best or satisfactory preservative identified from routine drug-excipient compatibility testing. In the present case, the ordinarily-skilled artisan would have harbored more than a reasonable expectation that the conventional preservative 2-phenoxyethanol would have been compatible with pneumococcal antigens in vaccine formulation.

D1 and D2 specifically teach pneumococcal conjugated vaccine formulations with 2-phenoxyethanol as preservative. One of ordinary skill in the art would have therefore understood from D1 and D2 that pneumococcal antigens were compatible with 2-phenoxyethanol as a preservative and would have maintained a reasonable expectation of success that such a formulation could be prepared via conventional methods employing conventional excipients for the 13-valent CRM-197 conjugated pneumococcal vaccine.

Upon endeavoring to formulate the 13-valent CRM-197 conjugated pneumococcal vaccine, the ordinarily skilled artisan would have chosen potential preservatives from a limited roster of conventionally-employed preservatives for vaccine formulations. Having chosen a limited number of prospective preservatives, the ordinarily skilled artisan would have conducted antigen-excipient compatibility testing to assess compatibility under stressed conditions. The ordinarily-skilled artisan would have thereafter selected those preservatives deemed satisfactory from compatibility testing for further formulation development. In other words, the prior art taught the ordinarily-skilled artisan to choose prospective preservatives from a finite list of well-known, pharmaceutically-acceptable ones, test them to confirm compatibility with the subject active, and, in an effort to optimize the formulation, select satisfactorily performing preservatives and excipients for further development. This is not the case where there are "numerous parameters" to try. Rather, the only parameter to be varied is the preservative with which to make the final pneumococcal vaccine composition. In T 0200/05 (EP Boards of Appeal), it was held that for assessing inventive step it is not necessary to establish that the success of an envisaged solution of a technical problem was predictable. It is enough to show that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success. Further Pfizer vs. Apotex 2006-1281 established that the suggestion, teaching or motivation to combine the relevant prior art need not be found explicitly in the prior art references but may be found in number of sources and that obviousness cannot be avoided, simply by showing of some degree of unpredictability as long as there is a reasonable probability of success. Discovery of an optimum value of a variable in a known process is obvious, hence the optimization of a specific preservative concentration would have been obvious since the prior art heavily suggests the particular preservative and specific dose range.

Obviousness does not require absolute predictability, but only a reasonable expectation that the beneficial result will be achieved. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). In the present case, the ordinarily skilled artisan would have maintained more than a reasonable expectation that 2-phenoxyethanol would be compatible with 13-valent conjugated pneumococcal vaccine because, as on April 2010 2-phenoxyethanol was a commonly-employed preservative in vaccine applications whose beneficial properties include safety, non-mercurial nature as compared to conventional preservatives like tiomerosal, its lack of reported incompatibilities in other vaccines and even pneumococcal vaccines in particular. See for example a post publication in Vaccine. 2011 Sep 22;29(41):7144-53. doi: 10.1016/j:vaccine.2011.05.074. Epub 2011 Jun 7 which states that "*Development of a Prev(e)nar 13™ multi-dose vaccine, in support of vaccinating populations against pneumococcal disease, required the addition of a preservative to the vaccine formulation that met antimicrobial effectiveness tests based on the European Pharmacopoeia (EP) requirements, including deliberate multiple challenge studies and recommendation by the WHO Open Vial Policy. In this study, the antimicrobial effectiveness of several preservatives in Prev(e)nar 13™ formulations was evaluated. A Prev(e)nar 13™ formulation containing 2-Phenoxyethanol (2-PE) at a concentration of 5.0mg/dose was stable and met EP recommended criteria for antimicrobial effectiveness tests when the formulation was kept over a 30 month period. In contrast, a recommended dose of Thimerosal, as a comparator, or other preservatives did not meet EP antimicrobial effectiveness acceptance criteria. The rate of growth inhibition of Thimerosal compared to 2-PE on Staphylococcus aureus, a resilient organism in these tests, was significantly slower in single and multi-challenge studies. These results indicate that 2-PE provides a superior antimicrobial effectiveness over Thimerosal for this vaccine formulation*".

However use of 2-phenoxyethanol as a safe and efficacious preservative is well documented in prior art, D6 provides a comprehensive summary of antimicrobial preservatives that are commonly used in licensed parenteral products to date. The information reviewed includes the general properties of the preservatives, the doses and frequency of their use, the classes of the preserved products (peptide, protein, vaccine, and small molecule products), the interactions with other formulation components, and the criteria commonly used for their selection in parental product formulations. It was revealed that phenol and benzyl alcohol are the two most common

antimicrobial preservatives used in peptide and protein products, **while phenoxyethanol is the most frequently used preservative in vaccines**. Benzyl alcohol or a combination of methyl paraben and propyl paraben are generally found in small molecule parenteral formulations. The key criteria for antimicrobial preservative selection are the preservative's dose, antimicrobial functionality, and effect on the active ingredient. Additionally, the use of spectroscopic techniques (circular dichroism (CD) and fluorescence) and differential scanning calorimetry (DSC) were identified as common techniques used in evaluating an antimicrobial preservative for its impact on the conformational stability of peptide, protein, and vaccine antigens. The future use of preservatives is also discussed, including antimicrobial agents such as peptides, and regulatory requirements for antimicrobial effectiveness testing. D7 further teaches that "the activity of the antimicrobial preservatives, phenoxyethanol and thiomersal, were compared in diphtheria, tetanus and pertussis (adsorbed) vaccine. Both chemicals were equally effective in inactivating challenge doses of Gram-negative and Gram-positive micro-organisms, as well as a yeast". D7 also states that "The usage of phenoxyethanol at 10% (v/v) on the skin in animal studies did not result in adverse events". D8 and D9 further confirm the safe use of 2-phenoxyethanol is marketed vaccine formulations.

Claim 2 which is dependent on claim 1 further specifies that " The multivalent immunogenic composition of claim 1, wherein said composition comprises seven or more capsular polysaccharides from Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F". This recital adds nothing more to the unpatentable claim 1 as the 13 valent conjugated pneumococcal vaccine incorporating the very same serotypes was already known and available before the priority date of the instant application see for example D14 and D15. D14 states on page 14 a " 13-Valent Pneumococcal Conjugate (Prevnar 13®) vaccine is a sterile liquid suspension of capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each saccharide individually conjugated to plasmid-derived Diphtheria CRM197 protein". Also D15 specifies on page 3 that "Prevnar 13 is a 13-valent pneumococcal vaccine for use in infants and young children for the prevention of pneumococcal disease. The pneumococcal 13-valent conjugate vaccine is a sterile suspension of the capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated by reductive amination to the non-

toxic diphtheria CRM197 protein. The vaccine includes the seven serotype conjugates included in the currently licensed Prevnar: 4, 6B, 9V, 14, 18C, 19F and 23F"

Claim 3 further recites that "The multivalent immunogenic composition of any one of claim 1 -2, wherein said composition comprises 2-PE at a concentration of between 7 mg/mL and 15 mg/mL", claim 4 further narrows down the concentration to about 10 mg/mL. Claim 5 recites "The multivalent immunogenic composition of any one of claims 1-4, wherein said composition comprises not less than 7 mg/mL of 2-PE" and claim 6 narrows down the concentration to not less than 10 mg/mL of 2-PE. Lastly claim 7 further adds "The multivalent immunogenic composition of any one of claims 1-4, wherein said composition comprises not less than 15 mg/mL of 2-PE".

It would be evident from D12 that these concentration ranges are nothing but routine experimentation. D12 already taught a range of 1-30 mg/ml, hence claims 3 to 7 add no further inventive feature to claim 1.

Claim 8 reads as "The multivalent immunogenic composition of any one of claims 1-7, wherein said composition further comprises and adjuvant, and wherein said adjuvant is aluminum phosphate".

However use of an aluminium phosphate adjuvant in 13-valent pneumococcal conjugate vaccine is already known from D14 and D15. D14 on page 14 specifies that "Prevnar 13 consists of the thirteen pneumococcal conjugates (Drug Substances) in 5 mM succinate, 0.85% NaCl buffer, pH 5.8, with 0.02% polysorbate 80 and aluminum phosphate at 0.25 mg/mL aluminum."D15 on page 6 recites that "Prevnar 13 is a 13-valent pneumococcal vaccine of use in infants and young children for the prevention of pneumococcal disease. The pneumococcal 13-valent conjugate vaccine is a sterile suspension of the capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated by reductive amination to the non-toxic diphtheria CRM197 protein. Each 0.5 mL dose contains a target of 2.2 µg each of the polysaccharides (except for 6B, formulated at 4.4

μg/dose), approximately 32μg of CRM197, 0.02% polysorbate 80, and 0.125 mg of aluminum as aluminum phosphate adjuvant"

Claim 9 recites "The multivalent immunogenic composition of any one of claims 1 -8, wherein the antigenicity of the immunogenic composition is stable for not less than 1 year, 1.5 years, 2 years or 2.5 years". However D14 already reports that the antigenicity of the vaccine is tightly controlled to a target value for each conjugate of 4.4 μg/mL for all serotypes except 6B for which the target value is 8.8 μg/mL. Since D14 discloses the same vaccine as currently claimed the claimed antigenicity value is an inherent feature and is also obvious from prior disclosures and is essentially a property of the known serotypes in known concentrations.

Claims 10 to 15 are directed to routine antimicrobial efficacy testing guidelines and measurement in terms of log reduction in the count of micro-organisms. But these guidelines are well documented in United States Pharmacopeia. USP <51>. Antimicrobial effectiveness testing. Rockville, MD and/or European Pharmacopeia. EP <5.1.3 > Efficacy of antimicrobial preservatives and/or Japanese Pharmacopeia. JP <19 > Preservative effectiveness tests. The antimicrobial effectiveness test, also known as the preservative effectiveness test, is a compendial test performed during formulation development and stability testing of a parenteral drug product intended as a multi-dose product. The test procedures and acceptance criteria are described in these three major compendia. During the development of a multi-dose parenteral product, formulation scientists and microbiologists routinely make a decision as to which preservative and what concentration will be utilized in the drug formulation. Interactions of the preservative with the drug product are usually considered as well as with the container and closure. The preservative must also remain effective, not just "present" or measureable, in the formulated product throughout its shelf life at the labeled storage conditions. Historical data from other marketed products are used as a general practice when choosing the appropriate preservative and concentration for the product. This is all routine procedure. A major consideration for selecting an antimicrobial preservative for a parenteral formulation is the "use period" or storage conditions and time after the initial product withdrawal. Some multi-use parenteral formulations, due to chemical or microbial stability, must be used within a 24-h period whereas others may remain stored for up to 1 week at 2–8 C following the initial use. The Ph.

Eur. requires testing of antimicrobial activity at 6 and 24 h after the microbial challenge. This activity ensures that any microorganisms inadvertently added to the product are killed prior to repeat administration. However, the USP tests are designed to evaluate antimicrobial activity after 7 days. Once a preservative has been chosen and the final formulation of the drug product has been established, the preservative levels in the drug product are chemically assayed at stability time intervals to assure that the preservative remains at effective concentrations in the drug product over the shelf life. It is also a regulatory requirement to measure the efficacy of the preservatives using the preservative effectiveness tests on the drug product in its final container through expiry. To establish the lower effective shelf life specifications, the product is formulated at 100%, 75%, and 50% of the labeled preservative concentration and its effectiveness at these concentrations confirmed using the AET. Based on these findings, future marketed product stability testing may be conducted using the chemical assay and not the microbiological challenge test.

The AET is performed by spiking a panel of challenge microorganisms (representing Gram-positive cocci, Gram-negative bacilli, yeast, and mold) individually into the product and determining the log reduction of organisms at prescribed time intervals to quantitatively evaluate the effectiveness of the antimicrobial preservative to prevent microbial proliferation and/or kill the organisms. Enumerations performed at 6 h, 24 h, 7 days, 14 days, and 28 days after the initial microbial challenge satisfy to determine the log reduction. See D16.

D17 teaches that the current general chapter <51> *Antimicrobial Effectiveness Testing* applies to vaccines in multi-use containers. Significant concern was expressed to the USP by the *Ph. Eur.* that, because of their nature and composition, most vaccines could not fulfill the requirements criteria proposed by the *Ph. Eur.* At the request of interested parties, USP developed a "stand-alone" chapter designed for the testing and evaluation of vaccines and is offering it as a point of departure for international harmonization discussions. This proposed chapter <52> appeared in the May – June 1998 issue of *PF* (53). In light of these disclosures it would be immediately apparent that claims 10-15 add nothing more than the known Pharmacopeia standard procedures to the claims and hence lack inventive concept.

For the same reasons cited above for claims 10-15, claim 29 which reads as follows is also invalid for being obvious from known Pharmacopoeial standard procedures

29. A method for measuring the efficacy of a vaccine formulation comprising one or more select preservative agents in the presence of some or all of the immunogenic and non-immunogenic components of the vaccine composition, wherein the test comprises at least two steps of inoculating the test composition with a select micro-organism population and comparing the log reduction of inoculated micro -organism(s) over time and under particular environmental conditions (e.g., temperature) to the log reduction in a control composition lacking the test preservative(s).

Claim 16 recites a multivalent composition as claimed in claim 1 which further comprises one or more of a buffer, a cryoprotectant, a salt, a divalent cation, a non-ionic detergent, and an inhibitor of free radical oxidation. D14 and D15 already teach 13-valent pneumococcal conjugate vaccines comprising adjuvant, buffer and non-ionic detergent, other agents like cryoprotectant, salt, cations, anti-oxidants etc., are routine and can be found in many textbooks like see for example D18, Chapter 18 on " Excipients used in Vaccines"

Claim 17 of the instant application reads as follows "A multivalent immunogenic composition formulation of pneumococcal capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, individually conjugated to CRM197, wherein the multivalent immunogenic composition is formulated in a sterile liquid to comprise: about 4.4 µg/mL of each polysaccharide, except for 6B at about 8.8 µg/mL; about 58 µg/mL CRM197 carrier protein; about 0.25 mg/mL of elemental aluminum in the form of aluminum phosphate; about 0.85% sodium chloride; about 0.02% polysorbate 80; about 5 mM sodium succinate buffer at a pH of 5.8; and about 10 mg/mL of 2-phenoxyethanol".

ıay be noted that D14 and D15 recite every element of the claim 14; exception 2-
vethanol.

D14 on page 15 states that "The antigenicity of the vaccine is tightly controlled to a target value for each conjugate of 4.4 µg/mL for all serotypes except 6B for which the target value is 8.8 µg/mL". Further on page 14 it is specified that "13-Valent Pneumococcal Conjugate (Prevnar 13) vaccine is a sterile liquid suspension of capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each saccharide individually conjugated to plasmid-derived Diphtheria CRM197 protein. The vaccine contains 2.2 µg/dose of each of the serotypes, except for serotype 6B at 4.4 µg/dose. The vaccine is formulated in 5 mM succinate buffer containing 0.85% NaCl and 0.02% polysorbate 80, at pH 5.8, and contains aluminum phosphate at 0.125 mg/dose aluminum, as an adjuvant. Each 1 mL syringe contains a single 0.5 mL dose of vaccine for parenteral administration, with no preservative".

D15 also refers to Prevnar 13 which contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each saccharide individually conjugated to plasmid-derived Diphtheria CRM197 protein. The reference on page 9 provides the composition wherein each ingredient which is component part of current claim is disclosed, the only difference is that the reference provides quantities per 0.5ml whereas the claim covers the quantities per 1ml.

The only difference between claim 17 and prior arts D14 and D15 is the addition of a preservative 2-phenoxyethanol. However this is obvious in light of the established fact that 2-phenoxyethanol is a well-known preservative used in the vaccine preparations and does not add inventive features to the current claims, see D6.

Claim 18 adds nothing more to claim 17 but merely recites a vial comprising composition according to claim 17, for the same reasons cited above claim 18 is obvious over D14 and D15 in light of D6.

Claims 19 to 28 relate to multi-dose preparation, further as pre-filled syringes presented in kits and containers. However these claims lack inventive feature in light D19, D20, D21 and D22.

D19 is a WHO target product profile for pneumococcal which discloses the 13 valent conjugated vaccine of the current application on page 9, table 1. On Page 26-27, D19 states that "*Based on this analysis the best presentation options are mono-dose and low multi-dose vials. Mono-dose presentations, in particular if available as non-reusable compact prefilled devices, help to assure safety of injection, reduce work load to health care workers, and reduce wastage of vaccines. Low multi-dose vials have reduced storage requirements and wastage rates. The selection of the number of doses per vial should be defined by the manufacturer. Preliminary analysis suggests that vials containing between 2-5 doses are appropriate. Any multi-dose presentation is subject to WHO multidose vial policy when they are used in the field (The use of opened multi-dose vials of vaccine in subsequent immunization sessions, WHO/V&B/00.09). **To allow for use through subsequent immunization sessions, the vaccine needs to contain preservative at appropriate concentration as outlined in the Global Advisory Committee of Vaccine Safety statement (http://www.who.int/vaccine_safety/topics/thiomersal/en/index.html; accessed 18.10.2007). In conclusion, for the TPP, mono-dose or low multi-dose vial presentations are considered essential.** For mono-dose presentations, either single dose vials or non-reusable compact pre-filled devices must be used. All presentations should be optimized for space efficiency in accordance with the WHO Guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23)*".

D20 discusses the impact of wastage on single and multi-dose vaccine vials: Implications for introducing pneumococcal vaccines in developing countries. D20 teaches that the optimal vial-size for PCV is dependent upon country specific wastage rates but few countries have these data. There may be a role for both single and multi-dose vials that is best determined by local management and storage capacities making local wastage data critical. Without effective wastage monitoring and control there is a risk that wastage costs will possibly exceed the savings from multi-dose vials' lower storage costs. Multi-dose vials can have 2, 5, 6, 10, 20, etc. doses of vaccine in a vial while a single- dose vial has just one dose of the vaccine. The manufacturing costs in a multi-dose vial are spread over many doses and therefore they tend to cost less per dose as compared to a single-dose vial. Further multi-dose vials have lower cold chain costs however they are also thought to be associated with higher wastage

D21 suggests multi-dose vials for PCV 13 valent strain on slide 22.

D22 on slide 10 proposes that the PCV vaccine must be available in mono-dose or low multi-dose presentations. Mono-doses must be either in single dose vial or in auto-disable compact pre-filled device. Low multi-dose presentations must be formulated and labelled in compliance with WHO policy or guidance. The preferred presentation for WHO is a monodose in vial or prefilled autodisable syringe or low multidose vial with preservative. If a low multi-dose vaccine contains no preservative, it needs to be discarded at the end of the immunization session, and at latest 6 hours after the vial has been opened. To distinguish such products from those containing preservative, specific labeling of the vial and training at field level will be required. WHO is currently revising its policy on the use of opened multi-dose vials (*The use of opened multi-dose vials of vaccine in subsequent immunization sessions,* WHO/V&B/00.09). Slide 13 refers to the13 valent pneumococcal vaccine that is currently claimed.

In light of the above discussions, all claims 1 to 29 of the instant application should be deemed unpatentable.

9. CLAIMS OF THE IMPUNGED APPLICATION ARE NOT PATENTABLE UNDER SECTION 25(2)(F) OF INDIAN PATENT ACT

The subject matter of all the claims of the alleged application is not an invention as per Section 3(e) of Indian Patent Act 1970 as amended by Patents (Amendment) Act 2005, so is opposed under Section 25(2)(f) of Indian Patent Act

Under Section 3(e) 'a substance obtained by a mere admixture resulting only in the aggregation of the properties of the compound thereof or a process for producing such substance', is not an invention under this Act.

It is humbly submitted that claimed composition is that of a known compound and a simple obvious and known process has produced the formulation with a known preservative. The final substance obtained is a mere admixture of the compound and the known preservative and is therefore not patentable. Without prejudice to and in the alternative to the above, the Opponent submits that all claims of the instant application are invalid as they relate to a substance that is not an invention under Indian law. All of the claims in the current Application relate to a

substance obtained by a mere admixture of two known components - (1) already known and marketed 13 valent conjugated pneumococcal vaccine and (2) well known preservative 2-phenoxyethanol - that results only in the aggregation of the properties of these two components. Therefore, they cannot be considered inventions under Section 3(e) of the Act and should be invalidated. As already demonstrated above the efficacy and properties of 13 valent conjugated pneumococcal vaccine were well known in the art. Similarly, the properties, safety and efficacy of 2- phenoxyethanol as a vaccine preservative were well documents in prior art. The substance obtained by the admixture of these two components as disclosed in the Application is nothing more than an aggregation of the properties of its two constituent components. There is nothing in the Application that states that the claimed substance exhibits any properties over and above the properties of the two constituent parts. A superior anti-microbial activity over other known preservatives is merely a routine experimentation.

Therefore, all claims relate to a substance obtained by a mere admixture that results only in the aggregation of the properties of the components thereof, and are invalid under Section 3(e) of the Act.

Further all the claims 1- 29, **do not satisfy the test of Section 3(d) under Indian Patent Act.** The subject matter of the instant application do not exhibit enhanced therapeutic efficacy over the efficacy of known substance which is the already known pneumococcal 13-valent vaccine conjugated to CRM-197. In fact D1, D2 and D23 also disclose such a vaccine with the claimed 2-PE preservative. Applicant has not established any known therapeutic efficacy in comparison with the prior art formulations articulated in this opposition. Accordingly claims 1- 29 do not involve any novelty or inventive step and also have no comparative efficacy vis-à-vis prior art compositions discussed earlier in this opposition document.

Under Section 3(d) of the Patent Act a new form of a known substance is not an invention, unless it results in enhancement of efficacy over the known efficacy of the known substance. Section 3(d) of the Patent Act was amended in 2005 to prevent patents based on modifications of known substances such as combinations and salts, esters,

ethers and derivatives of known substances. Under the law each claim that relates to a new form of a known substance has to satisfy section 3(d) of the Patents Act.

It is an established position of the law that the section 3(d) has to be satisfied independently of sections 2(1)(j) and 2(1)(ja) (see Novartis AG vs Union Of India and others (2013 6SCC 1)). As held by the Hon'ble Madras High Court, the burden of proof is on the patent applicant to satisfy the requirements of Section 3(d), ie., that of showing efficacy (see Novartis AG vs Union Of India and others, 2007 4 MLJ 1153, Para 13). As held by the Hon'ble IPAB, this data is required to be in the complete specification (see Novartis AG vs Union Of India and others, MIPR, 2009, (2) 0345, para 9(xvii).

It is also an established position of law that the term efficacy in section 3(d) means therapeutic efficacy for pharmaceutical products (see Novartis AG vs Union Of India and others (2013 6SCC 1)).

Without prejudice to other grounds raised herein claims of the instant application fail under section 3(d) of the Patent Act. These claims essentially cover formulations of substances already knows in prior art. The instant patent application does not contain any comparative efficacy data with respect to close prior art compositions disclosed and discussed herein from D1 D2 and D23. These prior arts belong to the same therapeutic category as instant application.

The compositions disclosed in D1 D2 and D23 are "same substances" as the claimed compositions of the instant application. Therefore in light of the above it is respectfully submitted that the applicant has failed to discharge the onus of fulfilling the requirement under section 3(d) of the Act. In view of the above, the compositions claimed in the present application is the same substance and/or derivatives of previously known substances and therefore not an invention in accordance with section 3(d) of the Patent Act

10. CONCLUSION

Given the foregoing, the Opponent humbly requests the Patent Office to reject the application on all or any of the following grounds:

- The alleged invention lacks novelty and inventive step over the prior art disclosures and hence it is not new;

- The subject matter of the alleged application is not an invention under the provisions of the Act.

All these grounds relate to material flaws that go to the heart of the Application and each is sufficient to for it to be rejected in its entirety, rather than requiring a claim-by-claim assessment.

The Opponent further requests that the Patent Office grant a hearing as per Rule 55(1) of the Patent Rules

Relief Sought

In the circumstances aforesaid the opponent prays for the following relief:

i) Revocation of the patent in entirety.

ii) Award of costs in favor of the opponents

iii) Such other relief or relief as the controller may deem appropriate.

Dated this 8th **day of** November **2016.**

Respectfully submitted

For Panacea Biotec Limited

The Controller of Patents,
The Patent Office,

Dr. Goutam Ghosh
Senior Vice President
Panacea Biotec Limited