

The Patents (Amendment) Act, 2005  
And  
The Patents (Amendment) Rules, 2006

In the matter of application no. 8081/DELNP/2007  
National phase entry on  
In the matter of hearing u/s 14  
In the matter of opposition u/s 25(1)

Wyeth LLC, USA ..... The Applicant

Panacea Biotech Ltd., India .....The Opponent

Hearing u/s 14 held on 18/03/2015

Present –

Ms Archana Shankar, Ms Arpita Kulshrestha, Gitika Suri.... Agents of the Applicant  
Of M/s Anand and Anand, NOIDA

Dr Peter Paradiso ... The Inventor

Ms Rajeshwari, Ms Chitra Arvind .... Agent of the Opponent

Leena Menghaney of Medecins Sans Frontieres (MSF), India..... Opponent

Representative from Panacea Biotec Ltd., New Delhi..... First Opponent

**Decision u/s 15**

1. The application for grant of patent titled “*MULTIVALENT PNEUMOCOCCAL POLYSACCHARIDE-PROTEIN CONJUGATE COMPOSITION*”, entered national phase in India on 19<sup>th</sup> October 2007. The international filing date of the instant application is 31<sup>st</sup> March 2006 (PCT no.: PCT/US2006/012354). The application claims priority from patent application Nos. PCT/US2006/012354 and 60/669,605 dated 31<sup>st</sup> March 2006 and 8<sup>th</sup> April 2005 respectively.
2. The application was examined under Sections 12 and 13 of the Indian Patents Act, 1970 and the first examination report was issued on 17<sup>th</sup> June 2013. The applicant submitted their reply to the first examination report on 17<sup>th</sup> June 2014 with the revised set of claims.

Panacea Biotech Limited filed an opposition, the Notice in respect of the Opposition was forwarded on 17<sup>th</sup> June 2013. A response was filed on 17<sup>th</sup> September 2013. Panacea filed a rejoinder around 6<sup>th</sup> January 2015.

3. Vide a letter dated 19<sup>th</sup> December 2014, a hearing was appointed on Feb 2, 2015. The oral hearing was adjourned and subsequently appointed for March 18<sup>th</sup>, 2015 in respect of the aforesaid application. Oral evidence was also led by Dr. Peter Paradiso (one of the inventor of the application) during the hearing. The applicant also filed written declaration of Dr. Peter Paradiso, particularly in response to the contentions taken by the Opponent in the rejoinder.
4. Claim revisions were also filed during the hearing. Original claims 1 to 6 were retained and the rest withdrawn. Pending claims are reproduced below:-

*Claim 1 - A multivalent immunogenic composition, comprising: 13 distinct polysaccharide-protein conjugates, together with a physiologically acceptable vehicle, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of streptococcus pneumoniae conjugated to a carrier protein CRM<sub>197</sub>, 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 aluminum-based adjuvant.*

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

*Claim 5 - The immunogenic composition as claimed in claim 4, wherein the adjuvant is aluminum 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: 2 µg of each saccharide, except for 6B at 4 µg; approximately 29 µg CRM<sub>197</sub> carrier protein; 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant; and sodium chloride and sodium succinate buffer as excipients.*

5. Oral hearing in respect of Opposition -1 was concluded on 18<sup>th</sup> March 2015.
6. Thereafter an opposition was filed by Medecins Sans Frontieres (MSF) on 11<sup>th</sup> March 2016 and the Notice in respect of the Opposition was forwarded on 21<sup>st</sup> March 2016. A response was filed on 21<sup>st</sup> day of June 2016. The Opponent a few days prior to the hearing, on 15<sup>th</sup> July 2016 filed the affidavits of Dr. Amulya K. Panda and Mr. Warren A. Kaplan.

List of documents Relied by MSF in representation

Document
WO 03/51392
WO 00/056359
US 4902506
US 5623057
Mbelle et al
William Hausdorff et al
S.K. Obaro et al
Cynthia Whitney et al
La Pena et al

Various additional documents were filed with the affidavits of Dr. Amulya K. Panda and Mr. Warren A. Kaplan:-

Document	Affidavit
WO 00/056359	Mr. Warren A. Kaplan
Jim P. BATTERY et al	
Moya Burrage et al	
Torben Barrington et al	
US 4902506	Dr. Amulya K. Panda
Mbelle et al	
William Hausdorff et al	
S.K. Obaro et al	
Cynthia Whitney et al	
La Pena et al	
US 4673574	
David Klein	
Mark A. Shelly	
US 5623057	
Robert S. Daum	
Tera L. Mc Cool	
Yu et al	
US 2004/0202668	
Cutts et al	
Overturf et al	
Malik et al	

- In response to the said affidavits of Dr. Panda and Mr. Kaplan, the applicant filed the affidavit of the inventor Dr. Peter Paradiso on 29<sup>th</sup> July 2016. The applicant also filed a copy of the affidavit of Dr. Ron Dagan that was submitted in the corresponding EP

appeal proceedings and forms a part of the record of the Indian patent office as it was submitted by the applicant under Section 8(2).

8. Another hearing on 5<sup>th</sup> August 2016 was appointed in order to enable the opponent deal with any new submissions that might be made by the inventor Dr. Peter Paradiso in his affidavit.

9. I also directed the Applicant on 5<sup>th</sup> August 2016, to file copy of the following 3 documents referred to by Dr. Ron Dagan in his affidavit in paras 2.4, 2.5, and 3.2.2, as requested by the Opponent, which are as follows:

- i. Henry R. Shinefield et al; Safety and Immunogenicity of Heptavalent Pneumococcal CRM<sub>197</sub> conjugate vaccine in infants and toddlers; *Pediatric Infect Dis J.* 1999; 18; 757-63, Volume 18, No. 9
- ii. Kenneth M. Zangwill et al; “Safety and Immunogenicity of a Heptavalent Pneumococcal Conjugate Vaccine in Infants”, *Vaccine* 21 (2003) 1894-1900
- iii. Menno R. van den Bergh et al; “Immunogenicity, Safety, and Reactogenicity of the 10-valent Pneumococcal Nontypeable Haemophilus influenza Protein D Conjugate Vaccine and DTPa-IPV-Hib when coadministered as a 3-dose Primary Vaccination Schedule in the Netherlands; *The Pediatric Infectious Disease Journal*, Volume 30, Number 9, September 2011.

10. I also directed the Opponent to submit the verified English translation of the document De La Pena (Annexure-10 of the pre-grant opposition Annexure-15 of Dr. Panda's Affidavit). The Opponent till date has not filed the verified translation of the document

11. I will first deal with the preliminary issues raised by the parties:-

11.1 The Applicants objected taking on record the belated filed documents/affidavits and any ground raised in respect of the said documents. As per the Applicant the delayed filing of affidavit is against the principles of natural justice, the same should not be taken on record as the

Act provides no such provision in a pre-grant proceeding. The applicant relied on the decision of the Delhi High Court in *Snehlata Vs. Union of India*. The Applicant also relied upon Salem Advocate Bar Assn. v. Union of India (which has also been relied upon by the Delhi High Court in Roche Vs. Cipla,) wherein according to the Applicant it has been clarified that before leave of the Court can be granted for receiving documents in evidence at a belated stage, the party seeking to produce the documents must satisfy the Court that the said documents were earlier not within the party's knowledge or could not be produced at the appropriate time in spite of due diligence.

The party seeking to produce the documents must satisfy the Court that the said documents were earlier not within the party's knowledge or could not be produced at the appropriate time in spite of due diligence. The documents therefore filed along with the rejoinder, as per the Applicant should not be considered and should be disregarded.

11.2 Decision: In the interest of natural justice and equity, I have taken the said affidavit and additional documents on record and also the documents filed by the Applicant on record. The Applicant received the affidavit from the opponent, just a few days before the appointed hearing date. I agree with the Applicant that this belated filing of documents of a technical nature does not permit the Applicant sufficient time to prepare a response. Further, if in the interest of natural justice I am taking the documents filed by the Opponent on record then, the Applicant's evidence led by the inventor himself should be taken on record as well.

## 12. ABOUT IN'8081

12.1 The applicant at the hearing provided several deliverables namely:

- a. An outline of the invention along with the summary of the documents relied upon by the applicant.
- b. The summary of the opponent's allegation in the opposition/ affidavits and the applicants reply.

- c. The “conclusion” to demonstrate that the invention of IN’8081 is novel, inventive and meets all the patentability criteria prescribed by the Indian Patents Act.

The applicant stated that the application relates to a 13-valent immunogenic composition for use as a vaccine, comprising polysaccharide-protein conjugates. The conjugates comprise capsular polysaccharides derived from *Streptococcus pneumoniae* serotypes (st) 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, each serotype being conjugated to CRM<sub>197</sub> carrier protein. The applicant has now commercialized the product of IN’8081 and the commercial product is Prevenar13<sup>®</sup> and has been approved in the US by the USFDA as well as in India by the CDSCO (Central Drugs Standard Control Organization).

The applicant also stated that IN’8081 is an invention that has been granted approximately 83 patents in various corresponding jurisdictions. The corresponding European patent was under opposition against which the applicant has filed an appeal as a result of which said European patent is also in force.

12.2 The challenges in vaccine development were also discussed by the applicant as I am summarizing the same below:

- In 1983 Merck developed a 23-valent polysaccharide vaccine (unconjugated) which was available under the brand name of Pneumovax23<sup>®</sup>.
- Since polysaccharides are weak antigens and are ineffective to immunize infants who are vulnerable to infection and further, since the polysaccharide vaccines do not induce B-cell derived immunogenic memory, they are disadvantageous since a follow-up administration does not boost up the antibody titre and the level of immune response is generally lower, conjugate vaccine (not pneumococcal polysaccharide conjugate) was developed for Haemophilus influenzae type b (Hib), using carrier detoxified diphtheria toxoid (DT) and tetanus toxoid (TT) proteins. In addition to DT and TT, a variety of other proteins were used for the development of conjugate vaccine such as CRM<sub>197</sub>, OMPC [Outer Membrane Protein Complex].

- Due to the problems associated with known carriers such as epitope suppression, Glaxo developed a new carrier protein D.
- The first pneumococcal polysaccharide conjugate vaccine was developed by the applicant in 1986 which was a 7-valent vaccine, Prevenar®. Thereafter, the applicant developed a 9-valent pneumococcal vaccine by adding serotypes (St) 1 and 5.

From 7 valent to 13 valent increase in serotypes and coverage

- Conjugate vaccines are associated with many challenges associated particularly while trying to increase the valency (antigen addition) into a single vaccine without diminishing/reducing an immune response provided by all the other antigens. There is sufficient documents that deal with the issues faced in conjugate vaccine development namely:
  - a) Carrier-induced epitope suppression (CIES) or Carrier mediated immune suppression (CMIS): It is suppression of an immune response to polysaccharide antigen due to the immune response to a conjugated carrier protein. It exists only when a carrier is conjugated to a Polysaccharide, i.e. for conjugate Vaccines. It is for this reason that it has been possible to develop a 23 valent Polysaccharide vaccine. However companies have struggled to develop a 13 valent conjugate Vaccine, or increase valency. Choo et al 2000 (Annexure-B4 of the reply statement) raised concerns with regard to the increase in CRM<sub>197</sub> and its use as a carrier.
  - b) In order to study the concerns of increasing CRM<sub>197</sub> content and its use as a carrier protein in a combination vaccine (pneumococcal conjugate vaccine and a Haemophilus influenza and Type b (Hib)), the author administered 7VPnC (7-valent+ CRM<sub>197</sub>) with Hib- CRM<sub>197</sub> conjugate (HbOC). Both the said vaccines had CRM<sub>197</sub> as a carrier protein. The said article on pages 85 / 92 concludes that a response for 5 of the 7BPnC in 7VPnC/HbOC recipients was low.
  - c) Buttery et al (Annexure-B 13) further confirms that the problem of immune interference, in particular immune interference with CRM<sub>197</sub> was a concern even after the priority date of the present application. Dr. Dagan states that this



document confirms the result of earlier studies like Choo et. al. that there were significant concerns of CIES associated with CRM<sub>197</sub>.

- d) Indian Patent Application no. 140/DEL/2011 of Panacea Biotec Ltd also recognize epitopic suppression/carrier suppression as being a major problem in developing multivalent conjugate vaccine due to the risk of immune suppression which leads to sub optimal response to the conjugated polysaccharide.
- e) WO'392 also recognizes the technical difficulties in combining multiple polysaccharide into a single vaccine formulation, including immune suppression as well as immune interferences by using the same carrier protein Further, the said document on page 19 in example 3 further recognizes that combination of vaccine into multivalent formulation results in decreased immunogenicity of one or more component of vaccine (CIES/CMIS) which mechanism is still not well understood.
- f) ANTIGEN COMPETITION: Further as carrier proteins are better antigens than polysaccharides, the carrier proteins in the conjugate vaccines or carrier proteins in other vaccines to be administered in combination suppress the immune response to polysaccharides or the immune response to polysaccharide antigens (which is called “antigen competition”).
- g) BY-STANDER EFFECT: CRM<sub>197</sub> is a derivative of DT. In addition of CMIS/CIES other mechanisms had also been observed that attributed to reduce responses seen with conjugate vaccine or with co-administration of conjugate vaccine or other vaccine. Dr. Dagan in his affidavit in para 4 has explained the so called “*By-stander effect*” which is the effect of DT or CRM<sub>197</sub> (related to DT) on the response to other co-administered vaccines. Dr. Dagan in para 4.2 further illustrates that if the DT or CRM<sub>197</sub> content is increased, the response to Hib conjugated to TT can be decreased which is not the result of CMIS/CIES.

- a) When the valency increases from 7 to 13, the amount of CRM<sub>197</sub> will increase in any given administration and it is this that can reduce the effect of PRP-T. For example, the effect on the response to DtaP when co-administered with PCV7-CRM<sub>197</sub> reported in Shinefield et al (1999) [Para 4.2 of Dr. Dagan affidavit].

The aforesaid challenges associated with the development of higher valent pneumococcal conjugate vaccines increase the unpredictability in the art and a person skilled in the art would be well aware of the same. Thus, those skilled in the field of vaccines would very carefully select a vaccine design, to overcome and avoid above problems, keeping in mind the following:

- the total number of serotypes,
- the specific serotypes to be included, and
- the respective carrier proteins for the specific serotypes, by considering both the benefit and the potential risk of adding antigens, i.e., the benefit of the increased coverage and the risk of not eliciting sufficient immune response for all antigens due to immune interference or suppression.

The Applicant concluded that in view of the aforesaid challenges, the person skilled in the art including experts in the field such as Glaxo, Merck, Aventis and Panacea Biotec Ltd. adopted various different strategies when attempting to increase the valency of a multivalent conjugate vaccine. (11 / 10 valency)

- Glaxo developed a new carrier protein derived from *Haemophilus influenza* which was the subject matter of the EP 0594610B1, protein D:
- WO2000/56358 – discusses a new carrier for use in preparation of vaccines that does not suffer from the above mentioned drawbacks and the same is Protein D. In fact the examples of the document also use Protein-D for an 11 valent vaccine.
- US 2004/0202668 –suggests that Protein D is the most advantageously used carrier as it may be used for 4 or more polysaccharide without marked carrier suppression effect.
- Glaxo tried to develop only an 11 valent with Protein D, but failed in developing an 11-valent vaccine using protein D as a sole carrier with St 3. Glaxo failed in this attempt as a result of which Glaxo dropped St3 from their vaccine formulation to produce a 10-

valent vaccine, and used the multiple carrier strategy by combining protein D with TT and DT. Reference was made to Nurkka et Al, 2004 (D7 of FER, B5 of Applicant's reply statement, also referred in Specification, and prymula et al.)

- SANOFI while developing a 11 valent PCV used a mixture of two carrier proteins wherein some serotypes are conjugated to DT while the remaining serotypes are conjugated to TT. Wuorimaa T et al, 2001 (before priority- D5 of FER and Annexure B3 of Applicant's reply statement) This paper therefore confirms that the state of the art was to use multiple carrier in case an increase in valency is to be achieved, as this paper describes a vaccine that uses two carrier proteins, DT and TT, for the purpose of avoiding immune interference.
- Wyeth, the applicant were working on developing a multivalent PCV as stated in paras 13 to 15 of Dr. Peter affidavit. Wyeth tested more than 20 new carrier proteins of which pneumolysin had an advantage of eliciting serotype non-specific immunogenicity and excellent properties in several aspects. De la pena document supports the fact that non-capsular proteins such as surface adhesion A, neuraminidase and autolysin may be used as carrier for conjugating polysaccharides of the St not included in earlier vaccines:
- Yu et al at page 159 of Dr. Amulya K. Panda affidavit clearly indicates that use of OMPC as a carrier protein in MK vaccine elicited better response to 19A as opposed to vaccines prepared by Wyeth using CRM<sub>197</sub> (PP and OP-5 Valent). Therefore, CRM<sub>197</sub> was never preferred choice of carrier.
- PANACEA BIOTEC LTD- Even after the priority date, companies such as Panacea were working on multiple carrier approach for developing higher multivalent PCV.

The applicant relied on several other publication which direct POSA to use multiple carrier strategy instead of a single carrier, to bypass CIES, reduce carrier overload etc include the following: (reference is made to para 10 of Dr. Peter affidavit)

- Fattom, *et al.* (1999)
- Dagan, *et al.* (1998) show that the pneumococcal conjugate vaccine, wherein 4 serotypes of capsular polysaccharide are conjugated to DT

and/or TT and given at the same time as a conjugate to *Haemophilus influenzae type b* (Hib) conjugated to TT.

- Wuorimaa, *et al.* (2001) (Sanofi Pasteur) suggests that the use of a single carrier protein in pneumococcal conjugate vaccine may cause overload of the carrier, and that it is preferable to use a mixture of protein carriers.
- KLEIN DAVID *et al.* (Annexure-4 to Dr. Amulya K. Panda) further supports the case of the Applicant and in particular the following
  - That when developing pneumococcal conjugates, the number of vaccine St must be limited.
  - Large concentration of antigen could be dangerous and promote serious local reaction.
  - High cost and technical defects are associated in developing and manufacturing multivalent conjugate vaccine.
  - It is difficult to apply the success of one conjugate vaccine to other vaccine formulations (unpredictability).
  - That all vaccine manufactures are working to produce PCV that contain 7 to 9 St (Page 87).
  - That pneumolysin was a good candidate.
  - This document further discusses the several consideration that a person needs to keep in mind while developing PCV

In view of the challenges associated with increasing the valency, of the PCV a person skilled in the art would not increase the valency of a PCV and instead rely upon the cross protection. 6B and 19F were added in Prevenar® [7-valent]. 6A and 19A are “non- vaccine serotypes” but related to 6B and 19F. 6B and 19F provide cross-protection to 6A and 19A. Therefore it was known that there was some cross-protection against 6A and 19A. Various documents such as the following prove the same:

- Antibody response to the structurally similar serotype 6A is cross-reactive, and that immunization with serotypes 6B elicits antibodies cross-reacting with polysaccharides from serotype 6A (Dagan 2002)
- Antibody response to the structurally similar serotype 19A is cross-reactive, and that immunization with serotypes 19F elicits antibodies cross-reacting with polysaccharides from serotype 19A (Harvard Jakobsen et al.).
- In fact, Whitney et al Annexure 14 of Dr. Paradiso's affidavit at page 280 relied upon by the Opponent itself proves that 6B & 19F provide cross-protection for 6A and 19A, as evident from Table 1 below:

**Table 1. Changes in Estimated Rates of Invasive Pneumococcal Disease among Children under Two Years of Age, According to Year and Serotype, from 1998 through 2001.\***

Serotype	Average for 1998 and 1999		2001		% Change in Estimated Rate (95% CI)‡	P Value§
	No. of Cases	Estimated Rate† cases/100,000	No. of Cases	Estimated Rate† cases/100,000		
All vaccine serotypes	563.5	156.1	124	33.6	-78 (-82 to -74)	<0.001
4	52	14.4	9	2.4	-83 (-91 to -67)	<0.001
6B	75	20.8	27	7.3	-65 (-76 to -48)	<0.001
9V	31.5	8.7	12	3.3	-63 (-79 to -35)	<0.001
14	228.5	63.3	39	10.6	-83 (-88 to -77)	<0.001
18C	51.5	14.3	12	3.3	-77 (-87 to -61)	<0.001
19F	78.5	21.8	14	3.8	-83 (-90 to -72)	<0.001
23F	46.5	12.9	11	3.0	-77 (-87 to -59)	<0.001
All vaccine related serotypes¶	70.5	19.6	36	9.8	-50 (-65 to -31)	<0.001
6A	32	8.9	18	4.9	-45 (-66 to -12)	0.02
9A	10.5	2.9	3	0.8	-72 (-89 to -11)	0.04
19A	20	5.5	12	3.3	-40 (-68 to +5)	0.09
All nonvaccine serotypes	44.5	12.4	58	15.7	+27 (-6 to +73)	0.14
1	2.5	0.7	1	0.3	-57 (-96 to +169)	0.43
3	2.5	0.7	4	1.1	-37 (-31 to +43)	0.33
5	0	0	1	0.3	Not defined	0.34
7F	5.5	1.5	6	1.6	+7 (-58 to +163)	0.89
12F	6.5	1.8	7	1.9	+6 (-56 to +145)	0.89

\* The data are from the Active Bacterial Core Surveillance.  
† The estimated rates were calculated on the assumption that the serotype distribution for cases with missing serotype data (12 percent of all cases) was the same as the distribution for cases with serotype data available.  
‡ CI denotes confidence interval.  
§ The P value was calculated by a chi-square test or Fisher's exact test that compared the estimated number of cases and noncases (the total surveillance population minus the number of estimated cases) in 2001 with the same figures for 1998 and 1999 combined. The estimated number of cases and totals were calculated on the assumption that the serotype distribution for cases with missing serotype data was the same as the distribution for cases with serotype data available. Repeated analysis with only cases with known serotypes included rather than the estimated number of cases did not change the results.  
¶ Types 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B are included.

The Table provides change in estimated rates of invasive Pneumococcal disease (IPD) among children under 2 years of age from 1998 through 2001 (before and after introduction of Prevenar® [7-valent]).

A decrease was observed for all 7 serotypes of Prevenar® [7-valent]. However, a decrease was also observed for all vaccine related serotypes [defined on para 3 on right hand column on page

1738], like 6A and 19A (-45% and -40%). These were not included in the vaccine, however were within the same serogroup (6, 9, 18, 19, and 23) as the vaccine types and could have been protected by cross protection.

Following are the advantages of the vaccine of IN'8081 that were highlighted by the Applicant:

- a. Vaccine with an increased valency compared with the prior vaccine
- b. A single carrier protein used in a 13-valent vaccine.
- c. Remarkable immunogenicity
  - i. Despite the addition of six serotypes, the 13-valent immunogenic composition of IN'8081 exhibits immunogenicity for the seven serotypes included in the prior 7-valent vaccine (Prevenar®) as well as remarkably excellent immunogenicity for the newly added six serotypes. Thus the addition of serotypes did not reduce the immune response of the other serotypes.
  - ii. STUDY #HT-01-1121 and #HT01-0036 in specification examine the immune response of 13 valent vaccine of the invention
    - the response observed to the seven core serotypes following immunization with 13 valent vaccine of invention with Aluminum adjuvant are consistent with historical response of rabbits to the 7 valent (Tables 3 and 4)
    - conjugation produces higher serum IgG titers and overall functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM<sub>197</sub> (Tables 5 and 6)
  - iii. Non inferiority studies (provided in Nunes et al. – B11 of the Applicant's Response and Product insert) indicate a similar immunogenicity profile between PCV-13 and PCV-7 recipients against most of the common

serotypes. Trials show that PCV-13 is safe, immunogenic and in general non-inferior to PCV-7. For overlapping Serotypes between PCV-7 and PCV-13, the OPA responses were comparable in both PCV7 and PCV13. For additional 6 serotypes PCV 13 elicits higher OPA.

- d. Immune protection for serotype 3
- e. Inclusion of Serotypes 6A and 19A

None of the experts working in the field experimented on adding 6A and 19A and instead relied on cross- protection from 6B and 19F. The inventors of present application, in contrast to other vaccine designers at the time, believed that the inclusion of serotypes 6A and 19A would provide substantial benefits, and that it might be possible to avoid major immune interference by the use for CRM<sub>197</sub> for each of the 13 serotypes (st), including st 6A and st 19A. The inventor's unique reasoning in this regard is set out in the patent application IN '8081 starting on page 5 under the heading "*Inclusion of Serotypes 6A and 19A*".

- f. Unexpected benefit of the addition of the serotype 6A to the multivalent: Since serotype 6A has greater structural similarity and immunological cross-reactivity with serotype 6C than does serotype 6B, the vaccine of the present invention, which contains a serotype 6A conjugate, elicits cross-protective responses to serotype 6C (as shown by Cooper D et al 2011).

13. I will now deal with the grounds of opposition;

#### 14. GROUND I- NOVELTY

##### 14.1 Opponent's arguments



The Opponent has relied on two documents WO 2003/051392 and WO 00/056359 for the purposes of establishing ground of anticipation. WO 00/056359 was essentially relied during the hearing and in the submissions.

The Opponent relied on WO 00/56359. According to the Opponent, the said document discloses

- a 13 valent immunogenic composition;
- a multivalent composition;
- conjugation of protein to CRM197 carrier disclosed, polysaccharide is prepared from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

As per the Opponent even dependent claims are not novel. The content of protein antigens in the vaccine will typically be in the range 1 -100µg, preferably 5-50, most typically in the range 5 - 25. Quantities of aluminium-based adjuvant added per dose should preferably be less than 50 µg, more preferably less than 30 µg, still more preferably less than 10.

#### 14.2 Applicant's submissions

The Applicant relied on the IPAB decision in *Ideal Cures Vs. M/S.Colorcon Ltd.* to describe the legal principle of anticipation. According to this document, for any prior art document, in order to be an anticipating document, it has to enable a person skilled in the art to perform the invention without exercise of any inventive ingenuity. The said disclosure has to be an “*unambiguous clear and a direct disclosure (enabling disclosure).*”

In this regard, the Applicant relied on several other cases: -

- Lallubhai Chakubhai Jariwala Vs. Chimanlal Chunilal and Co. [AIR1936Bom99], at para 10
- E.I. Du Pont De Nemours & Co. application FSR [1982] 303, at page 311
- Apotex vs. Sanofi [2008] 3 S.C.R. 265, 2008 SCC 61,
- Hon'ble IPAB in *Ideal Cures*.
- *Endo Pharmaceuticals Inc. Vs. Mylan Pharmaceuticals Inc*, Pages 12-14

The Applicant also highlighted that the following factors should normally be considered for anticipation:

1. Enablement is to be assessed having regard to the prior patent as a whole including the specification and the claims
2. The skilled person may use his common general knowledge to supplement information contained in the prior patent. Common general knowledge means knowledge generally known by persons skilled in the relevant art at the relevant time.
3. The prior patent must provide enough information to allow subsequently claimed invention to be performed without undue burden. When considering whether there is undue burden, the nature of the invention must be taken into account. For example, if the invention takes place in a field of technology in which trials and experiments are generally carried out, the threshold for undue burden will tend to be higher than in circumstances in which less effort is normal. If inventive steps are required, the prior art will not be considered as enabling. However, routine trials are acceptable and should not be considered undue burden.

#### 14.3 WO 2003/051392

The Opponent during the hearing did not rely on this document

14.4 According to the applicant, WO 00/056359 relates to pneumococcal polysaccharide conjugates with a protein antigen from Streptococcus Pneumoniae and optionally a Th1 inducing adjuvant. The inventors of the prior art found that for certain pneumococcal polysaccharide conjugates the immunogenicity of the vaccine is greater when the antigen is formulated with 3D-MPL alone rather than in conjunction with aluminum-based adjuvant. The Opponent has done cherry picking and has not looked at the entire disclosure. Even while cherry picking, the Opponent has failed to recognize that as per the prior art polysaccharides are preferably conjugated to protein D.

Further the applicant pointed that the teaching of the document is directed towards the adjuvant that is to be used in a pneumococcal vaccine and teaches the use of 3D-MPL alone without any aluminium-based adjuvant. The document does not teach the use of a single carrier for a 13 valent vaccine. The examples are also directed to 11 valent vaccines in which the polysaccharide is conjugated to protein D. The document therefore discloses and enables a person ordinarily skilled in the art towards a protein D conjugated 11 valent vaccine and provides no teaching or

suggestion or motivation towards a 13 valent vaccine which uses a DT modified CRM197 as a single carrier.

**14.5 Decision: I have extensively heard the opponents and the applicant as well as gone through the written submissions. Serotypes are added to a vaccine but we cannot ignore that there is no disclosure in any prior art document that discloses 13 valent vaccine with specific serotypes conjugated to CRM197. Thus none of the prior arts including WO '359 renders the claims of 8081 as lacking in novelty as the prior art does not disclose or enable a 13 valent vaccine with a single carrier, like CRM197. I therefore dismiss the ground of anticipation.**

## **15. LACK OF INVENTIVE STEP**

15.1 The Opponent made the following submissions with regard to the application being obvious. The Opponent particularly submitted that even prior to 1990s use of multi valent vaccines were common.

- 1990-US 4902506: Serotype 3 conjugated to CRM197 was known and well established.
- 1997-US5623057: Proposal of various serotypes conjugated to an immunogenic protein was known.
- 1999- Mbelle et al: Proposal of various serotypes conjugated to the immunogenic protein CRM197 was known.
- 2000- Hausdorff et al: disclosed the serotypes of hepta, nona- and undeca-valent conjugated pneumococcal vaccines. Hausdorff et al. teaches that adding 6A and 19A serotypes to future vaccines would be beneficial. The author also discloses a PCV7 vaccine including serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, as well as 9-valent formulations further including serotypes 1 and 5 and 11 -valent formulations further including serotypes 3 and 7F.
- 2003- Whitney et al: Serotypes 6A and 19A can be added to 11-valent (containing serotypes 3 and 7F) to broaden the protection

- 2004-De La Pena et al: discloses 13-valent vaccine with 6A and 19A serotype conjugated-to CRM-197

15.2 The Opponent has also relied on expert evidence of Dr. Amulya K. Panda and affidavit of Dr. Warren A. Kaplan to conclude that the multivalent vaccine as claimed is obvious and deducible from prior art for various reasons including:

- Carrier Proteins-that can be conjugated in the prior art are well known and limited. The commonly used carrier proteins were DT, TT and CRM197 (Prior art WO 00/56358).
- It was routine to prepare vaccine based on multiple serotypes: A summary of serotypes used in the vaccines in prior art is given below:

Valency	Serotype	Carrier	Reference
4 valent (1945)	Not Available	Not disclosed	Obaro et al. 2002 (Page 251 of Annexure) (O)
5 valent	6B, 14, 18C, 19F and 23F	CRM <sub>197</sub>	Klein et al., 1995 (Page 86 of Annexure) (A) Shelly et al.,1997 (Page 95 of Annexure) (A) Daum et al.,1997 (Page 134 of Annexure) (A)
6 valent	Not Available	Not disclosed	Obaro et al. 2002 (Page 251 of Annexure) (O)
7 valent (Prevnar)	4, 6B, 9V, 14, 18C, 19F and 23F	CRM <sub>197</sub>	Mbelle et al., 1999 (Page 221 of Annexure) (O) Obaro et al. 2002 (Page 252 of Annexure) (O) Pena et al., 2004 (Page 281 of Annexure) (O) Yu et al., 1999 (Page 157 of Annexure) (A) Hausdorff et al., 2000 (Page 166 of Annexure) (A) Obrien et al., 2000 (Page 321 of Annexure) (A) Overturf et al. 2002 (Page 326 of Annexure)

			(A)
9 valent	1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F	CRM <sub>197</sub>	Mbelle et al., 1999 (Page 221 of Annexure) (O) Overturf et al. 2002 (Page 326 of Annexure) (A) Hausdorff et al., 2000 (Page 166 of Annexure) (A)
10 valent (Synflorix- Glaxo)	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F	Protein D, Tetanus toxoid and Diphtheria toxoid	Synflorix Product Brochure
11 valent	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F	Protein D  CRM <sub>197</sub>	WO2003/51392 (Page 55 of Annexure) (O) WO2000/056359 (Page 109 of Annexure) (O) Pena et al., 2004 (Page 289 of Annexure) (O) Overturf et al. 2002 (Page 326 of Annexure) (A)
			Hausdorff et al., 2000 (Page 166 of Annexure) (A)
13 valent (Prevnar)	1, 3, 4, 5, 6B, 7A, 7F, 9V, 14, 18C, 19A, 19F and 23F	CRM <sub>197</sub>  Protein D	Prevnar Product Brochure Pena et al., 2004 (Page 281 of Annexure) (O) WO2000/056358 (Page 199 of Annexure) (A)
14 valent (1977)	Not Available	Not disclosed	Obaro et al. 2002 (Page 251 of Annexure) (O)
23 valent (1981)	Not Available	Not disclosed	Obaro et al. 2002 (Page 251 of Annexure) (O)

\* Annexure (O) – Annexures of Opposition

\* Annexure (A) – Annexures of Affidavit

- iii) Art also suggested a 13-valent vaccine and the use of CRM 197 as a carrier of choice
- iv) WO'392 discloses that it is possible to advantageously develop a 13-valent vaccine along with CRM 197 as carrier protein.
- v) WO'359 discloses that one of the carrier proteins that may be considered for this vaccine includes CRM197.
- vi) De La Pena et al.: a paper by the impugned applicant discloses a 13-valent vaccine. conjugated individually with a protein, a nontoxic mutant of the diphtheria toxin, CRM 197, and forming glycoconjugates.

Thus, the Opponent stated that increasing the valency of the vaccine and inclusion of serotypes 6A/19A was suggested in prior art. The prior art also suggests that the serotype 6A and 19A may be advantageously included to offer protection against various sub-serotypes of serotype 6 and serotype 19.

15.3 The Opponent also made the following conclusions:

- (a) That on priority date, the interaction of various serotypes with various carrier proteins were available.
- (b) Multiple carrier protein approach was the strategy of choice;
- (c) Different serotypes could be easily combined without much interaction problems;
- (d) 13-valent system was conceived by the art and there were many workers trying to improve it;
- (e) PD, DT and TT is not a suitable carrier for serotype 3; rather CRM 197 was the carrier of choice and frequently used without adverse reactions;
- (f) PD is not a suitable carrier for 18C and 19F.

The Opponent also produced a table in their written submissions with respect to the documents relied on by Dr. Paradiso and I am reproducing the same as such.

<b>Reference relied upon Dr. Peter Paradiso Affidavit and relevant teaching</b>	<b>Conclusion: Reasons why it cannot serve as discouraging factor</b>
<p data-bbox="230 310 782 348"><b>Fattom et al. Vaccine 17 (1999) 126-133</b></p> <p data-bbox="230 365 782 512">“Clearly showed that combining conjugate vaccines on the same carrier results in interference and suggests the need for</p>	<ul data-bbox="873 310 1430 512" style="list-style-type: none"> <li data-bbox="873 310 1430 457">• Pertains to the immunogenicity of different proteins with different carriers.</li> <li data-bbox="873 474 1430 512">• Does not refer to pneumococcus or to</li> </ul>

multiple carriers”.	CRM <sub>197</sub> entirely irrelevant to present case.
	(Internal Page 127 materials and methods, Internal Page 128 Table 1, Internal Page 131)
<p><b>EP 0497 525 B2</b></p> <p>Suggested that the way to circumvent immune interference is to use OMPs as the carrier.</p>	<ul style="list-style-type: none"> <li>• Irrelevant factor because immune suppression occurs when two different vaccines administered whereas in this case, only one being used.</li> <li>• Pertains to pneumococcal capsular polysaccharide conjugated with different carrier proteins.</li> <li>• Does discourage use of CRM<sub>197</sub> as a carrier protein; does not advocate use of any specific carrier protein over CRM<sub>197</sub>.</li> </ul> <p>(Internal page para 13 (Objects of the Invention))</p>
<p><b>Ron Dagan et al., Infection &amp; Immunity, May 1998, p. 2093-2098</b></p> <p>Using 4-valent DT and TT conjugates showed interference with concomitantly used Hib-TT vaccine and strongly suggested a mixed carrier approach to conjugate vaccines.</p>	<ul style="list-style-type: none"> <li>• For these reasons, skilled person would prefer CRM<sub>197</sub> than DT or TT as carrier.</li> <li>• Studies immunogenicity of DT and TT carriers only discusses immunologic interference when combined with Hib TT vaccine.</li> <li>• Discusses mixed carrier approach only when different vaccines are co-administered – not applicable to present case where only one vaccine is being administered.</li> </ul> <p>Internal Page 2093 (Abstract), Internal page 2093, Internal page 2096 (2</p>





	<p>column, para 1), Internal page 2097 (1<sup>st</sup> column, para 1), Internal page 2097 (1<sup>st</sup> column, last para), Internal page 2097 (last few lines of the Article)</p>
<p><b>US 2001/0048929</b> Suggests using carbohydrate carbons rather than polysaccharides and an mixed carrier approach using DT and TT as carriers.</p>	<ul style="list-style-type: none"> <li>• Even though mixed carrier approach discussed single carrier protein as a good strategy.</li> <li>• Internal page 1, column 1, para 2, Internal page 3, column 1, para 1, Internal page 15, column 2, para 1</li> </ul>
<p><b>Wuorimaa et al.</b> <b>The Paediatric Infectious Disease Journal</b>, Vol. 20(3), page 272-277 11-valent mixed carrier vaccine developed by Sanofi, which was “designed to circumvent carrier related problems”.</p>	<ul style="list-style-type: none"> <li>• Discusses immunogenicity and tolerability of 11-valent PCV with and without adjuvants.</li> <li>• Admits that CRM<sub>197</sub> protein is safe and immunogenic in toddlers and infants.</li> <li>• Concludes adjuvant does not have significant benefit and that there is a need to increase valency (from 13 to higher).</li> </ul>
	<p>Internal page 1, Objective (para), Internal page 1, Conclusions (para), Internal page 2, Introduction (para),</p>
<p><b>Nurkkä et al. The Pediatric Infectious Disease Journal</b>, Volume 23, Number 11, November 2004 11-valent formulation failed to be immunogenic against serotype 3 and was ultimately abandoned for this reason.</p>	<ul style="list-style-type: none"> <li>• Discusses immunogenicity and safety of 11-valent vaccine.</li> <li>• Admits licensed pneumococcal vaccine with CRM having 7 serotypes is safe.</li> <li>• Discusses increase in coverage would be beneficial in many countries.</li> </ul> <p>Internal page 1008, column 1, background, Internal page 1008, column 2, Para 2, Internal page 1008, column 2, Para 3, Internal page 1013, column 1, Para 2</p>



<p><b>Prymula et al., Vol. 367, March 4, 2006</b> Lack of efficacy of 11-valent vaccine.</p>	<ul style="list-style-type: none"> <li>• Discusses effect of pneumococcal serotypes conjugated with protein D in acute otitis media.</li> <li>• Submits effect in respiratory tract infection needs investigation.</li> <li>• <u>Suggests that combination of serotype 3 with PD is not immunogenic.</u></li> </ul> <p>Internal page 740, para (Summary), Internal page 740, para (Interpretation), Internal page 740, column 2, para 1, Internal page 747, column 2, last para,</p>
<p><b>WO 03/051392</b> Contained protein D, DT, TT, carriers in the same vaccines.</p>	<ul style="list-style-type: none"> <li>• Discloses all serotypes, carriers, lyophilisation, formulation of impugned patent application.</li> <li>• Suggests mixed carrier approach <u>but does not discourage use of single carrier approach.</u></li> </ul>
<p><b>Choo et al., Pediatr Infect Dis J., 2000; 19:854-82</b> On combination of two vaccines (Hib-CRM7 with prevenar 7), five of seven pneumococcal antigens showed reduced response.</p>	<ul style="list-style-type: none"> <li>• Assesses immunogenicity of 7 VPnC with and without the presence of Hib vaccine.</li> <li>• Concludes 7 VPnC same was found to be safe and immunogenic with and without Hib vaccine.</li> </ul> <p>Internal page 854, column 1, para (Objectives), Internal page 854, column 2, para (Conclusion),</p>
<p><b>Anderson et al., Vaccine 21 (2003), 1554-1559</b> This formulation contained less than 50 u.g.</p>	<ul style="list-style-type: none"> <li>• Compares carrier tetanus toxoid and CRM<sub>197</sub>.</li> <li>• Suggests one possibility is to use two or more carriers with PS serotypes does</li> </ul>

<p>limit of CRM suggested by Anderson et al. and yet interference was clear.</p>	<p>not discourage use of single carrier.</p>
	<ul style="list-style-type: none"> <li>• Suggests tetanus and conventional diphtheria toxoid where more or less equally potent as carrier depending on pneumococcal serotype.</li> </ul> <p>Internal page 1554 (Abstract), Internal page 1554, column 2, para 2, Internal page 1558, column 1, para 2</p>
<p><b>Ron Dagan et al.</b> <b>The Journal of Infectious Diseases, 2002;</b> <b>185:927-36</b></p>	<ul style="list-style-type: none"> <li>• Discusses carriage rate of nasopharyngeal infections.</li> <li>• States that in a 9 valent vaccine study in South Africa, CRM as a carrier protein showed protection against all vaccine serotypes.</li> </ul> <p>Internal page 927 (Abstract), Internal page 933, column 1 last para, Internal page 934, column 1 para 1, Internal page 935, column 1, para 2</p>
<p><b>Jakobsen et al.</b> <b>Infection and Immunity, May 2003, p.</b> <b>2956-2959, 2003</b></p>	<ul style="list-style-type: none"> <li>• Discusses cross reactivity between 19F and 19A.</li> </ul> <p>Internal page No. 2958, column 2, last para</p>
<p><b>Cooper et al., Vaccine 29 (2011) 7207-7211</b></p>	<ul style="list-style-type: none"> <li>• Discusses cross reactivity between 6A, 6B and 6C but does not discourage use of these serotypes together.</li> </ul> <p>Title, Internal page 7210, column 1, para 1, Internal page 7211, column 1, para 1</p>
<p><b>Nunes et al., Expert Rev. Vaccines 10(7), 951-980 (2011)</b></p>	<ul style="list-style-type: none"> <li>• Discusses immunogenicity and safety of PCV-13 in infants and children.</li> <li>• Noninferiority studies indicate a similar immunogenicity profile between PCV-13 and PCV-7 recipients against most</li> </ul>

	<p>of the common serotypes.</p> <ul style="list-style-type: none"> <li>• <u>An attenuated anamnestic response to serotype 3 was reported in five out of 14 studies.</u></li> </ul> <p>Internal page 951 (Abstract)</p>
<p><b>Ron Dagan et al., Vaccine 28 (2010) 5513-5523</b></p>	<ul style="list-style-type: none"> <li>• Discusses co-administration of vaccines.</li> <li>• Abandons development of mixed carrier approach as a result of reduce immune response for the TT conjugates.</li> </ul> <p>Internal page 5513, column 2, para 1, Internal page 5519, column 1, para 2</p>
<p>Buttery et al.</p>	<ul style="list-style-type: none"> <li>• There is no teaching away</li> <li>• From Warren A. Kaplan's affidavit, paras 21-23</li> </ul>

#### 15.4 Applicants submissions

The Applicant explained that obviousness is to be determined through the eyes of a hypothetical construct, POSA who has certain attributes namely

- (a) that POSA is conservative;
- (b) Does not undertake risk;
- (c) Is not imaginative;
- (d) considers teaching of document as a whole rather than cherry picking,
- (e) is aware of the general state of art through his common general knowledge and
- (f) does not tread the path which teaches away.

The above attributes of a person skilled in the art have been held in several decisions namely,

- i. POSA is A Conservative Person, reliance is placed on T455/91
- ii. OA/8/2009/PT/CH,
- iii. Teaching away: In paras 11 and 12 on page 10 of In re Icon Health and Fitness Inc. [496 F.3d 1374], the Federal Circuit, held that
- iv. The Hon'ble IPAB in para 42 of OA/08/2009/PT/CH, held that a person skilled in the art is not a dullard.
- v. It is not to be determined by an expert or an applicant or the inventor and their knowledge is not to be looked into while determining inventive step.

The applicant submitted that the reasonable expectation of success seems to have been confused with the hope to succeed. The Applicant also stated that the filing of 25 documents by the Opponent is demonstrative of the fact that this field is highly complex and unpredictable

The applicant stated that the approach of the opponent was that of simple addition of St of the existing vaccine and adding it with CRM<sub>197</sub>. A person skilled in the art would not do this as there would not be any reasonable expectation of success and infact he would be confronted with the challenges and problems referred to above. Reliance was placed upon T296/93 - Page 40, para 3

Further the Opponent relied on the EP decision during the hearing. The Applicant submitted that the opponent did not verify their facts at the hearing and made a casual remark that the EP patent was revoked despite Prof. Dagan's affidavit. In relation to EP proceedings, the applicant submitted that

- The EP patent is not revoked in view of Article 106 of the EP patent convention due to the pendency of an appeal.
- That Prof. Dagan's affidavit was filed by the applicant in the appeal proceedings and not in the opposition in EP and, therefore, the EP patent was not revoked despite Prof. Dagan's affidavit.

- In any event, the Applicant submitted that the EP patent is back in force and patents have also been granted in almost 83 countries. Even in Japan invalidation action was filed but despite the invalidation action the patent was upheld as being valid.

15.5 Having said this, I am considering all the prior documents filed by the Opponent in the representation as well as with the affidavits and am dealing with them after due consideration of the oral arguments made at the hearing, pleadings and evidence.

1. US 4673574 & US4902506

- I don't consider these as relevant documents and is for a single valency conjugate

2. David L. Klein et al - Published: 1995- Klein et al is a review and update article on pneumococcal conjugate vaccines. The carrier protein indicated by said article are DT, TT, CRM197 and Outer Membrane Protein Complex. I have seen this document which stated not to increase valency and use a single carrier protein of PCV, limiting the number of serotypes and unpredictability in the art and adopting a multiple carrier strategy to reduce carrier load and enhance immune response. In this document, Praxis that used CRM197 as carrier protein only involved 7 serotypes while the vaccine developed by University of Rochester used multiple carrier proteins CRM197 and TT and involved only 4 serotypes.

3. Mark A. Shelly et al - Published: 1997 is not relevant as it relates to pneumococcal conjugate vaccines and polysaccharide vaccines.

4. US 5623057 [Merck & Co.] - Published: 22-Apr-1997 I have seen this document that relates to a single valent vaccine comprising carriers such as OMPC and MIEP and a process for preparing the same..

5. Robert S. Daum et al - Published: 1997: This is not a relevant document as all it teaches is that the polysaccharides conjugate vaccines are more immunogenic than their oligosaccharide counterparts.



6. Nontombi Mbelle et al – discusses a randomized double blind study of the safety, immunogenicity and impact on carriage of a 9-valent pneumococcal conjugate vaccine and does not teach the vaccine of IN ‘8081.
  
7. Tera L. McCool et al - Published: 1999 As suggested by the Applicant, this document examines the immunogenicity of three PnPs-protein conjugate vaccines in a mouse model. The three vaccines were 6B, 19F and 23F conjugated to CRM197. This document shows that good immune response was observed for some serotypes but not for others. In fact the same carrier protein did not produce significant immune response for 23F serotype.

Based on this document, I am of the opinion that there is unpredictability in the field. A person skilled in the art would only be directed to not use a single carrier CRM197 for all serotypes which is a teaching away.

8. Xinhong Yu et al – is a study wherein young children were immunized with three different conjugate vaccines containing 6B and 19F polysaccharides namely [see table 1]:
  - PV: polysaccharides of 6B + 19A + 19F serotypes
  - PP: pentavalent conjugate vaccine conjugated to CRM197
  - OP: pentavalent conjugate vaccine wherein oligosaccharides are coupled to CRM197
  - MK: heptavalent conjugate vaccine wherein polysaccharides are conjugated to outer membrane complex protein (OMPC).

From this document I note that It MK vaccine elicited opsonophagocytic responses to 19A serotype but OP and PP vaccines did not MK vaccine elicited antibodies reacting with both 19F and 19A. The study was done to examine that 6B and 19F conjugate elicit antibodies cross reacting with 6A and 19A serotypes. OMPC according to this document is preferred carrier and also shows 6B and 19 F provide cross reactivity to 6 and 19A

9. William P. Hausdorff et al - Hausdorff is a study to optimize the formulations of future conjugate vaccines and to evaluate the appropriateness of their use in various geographic areas and age group,  
This is a document that is not relevant for obviousness as the purpose of this study was not to determine the vaccine formulation but to understand the serogroup epidemiology of the pathogens. The inventor, Dr. Peter Paradiso (inventor of IN'8081) was also involved in study
10. WO 2000/56358 [Smithkline Beecham Biologicals S.A: WO '358 provides polysaccharide antigen vaccines. The inventors of WO '358 surprisingly found that for certain pneumococcal polysaccharide conjugates the immunogenicity of the vaccine is significantly greater when the antigen is formulated with 3D-MPL alone rather than with 3D-MPL used in conjunction with a carrier adjuvant. WO '358 provided a new carrier protein D
11. Obaro et al - Published: 2002. This document merely discusses the success of Prevenar®
12. Choo et al. obtained experimental results showing immune interference in 7+1 valent-CRM197 conjugate vaccine under appropriate experimental conditions. Accordingly, a person skilled in the art as of the priority date, who understands the experimental designs and results of Obaro (2002) and Choo (2000), would seriously consider the immune interference.
13. Cynthia G. Whitney et al - Published: 2003. This document examines the burden of pneumococcal invasive disease. I agree with the Applicant that this document proves that 6B, 19F provide cross-protection for 6A and 19A.
14. De la Pena : This document cannot be relied upon by the Opponent as no verification certificate was filed. Having said this I note that there is not scientific discussion of

immune interference in this document. This document discusses epidemiology of pneumococcal disease

15. On a careful reading of this document, I note that with the addition of serotypes, mixed carrier strategy such as pneumolysin, neuraminidase, autolysin etc is recommended. How to develop a more highly valent, effective vaccine (while avoiding immune interference) is not addressed in this document.
16. US 2004/0202668 - Published: 14-Oct-2004 US '668 is directed to combination vaccines.
17. Cutts et al - Published: 26-Mar-2005 is not a relevant document..
18. O'Brien et al - Published: 2000 I am not considering this document as opponent only filed an extract of the publication.
19. Overturf et al - Published: 2002
20. Overturf et al relates to the advent of pneumococcal protein conjugate polysaccharide vaccines in particular the 7-valent pneumococcal conjugate vaccine Prevenar® developed by Wyeth for children beginning 2 months and also for children between 24 and 59 months of age.

Overturf realizes that the addition of larger serotypes would bring in the phenomena of immune interference.

The inventor further stated that Wyeth never developed an 11-PCV

21. Malik et al - Published: 2013 was published after the priority date and therefore not a relevant prior art for inventive step.
22. Buttery et al - Published: 13-Apr-2013 is a later published document

The applicant also highlighted towards the various advantages and commercial success associated with the claimed vaccine.

## **15.6 Decision:**

I have considered all the documents, pleadings and affidavit filed by both the parties in relation to inventive step. I have also given my opinion in relation to each prior art document relied upon by the Opponent with respect to lack of inventive step in the aforesaid paragraphs.

After due consideration of everything before me, I dismiss the ground of lack of inventive step for the following reasons:

1. It is an established position that multivalent conjugate vaccines is a very complex and unpredictable field and all the prior arts and documents filed by both the opponent are demonstrative of the same. A person skilled in the art (POSA) would be aware of the challenges associated with multivalent conjugate vaccines and the problems associated with having the same type of carrier protein when increasing the valency of the conjugate vaccine. I would deal with the issue of inventive step at two levels:
  - (i) whether POSA would develop a 13 valent multivalent vaccine that comprises serotypes 1,3,4,6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. In other words, whether the person skilled in the art would include the following 4 serotypes to a 9 valent vaccine that was already known in the prior art document namely 3, 7F, 6A, 19A.
  - (ii) The 2<sup>nd</sup> issue that I would deal is that whether a POSA would use CRM 197 when increasing the valency from 9 valent to 13 valent.
2. The law with regard to obviousness in India is well settled which is a mix question of law and fact. The inventive step has to be looked through the eyes of POSA who is a hypothetical person, not an inventor or an expert, conservative and is aware of the state of art.
3. Also, the opponent has to demonstrate that POSA based on the prior art and common general knowledge would have any teaching, suggestion or modification with a reasonable expectation of success to develop a 13 valent vaccine with a single carrier protein CRM 197 from a 9 valent pneumococcal vaccine with CRM.

4. In my opinion based on the documents before me, POSA was aware of the challenges in developing a multivalent conjugate vaccine with a single carrier protein. The said person is aware of the state of art what others are doing in this field and the challenges associated in relation thereto.
5. POSA would be aware of including additional serotypes in a vaccine to provide broader coverage but is also aware of the challenges faced in relation thereto such as carrier induced epitope suppression, antigen competition, immune interference and epitopic load and by standard effect.
6. As on the priority date POSA is aware of the fact that serotypes 6B and 19F provided cross protection to 6A and 19A and therefore POSA would not undertake any risk associated with increasing the valency by including 6A and 19F as cross protection was already provided to the serotypes and there was increased the chances of encountering immune interference. No expert in the field had developed a vaccine more than 10 valent with a single carrier protein and including serotypes 6A, 19A and 3.
7. The cross protection to serotype 6A and 19A by 6B and 19F is clearly provided by Whitney et al; Dagan 2002 and Jakaobsen et al as wellas Hausdroff
8. I also note that the article submitted by Dr. Amulya Panda expert of the Opponent clearly suggest that when developing pneumococcal conjugate, the number of vaccines should be limited and that large concentrations of antigen could be dangerous. The said document also demonstrated unpredictability in the art.
9. Further, the Applicant has demonstrated surprising effects that have to be considered by me as establishing that the invention is inventive. The patent specification includes data to show that the claimed composition is able to show immunogenic response for all 13 serotypes. The Applicant also demonstrated through studies that by adding serotypes to PCV7, the immunogenic response was not reduced for any of the existing serotype including in PCV7 or the new serotypes included in 13 valent.
10. The Applicant also relied upon Cooper et al that shows an unexpected benefit by adding serotype 6A to multivalent conjugate vaccine. It was seen that serotype 6A which has structural similarity and immunological cross reactivity with serotype 6C and serotype 6A elicits cross protective response to serotype 6C. With regard to serotype 3, POSA

would be aware of the failures of others in being unsuccessful in adding serotype 3 to a pneumococcal multivalent conjugate vaccines as it was not showing any results.

11. Therefore, in my opinion, POSA would not undertake any risk; would not add serotype 3 to existing vaccine as others had failed in doing so; would not add 6A and 19A as these serotypes were being provided a cross protection through 6B and 19F and to number of vaccine serotype must be limited.

On a Single carrier protein strategy arguments were advanced by the Applicant that a POSA would not add a single carrier protein to a multivalent vaccine.

12. The Opponent and the evidence was filed in relation thereto to demonstrate that POSA based on several prior arts would be motivated to use a single carrier protein and there was a reasonable expectation of success, I disagree with the approach of the Opponent.
13. While I have dealt with each of the documents in the preceding paras, I would like to summarize that POSA would be aware of carrier induced epitopic suppression, antigen compound, immune interference and epitopic load which could result in diminishing the immune response for each serotype in vaccine and therefore POSA would adopt a mix carrier protein strategy as all the prior art documents are in this direction including what the experts were doing.
14. None of the documents relied upon by the Opponent teach towards adding a single carrier protein when increasing the valency of a multivalent conjugate vaccine. In fact the prior art such as Choo et al and Obaro et al would be aware of immune interference caused by increasing carrier protein CRM 197.
15. Even experts such as Panacea and Glaxo were using a multiple carrier strategy of including DT, TT, and protein D. De la pena also recognizes the multiple carrier protein which is the document of the Applicant to suggest that increasing the valency of multivalent conjugate, multiple carrier protein strategy should be the approach and preferably including pneumolysin.
16. Sanofi also used a mixture of 2 carrier proteins DT and TT.

17. Therefore using a single carrier protein was clearly not taught by any of the prior art documents when increasing the valency and there was no reasonable expectation of success

I therefore dismiss the ground of “lack of inventive step”

## 16. NOT AN INVENTION/NOT PATENTABLE

16.1 The applicant argued that the Ground *Not an invention/ Not Patentable* were not argued during the hearing by the Opponent and therefore should be dismissed. The Applicant however submitted that claims do constitute an invention as they are novel and inventive for reasons provided in preceding paragraphs. The opponent admits that one embodiment of the invention is a commercial vaccine, therefore utility at least for this reason cannot be challenged.

16.2 Decision: For reasons stated above, I believe the present invention is novel and inventive. It definitely has industrial applicability.

## 17. Section 3(e)

17.1 The opponent further held that claims 1-21 are not patentable under Section 3(e) as composition claimed is not synergistic. It was submitted that all claims 1-6 are drawn to a composition. However, there is no synergy data in the impugned specification. In absence of synergy data, all claims 1-6 ought to be rejected on this ground only

17.2 The applicant argued that a person skilled in the art upon reading the patent specification and based on his common general knowledge will appreciate that the vaccine/multivalent immunogenic composition is a conjugate of 13 distinct polysaccharides and a carrier protein CRM197 and in that sense is not an admixture under Section 3(e) of the Indian Patents Act. Even otherwise, the components of the vaccine of IN’8081 are various advantages/surprising effect which are summarized below:

- a. Vaccine with an increased valency compared with the prior vaccine – protection against more strains, i.e. a higher coverage without causing any reduction in immune response due to interference
- b. Remarkable immunogenicity
- c. Unexpected benefit of the addition of the serotype 6A to the multivalent:

17.3 Decision: -I agree that vaccine/multivalent immunogenic composition is a conjugate of 13 distinct polysaccharides and a carrier protein CRM197 and is not an admixture under Section 3(e) and is a synergistic vaccine composition. I therefore dismiss this ground.

## 18. INSUFFICIENCY & CLARITY

18.1 The applicant stated that the ground was not argued during the hearing by the Opponent and therefore should be dismissed. It was submitted by the Opponent that claim 1 as drafted and pending does not have antecedent basis for the dependent claim and therefore, the claims in the current form cannot be allowed.

18.2 Decision: I do not agree. The dependent claims define further embodiments of main claim 1 and have correct antecedent. Further, the specification claims a 13 valent composition which has been specifically described and also the advantages have been elaborated by evidence and other documents.

## 19. GROUND – V: SECTION 8

19.1 The applicant argued that the ground was not argued during the hearing by the Opponent and therefore should be dismissed. The Opponents seem to rely on EP revocation.

19.2 Decision: The opponents have only mentioned the ground of section 8, but have no pleadings in that respect, and nor do the opponents elaborate/prove as to how the ground has not been met. EP details and documents related revocation have already been filed by the Applicant.



The ground therefore cannot stand as the same has not been pleaded or proved. I note that section 8 details have been filed by the Applicant on various occasions.

20. In view of the above discussion I dismiss the pre-grant opposition filed under Section 25(1) of the Indian Patents Act and allow the application to proceed to grant on claims 1 to 6 as stated above

Date – 11/08/2017

(Dr Nilanjana Mukherjee)  
Assistant Controller of Patents and Designs