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

Dr Anushree Gupta of M/s ANA, New Delhi …. Agent of the Opponent

Mr Rajesh Jain, Dr Mahalaxmi Andheria, Mr Arindam Purokayastha
….Representatives of the 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 19th October 2007. The international filing date of the instant application is 31st March 2006 (PCT no.: PCT/US2006/012354). The application claims priority from patent application Nos. PCT/US2006/012354 and 60/669,605 dated 31st March 2006 and 8th 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 17th June 2013. The applicant submitted their reply to the first examination report on 17th June 2014 with the revised set of claims.

3. Panacea Biotech Ltd. filed an opposition on 31st August 2010. The Notice in respect of the Opposition was forwarded on 17th June 2013. A response was filed on 17th September 2013. Panacea filed a rejoinder around 6th January 2015 wherein additional documents were relied upon. D1 to D3 were relied in the pre grant representation:-

WO 2003051392	D1
AU 199877730	D2
A trail of a 9-Valent Pneumococcal Conjugate Vaccine in children with and those without HIV infection by Keith P. Klugman, N Engl J Med 2003 349: 1341-8, October 2, 2003	D3

The following additional documents were filed with the rejoinder:-

WO 00/56358	D4
Overturf *et al*, (2002) *Seminars in Pediatric Infectious Diseases;* 13: 155-164	D5
Xinhong Yu et al. (1999) *The Journal Of Infectious Diseases*; 180: 1569-1576	D6
Hausdorff *et al.* (2000) *Clinical Infectious Diseases*; 30: 100-121	D7
Mbelle et al. *The Journal Of Infectious Diseases;* 180: 1171- 1176	D8
Ada et al. (2003) *Clin Microbial Infect*; 9: 79-85	D9
Rennels *et al.* (1998) *Pediatrics;* 101: 604-611	D10
WO0062801	D11
Declaration by Dr. Talaga, Head of an Analytical Research Unit for Sanofi Pasteur	D12
WO2002022167	D13
WO0200249	D14
De La pena	D15
O'Brien et al	D16
Obaro et al	D17

Whitney et al	D18
Daum et al	D19
Cutts et al	D20
WO 00/56359	D21
Nurkka et al	D22
Wuorimaa et al	D23
Reinert et al	D24
Hausdorff (2002)	D25
Block et al	D26
Joloba et al	D27

4. Vide a letter dated 19th December 2014, a hearing was appointed on Feb 2, 2015. The oral hearing was adjourned and subsequently appointed for March 18th, 2015. 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.

5. Claim revisions were also filed during the hearing. Original claims 1 to 6 were retained and the rest withdrawn without prejudice. 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_{197}, the capsular polysaccharides are prepared from serotypes 1, 3,4, 5, 6A, 6B,7F, 9V, 14, 18C, 19A, 19F and 23F.

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

   Claim 3 - The immunogenic composition as claimed in claim 2, wherein the adjuvant is an 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_{197} carrier protein; 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant; and sodium chloride and sodium succinate buffer as excipients.

6. Before I deal with the substantive issues, I will deal with certain preliminary objections raised by the parties:-

6.1 Rejoinder in a pre-grant opposition

6.1.1 The applicants objected taking on record the belated filed documents and any ground raised in respect of the said documents. It was argued that representation by Panacea was notified to the applicant by the Patent office on 17th June 2013. The reply statement to the representation was filed by the applicant on 17th September 2013 and still the Opponent choose to sit back for one year and filed a rejoinder to the reply statement few days before the first hearing was appointed.

As per the Applicant the delayed filing of rejoinder is against the principles of natural justice, the same should not be taken on record as the Act provides no provision of filling a rejoinder 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 submitted that all grounds have to be averred in the first instance itself rather than in rejoinder because latter is not a part of the pleadings.

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.

6.1.2 As per the Opponent the original claims 1 to 27 of the impugned patent application were directed to multivalent immunogenic composition of valencies beyond 7 and beyond 13. Further there was no recital whatsoever about the limitation of conjugating protein as CRM-197 in claim 1. The Opponent further stated that they are not barred by the Patents Act, 1970 to file further pre-grant opposition to the

same application on different grounds or same grounds with different citations or fact or as substantive right under the Statute, pre-grant opposition is available any time before the grant of patent against the grant of patent on any invention. The Opponent in the submissions also relied upon decision in respect of 2899/DELNP/2005 wherein the additional documents were taken on record *in public interest*

6.1.3 **Decision: In the interest of natural justice and equity, I have taken the said rejoinder along with the affidavits on record. Also, I have also exercised my discretion and taken the affidavit of Dr. Peter Paradiso on record to respond to the allegations of the Opponent. Dr. Paradiso is an inventor and explained the invention and distinguished the prior arts. However, I certainly discourage the filing of documents several months after the filing of the pre-grant opposition unless the opponent can provide sufficient cause for the delay. This will however not serve as a precedence to future cases.**

6.2 Oral/written evidence led by the Inventor

6.2.1 The Opponent has objected to the oral and written evidence of the inventor and stated that it should not be taken on records on the basis of the IPAB order (No.41 of 2013) that held in para. 13, page 3 that "*the expert witness should give his opinion which will be independent without any inference. The opinion shall be unbiased. The expert evidence must be necessary in assisting the trial on facts and in law."*

6.2.2 Decision: The Applicant received the rejoinder to the reply statement 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 natural Justice I am taking the documents filed by the Opponent on record then, the Applicant's Oral evidence led by the inventor himself and the written declaration should be taken on record as well. Declarations of inventors have been considered by me in the past, and also I understand that the Courts accept them as inventors are the best persons to provide evidence.

6.3 Admission Best Form Of Evidence

6.3.1 The applicants also relied upon Opponent Panacea Biotech's Patent Application No. 140/DEL/2011. As per the Applicant, in said document the Opponent, admit that it is not an easy task to develop a multivalent conjugate vaccine, because there is a risk of immune suppression leading to suboptimal response to the conjugated polysaccharide due to the presence of too much of a particular carrier protein in a multi-conjugate vaccine. The Applicant

urged that admission under the evidence act is the best form of evidence and operates as an estoppel. The Applicant relied upon Nagubai Ammal & Ors. v. B.Shama Rao & Ors., AIR 1956 SC 593, wherein the supreme Court held that admission made by a party is admissible and best evidence, unless it is proved that it had been made under a mistaken belief.

6.3.2 The Opponent disagreed with the Applicant and relied on the following cases:-

a) Himani Alloys Ltd. vs. Tata Steel Ltd.(2011)7 SCR, para 10,page 2
b) Nagubai Ammal and others vs. B. Shama Road and others 1956 AIR 593,1956 SCR 451, page 10
c) Razia Begum v. Sahebzadi Anwar Begum, 1958 SC, page 6,last para
d) In M/s Puran Chand Packaging Industrial Pvt. Ltd. vs. Smt. Sona Devi and another, 2008,
e) Raj Kumar Chawia Vs. Lucas Indian Services AIR 2006, in para 5,on page 2
f) Para nos. 20 and 23 on page nos. 16 and 18 of the judgment by Hon'ble Supreme Court of India in UOI Vs. Ibrahim Uddin & Anr (Civil Appeal No. 1374 of 2008)

Based on the above the Opponent stated that the law on admissions requires that unless the admission is clear, unambiguous and unconditional, the discretion of the Court should not be exercised to deny the valuable right of a defendant /opponent to contest the claim and the law would not permit admission by inference as it is a matter of fact.

6.3.3 Decision: Patent application 140/del/2011 is a postdated document, I will only consider it to the limited extent that it provides certain details about the state of the art in the vaccine technology as the background.

6.4 Corresponding EP patent

6.4.1 The Opponent also submitted that the European equivalent of applicant's Indian patent application was opposed and the patent was revoked on Dec. 22, 2014. The Opponent also submitted that the proceedings and all the documents including Dr.Talaga's declaration submitted during the revocation of the corresponding EP patent is persuasive in nature while considering the examination of the alleged invention by the Learned Controller.

6.4.2 The Applicant submitted that:-

- In accordance with Article 106 of the EP Patent Convention, if an appeal has been filed against the order of revocation, the order has suspensive effect.
- Reliance on EP decision by the Opponent is in complete ignorance of the fact that the same application has been granted patent in other jurisdictions such as Australia, US and many more.

- Patent rights are territorial in nature. The grant or rejection of the patent application in foreign jurisdiction does not influence the examination procedure of the Indian Patent Application. Where the Applicant is not given the benefit of corresponding patents granted in foreign jurisdiction, the same could not even be deprived of his right to patent in light of revoked patents or applications not granted in foreign jurisdictions.
- Reliance was placed on the decision of the US District Court in Quad/Tech, Inc vs Q.I. Press Controls B.V. et al wherein the Court held that "foreign patent determinations are not binding in litigation concerning United States patents and patent law". Similarly reliance was also placed on the decision of the US court of Appeals, Federal Circuit in Medtronic, Inc and Medtronic Puerto Rico Inc. vs Daig Corporation.
- The applicant further stated that the evidence of Dr. Talaga filed in the present proceedings is a copy of the evidence filed in EP proceedings and is not in accordance with Section 79 and Rule 126 of Indian Patent Act and Rule. Further, the copy of the declaration has no exhibits and no documents relied on in the declaration have been filed along with the declaration.

6.4.3 Decision: The Applicant has provided details of EP under section 8. I will be assessing the Novelty and inventive step based on the case before me and all the documents placed before me.

6.5 Inventor's submissions

6.5.1 The Applicant highlighted few points about the invention. Dr. Peter Paradiso also highlighted advantages and surprising effects about the invention:-

- IN'8081 relate to a 13-valent immunogenic composition for use as a vaccine, comprising polysaccharide-protein conjugates derived from *Streptococcus pneumoniae* serotypes **1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F**, each serotype being conjugated to a **CRM_{197}** carrier protein. The commercial embodiment of the invention is **Prevenar13®**.

- Studies on pneumococcal polysaccharide conjugate vaccine (PCV) started in 1986.

- Two types of 7-valent vaccines were studied, the development of a 7-valent vaccine using OMPC as a carrier protein was stopped at the trial stage while a 7-valent vaccine using CRM_{197} was finally commercialized. 7-valent vaccine, Prevenar®, was the first approved pneumococcal polysaccharide conjugate vaccine to be approved by FDA and has capsular polysaccharides from serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, each conjugated to a carrier protein CRM_{197}.

- Applicant prepared a 9-valent vaccine further comprising serotypes 1 and 5 conjugated to the same carrier protein CRM_{197} and added to the 7-valent vaccine, which was under development at that time.

- In case of pneumococcal vaccines, due to the existence of various serotypes (over 90 types) that cause very specific immune responses, it is an important, yet difficult task to increase the scope of immune protection, particularly due to:

    - **Carrier-induced epitope suppression** It is suppression of an immune response to polysaccharide antigen due to the immune response to a conjugated carrier protein. This appears to result from competition for Th-cells, by the B cells to the carrier protein, and B cell to polysaccharide. If the B cells to the carrier protein predominate, there are not, there are not enough Th-cells available to provide necessary help for the B-cell specific to the polysaccharide. Therefore, when due to increase in valency of a vaccine there is an increase in dosage of the carrier protein, there is a risk of facing issues relating to carrier induced epitopic suppression.

    - **Antigen Competition:** since the 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").

- Those skilled in the field of vaccines would very carefully select a vaccine design, that is (1) the total number of serotypes, (2) the specific serotypes to include, and (3) 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.

- To avoid the above problems, as per the applicant attempts to use at least two mixed carrier proteins were made so as to reduce the effect of individual carrier protein. (use of mixed carrier proteins was suggested in **Fattom, *et al.*** (1999), **Dagan, *et al.*** (1998) **Wuorimaa, *et al.*** (2001))

- Concern was growing for CRM_{197} after a significant suppression of pneumococcal antigen-specific response was observed in co-administered CRM_{197}-conjugated vaccines, which was later published in **Choo et al. (2000).**

- Wyeth was looking for other candidate proteins, in particular for a mixed carrier strategy. Wyeth considered pneumolysin as one of the most desirable candidates and tested it as a potential carrier protein that could be used in combination with the previously used CRM197.

- In the early 2000's (before the priority date of 2005 of the present application), GlaxoSmithKline ('Glaxo') and Sanofi-Pasteur ('Sanofi') conducted studies to develop an 11-valent vaccine, which further comprises serotypes 3 and 7 in addition to the prior 9-valent vaccine.

- Sanofi developed an 11-valent vaccine using a mixture of two carrier proteins, wherein some serotypes are conjugated to DT while the remaining serotypes are conjugated to TT. (**D5 of FER: Wuorimaa T et al, 2001** (before priority)) describe the 11v vaccine, developed by Sanofi, as being "*designed to circumvent carrier related problems*. Paper describes a vaccine that uses two carrier proteins, DT and TT, for the purpose of avoiding immune interference.

- However, the 11-valent conjugate vaccine designed by Sanofi on further study as such showed significant immune suppression to acellular pertussis antigens when co-administered with the universal DTP vaccine.

- Further, Glaxo chose to use Protein D (PD) from *Haemophilus influenzae* as a single carrier protein. This was to resolve the problem of lowered immunogenicity by using a new carrier protein that was not included in the co-administered universal vaccine. Nurrka et al studied a 11-valent conjugate vaccine developed by GSK using Protein D as the carrier. In their studies, the serotype 3 conjugate was not able to prime the immune system as were the other conjugates suggesting that it might not be efficacious. (**WO2003051392** the patent application filed by GSK also suggests the need for multiple carrier proteins and suggests a combination of protein D, DT and TT in a formulation)

- Subsequent studies (**D8: Prymula et al**) further confirmed that was in fact the case, and serotype 3 conjugate was not able to prime the immune system and it was not efficacious. GSK eventually dropped serotype 3 from this vaccine formulation. In addition, they used DT and TT as carriers for their 18C and 19F conjugates, respectively, to improve the immunogenicity. **Thus GSK went from one preferred carrier to a multiple carrier approach.**

- Thus, after modifying the vaccine design to a great extent by excluding serotype 3 from the vaccine and changing the carrier proteins for serotypes 18C and 19F to DT and TT,

respectively, in an attempt to improve the immune response to these two serotypes, Glaxo was able to develop a vaccine eliciting immune responses at a required level. Thus, Glaxo had to reduce the valency of the vaccine and obtained an approval for a 10-valent vaccine conjugated to a mixture of three types of carrier proteins (PD, DT and TT) in 2009 in the EU. This 10-valent vaccine has been imported and sold under the trade name "Synflorix" in Korea since 2010. Therefore, till date the vaccine developed by Glaxo is only a 10 valent vaccine with multiple carriers.

- From the above, the Applicant essentially highlighted the following:-

    a. that as on the priority date and even till today, the field of polysaccharide-protein conjugates vaccine is extremely complicated and unpredictable;

    b. there was a clear direction (teaching away) as on the priority date

        i. not to increase the valency;
        ii. to use a multiple (mixed) carrier approach strategy to avoid immune interference;
        iii. not to include serotype 3 (GSK dropped this serotype in their commercial product "Synflorix" only buttresses the stance of the applicant to limit the serotypes to 10v with a mixed carrier strategy) and
        iv. for serotypes 18C and 18F, use another carrier protein.

7. I will now deal with each of the grounds raised by the Opponent:-

8. GROUND - NOVELTY

8.1 Opponent's argument

The first ground raised by the Opponent was that the invention lacks Novelty. Various documents were cited in the representation and rejoinder. At the hearing and in the submissions, the Opponent relied on:-

D4: Capiau et al 2000 (WO00/56358)
The Opponent submitted that D4 claims exactly 13 valent streptococcus pneumonia vaccine. In addition the prior art claims that the polysaccharides are conjugated to carriers from the group consisting of TT, OMPC, DT, pnemolysin or CRM197. Thus the serotypes in D4 may be attached to any of the carrier which includes CRM 197 as well out of a limited option.

D15: De La Pena et al, 2004.

The Opponent submitted that D15 is an article authored by a scientist from Wyeth (the Applicant). Page 1 last line in the summary mentions - Currently, there are two available vaccines to prevent invasive pneumococcal illness in Spain: 23-valent polysaccharides (VNP-23v) and 7-valent conjugated (VNC-7v). Other conjugated vaccines, 9, 11 and 13-valent, are being developed, although they have not yet been marketed. Since all of the Applicant's developments were using CRM 197 as the carrier, hence it can be understood that the 13-valent under development will also be using CRM 197 only as the carrier protein in this article.

D25: Hausdorff et al, 2002
The Opponent submitted that Hausdorff is one of the co-inventor of the impugned application and one of the author of the D25, which discloses various high valency conjugated pneumococcal vaccines. D25 on Page 1009 discloses how the serotypes are incrementally added to PCV7. D25 on page 1013 discloses 7, 9 and 11 valent conjugated vaccines. D25 on page 1014 discloses that PCV11 plus 6A and 19A comprise all major serotypes. In light of above disclosure even 13 valent vaccines is anticipated as 6A and 19A addition in an 11 valent vaccines lead to 13 valent vaccine.

8.2 Applicant's arguments;

The Applicant stated as to how novelty has to be assessed and the law in relation thereto.

For any prior art document, in order to be an anticipating document, 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 the following 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

8.3 The Applicant also highlighted that from this jurisprudence, 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.

8.4 With regard to the documents relied by the Opponent at the hearing and the submissions, the Applicant submitted as follows: -

D4: The prior art relates to pneumococcal polysaccharide conjugates adjuvanted with 3D-MPL. The vaccine is devoid of any aluminium-based 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 aluminium-based adjuvant. The bacterial polysaccharide as per the prior art are preferably conjugated to protein D conjugate. The Applicant also pointed that the prior art acknowledges problems relating to antigen specific immune response suppression on pages 7 and 8 of the prior art. Further on reviewing page 28 of the prior art, it is amply clear that the invention disclosed and claimed essentially lies in using conjugated polysaccharide conjugate with protein D and the use of 3D-MPL as an adjuvant. The examples are also for **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 CRM-197 as a single carrier. The document does not teach the use of a single carrier for a 13 valent vaccine.

D15: D15 is a publication that discusses the present and future pneumococcal vaccine. The document discussed epidemiology of pneumococcal disease. It further goes on efficacy of heptavalent pneumococcal conjugate vaccine (PCV-7). **D15 discusses PCV9** which at that time was in advanced stages of study. Under the section "The *future of pneumococcal vaccination*", the authors of D15 suggest development of 11, 13 valent vaccine which could broaden the spectrum of ages and countries. In order to achieve much diversity in coverage, however, D15 merely makes suggestion of development of 11-valent and 13-valent vaccines and does not discuss carrier protein for that matter that may be carrier protein in the development of pneumococcal vaccine. The Applicant also pointed that the need for forming a higher valent conjugate vaccine existed in the art, but researches were unable to solve the said need due to the complexity in the field and the problems the immune interference and suppressions, which

increase with the increase in valency of the vaccine. The document does not teach the use of a single carrier for a 13 valent vaccine.

D25: The opponent from this document tries to suggest that serotypes should be added to the 7 valent vaccines to form 13 valent vaccines The Applicant submitted that, the document does not disclose any 13 valent vaccine with a single carrier. It was only the inventors of the present application that they tried to increase the valency till 13 using a single carrier CRM-197. The Applicant also submitted that, though various serotypes that would be important and needed to be included in the vaccines were known to scientists, scientists did not know how to increase the valency further. The scientists were particularly skeptical about adding 3, 6A and 19A to a vaccine formulation as they were not producing results or were cross protected. In addition, the addition of a serotype possessed more risk than the advantage that the scientists expected to achieve from the inclusion of for instance 6A and 19A. The scientists therefore preferred not adding these serotypes and relying on the cross-protection.

The Applicant also provided submissions for documents like D13, D14, and D11 etc. which were relied in the rejoinder for Novelty.

8.5 Decision:

I have considered the arguments and submissions made by the Opponent and the Applicant and I am of the opinion that D4 teaches POSA towards a pneumococcal polysaccharide conjugates adjuvanted with 3D-MPL and and a vaccine composition lacking any aluminium-based adjuvant. Also the conjugated polysaccharide conjugate is with protein D and the use of 3D-MPL as an adjuvant. No 13 valent vaccine with CRM197 is disclosed in this document. Authors of D15, disclosed 7 valent and 9 valent (which on the priority date of IN 8081 was in advanced stages of study) and suggest development of 11, 13 valent vaccine in future could broaden the spectrum of coverage. There is no disclosure that will direct POSA to develop an 11-valent or 13-valent vaccines with CRM197. D25, only suggests the need to increase coverage by adding serotypes. No 13 valent vaccine with CRM197 is disclosed in this document as well. Therefore in my opinion none of these documents provide enabling disclosure of a 13 valent vaccine conjugated to a single carrier, CRM197. A person skilled in the art would not be able to arrive at the invention from any of the documents to carry out the invention without undue experimentation. I therefore hold the claims as being novel.

9. <u>Ground - Inventive Step</u>

9.1 The Opponent submitted that the alleged invention relates to nothing more than the addition to the 7-valent pneumococcal polysaccharide CRM 197 conjugated vaccine (already known and

marketed successfully by the Applicant as PCV7, Prevnar®, since Feb 2000, having serotypes 4, 6B, 9V, 14, 18C, 19F, 23F), six further serotypes, namely 1, 3, 5, 6A, 7F and 19A, all readily identifiable in art (and by the Applicant themselves through prior art publications) to provide a wider vaccination coverage, as suggested in art, to produce a 13-valent vaccine.

9.2 The Opponent stated that there was clear prior knowledge and systematic development of pneumococcal conjugated vaccine with CRM197 carrier protein in increasing order of valency (5, 7, 9 were developed with clinical data published, while 11 valent was under development and 13 valent was suggested as future vaccine to develop) know since 1997 until 2005, when the priority patent application of the Applicant was filed:-

Table 4: Relevant prior arts showing systematic development of pneumococcal multivalent vaccine conjugated with CRM_{197} protein (publications supported by the Applicant's Labs)

Type of Conjugations Disclosed in Prior Art	Serotypes known in the Vaccine	Prior Art Document	Disclosure Page/Line
5 valent CRM_{197} conjugated vaccine	**6B, 14, 18C, 19F, 23F**	D19 (Daum et al, 1997)	*See abstract, 1st line*
7 valent CRM_{197} conjugated vaccine	**6B, 14, 18C, 19F, 23F, 4, 9V**	D10 (Rennels et al, 1998)	*See page 604, right hand Col , top 3 lines*
9 valent CRM_{197} conjugated vaccine	**6B, 14, 18C, 19F, 23F, 4, 9V**, 1, 5	*D8* (Mbelle et al, 1999)	*See page 1171, right hand Col., 1st paragraph*
11 valent CRM_{197} conjugated vaccine	**6B, 14, 18C, 19F, 23F, 4, 9V, 1, 5**, 3, 7F	D5 (Overturf, 2002) (see **Annexure 30**) & D16 (O'Brien et al 2004)	See *page 158, table 4, and right hand Col , 2nd last paragraph, last 5 lines* & *Page 638, table 3*
13 valent CRM_{197} conjugated vaccine	**6B, 14, 18C, 19F, 23F, 4, 9V, 1, 5, 3, 7F, 6A**, 19A	D15 (De La Pena et al, 2004)	*See Page 10, last two lines; Page 11-first 4 lines; Page 12, 2nd last paragraph, line 4-6*

It was submitted that the alleged invention is not inventive as –

(i) It involves combining prior art elements according to known methods to yield predictable results.

(ii) It involves "obvious to try" rational - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

(iii) It even satisfies the relatively stringent "Teaching Suggestion Motivation" criteria for obviousness.

The process of conjugation of serotypes was well known from prior arts disclosing 7 valent CRM 197 conjugated commercial vaccine. D5 and D17 expressly disclose 11 valent CRM197 conjugated vaccines. It was a mere decision to add two more serotypes which were well recognized as a substantial cause of disease and prior arts advocated the addition of these serotypes as well.

Present case involve "Obvious to try" rational - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success (KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 415-421, 82 USPQ2d 1385, 1395-97 (2007))

9.3 Addition of 6A and 19A

The Opponent stated that in light of importance of serotype 6A and 19A disclosed in prior arts and certain prior arts expressly advocated the inclusion of these serotypes, it was obvious to try rational for a person of ordinary skill in the art to add serotypes 6A and 19A with a reasonable expectation of success as has been seen with 7 valent and 9 valent CRM 197 conjugated vaccines.

Further it was submitted that the pneumococcal conjugate vaccines utilize mainly the well-recognized carriers for conjugation of serotypes, which include DT, TT, CRM 197, protein D etc., where these are finite number of carriers used, CRM197 has been described as single carrier where up to 11 valent vaccines conjugated to CRM 197 are disclosed in the prior arts. Hence where there is finite number of carriers and there is only one carrier which has been used singly in highly multivalent vaccines it was obvious to try or obvious for a person of ordinary skill to get 13 valent vaccine with CRM197 as a carrier.

The Opponent also relied upon test of "Teaching Suggestion Motivation" criteria for obviousness described- In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)

It was submitted that prior art taught that 7 valent CRM 197 conjugated vaccine has been successfully commercialized. Followed by this prior arts taught the excellent results with 9 valent CRM 197 conjugated vaccines which further incorporates serotype 1 and 5 in 7 valent vaccine. Prior arts suggested that 11 valent CRM 197 conjugated vaccines are also in progress which further incorporates serotype 3 and 7F. Hence there was unambiguous motivation to add serotype 6A and 19A in the prior art vaccines.

Prior arts expressly disclose 11 valent pneumococcal CRM 197 conjugated vaccine in preclinical phase (see Table 5), mentioning it to induce good immune response and expressly stating requirement of addition of serotypes indicating the importance of 6A and 19A due to modest cross protections (see Table 6), clearly leads a person skilled in the art to a 13 valent CRM 197 conjugated vaccine. And such a 13 valent vaccine being under development is also mentioned in the Applicant's own prior art publication and other prior arts (see Table no.7).

Table 5: Relevant Prior arts disclosing 11 valent vaccine with CRM_{197}

Sr No.	Author/Inventor	Year	Disclosures	Refer
D5	Overturf	2002	-11 valent with CRM_{197} in preclinical stage -found to induce good immune response	pg 158, table 4 pg 158, 2nd last para, last 5 lines
D16	O'Brien et al	2004	11 valent with CRM_{197} in preclinical stage	pg 638, table 3
D7	Hausdroff et al (see Annexure 33)	2000	11 valent is 9-V plus serotype 3 & 7F	pg 101 right hand col; 2nd last para, see pg 113 fig 3, pg 115, fig 4
D15	De La Pena et al	2004	11-valent (adding 3 and 7F)	pg 11 first 4 lines; pg 12 2nd last para, lines 4-6
D25	Hausdroff et al	2002	Incremental increase with serotype 3 & 7F (included in PCV-11)	pg 1013 fig 2 & pg 1014 fig 3
D27	Joloba et al	2001	7,9,11 valent protein conjugated vaccine are immunogenic in children	Pg 1489 last para last 4 lines

Table 6: Relevant Prior arts disclosing inclusion of serotypes 6A and 19A to a 11 valent conjugated vaccine

Sr No.	Author/Inventor	Year	Disclosures	Refer
D15	De La Pena et al	2004	13 valent vaccine (adds serotype 6A & 19A)	pg. 11 first 4 lines
D7	Hausdroff et al	2000	future vaccine may need serotype 6A and 19A	pg.117, 2nd last para lines 3-5
D25	Hausdroff et al	2002	PCV 11 plus 6A & 19A covers all major serotypes	pg. 1014, right hand Col., lines 12-15

D8	Mbelle et al	1999	6A is necessary because 6B does not provide sufficient cross protection.	pg. 1174, 2nd paragraph, lines 4-13
D6	Xinhong Yu et al (see **Annexure 34)**	1999	states modest cross protection to 6A and 19A in existing vaccines	pg.1571, left hand Col., last para., line 4-5, right hand Col., 1st para., lines 1-2
D26	Block et al (see **Annexure 35)**	2002	marginal cross protection for serotypes 6A and 19A in existing vaccines	pg. 863, right Col. 2nd last para.
D4	Capiau et al	2000	6A & 19A serotypes are advantageously added in 13 valent vaccines	pg. 12, lines 7-8
D5	Overturf	2002	Discloses upto 11 valent CRM_{197} conjugated vaccine and discloses that serotype 6A & 19A cause significant amount of invasive disease in developing country	page 158, table 4, and right hand Col., 2nd last paragraph, last 5 lines and See D5- page 162, right hand Col., first 5-8 lines and page 157, right hand Col., table 3
D24	Reinert see **Annexure 36)**	2004 Apr	Discloses importance of adding 6A and 19A	Page 281, left hand Col., lines 8-11

Table 7: Relevant Prior arts disclosing a 13 valent conjugated vaccine (suggesting CRM_{197} as a carrier)

Sr No.	Author/Inventor	Year	Disclosures	Refer
D15	De La Pena et al	2004	13 valent vaccine (adds serotype 6A & 19A)	pg. 11 first 4 lines; pg. 12, 2nd last para., line 4-6
D6	Xinhong Yu et al	1999	7 valent CRM_{197} vaccine and exact 6 serotypes to be added to increase the coverage	pg. 1569, right hand Col., lines 2-8
D7	Hausdroff et al	2000	to maximize coverage of IPD in young children future vaccine may need serotype 6A and 19A.	pg. 117, 2nd last para. lines 3-5
D25	Hausdroff et al	2002	PCV 11 plus 6A and 19A covers all major serotypes	pg. 1014, right hand Col., lines 12-15

9.4 The Opponent relied on Hausdorff et al, 2002 (D25) to show that it fully discloses and makes it obvious the claimed 13 valent CRM197 conjugated vaccine. The Opponent submitted that Hausdorff is one of the inventors of the impugned patent application and one of the author of the prior art D25, which discloses various high valency conjugated pneumococcal vaccines. Though the carrier is not specifically mentioned for those vaccines it is implied that those higher vaccines are disclosed in the context of CRM 197 carrier only. D25 on Page 1009 discloses how the serotypes are incrementally added to PCV7. PCV-7 pneumococcal conjugate vaccine formulation contains serotype 4,6B,9V,14,18C,19F, 23F conjugated with carrier protein CRM197 and from the above disclosure it is clear that PCV- 7 serotypes plus 1 and 5

made PCV-9 and PCV-ll (11-valent pneumococcal conjugate vaccine formulation) was made by adding 3 and 7F to PCV-9. D25 on page 1013 discloses 7, 9 and 11 valent conjugated vaccines and their age dependence on vaccine serotype coverage.

In light of above disclosure, up to 11 valent vaccines are disclosed. D25 on page 1014 discloses that PCV11 plus 6A and 19A comprise all major serotypes. In light of above disclosure even 13 valent vaccines is obvious as addition of 6A and 19A in 11 valent vaccines lead to 13 valent vaccine. It is evident from page no. 1009 of the article that the higher vaccines mentioned on D25 are additions to PCV7-CRM197 conjugated licensed vaccine.

9.5 Addition of Serotype 3 and its protection in the alleged multivalent composition is known:

The Opponent further stated during the hearing, that the addition of serotype 3 and its protection in the alleged multivalent composition is known and obvious to the person skilled in the art and also have been suggested in the prior arts that it may be added in a multivalent immunogenic conjugated vaccine and also in the 13 valent conjugated vaccine as shown in table 8:

Sr No.	Author/Inventor	Year	Disclosures	Refer
D15	De La Pena et al	2004	11 valent and 13 valent vaccines which consists serotype 3 also in various stages of research	pg. 12, 2nd last paragraph, line 4-6.
D5	Overturf	2002	11 valent vaccines which include serotype 3 also in various research stages	pg. 158, table 4, and right hand Col., 2nd last para. last 5 lines.
D7	Hausdroff et al	2000	11 valent vaccines which include serotype 3 also in various research stages	pg. 101 right hand Col., 2nd last para.; see page 113 figure 3, 115 figure 4
D16	O'Brien et al	2004	11 valent vaccines which include serotype 3 also in various research stages	pg 638, table 3
D25	Hausdroff et al	2002	incremental increase with serotype 3 & 7F (included in PCV-11)	pg 1013 fig 2 & pg 1014 fig 3
D6	Xinhong Yu et al	1999	To increase coverage of 7-valent vaccine (eg serotypes 4,6B,9V,14,18C,19&23F); additional 6 serotypes is suggested which includes serotype 3 (eg serotypes 1,3,5,6A.7F&19A)	pg 1569, right hand Col; lines 2-8

The Opponent further relied on, prior art De La Pena et al, 2004 (D15) to show that it suggests add serotype 3 in 13 valent conjugated vaccine and anticipates the 13 valent vaccine. Dl 5 is an article authored by a scientist of the Applicant (Wyeth).

Page 1 last line in the summary mentions -*Currently, there are two available vaccines to prevent invasive pneumococcal illness in Spain: 23-valent polysaccharides (VNP-23v) and 7-valent conjugated. Other conjugated vaccines, 9, 11 and 13-valent, are being developed, although they have not yet been marketed.* Since all of the Applicant's developments were using CRM197 as the carrier, the Opponent submitted that it can be understood that the 13-valent under development will also be using CRM197 only as the carrier protein in this article.

9.6 Fear of immune suppression

The Opponent submitted that, there is as such no fear of immune suppression with respect to multivalent conjugate vaccine, which is conjugated with CRM197, particularly at the concentration used in the alleged composition. Further, it is submitted that it is well-known in the field of vaccines that as per the guidelines of World Health Organization (WHO), for pneumococcal conjugate vaccines the polysaccharide-protein ratio is typically in the range 0.3-3.0 but vanes with the serotypes (see Annexure 37). Therefore, it is obvious for the person skilled in the art to keep the ratio within such range while making the conjugated polysaccharide vaccines.

Table 9: Prior arts disclosing that concentration of CRM197 is important to avoid Immunosuppression

Sr No.	Author/Inventor	Year	Disclosures	Refer
	Fattom et al (see Annexure 38)	1997	extent of interference is related to the concentration of carrier protein	pg. 131 left Col. 3rd para.
	Dagan et al (see Annexure 39)	1998	content of carrier protein in conjugate vaccine should be restricted in light of interference	pg. 2097, right Col., final 4 lines
	Anderson et al see Annexure 40)	2002	carrier amount of 50µg may not cause interference	pg. 1558 left col., 3rd para.
D17	Obaro et al	2002	Enhancement of response to antigens like Hib and diphtheria used in combination with CRM_{197} conjugated 9 valent vaccine	Pg. 945, right hand Col., 2nd paragraph, last 7 lines

The Opponent also relied upon Obaro et al. (D17), to show that it uses 9 valent CRM197 conjugated preparation with CRM197 45ug and the skilled person would conclude that this amount is not sufficient to cause immune suppression, whereas the Applicant, has used 29u.g,

in the alleged composition, which clearly shows that immune suppression will not be caused at such low concentration.

The Opponent also relied upon:-

- Anderson et al., which as per the Opponent shows that that there is no difference in effectiveness regardless of whether CRM 197 on its own or mixture of CRM197 and TT is used as carrier, at least in composition comprising less than 50ug of carrier protein (see page 1558, left col.3rd para.).

- Fattom et al. 1999, which as per the Opponent shows that concentration of carrier protein had a significant effect on extent of interference of the immune response

- Wuorimaa et al. 2001 (D23), which as per the Opponent shows, that only large amount of carrier protein has a role for immunosuppression and no carrier specific differences existed in immunogenicity for types 6B, 18C, 19F and 23F serotypes.

- Dagan et al. 1998, which as per the Opponent shows, that the immune suppression is due to the use of TT carrier protein compared to vaccine with DT carrier protein.

Thus, as per the Opponent none of the prior arts supports that there is immune suppression due to the carrier protein CRM197 and that too at such a low concentration.

Opponent argued and submitted that there is no prior art which states that immune interference discredited the use of single carrier in multivalent preparation and certainly there is no reference which suggests that CRM 197 should be avoided as a single carrier because of fear of immune interference.

Opponent also argued and submitted that Wyeth's position that Aventis and GSK utilized more than one carrier in the PCV vaccines they developed in order to avoid the risk of utilizing single carrier and that they failed to develop higher serotypes vaccines is not persuasive.

Aventis's 11 valent vaccine with mixed carrier DT and TT was undergoing trials in Philippines when the company decided to discontinue its commercialization for the following reasons:

i. Although the vaccine produced a strong immune response, when given at the same time as DTwP vaccine, it performed disappointingly when given at the same times as

DTaP. Since some further trials were required and the development time would be extended, they decided to discontinue it.

ii. Aventis had another candidate, a protein vaccine that could be used with DTwP as well as DTaP, hence they decided to focus on the development of this protein vaccine candidate.

GSK's product:GSK marketed a 10-valent pneumococcal conjugated vaccine using protein D as carrier protein (except for two serotypes wherein DT and TT were used). It seems to be a business driven decision for GSK to develop majorly using protein D as carrier as they also had IP protection on protein D. Initially GSK was developing a 11 valent vaccine using only Protein D as single carrier. Then they shifted to 10 valent, by removing serotype 3 since it was poorly bioactive (a point to note here is that serotype 3 was conjugated with protein D and not with DT) and used DT and TT carriers in two of the serotypes, to develop the 10-valent vaccine. This was around the year 2006. By then Wyeth had already developed their 13 valent CRM based product and was in Clinical studies.

9.7 Postdated Articles

The applicant took support of articles which are post-dated (support of which is also taken in the affidavit submitted by the technical expert during the hearing), to counter the Opponent's patent challenge. The Opponent submitted that these documents should not be considered and taken on record.

During the hearing, the Applicant's attorney, quoted Copper et al 2011 (Annexure A10 in the affidavit), Park et al 2008 (Annexure A9 in the affidavit), Prymula et al 2014 (Annexure A8 in the affidavit), Nunes et.al 2011 (Annexure All in the affidavit), Dagan et al 2010 (Annexure A12 of the affidavit) and Buttery et al 2005 (Annexure A13 in the affidavit). These are the articles which are post-dated to the priority date April 08, 2005 and cannot be considered of relevance to the understanding and thought process of a person skilled in art at the time of filing of the impugned application.

9.8 Applicant’s submissions:

Applicant submitted the main attributes for determination of obviousness, with the help of case law, are that:

- Obviousness is a mixed question of fact and law (Roche v Cipla, para 63
- If the alleged invention is so much out of track of what was known before so as not to naturally suggest itself to a person skilled in the art it is not obvious (Bishwanath Prasad Radhey Shyam v Hindustan Metal Industries [AIR1982SC1444])

- A person of ordinary skill in the art is conservative and does not take risks or go against the established prejudices and is not a dullard (Hon'ble IPAB in para 42 of OA/08/2009/PT/CH
- For determination of obviousness, teaching of a document has to be seen as a whole;
- Hindsight is not permissible; one cannot use the knowledge of the invention to assess obviousness;
- There has to be a teaching, suggestion or motivation to combine prior art documents;
- Teaching away and unexpected results are indicators of non- obviousness;
- Caution needs to the taken when there are prior art that teach away from the invention
- Inventors knowledge is also immaterial. The problems the inventor encountered during the development of the invention and his knowledge is immaterial

Inventive step of IN 8081

9.9 With regard to Inventive step, the Opponent relied on various documents and therefore the applicant presented their argument on each of the cited documents separately. The Applicants Counsel and the inventor explained the background of the technology and priority date, and the highlighted the advantages of the invention:-

a. Vaccine with an increased valency compared with the prior vaccine

The applicant submitted that immunogenic composition of IN'8081 is a high valency pneumococcal polysaccharide conjugate vaccine composition prepared by adding six types of serotypes 1, 3, 5, 6A, 7 and 19A to the prior 7-valent vaccine (Prevenar), This invention has 3 valency higher than 10-valent vaccine which has been imported and sold under the trade name "*Synflorix*" by GSK using multiple carrier protein.

The applicant submitted that it is important to consider that there was never an 11-valent that could be effective enough to reach the market. An attempt to make effective 11 valent failed for both Sanofi and GSK, and the applicant never made an 11-valent. The jump was using a single carrier protein was directly from 9 to 13 valent. 10 and 11 valent that were being developed by Sanofi and GSK were also based on a mixed carrier strategy approach.

b. A single carrier protein used in a 13-valent vaccine as opposed to mixed carrier strategy of prior art

The applicant submitted that as of the priority date of IN'8081, the use of a mixed carrier protein was considered favorable as the vaccine valency increases. Thus, it was surprising that the 13-valent immunogenic composition of IN'8081chose CRM_{197} as a sole carrier protein.

c. Remarkable immunogenicity

The applicant submitted that, the constitution described above allows the 13-valent immunogenic composition of IN'8081 to exhibit superior immunogenicity for all the serotypes included therein. Despite the addition of six serotypes, the 13-valent immunogenic composition of IN'8081exhibits immunogenicity for the seven serotypes included in the prior 7-valent vaccine (Prevenar®) comparable to Prevenar® as well as **remarkably excellent immunogenicity for the newly added six serotypes.**

d. Immune protection for serotype 3

The applicant submitted that, the immunogenic composition of IN'8081 exhibits an excellent effect since it provides sufficient immune protection for serotype 3, which could not have been expected from the prior art. **There was no pneumococcal conjugate vaccine that provided sufficient immune protection for serotype 3** before the priority date of IN'8081. Even today, Prevenar13®, is the only vaccine that provides such immune protection. Nurrka et al studied an 11-valent conjugate vaccine developed by GSK using Protein D as the carrier. In their studies, the serotype 3 conjugate was not able to prime the immune system as were the other conjugates suggesting that it might not be efficacious.

e. Inclusion of Serotypes 6A and 19A

The applicant submitted that more than 90 different serotypes are known, and these types differ in virulence, prevalence, and extent of drug resistance. Also, 23 out of the 90 have been widely studied and were also included in the non-conjugated pneumococcal vaccines. After the success of 7 valent Prevenar, scientists were thinking on which serotypes to be added and how many can be added so that there is no interference with or suppression of the immune response of the existing 7. It was not simply to add serotypes and the scientist did not want any interference with the existent 7 serotypes. For these reasons a balanced approach was required on what serotypes and how many additional can be added.

f. **Cross-protection to 6A and 19A through st 6B and 19F**:

The applicant submitted that, though the scientist knew that adding 6A and 19A would have benefits and would provide better immune repose for said serotypes, however when assessing potential benefits against the increased risks of complexity, such as possible immune interference, others in the field had decided not to include st 6A and st 19A, but to rely on the cross-protection afforded by st 6B and st 19F instead. Therefore, the scientists developing the vaccine or Sanofi and GK also tried to avoid these and preferred to work on a 10 or 11 valent vaccine.

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_{197} 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*".

g. **<u>Unexpected benefit of the addition of the serotype 6A to the multivalent</u>**:

The applicant submitted that a newly identified pathogen serotype named serotype 6C has been described recently. Said serotype has greater structural similarity and immunological cross-reactivity with serotype 6A than does serotype 6B. Additionally, it has been shown recently that serotype 6B conjugate does not provide cross-protection against serotype 6C (see Park et al 2008). Therefore, the vaccine of the prior art although provided cross-protection to serotype 6A by the presence of the 6B conjugate, does not provide protection against serotype 6C. 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).

9.10 Further, there are certain specific issues that were raised by the Opponent with regard to the obviousness of the present invention. The arguments raised by the opponent and the responses of the applicant are herein below:-

13-valent vaccine of the instant application has been developed by the step-wise addition of further polysaccharide conjugate to 7v, 9v, 11v, being developed by the applicant

The opponents have alleged that the 7valent Prevenar, 9v has been disclosed and 11v being disclosed, the 13 v with CRM 197 was an obvious addition. (Various documents were relied for each)

The Applicant disagreed and submitted that vaccine development is not as simple as has been presented by the opponent. The field of vaccine development is very complex. The addition of even a single serotype, can cause serious issues like immune suppression and interference. In case of pneumococcal vaccines, due to the existence of various serotypes (over 90 types) that cause very specific immune responses, it is an important task to increase the scope of immune protection by adding as many serotype antigens as possible to a single vaccine while providing a sufficient immune response to all of the antigens, particularly due to:

- **Carrier-induced epitope suppression- subject previously immunized against carrier proteins**.
- **Antigen Competition**:

9.11 Further, the Applicant also submitted that even if the step wise addition approach suggested by the opponent is considered, it is important to consider the following , that clarify that it cannot be a simple addition of serotypes:-

a. 11v with CRM 197 never existed, no such vaccine was being prepared by Wyeth. The document cited by the opponent in this regard does not provide the source for such information and cannot be relied on. Reference was also made to the evidence of Dr. Peter Paradiso;
b. the state of the art at the time of the invention was to develop a vaccine with higher valency from 7 and 9 v. However the researchers feared that increasing valency with single carrier would be difficult as problems of immune interference and suppression would stem up.
c. the 11 v that was being developed by Sanofi followed a mixed carrier strategy and not single carrier and therefore teaches away from the invention
d. the 11v that was being developed by Glaxo uses protein D as a carrier and before the priority date it was clear that the vaccine did not give good result for serotype 3
e. even till date no other commercial product except the one covered by the present application provides more than 10valent
f. the jump is therefore from 9 to 13 with a single carrier.

7, 9, 11v existed and addition of 6A and 19A is suggested by prior art to arrive at present invention.

The Applicant submitted that 11v with CRM 197 never existed, no such vaccine was being prepared by Wyeth. The document cited by the opponent in this regard does not provide the source for such information and cannot be relied on. Reference was also made to the evidence of Dr. Peter Paradiso;

The Applicant submitted that even otherwise it is not obvious to add 6A and 19 A to the 11 v serotypes, for following reasons-

a. People at the time of the invention though wanted immune response against 6A and 19 A however preferred that such a protection be afforded from the cross-protection by 6B and 19F.

b. The mere fact these serotypes were known, does not make this decision related to the vaccine design obvious. The published data on cross protection between st 6A and st 6B, as well as 19A and 19F, prima facie discouraged the inclusion of these serotypes as compared to serotypes that do not benefit from cross-protection.
c. Given the enormous investment behind the development of such a multivalent PCV, one cannot talk of a "try and see" situation. In this field, if one believed that for a specific vaccine design the risks outweighed the benefits, one would not try and see, but would not implement such design.
d. For this reason the GSK and Sanofi-Pasteur sponsored vaccines did not include these serotypes.
e. A small decrease in immunogenicity of one of the 'common serotypes' already included in the licensed PCV7-vaccine could easily outweigh any benefit from including any additional serotypes.

These choices of serotypes by Sanofi and GSK, as referred to above in para reflect that the skilled person at the time believed that the possible benefits of including further serotypes (such as possibly 6A and 19A) did not balance the increased risks of encountering immune interference if these serotypes were included.

9.12 As per the Applicant, the choice of the addition of serotype 6A conjugates to the formulation was not obvious:

- The prior art discloses a nine valent pneumococcal conjugate vaccine where serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F are conjugated to CRM197.

- The vaccine of the present invention differs by the addition of conjugates and in particular the addition of serotype 6A. The person skilled in the art being aware of the potential issues associated with the addition of conjugates would not have added serotype 6A conjugate to the multivalent vaccine.

- Indeed, serotypes 6A and 6B share similarity in polysaccharide structure and the prior art taught that serotype 6B conjugate provides cross-protection against serotype 6A (see e.g. Dagan R et al, 2002, in particular page 934 left column, last paragraph).

- Therefore, POSA would have found superfluous to add serotype 6A conjugate to the vaccine and being aware of the potential issues associated with the addition of conjugates would have selected another serotype. *This is especially in view of the fact that the 11-valent vaccines of D1 and D2 cited by the opponent themselves did not contain serotype 6A conjugate. Even the vaccines being develop by Sanofi and GSK did*

not contain 6A. If it were so obvious inventors of the prior art would have included serotype 6A conjugate.

- Unexpected benefit of the addition of the serotype 6A to the multivalent:

9.13 As per the Applicant, the addition of serotype 19A conjugates to the formulation was not obvious:

- The vaccine of the present invention differs by the addition of more conjugates and in particular the addition of serotype 19A. The person skilled in the art being aware of the potential issues associated with the addition of conjugates would not have added serotype 19A conjugate to the multivalent vaccine.

- Indeed, when serotype 19F was selected for inclusion in the vaccine of the prior art, it was thought that antibody responses to the structurally similar serotype 19A would be cross-reactive, and that immunization with serotypes 19F would elicit antibodies cross-reacting with polysaccharides from serotype 19A (Jakobsen H et al. Infect Immun, 2003;71(5):2956–9). Jakobsen et al. have shown that pneumococcal serotype 19F conjugate vaccine induces cross-protective immunity to serotype 19A in a murine pneumococcal pneumonia model.

- Therefore the man skilled in the art, being aware of the potential issues associated with the addition of conjugate, would have found superfluous to add serotype 19A conjugate to a vaccine already comprising serotype 19F conjugates and would have added another serotype. This is especially in view of the fact that the 11-valent vaccines of D1 and D2 cited by the opponents themselves also did not contain serotype 19A conjugate. Even the vaccine being developed by Sanofi and GSK If it were so obvious inventors of the prior art would have included serotype 19A conjugate.

- Only the inventors of the instant application tested a 13-valent vaccine that included serotypes 6A and 19A and showed success in vaccine based uniquely on the single CRM197 carrier.

9.14 Prior art teach addition of serotype 3

The opponents argued that the prior art taught the addition of serotype 3. The Applicant disagreed and submitted that:-

- The immunogenic composition of IN'8081 exhibits an excellent effect since it provides sufficient immune protection for serotype 3, which could not have been expected from the prior art.

- There was no pneumococcal conjugate vaccine that provided sufficient immune protection for serotype 3 before the priority date of IN'8081. Even today, Prevenar13®, is the only vaccine that provides such immune protection.

- Nurkka Anu Et Al, 2004 (before priority) Nurrka et al studied a 11-valent conjugate vaccine developed by GSK using Protein D as the carrier. In their studies, the serotype 3 conjugate was not able to prime the immune system as were the other conjugates suggesting that it might not be efficacious.

9.15 No reference is there that teaches away from use of CRM_{197}

The opponents argued that none of the references teach away from use of CRM_{197}. The Applicant disagreed and submitted that, immune interference was an issue with multivalent vaccines, and with CRM 197 as a carrier as well:-

- Immune interference was considered a major problem and there was a growing apprehension in increasing valency especially for CRM197 after a significant suppression of pneumococcal antigen-specific response was observed in co-administered CRM197-conjugated vaccines, which was later published in Choo et al. (2000).

- Considering the above, even the applicant was looking for other candidate proteins, in particular for a mixed carrier strategy. They started work on a potential carrier based on either wild-type or detoxified pneumolysin, a protein derived from pneumococci, and evaluated the utility of Pn-polysaccharide-pneumolysin conjugates for eventual inclusion in highly multivalent PCVs. Wyeth considered pneumolysin as one of the most desirable candidates and tested it as a potential carrier protein that could be used in combination with the previously used CRM197.

- The decision to follow a CRM197-based single carrier strategy for the clinical development of a PCV13 pneumococcal vaccine was only made after the data in the Subject Patent Application Wyeth obtained promising result from a CRM197-based single carrier strategy.

9.16 Immune interference is expected only when the amount of carrier protein is above 45 µg

The opponents argued that immune interference is expected only when the amount of carrier protein is above 45 μg. The Applicant disagreed and submitted that,

- The opponents rely on the "45ug threshold theory" of Dr. Talaga that immune interference is expected only when the amount of carrier protein is above 45 μg. This is an in-correct reading of a scientific document, ignoring important considerations. Dr. Talaga however ignores the fact that, any immune-suppressive effect of the CRM197 would not be seen in the Obaro et al. study because the *"co-administered whole cell pertussis compound ("wP")"* provides a strong adjuvant effect that would mask any such interference.

- This oversight is surprising as Dagan 2004, introduced by Dr. Talaga, clearly explains and confirms this effect of wP as well (see e.g. abstract, lines 11-15). Under these circumstances the skilled person would not have deduced any absolute '45ug threshold' from D16, or that CRM197 was in some way superior to other carriers.

- Applicants relies on Choo et al., 2000. Choo is an article referenced in the passage of Dagan 2010 (page 5519, lines 29-33, citation no. 83) that concisely summarized the CRM197-relevant interference. Choo et al. reports a study where PCV7-CRM is used with Hib-CRM either separately or combined. Immune suppression is found for 5 specific pneumococcal serotypes out of the total of 7 pneumococcal serotypes (see 'Results' of the abstract on page 854, lines 34-37). In contrast to Obaro et al., the effect here is not masked by the use of a whole cell pertussis component (wP), because wP is always administered at a separate limb. The results are thus similar to Buttery's study when combining PCV7-CRM with MnC-CRM and reporting suppression of immunogenicity (immune interference).

9.17 Results show that immune suppression is only in TT and not in DT or CRM_{197}.

The opponents argued that immune suppression is only in TT and not in DT or CRM_{197}. The Opponents also rely on Dr. Talaga's declaration to infer that immune suppression is only in TT and not in DT or CRM_{197}. The Applicant disagreed and submitted that,

- Dr. Talaga's declaration actually confirms that immune interference was a relevant consideration, at the very least for his employer, Sanofi Aventis, when stating that "*Sanofi Pasteur did not utilize more than one carrier in its development of an 11-valent PCV only to limit the potential for carrier suppression.*" (Emphasis added).

- If Sanofi, who is not a POSA believed that using DT or CRM197 in a single carrier strategy would have been the more advantageous path, then it had all the means to do so. However, it did not, but rather it followed the conventional wisdom to reduce carrier dose by applying a multi-carrier strategy (as is confirmed in Dagan, 2004).

- The Opponents assume that from Obaro it can be inferred that the immune interference was completely resolved since no immune interference was observed in PCV9+1/CRM197. However, such an assertion is highly improper since it is based on a wrongful interpretation and illogical generalization of the Obaro reference.

- The Applicant submitted that, it is evident to the skilled person that Obaro's trial was clearly not designed to confirm that immune interference was not observed in the combined administration group. Although no immune interference was reported, it is submitted that the immune interference due to the addition of Hib-CRM197, the effect of the interference was masked because of DTwP, especially through the wP component, which was known to have an adjuvant effect. This is clearly explained and confirmed in Dagan 2004 cited therein (see e.g. abstract, lines 11-15).

- In contrast, in Choo et al, 2000 the trials were designed to confirm whether or not PCV7-CRM197 plus Hib-CRM197 shows immune interference, by way of only varying the factor of adding Hib-CRM197, i.e. PCV7-CRM197 was compared with PCV7-CRM197 plus Hib-CRM197, while all the other factors were properly controlled. Choo et al. indeed 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, which was observed in Choo.

The Opponents also relied on Housdorff et al. (D7) to supports that 11 valent vaccines with CRM197 was being develop by Wyeth. Inventors of present application are authors of paper. The Applicants disagreed and submitted that

- The Opponents (D7) have completely misinterpreted the Housdorff to meet their ends. The document does not disclose leave alone suggest an 11 valent with CRM-197 or any 11 valent being develop by Wyeth in particular. D7 relates to an analysis of data set to prepare 70 recent data sets to compare the serogroups causing invasive pneumococcal disease (IPD) with those represented in conjugate vaccine formulations. The idea behind the study is to optimize the formulations of future conjugate vaccines and to evaluate the appropriateness of their use in various geographic areas and age group, it is

necessary to better understand the serogroup specific epidemiology of this pathogens. Page 101, column 2 lines 11 to 15 are reproduced below.

- The analyses presented here indicate that introduction of effective pneumococcal conjugate vaccines containing at least 7 serotypes could potentially have a clinically important impact on the incidence of IPD in all regions, both in young children and in older children and adults. They also indicate that the magnitude of this impact would vary significantly, depending on the age group and geographic region.

- The study only suggests that 9 valent 11 valent might emerge in future. Page 118 column 1 lines 1 to 5. It is asserted that there is no whisper on stability, preparation and possibility of 13-valent pneumococcal vaccine, leave apart with a single or multiple carrier. As can be seen Dr. Peter Paradiso (inventor of IN'8081) was also involved in study, which merely focuses on incidence of IPD due to various serotypes in different geographical areas.

- At the hearing, through oral evidence that has a greater evidentiary value as opposed to mere statements by the Opponent's counsel, Dr. Paradiso confirmed that the study was a general study that did not focus on the work being done by Wyeth in particular in the field. He also confirmed that Wyeth never worked on an 11-valent vaccine. Dr. Paradiso stated and confirmed that in the said document there is no whisper in the said document whatsoever of any 11 valent being worked by Wyeth or being made with a single carrier like CRM 197.

9.17 Decision:

I have considered the arguments made by both the parties as well the evidence of Dr. Paradiso and am of the following opinion:

The question before is whether POSA would increase the valency of the available 7 and 9 valent pneumococcal conjugate vaccine to 13 valent, and if he does so would hat be with the use of a single carrier CRM197.

POSA based on his common general knowledge and prior art documents is aware that there is always a need to include additional serotypes in a vaccine based on serological studies. POSA is also aware of various issues faced in multivalent conjugate vaccine formulations namely: Carrier induced epitope suppression, Antigen competition, Immune interference, and Epitopic load. These problems were being faced also with regard to CRM197. Choo et al. and affidavit of Peter Paradiso clearly point to the same.

I agree with the Applicant, that POSA being aware that increasing the same carrier protein in a multivalent conjugate can diminish the response, and therefore would be directed towards/motivated to a mixed carrier strategy approach like that used by Sanofi or use of a new carrier like Protein D like that used by GSK.

Starting from Prevenar 7/9, a person skilled in the art would be aware that cross protection is conferred upon serotypes 6A, 9A and 19A (Dagan and Jakobsen). Therefore he would not take a risk of increasing these serotypes and increasing the epitopic load. Instead, a person skilled in the art would add other serotypes for which coverage was not being provided through cross protection such as serotype 3 and 7F.

I note that, Glaxo did exactly the same and tried to develop an 11v by adding 3 and7F, but failed ailed with serotype 3 and subsequently only retained serotype 7F resulting in 10 valent vaccine (Synflorix-Nurkka). Aventis also tried 11 valent vaccine while including serotype 3, 7F.

The present application claims a higher 13 valent vaccine that not only increased the coverage (from 9 to 13) but was also successful in including serotype 6A (which unexpectedly protects 6C as well), 19A and serotype 3 in addition to 7F. This does not seem to be achievable by reasonable expectation of success.

I disagree that in a complex and unpredictable field like vaccine, an attempt by the opponent to portray the inclusion of serotype in a vaccine formulation as being a "simple arithmetic progression". This seems to be only a speculation or a statement made in hindsight and speculation and hindsight cannot form a basis of obviousness enquiry. There was no Reasonable expectation of success as a POSA is aware of various issues faced in multivalent conjugate vaccine formulations namely: Carrier induced epitope suppression, Antigen competition, Immune interference, and Epitopic load. These issues were existing for CRM197 as well as has been stated and shown by Dr. Peter Paradiso. In fact a POSA would be motivated to use mixed carrier approach or use of Protein D as a carrier in view of the teachings of the prior art. The applicant has also demonstrated the remarkable immunogenicity, increased coverage, protection for serotype 3 etc and unexpected benefit of the addition of the serotype 6A to the multivalent: elicits cross-protective responses to serotype 6C, which is demonstrative of non-obviousness. In view of the above, I hold the claims of IN 8081 as inventive

10. Ground of Section 3(e)

10.1 The Opponents alleged in the written submissions that, the claimed invention is directed to 13 valent CRM197 conjugated pneumococcal vaccines wherein 13 serotypes are conjugated to

CRM197 carrier protein. At the time and well before the priority of instant application the phenomenon of conjugation of carriers to serotypes was well recognized as, 7 valent conjugated vaccine was marketed and other higher valency vaccines were also being developed. In addition to serotypes in 7 valent vaccines other serotypes were well recognized as being important to improve the disease coverage. The opponent stated that the alleged invention is nothing more than the addition to the 7-valent pneumococcal polysaccharide CRM197 conjugated vaccine with six further serotypes, namely 1. 3. 5. 6A. 7F and 19A, to provide a wider vaccination coverage, as suggested in art, to produce a 13-valent vaccine.

The process of conjugation was well known by use of which further serotypes have been added to get a 13 valent vaccine and the resultant vaccine is nothing more than an admixture where each component serotype performs their individual function to provide immunity to the respective antigens leading to aggregative effect of serotype coverage. Therefore, the claimed invention is not patentable under section 25 (1) (f) and pursuant to section 3 (e) of the Patent Act. The applicants submitted that the vaccine/multivalent immunogenic composition comprising a conjugate of 13 distinct polysaccharides and a carrier protein CRM197 is not an admixture as there is synergism and data is provided in the specification demonstrating this as has been discussed in the preceding paragraphs

10.2 Decision. The serotypes of the vaccine of IN'8081 are synergistic in the sense that they produce various advantages/surprising effect which are summarized:

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. **The response observed to the core 7 serotypes following immunization with 13v polysaccharide conjugates of the present invention are consistent with historical responses of the heptavalent formulation.**
c. **Remarkable immunogenicity: 13-valent pneumococcal vaccine polysaccharide produces higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM 197 (Page 48 of specification)**
d. **Immune protection for serotype 3**
e. **Inclusion of Serotypes 6A and 19A**
f. **Unexpected benefit of the addition of the serotype 6A to the multivalent: elicits cross-protective responses to serotype 6C**

In view of the above, I dismiss the ground of opposition of the invention not being patentable under Section 3 (e) of the Indian Patents Act.

11. SUFFICIENCY

11.1 The Opponent stated that the patent applicant claims that vaccines of present invention overcomes and/or do not show immune interference and therefore the claims are not sufficiently supported by the complete specification.

11.2 The applicant submitted that the specification claims a 13 valent composition which has been specifically described and also the advantages have been elaborated by evidence and other documents.

11.3 Decision:

In view of the discussion, I hold that the specification sufficiently described the invention and the claims are also supported by the patent specification. I therefore dismiss this ground

12. SECTION 8

12.1 The opponents have only mentioned the ground of section 8 , but have no pleadings in that respect, and nor does the Opponent elaborate/prove as to how the ground has not been met. 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 Opponent on various occasions.

12.2 Decision: I therefore dismiss this ground

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