The Respondent submits the following arguments in the above-identified case.

1. **Unique aspects of glycoconjugate vaccine development**

   Development of vaccines, especially glycoconjugate vaccines, has distinctive features in many aspects compared to those of general drug development, as shown by many papers and articles in this field and the declaration from Dr. Peter Paradiso (Exhibit No. Eul-25) who has been engaged in vaccine developments for over 30 years and significantly involved in the development of Prevenar®, the first pneumococcal conjugate vaccine (7-valent PCV), and also the 13-valent conjugate vaccine composition of the Subject Patent. The specification of the Subject Patent describes the patented invention in consideration of such unique aspects of the vaccine development.

   As already known, more than 90 pneumococcal serotypes that cause pneumococcal diseases (e.g., pneumonia, otitis media, etc.) have been discovered, and the distribution and severity of serotypes have been also well established through epidemiological studies. A person designing a new PCV would select vaccine serotype candidates in view of the serotypes included in the previously available PCVs as well as the distribution and severity of serotypes, and then choose a candidate carrier protein(s) suitable for the selected serotype candidates to confirm immunogenicity.

   First, each serotype antigen has a different level of immunogenicity, and as the number of vaccine serotypes increases, the risk of immune interference also increases. In a high multivalent vaccine as high as the 13-valent composition of the Subject Patent, the immune response becomes very complex, and thus, it is not easy even to choose serotype candidates that may show proper immunogenicity. For such reasons, the inventors of the Subject Patent elaborated the reasons why they decided to select and add serotypes 1, 3, 5, 6A, 7F and 19A on pages 7 to 11 of the specification.

   * For **serotypes 6A and 19A**, it was already known that serotypes 6B and 19F, which were included in Prevenar®, may not provide sufficient cross-protection (see paragraphs [0029] and [0030] of the Subject Patent). However, the competitors (e.g., Sanofi and Glaxo) did not choose to add these serotypes in their vaccines. It was also known that addition of serotypes 12 and 15 is preferable to optimize global coverage of the vaccine (Exhibit No. Kap-14; CR5, Hausdorff, 2000). However, the inventors of the Subject Patent decided to choose serotypes 6A and 19A, rather than serotypes 12 and 15 that were more advantageous in terms of expanding coverage. This indicates that a person skilled in the art does not simply choose vaccine serotypes only since they are known to show high incidence in epidemiological studies, or because they may not be cross-protected by the serotypes
included in the previous vaccines.

- For **serotype 3**, it was known that Glaxo's PCV11-PD failed to exhibit sufficient immune response, in particular with regard to immunologic memory (Exhibit Nos. Eul-2, Gatchalian (2001), and Kap-29, Nurkka (2004)). Thus, addition of serotype 3 was also not one that a person skilled in the art at the time would have chosen to include, but might have decided to replace it with another serotype, or even opt for a less multivalent vaccine in order to increase likelihood of success, as Glaxo eventually did (see Exhibit No. Eul-3, Prymula (2009)).

Moreover, there is no way to anticipate which serotypes would show interference with which carrier protein(s) since the mechanism of immune interference has not been established. Thus, it is never an easy work to select specific serotype(s) and specific carrier protein(s) to build a specific combination thereof.

Furthermore, one cannot expect whether all of the selected serotypes would exhibit satisfactory immunogenicity since the ability of each serotype to induce immune response varies when conjugated to a specific carrier protein. Further, newly added serotype(s) may alter the immune response to the serotypes already included in the vaccine. However, it would not be desirable if the serotypes added to a new formulation cause a negative impact on the immunogenicity of the vaccine serotypes included in the previously available vaccine (e.g., the 7-valent Prevenar®). Accordingly, a new vaccine formulation is assessed with "non-inferiority" criteria to insure that the immune response to the original components is not compromised because these are globally the most prevalent disease causing types.

In another aspect, the general complexity of conjugate adds to the unpredictability of success for highly multivalent conjugate vaccines. While various conjugation methods are generally known in the art, it is still important to find manufacturing conditions suitable for each conjugate to yield a successful conjugate vaccine since the manufacturing conditions may differ depending on the serotypes and carrier proteins.

The specification of the Subject Patent describes processes and conditions suitable for preparation of conjugates for all 13 serotypes in great detail in Examples 1 to 14, in almost the half volume of the specification (pages 13-26). Specifically, preparation of capsular polysaccharides of each serotype is described on a step-by-step basis as (i) preparation of master and working cell banks, (ii) fermentation and harvesting, (iii) purification, and (iv) characterization. Preparation of saccharide-CRM_{197} conjugate is also described in the steps of (i) activation and conjugation, and (ii) characterization. It can be easily understood, that although chemical activation and conjugation methods are generally known, it may not be easy to find the specific process and conditions as shown in the examples of the Subject Patent from such general knowledge.

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1 The original vaccine serotypes are the most prevalent disease causing types throughout the world. Thus, regardless of how many new serotypes were added in the new vaccine, it would not be considered valuable if the newly added serotypes deteriorate the immunogenicity of the original components.
As such, the inconsistent immune responses observed in the prior art during the development of glycoconjugate vaccines may have rooted from the complexity of our immune system and immunological interference yet to be established, and thus cannot be anticipated or prevented in the development of eventual even more complex conjugate vaccines. Thus, it is understood that the development of a new glycoconjugate vaccine is not completed by simply choosing the serotypes and carrier proteins to include in the vaccine, but only after the immune response of a conjugate vaccine from a specific combination of serotypes and carrier proteins is confirmed.

The difficulties in the prior art are further compounded by the fact that vaccine developers tend not to disclose much information on their new vaccines (except for the vaccine serotypes and carrier design) to the public. Rather, they often prefer to keep the information on conjugation process and conditions as a trade secret.2

Another specific aspect of vaccines that adds to the general risk of development, is the need for immunological compatibility with other infant vaccines is another important factor for the development of a new vaccine product. Thus, not only is the clinical evaluation made to license the vaccine deemed important, the post-surveillance data is also considered to be very important when developing a new vaccine.

Accordingly, it took a very long time to increase only a few valency in the next commercial PCV (i.e., Glaxo's PCV10) after the licensure of the 7-valent Prevenar® in 2000, although all the serotypes and carrier protein candidates were known in the art as such.3

2. A person skilled in the art as of the priority date would not have selected CRM197 as a single carrier in multivalent PCVs with 11-valent or higher.

A. Since 2000's, prejudice against a single carrier protein was widely spread since the risk of immune interference from carrier overload increases as the number of conjugates in a single formulation increases.

In the vaccine field, it was commonly accepted that the risk of immune interference increases as more antigens are added to a formulation since interaction between the antigens are expected to increase. In particular, in glycoconjugate vaccines like the Subject Patent, there are a lot of factors affecting the immunogenicity of formulation since polysaccharide antigens and carrier proteins with distinct immunological

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2 For this reason, in the vaccine field, it is not uncommon that review articles make incorrect statements based on wrong information or pure speculation. Sometimes, such an incorrect statement is referred to by other review articles multiple times. For example, Exhibit No. Kap-11(O'Brien, 2004) is a review article relating to PCV11-CRM1, developed by Wyeth in a preclinical stage. However, as noted in Dr. Paradiso's declaration, Wyeth never attempted to develop PCV11 (Exhibit No. Eul-25; see Item 13).

3 PCV10 by Glaxo was licensed in 2009, followed by PCV13 by Wyeth in 2010. No other higher-valent PCVs have been licensed ever since (even now after four years from PCV13).
properties are included in a single formulation, and are conjugates with different conformations. Thus, the immune response of glycoconjugate vaccines is much more complex and unexpected compared to the vaccines with a mere mixture of antigens. The risk of interference therefore is highly unpredictable.

Other glycoconjugate vaccines available at the priority date, including *H. influenzae* type b vaccines and meningococcal vaccines, were merely monovalent or tetravalent. On the contrary, pneumococcal vaccines were designed to cover 7 serotypes from the first commercial product (Prevenar®) as there were over 90 serotypes known to cause pneumococcal diseases. In the process, the development of a 7-valent vaccine by Merck, where OMPC was used as a single carrier, was halted. Further, a case of 12-valent *E. coli* glycoconjugate formulation with a single rEPA carrier was reported to exhibit significant immune suppression (i.e., 30~90% reduction in the immune response compared to administration of a monovalent conjugate) in 6 antigens included in the formulation (Exhibit No. Eul-4, Fattom, 1999; see Abstract). Thus, the vaccine developers at that time clearly recognized the technical difficulty of achieving a higher multivalent conjugate vaccine with more than seven conjugates as well as the significance of interference problem.

Accordingly, studies were performed to analyze the cause of interference in the multivalent conjugate vaccines. Such studies include those described in Exhibit No. Eul-4 (Fattom, 1999) and Exhibit No. Eul-5 (Dagan, 1998).

(1) Eul-4 reference (Fattom, 1999) described that the reason of immune suppression to polysaccharide antigens observed in the multivalent conjugate vaccines resides in the excessive amount of carrier protein in the co-administered vaccines. Thus, the authors suggested using multiple carrier proteins when designing a multivalent conjugate vaccine to reduce interference (see Abstract). This reference also provides experimental results where rEPA-conjugated *Staphylococcus aureus* vaccine co-administered with free carrier protein (rEPA) showed immune suppression to polysaccharide antigens, unlike the co-administration of a heterogenous protein (DT), thereby confirming that mixed carrier proteins can be an effective way of avoiding interference in a multivalent conjugate vaccine.

(2) The authors of Eul-5 reference (Dagan, 1998) studied the same issue in PCVs. Eul-5 shows that when PCV4-TT or PCV4-DT (where polysaccharide antigens of serotypes 6B, 14, 19F and 23F conjugated either to TT or DT) is co-administered with PRP-TT and DTP vaccines, anti-Hib response is significantly suppressed only in the PCV4-TT group, and that the level of suppression correlates to the dose of co-administered TT. Further, Eul-5 mentions a prior study where the co-administration of PCV7-OMPC with PRP-OMPC caused significant interference compared to the co-administration with PRP-CRM197 (see Eul-5, page 2097, left column, 3rd paragraph; Reference 14: Greenberg, *et al.* (1997)). Based on these results, Eul-5 indicated that the immune interference occurs in multivalent conjugate vaccines when the same carrier protein is used in more than two antigens administered concomitantly. Moreover, the authors stated that this
issue should be considered when introducing an immunization program that includes multivalent conjugate vaccines, while emphasizing that, to solve this problem, the amount of same carrier protein in the multivalent formulation should be restricted or other protein or non-protein carriers should be developed.

As discussed above, in the vaccine field at the priority date, there was a general recognition that the amount of same carrier protein should be limited to avoid interference from carrier overload. That is, it was recognized that the use of mixed carrier proteins was considered favorable to a single carrier design, or that entirely new carriers needed to be developed. Such recognition was fully reflected in the competitors' development of next-generation vaccine products, which faithfully followed these concepts.

B. Since 2000, the competitors that attempted to develop more than 9-valent PCVs adopted mixed carrier designs in consideration of problems associated with the carrier overload and/or sought to develop alternative carriers.

The competitors could not be free from the carrier overload problem as the number of conjugates to include in the next generation PCVs got higher. Thus, from the conventional single carrier design, they had to move on to find a new vaccine design that can lead to successful PCVs with higher than 9-valent. Such attempts resulted in the use of mixed carriers, instead of single carriers, as the use of a new carrier protein that had not been included in the routine vaccines for infants or as a combination thereof.

(1) Sanofi's development of a mixed-carrier PCV (Eul-5, Kap-24, Eul-6 and Eul-26) – PCV11-DT/TT

Many prior art references show that Sanofi gave a careful consideration on the selection of carrier proteins when it tried to develop PCV11 as a first runner. After confirming the idea of using mixed carriers in a multivalent conjugate vaccine from Exhibit No. Eul-5 (Dagan, 1998), Sanofi prepared a higher valent PCV for serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F with a single carrier of TT or DT (i.e., PCV8-TT and PCV8-DT) and evaluated the serotype-specific immunogenicity in infant clinical trials (Exhibit No. Kap-28; Nurkka, 2001). As a result, it was confirmed that serotypes 3, 9V, 14 and 18C showed a better immune response when conjugated to DT, while serotype 4 had a higher immunogenicity when conjugated to TT. This result was reflected when designing Sanofi's PCV11.4

4 "Response to PncD and PncT differed to certain serotypes, especially during the primary course of vaccination. PncD induced higher and/or earlier responses to types 3, 9V, 14, and 19C, while responses to type 4 were higher in the PncT group. For serotypes 6B, 19F, and 23F, no clear differences could be found. This information has now been used for development and optimization of new 11-valent mixed carrier PncD/T vaccines. The 11-valent PncD/T vaccine is a mixture of both PncD and PncT conjugates containing PSs 3, 6B, 14, and 18C conjugated to diphtheria toxoid and 1, 4, 5, 7F, 9V, 19F, and 23F to tetanus toxoid" (Exhibit No. Kap-28,
That is, it is apparent that although Sanofi obtained clinical results supporting an acceptable level of immunogenicity in PCV8 with a single carrier, they did not expect similar results from PCV11. As such, in an earlier study where PCV11 with mixed carriers of TT and DT was tested in a clinical trial (Exhibit No. Eul-6; Wuorimaa, 2001), Sanofi explained that its decision to use mixed carriers was to prevent immune suppression that might occur from carrier overload. A later published review article, Finn (2004), also confirmed that Sanofi's choice of mixed carrier design was based on the fear of immune interference from carrier overload (Exhibit No. Eul-26).

(2) Glaxo's development of PCVs with a new carrier and mixed carriers (Eul-2, Eul-3, Kap-29 and Eul-27) – PCV11-PD, PCV11-PD/XX and PCV10-PD/DT/TT

Glaxo made a bold decision to develop a new carrier protein, Protein D (PD), which had not been included in the conventional infant vaccines, and to use it as a single carrier. PD, which was isolated from non-typeable H. influenzae (NTHi), performed as an effective carrier protein, as well as possessing an additional merit of preventing acute otitis media (AOM) caused by NTHi since it has its own immunogenicity (Exhibit No. Eul-3; Prymula, 2009). It took a considerable time and effort to develop a new carrier, while abandoning the conventional carriers such as DT, TT, CRM197 and OMPC, for which safety and efficacy have been well established. Thus, Glaxo's selection shows that it was a very critical issue to solve the overload problems with the conventional carrier proteins in the next-generation high multivalent vaccines.

Glaxo's PCV11-PD was reported to show an insufficient response to serotype 3 in an early clinical trial (Exhibit No. Eul-2; Gatchalian, 2001). In subsequent large-scale trials, the vaccine showed immunogenicity either comparable to a control

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5 "The use of a mixed carrier vaccine reduces the load of an individual protein and might reduce interference in immunogenicity when multivalent conjugate vaccine is formulated into a single dose" (Exhibit No. Eul-6, page 2, "Introduction," 2nd paragraph, the last three lines).

6 "Several other combined PS-conjugates containing up to 11 serotypes are under development (Table 1) but there must be some limit to the number that can practically be included. Concerns about possible interference or inhibitory effects of using large quantities of the same carrier protein for all the different conjugates have already led to come formulation with two distinct protein carriers (Table 1)" (Exhibit No. Eul-26, page 8, the last paragraph, lines 3-9).

7 "The use of the novel protein D (PD) carrier protein instead of carrier proteins closely related to coadministered antigens therefore minimizes the risk of interference related to the carrier protein and, importantly, by virtue of its antigenic properties, may prevent AOM due to NTHi" (Exhibit No. Eul-3, page 1480, right column, Section "Why select a new carrier protein," 1st paragraph, lines 4-9).
group (post-primary) or inferior (booster immunization) for serotype 3 (Exhibit No. Kap-29; Nurkka, 2004; see Table 4). A noticeable fact is that as soon as the early clinical result in 2001 indicated an insufficient immune response to some serotype antigens, Glaxo filed a patent application on 11-valent or higher PCVs characterized with the use of PD mixed with one or two additional carrier(s) (Exhibit No. Eul-27: WO2003/051392; see bibliographical data).8

That is, Glaxo filed such a patent application since it believed that the suppression to some pneumococcal serotype responses in its PCV11 might have occurred due to the use of a single carrier, and that mixed carrier strategy as adopted by Sanofi might be able to solve the problem. Actually, Glaxo later changed the design of its vaccine to include three different carriers (PD, DT and TT) for ten serotypes and obtained a licensure for PCV10-PD/DT/TT (Exhibit No. Eul-3, Prymula, 2009).

Although Glaxo's mixed carrier PCV10 was licensed after the priority date, it is evident that Glaxo decided to use mixed carriers to solve the immune interference problem reported in the early clinical results of Eul-2, in view of the filing date and content of the Eul-27 patent application. Furthermore, since the patent application was published before the priority date, the vaccine developers as of the priority date would have recognized that it was inevitable to use mixed carriers in the vaccines with 11-valent or higher.

C. As cases of immune interference began to rise with multivalent conjugate vaccines with a CRM197 single carrier since 2000, it was difficult to expect that CRM197 could be further used as a single carrier.

PCV7 and PCV9, which were developed by the patentee of the Subject Patent, used CRM197 as a single carrier, and both vaccines were reported to be safe and effective in the clinical trials conducted in late 1990's (e.g., Exhibit Nos. Kap-4 to Kap-8, Kap-12, Kap-13, Kap-17 and Kap-18). However, since 2000, reports on the interference among CRM197-conjugated vaccines were accumulating.

In Choo (2000), which is submitted as Exhibit No. Eul-28, the immune response of a separate co-injection of PCV7-CRM197 and HbOC (i.e., Hib-CRM197) was compared with that of a combined administration of PCV7-CRM197 and HbOC. In this study,

8 Eul-27 application was filed as an international patent application on December 18, 2002 while claiming a priority based on a UK application filed on December 18, 2001. It was later published on June 26, 2003, i.e., before the priority date of the Subject Patent, as an international publication. While demonstrating a PCV11 using PD and DT as mixed carriers, Eul-27 application has Claim 1, which relates to 11-valent or higher PCV characterized by using two or more carrier proteins and reads as follows:

"1. An improved Streptococcus pneumoniae vaccine comprising 11 or more polysaccharides from different S. pneumoniae serotypes conjugated to 2 or more carrier proteins wherein, serotypes 6B, 19F and 23F are conjugated to 1 or 2 secondary carrier proteins, and wherein the secondary carrier proteins are different from the first carrier protein."
both test groups were evaluated for immunogenicity after primary series at 2, 3 and 4 months as well as for ability to induce immunological memory after booster immunization with 23-valent polysaccharide vaccine (PnPV23) at 13-16 months. As a result, while both groups were not distinguishable in terms of the ability to induce immune memory, the combined administration resulted in a severe suppression to five out of seven serotype polysaccharides after primary series (i.e., 29-46% reduction in IgG level compared to the separate co-injection group; see Exhibit No. Eul-28, Table 1).

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Separate co-injection group (µg/ml)</th>
<th>Combined administration group (µg/ml)</th>
<th>Reduction (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2.40</td>
<td>2.06</td>
<td>14</td>
</tr>
<tr>
<td>6B</td>
<td>1.11</td>
<td>0.64</td>
<td>42</td>
</tr>
<tr>
<td>9V</td>
<td>1.50</td>
<td>1.06</td>
<td>29</td>
</tr>
<tr>
<td>14</td>
<td>2.23</td>
<td>1.39</td>
<td>38</td>
</tr>
<tr>
<td>18C</td>
<td>1.42</td>
<td>1.18</td>
<td>17</td>
</tr>
<tr>
<td>19F</td>
<td>2.45</td>
<td>1.58</td>
<td>36</td>
</tr>
<tr>
<td>23F</td>
<td>1.52</td>
<td>0.82</td>
<td>46</td>
</tr>
</tbody>
</table>

*: Calculated based on the 5-month data in Table 1 of Choo (2000)

The above result was unacceptable in terms of "immunogenicity after primary series," which was the most important criterion to evaluate the efficacy of PCVs as of 2005 as described by Jodar et al (2003) and adopted by the WHO. Further examples of immune interference are reported by Exhibit No. Eul-8 (Buttery, 2005). In particular, such interference was seen for the combined formulation of two CRM197-conjugated vaccines (i.e., PCV9-CRM197 and MenC-CRM197) co-administered with the other routine vaccines (Hib and DTP vaccines). Based on such observations, concerns on CRM197 as a single carrier grew.

9 The Choo reference was published in 2000 and does not provide data required to evaluate the efficacy of PCVs according to the criteria established at the priority date (2005), i.e., percentage of subjects with serotype-specific IgG level (determined by ELISA) of ≥ 0.35 µg/ml after primary series (see footnote 10 below). Thus, the only plausible way of comparing the efficacy of two test groups is to directly compare the IgG levels as shown above.

10 “Primary end point. The following criteria are recommended for use as the primary end-point for demonstration of non-inferiority against a registered vaccine:

- IgG antibody concentration, as measured by ELISA, in sera collected 4 weeks after a three-dose primary series is considered to be the optimal primary end-point and main licensing parameter.”

After the results of Eul-8 came out, even the patentee’s research group internally considered that CRM\textsubscript{197} cannot be used further as a single carrier. Thus, various candidate carriers were considered and evaluated to replace and/or supplement CRM\textsubscript{197} in the next-generation PCV or combination vaccines (see Exhibit No. Eul-25; Dr. Paradiso’s declaration, Items 17-21).

D. Sub-conclusion

As discussed above, the vaccine developers at the priority date were reluctant to adopt a single carrier design in high multivalent PCVs so that they could avoid immune interference due to carrier overload. Such recognition led to the use of mixed carriers and/or development of a new carrier protein. Further, CRM\textsubscript{197}, which was known to be relatively compatible with other vaccines in PCV7 and PCV9, was reported to cause severe suppression in 7+1 (Eul-29, Choo (2000)) and 9+1 combination vaccines (Eul-8, Buttery (2005)). Thus, it was considered risky to use CRM\textsubscript{197} as a single carrier for a 11 or higher valent PCVs. It is apparent that the competitors at that time did not use CRM\textsubscript{197} as a single carrier due to the concerns on immune interference, and not because of a patent barrier as argued by the Petitioner.\textsuperscript{11} Moreover, the new carrier PD, which was developed as an alternative, has been reported to show immune suppression when used as a sole carrier.

Given the above, a person skilled in the art would even less have adopted any carrier protein (including CRM\textsubscript{197}) as a sole carrier when designing a multivalent PCV of 11-valent or higher. Especially, the conventional carrier proteins such as DT, TT, and CRM\textsubscript{197} were not only included in the routine vaccines such as DTP, but were also used as a carrier protein for other conjugate vaccines for infants such as Hib and meningococcal vaccines. Thus, if any of them were to be chosen as a candidate carrier, it would have been used at least not as a sole carrier.

Accordingly, the Petitioner’s argument that there was no difficulty in selecting CRM\textsubscript{197} as a single carrier for PCV13 based on the vaccine designs disclosed in Cited References 1 to 4 is completely groundless. Thus, such an argument has no merit since it does not consider the technical circumstances at the priority date and merely chooses and compares prior art references based on hindsight.

3. Even the serotype selection is not obvious as the Petitioner argued. The immunogenicity of a polysaccharide conjugate vaccine differs depending on each serotype and the multivalency of the conjugate vaccine makes the serotype-specific immunogenicity profile even more complex. Thus, a skilled person would more likely have developed a lesser valent vaccine.

A. The immunogenicity of a polysaccharide conjugate vaccine differs depending on each serotype.

Exhibit No. Eul-31 examined the immunogenicity of three 1-valent conjugate vaccines containing pneumococcal serotype 6B, 19F and 23F, respectively, conjugated to CRM197, and found that serotypes 6B and 19F produced a strong anti-polysaccharide antibody response, whereas serotype 23F conjugated to CRM197 failed to produce a significant anti-polysaccharide antibody response (Exhibit No. Eul-31, page 4863, Figure 112, etc.). Particularly, immunization with 23F-CRM197 resulted in a significant carrier-specific antibody response, whereas 23F-specific antibody response was poor. This means that T-cell immune response was successfully induced due to the carrier protein, although the immune response specific to serotype 23F conjugated thereto was not stimulated. This is one good example showing that the conjugation of a certain polysaccharide to a carrier in a conjugate vaccine does not necessarily induce immune responses specific to the polysaccharide.

B. The multivalency of the conjugate vaccine makes the serotype-specific immunogenicity profile even more complex

As described in the specification of the Subject Patent, serotype 19F-specific efficacy was not demonstrated in the Finnish clinical trial for otitis media using a 7-valent pneumococcal CRM197 conjugate vaccine (Paragraph [0036] and Table 1 of the patent specification). According to Exhibit No. Eul-32, the report of the Finnish clinical trial, the efficacy of serotype 19F was merely 25% (95% CI: -14 to 51%) while other serotypes showed 49~84% (Exhibit No. Eul-32, page 406, Table 2).

If multiple different carbohydrate antigens are conjugated to the same protein, then the B cells specific for different carbohydrates may compete with each other. Further, different serotypes have different structural influences on antigen processing and presentation of the same vaccine conjugate. As such, in a multivalent conjugate vaccine, the serotype-specificities in immunogenicity further change.

In a 9-valent pneumococcal conjugate vaccine, serotype 1 became a problem. According to Exhibit No. Eul-33 (2005), which is a commentary article regarding large clinical trials using the 9-valent pneumococcal CRM197 conjugate vaccine conducted in Africa before the priority date of the Subject Patent, there were doubts about whether this type of vaccine is effective against diseases caused by serotype 1. The reason was that in the Gambian trial, in the latest trial using serotype 1, there was a small increase in serotype 1 disease, while the only other trial of a serotype 1 containing vaccine (South Africa) did not have enough cases of serotype 1 disease to evaluate efficacy (Exhibit No. Eul-33, page 498, right column, last paragraph to page

Serotype 6B induced a slightly stronger immune response than serotype 19F.
A review article, Exhibit No. Eul-34, also made a statement to the same effect, i.e., the Gambian trial revealed the efficacy of 9-valent vaccine to be incomplete for certain serotypes such as serotype 1 (Exhibit No. Eul-34, page 208, right column, lines 12-16).\(^\text{13}\)

C. Thus, the serotype combination according to the Subject Patent could not have been easily conceived with a reasonable expectation of success.

As clearly shown by the above examples, the conjugation of a certain polysaccharide to a carrier in a conjugation vaccine does not consistently induce immune responses specific to the polysaccharide. Even if a need to add certain serotypes in a vaccine is acknowledged by an epidemiological study, whether the addition of such serotypes in the vaccine can actually provide the desired immunogenicity could not have been reasonably expected.

- In fact, serotype 6A was known as one of the commonly found in North America in 1980s (Exhibit No. Eul-35). However, serotype 6A was also known to show a poor immunogenicity when being included in a 14-valent polysaccharide vaccine or a 2-valent CRM197 conjugate vaccine (Exhibit Nos. Eul-35 and Eul-36). Thus, there was no reasonable expectation of success in adding serotype 6A, and thus, none of the pneumococcal vaccines developed before the Subject Patent contained serotype 6A.

- The 11-valent vaccine that Glaxo developed did not provide any significant immunogenicity against serotype 3, which was eventually excluded from the commercial formulation (Exhibit Nos. Eul-2 and Kap-29).

Further, when the valency is increased to more than 9-valency, there is no guarantee that the comparable efficacy with existing lower-valent conjugate vaccines would be seen (in fact, serotype 19F successfully induced its immunogenicity when being solely conjugated to CRM197 (Exhibit No. Eul-31), while in the 7-valent vaccine, the efficacy was not shown (Exhibit No. Eul-32). Thus, there was no expectation of success that significant immunogenicity against each of the 13 serotypes would be obtained when adding new serotypes 3, 6A, 7F and 19A to the existing 9-valent CRM197 conjugate vaccine (while maintaining other constitutions).

Moreover, as explained on page 21 of the Respondent's brief submitted on September 30, 2014, addition of other serotypes such as serotypes 12 and 15 was considered to be more preferable. Given this, it was not easy to select the serotype combination according to the Subject Patent to those skilled in the art at the time of the priority date. Thus, the inventiveness of the vaccine according to the Subject Patent, which can induce specific immune responses for all of the 13 different

\(^\text{13}\) Although Exhibit Nos. Eul-33 and 34 were published after the priority date of the Subject Patent, they all refer to the clinical trial report in Gambia published before the priority date.
serotypes, cannot be denied.

4. Further, immunogenicity of a conjugate is affected by various factors including manufacturing processes and conditions.

Components in a conjugate vaccine (a serotype and a carrier protein) are not simply combined. Rather, they are chemically conjugated through random reaction between functional groups present along the polysaccharide chain and functional groups present along the polypeptide chain, forming a new conformational structure.

To prepare polysaccharide conjugate vaccine, the polysaccharide is isolated and purified through fermentation of polysaccharide-producing microorganism, a carrier protein is isolated and purified via a separate biological process, and then the two components are chemically conjugated to each other. Polysaccharides require activation before conjugation to the carrier protein so that the functional groups necessary for the conjugation can be exposed, where a glycosidic bond may be cleaved to thereby depolymerize the polysaccharide. **Such processes affect the three-dimensional structure, and in turn, the immunogenicity of conjugates** (Exhibit No. Eul-25: Declaration, Paragraphs 9 and 10; and Exhibit No. Eul-37: Kiberan, 2000).

The specification of the Subject Patent provides detailed descriptions regarding different activation conditions and CRM197 conjugation conditions suitable for each serotype (see Examples of the patent specification). For example, whether hydrolysis is to be carried out in activating the polysaccharide, what reagents to be used for activation, whether a special treatment should be employed for activation, how the polysaccharide and carrier protein should be admixed for conjugation, whether aqueous or DMSO condition to be employed for conjugation, etc. are all differently described for each of the 13 serotypes (provided below is a table summarizing some representative differences).

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Hydrolysis prior to activation</th>
<th>Reagent for hydrolysis</th>
<th>Additional reagent for activation</th>
<th>Lyophilization</th>
<th>Resuspension for conjugation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydrolysis</td>
<td>Sodium carbonate</td>
<td></td>
<td></td>
<td>In water</td>
</tr>
<tr>
<td>3</td>
<td>Hydrolysis</td>
<td>Acetic acid</td>
<td>Magnesium chloride</td>
<td></td>
<td>In water</td>
</tr>
<tr>
<td>4</td>
<td>Hydrolysis</td>
<td>Hydrochloric acid</td>
<td></td>
<td></td>
<td>In water</td>
</tr>
<tr>
<td>5</td>
<td>No Hydrolysis</td>
<td>-</td>
<td></td>
<td></td>
<td>In water</td>
</tr>
<tr>
<td>6A</td>
<td>Hydrolysis</td>
<td>Acetic acid</td>
<td></td>
<td>Discrete lyophilization</td>
<td>In DMSO</td>
</tr>
<tr>
<td>6B</td>
<td>No Hydrolysis</td>
<td>-</td>
<td></td>
<td>Discrete lyophilization</td>
<td>In DMSO</td>
</tr>
<tr>
<td>7F</td>
<td>No Hydrolysis</td>
<td>-</td>
<td></td>
<td>Discrete lyophilization</td>
<td>In DMSO</td>
</tr>
</tbody>
</table>
As such, the conditions for preparing effective conjugates differ depending on each serotype, which should be explored on a serotype-by-serotype basis. While it may not be difficult to explore such processes and conditions suitable for some serotype conjugates, there may be some other serotypes that are difficult to be prepared as effective conjugates for use as vaccine.

Specifically, serotype 19A was never included in a conjugate vaccine until the inventors of the Subject Patent discovered that co-lyophilization of the activated polysaccharide with a carrier protein followed by resuspension in DMSO improves conjugate characteristics in terms of molecular size and the percentage of free saccharide\textsuperscript{14}, compared to the use of discrete lyophilization of polysaccharides and carrier proteins in DMSO or aqueous co-lyophilization of polysaccharides and carrier proteins without DMSO. By adopting a suitable conjugation process and conditions for preparing an effective 19F conjugate in the Subject Patent, a multivalent conjugate vaccine including serotype 19F became possible. The above process of preparing 19A conjugate was separately patented (Exhibit No. Eul-38\textsuperscript{15}), which clearly shows that such a process could not have been easily conceived by a skilled person at that time.

Further, serotype 3 was known as a difficult serotype to work with due to the structure of the polysaccharide and the tendency to aggregate. The specification of the Subject Patent describes: "Attempts to produce a multivalent pneumococcal conjugate vaccine that exhibits significant immunogenicity with respect to serotype 3 polysaccharides have been unsuccessful" (Paragraph [0024] of the patent specification). It was well known in the art at the priority date that Glaxo included serotype 3 in its pneumococcal conjugate vaccine but failed to achieve a desirable immune response against serotype 3 (Exhibit Nos. Eul-2 and Kap-29). However, the inventors of the Subject Patent adopted hydrolyzing the polysaccharide, but with mild acid such as acetic acid, to control viscosity, and adding magnesium chloride with periodate to obtain reasonable levels of activation, whereby an effective serotype 3 conjugate for

\textsuperscript{14} Free saccharides are undesirable byproducts produced during the conjugation step, which deteriorate the immunogenicity of a conjugate vaccine.

\textsuperscript{15} It belongs to the same patent family as the Subject Patent.
use in a multivalent CRM197 conjugate vaccine became possible (Exhibit No. Eul-25, paragraph 15).

Prior to the Subject Patent, it was not apparent that suitable processes for all 13 serotypes could be found. Although there was a need for a conjugate vaccine for pneumococcal serotypes of more than 9 serotypes that were included in the 9-valent vaccine, i.e., 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F, there were also high technical barriers as to how a multivalent conjugate vaccine effective against all of the serotypes included can be provided, i.e., what carrier protein(s) to be used, how many and which serotypes to be included and how the carrier and polysaccharides to be conjugated.

However, the inventors of the Subject Patent finally discovered suitable conditions for providing a pneumococcal conjugate vaccine containing as many as 13 different serotypes and effective for all of them, whereby a 13-valent pneumococcal conjugate vaccine as claimed, which never existed before the Subject Patent, became possible.

5. Conclusion

As discussed above, the Petitioner’s arguments are clearly groundless. Accordingly, the Respondent respectfully requests for a decision according to the tenor of response.

January 9, 2015

Counsels for the Respondent

EXHIBITS

| Eul-25 | Declaration of Dr. Peter Paradiso |
| Eul-26 | Finn, A., British Medical Bulletin 2004; 70:1-14 |
| Eul-27 | WO 03/051392 A2 |
| Eul-28 | Choo et al., The Pediatric Infectious Disease Journal 2000; 19(9):854-862 |
| Eul-38 | U.S. Patent No. 7955605 |