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Case No: A3/2021/0238

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGH COURT OF JUSTICE, BUSINESS AND PROPERTY COURTS, INTELLECTUAL PROPERTY LIST (CHANCERY DIVISION), PATENTS COURT
Meade J
[2020] EWHC 2636 (Pat)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 22 July 2021

Before :

LORD JUSTICE NEWEY
LORD JUSTICE ARNOLD
and
SIR CHRISTOPHER FLOYD

- -

Between :

WYETH LLC	**Appellant**
- and -	
MERCK SHARP & DOHME (UK) LIMITED	**Respondent**

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- -

Michael Tappin QC and **Andrew Lykiardopoulos QC** (instructed by **Marks & Clerk Law LLP**) for the **Appellant**
Thomas Hinchliffe QC and **Katherine Moggridge** (instructed by **Hogan Lovells International LLP**) for the **Respondent**

Hearing dates : 14-15 July 2021

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Approved Judgment

Covid-19 Protocol: This judgment was handed down remotely by circulation to the parties' representatives by email, release to BAILII and publication on the Courts and Tribunals Judiciary website. The date and time for hand-down is deemed to be at 10:30am on 22 July 2021

Lord Justice Arnold:

Introduction

1. The Appellant ("Wyeth") is the registered proprietor of European Patent (UK) No. 2 676 679 entitled "Formulations which stabilize and inhibit immunogenic compositions" ("the Patent"), which has a priority date of 26 April 2006. Wyeth appeals against an order of Meade J dated 15 December 2020 declaring, for the reasons given in the judge's judgment dated 15 October 2020 [2020] EWHC 2636 (Pat), that (i) all the claims of the Patent (as unconditionally proposed to be amended) are invalid on the ground of obviousness in the light of C. de la Pena *et al*, "Present and future of the vaccination against pneumonia", *Pediátrika*, 24(4), 147-155 (2004) ("de la Pena") and (ii) a vaccine referred to as "V114" which the Respondent ("MSD") intends to market if it receives a marketing authorisation would not infringe any claim of the Patent even if valid. Wyeth contends that none of the claims of the Patent is obvious over de la Pena and that V114 infringes at least claim 1. MSD supports the judge's conclusions, and also contends by a respondent's notice that, if the Patent is not obvious over de la Pena, it is insufficient because the specification does not contain any more information than de la Pena to make it plausible that a vaccine of the kind claimed would be worth trying to make.

Technical background

2. Pneumococci are bacteria which cause a range of diseases such as bronchitis, meningitis and pneumonia. Each bacterium is encapsulated by a shell of polysaccharides. This polysaccharide shell can be used for vaccines because it can produce an immune response, and thus be recognised and bound by antibodies of the immune system. The Patent is concerned with "conjugated" polysaccharide vaccines. This refers to the fact that the immunogenicity of polysaccharides is improved by conjugation (covalent linkage) to a carrier protein.

3. Within a species of such bacteria, "serotypes" are used to classify the variations that occur in the particular polysaccharides displayed on their surface. More than 90 pneumococcus serotypes have been identified. Some serotypes are classed together into serogroups (there are around 40). Serogroups are given numerals by which to identify them. Where a serogroup has only one serotype within it, only a numeral is used. Where a serogroup contains more than one serotype, then a letter is given as a suffix (e.g. serogroup 19 includes the serotypes 19A, 19B, 19C and 19F).

4. At the priority date, pneumococcal vaccines could be "multi-valent", meaning that they included polysaccharides from more than one serotype (i.e. targeting different strains of the pneumococcus). Where a vaccine contains seven serotypes, it is commonly referred to as a 7-valent or 7v vaccine. Similarly, one with nine serotypes is a 9v vaccine, and so on.

5. Although, in principle, it was desirable to include as many serotypes as possible in a vaccine to obtain the greatest coverage possible, it was known that there were practical limitations to this, particularly with conjugated vaccines. In reality, a more limited choice of serotypes had to be made.

6. At the priority date only two pneumococcal vaccines were commercialised. The first was MSD's Pneumovax 23v vaccine. This was not conjugated, and so could include a greater number of serotypes (23). Because it was not conjugated, it was less effective in protecting certain patient populations, particularly children under two years old who produce a poor immunogenic response because their immune system is still developing. For this age group, a conjugated vaccine is preferable.

7. The only successfully commercialised conjugated pneumococcal vaccine at the priority date was Wyeth's 7v vaccine called Prevenar 7. Prevenar 7 was approved in the US in 2000 and in the EU in 2001. It contained serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. As explained in more detail below, two 11v vaccines containing serotypes 1, 3, 5 and 7F had been in development, but had failed their Phase III trials.

8. All vaccines need to be incorporated into formulations which enable them to be stored (even if only at low temperatures) and administered to patients.

The Patent

9. Under the heading "Field of the invention", the specification states at [0001] that the invention "generally relates to the fields of immunology, bacteriology, vaccine formulation, protein stability and process development". "More particularly", it relates to "novel formulations which inhibit precipitation of immunogenic compositions".

10. Under the heading "Background of the invention", the specification states at [0002] that "improving the stability of an immunogenic composition (e.g., a protein immunogen, a polysaccharide-protein conjugate) is a necessary and highly desirable goal". At [0003]-[0004] the specification explains that many factors must be considered in order to achieve this goal. At [0005] the specification notes that it has been suggested that "silicone oil, which induces protein secondary and tertiary conformational changes, might be responsible for the aggregation/precipitation seen in certain protein pharmaceutical preparations". As the specification explains, however:

> "… Paradoxically, silicone oil is a necessary component of plastic syringes, as it serves to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel (i.e., silicone oil improves the syringeability of the formulation).
>
> [0006] Furthermore, the use of silicone oil is not limited to syringes, as it is used as a coating for glass vials to minimize protein adsorption, as a lubricant to prevent conglomeration of rubber stoppers during filing procedures, as a lubricant critical to the processability/machinability of glass and elastomeric closures and as a lubricant to ease needle penetration of vial rubber stoppers. Additionally, the siliconization of syringes, glass vials, rubber stoppers and the like, is not a well controlled nor standardized process, and as such, there is a high degree of variability of the silicone oil content from one lot to another."

11. Under the heading "Summary of the invention", the specification states at [0008]:

> "The present invention broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions. More specifically in certain embodiments, the present invention is directed to novel formulations which inhibit precipitation of immunogenic compositions comprised in container means. In one specific embodiment, the invention is directed to novel formulations which stabilize immunogenic compositions against silicone oil interactions, shear forces and shipping agitation."

12. This is followed by a number of consistory paragraphs. The key features of the claimed invention are that the formulations comprise (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) an aluminium salt and optionally (iii) a surfactant. The amendments limit the claims to formulations which contain 13 specified serotypes, although there is a dispute as to whether the claims preclude the presence of additional serotypes.

13. Under the heading "Detailed description of the invention", the specification describes at [0030]-[0070], among other things, certain experiments examining the effect of different formulations on the stability of (i) a streptococcal C5a peptidase and (ii) a 13-valent pneumococcal conjugate ("13vPnC"). The 13vPnC contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

14. Sections of the specification with the sub-headings "Surfactants", "Container means" and "Adjuvants and pharmaceutical carriers/excipients" describe suitable surfactants, containers, adjuvants and excipients for use in the invention. A section of the specification under the sub-heading "Immunogens" states that in certain embodiments of the invention the immunogen is the 13vPnC. Although methods for the preparation of the 13vPnC are described in general terms at [0062]-[0069], this adds nothing to the description quoted in the next paragraph.

15. Under the sub-heading "Examples", the specification describes at [0071]-[0111] three reference examples (which fall outside the granted claims because they do not include aluminium salts) and two examples of the invention. The description of Reference Example 1 includes the following passage:

> "[0072] The polysaccharide-protein conjugate used in this example was a thirteen-valent pneumococcal polysaccharide conjugate (13vPnC) comprising capsular polysaccharides from *S. pneumoniae* serotypes 4, 6B, 9V, 18C, 19F, 14, 23F, 1, 3, 5, 6A, 7F and 19A, each of which were conjugated to CRM_{197}. The capsular polysaccharides were prepared by standard techniques known to those skilled in the art. Briefly, each pneumococcal polysaccharide serotype was grown in a soy-based medium, the individual polysaccharides were then purified through centrifugation, precipitation, ultra-filtration, and column chromatography. The purified polysaccharides were chemically activated for conjugation and each polysaccharide was separately conjugated to a CRM_{197} carrier protein to form a glycoconjugate and formulated into a single dosage formulation.

> [0073] The chemical activation of the polysaccharides and subsequent conjugation to the carrier protein were achieved by conventional means (e.g., see U.S. Patent No. 4,673,574 and 4,902,506). CRM_{197} (Wyeth, Sanford, NC) is a non-toxic variant (i.e., toxoid) of diphtheria toxin isolated from cultures of *Corynebacterium diphtheria* strain C7 (β197) grown in casamino acids and yeast extract-based medium. CRM_{197} is purified through ultra-filtration, ammonium sulfate precipitation, and ion-exchange chromatography.
>
> [0074] The antigenicity experiments described below were performed by mixing the 13vPnC samples with one of thirteen antisera (Ab) specific to the each of the polysaccharide serotypes and detecting the immune complexes via light scattering measurements on an Array® 360 system (Beckman Coulter, Inc.; Fullerton, CA). The detected light scattering measurements for each of the thirteen serotypes were then compared to a standard curve and reported as antigenicity (µg/mL)."

16. It is to be noted that the specification states that the 13 serotypes were prepared "by standard techniques" and that they were conjugated to the carrier protein "by conventional means". The antigenicity experiments referred to are *in vitro* experiments used to assess the stability of the formulations over time.

17. The specification and claims of the Patent are focussed on the formulations. There is nothing in the specification to suggest that the selection of the 13 serotypes was regarded as inventive. Thus there is nothing which explains why the 13 serotypes were chosen, and in particular whether there is any value in adding 6A and 19A. Nor is there anything to suggest that the preparation and conjugation of the 13 serotypes required invention. On the contrary, as noted above, it is said that this was achieved by conventional means. Nor is there anything in the specification about the efficacy or safety of the 13v vaccine. Thus there is no report of any trials of the vaccine.

<u>The claim</u>

18. The only claim of the Patent which it is necessary to consider for the purposes of the appeal is claim 1 as unconditionally proposed to be amended. Broken down into integers, this reads:

> "[A] A siliconized container means filled with a formulation which inhibits silicone induced aggregation of a polysaccharide-protein conjugate comprised in a siliconized container means, the formulation comprising:
>
> [B] (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5,
>
> [C] (ii) an aluminium salt and
>
> [D] (iii) one or more polysaccharide-protein conjugates

[E] wherein the polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides

[F] and wherein the one or more pneumococcal polysaccharides are a *S. pneumoniae* serotype 4 polysaccharide, a *S. pneumoniae* serotype 6B polysaccharide, a *S. pneumoniae* serotype 9V polysaccharide, a *S. pneumoniae* serotype 14 polysaccharide, a *S. pneumoniae* serotype 18C polysaccharide, a *S. pneumoniae* serotype 19F polysaccharide, a *S. pneumoniae* serotype 23F polysaccharide, a *S. pneumoniae* serotype 1 polysaccharide, a *S. pneumoniae* serotype 3 polysaccharide, a *S. pneumoniae* serotype 5 polysaccharide, a *S. pneumoniae* serotype 6A polysaccharide, a *S. pneumoniae* serotype 7F polysaccharide and a *S. pneumoniae* serotype 19A polysaccharide."

Integer F derives from granted claim 10.

The skilled team

19. The judge found at [65]-[79] that the Patent was addressed to a skilled team consisting of a vaccinologist and a formulator.

Common general knowledge

20. The judge made extensive findings as to the common general knowledge of the vaccinologist (at [88]-[134]) and of the formulator (at [135]-[248]). Given the issues on the appeal, it is not necessary to set out any of the common general knowledge of the formulator.

21. For the purposes of the appeal, the judge's key findings as to the common general knowledge of the vaccinologist were as follows:

> "110. Antibodies can be serotype-specific, recognising the specific structure of that polysaccharide. Antibodies against a polysaccharide from one serotype may not be cross-protective (or may only be weakly cross-protective) against different serotypes. Because of this lack of cross-protection, vaccines may be multivalent, i.e. they include polysaccharides from more than one serotype.
>
> 111. There may be progression in the development of multivalent vaccines in relation to the number of serotypes used. The earliest version would generally utilise the most prevalent and most virulent serotypes. Over time, later vaccine versions will incorporate additional clinically-relevant serotypes for broader protection when a sufficient clinical need is identified and considerations such as manufacturability, marketability and cost allow.

…

113. As early as the 1920s, it had been shown that the antibody immune response to the polysaccharide capsule of bacteria could be improved by conjugating polysaccharides with carrier proteins. … Common carrier proteins for such polysaccharide-protein conjugates [included] CRM197 …

…

122. At the priority date, it was, it is common ground, CGK that it would be desirable to add more serotypes to pneumococcal conjugate vaccines. The reasons would include, in particular, adding serotypes for which cross-protection from those already in Prevenar (for example) was either weak or absent.

123. It was also CGK however that there were practical limitations to doing that, and that a choice had to be made of which serotypes to try to include.

124. Further, it was CGK that various 9v pneumococcal vaccines were in development, which would add serotypes 1 and 5. But at the same time, it was CGK that two 11v vaccines, from Aventis and GSK, which would add serotypes 1, 5, 3 and 7F to Prevenar's list, had failed, for different reasons (Aventis had given up and GSK had dropped down to 10v, omitting serotype 3). The precise reasons for failure do not matter, save to say that they were specific to the efforts of those companies, and not regarded as reasons why that combination of serotypes could never be added.

125. Against this backdrop, MSD submits that it was CGK that the overall direction of travel was to increase the number of serotypes. In my view this is much too simple … It is true that the skilled vaccinologist would not progress a vaccine that left out serotypes which were present in Prevenar (or whatever the state of the art starting point might be), but that does not mean that they would be wedded to adding further serotypes, let alone multiple serotypes, or that they would think that any combination with added serotypes could easily be achieved without problem. They would know that there could well be problems.

126. Similarly, 11v pneumococcal vaccines were not common general knowledge in the usual sense of being widely accepted as a good place to start. On the contrary, they had failed. MSD point out that, as I have said, they had failed for reasons specific to those workers, but that is not the same as there being a confidence that they could readily be done. …

…

> 128. It was essentially common ground that it was CGK that the existing serotypes did not give cross-protection for 19A and that, for reasons that I need not go into in any greater detail, 19A was an important serotype clinically. I can and do accept that in principle that is the sort of thing that could be CGK: not that 19A could necessarily be added with ease in practical terms, but that immunologically speaking it would, if it could be added, provide important benefits.
>
> …
>
> 131. … it was CGK, that while a case for the utility of 6A could be made, the situation was still developing. …"

De la Pena

22. De la Pena is a paper by three workers from Wyeth Farma SA in Madrid. The paper was published in Spanish, but I shall refer to the agreed translation. It is about pneumococcal vaccination in Spain. The abstract states:

> "Pneumococcal infections are an important cause of morbidity, mortality and hospitalization around the world; it is one of the tenth [sic: ten] main causes of mortality and represents 40 % of pneumonia deaths in subjects under 5 years of age. Universal vaccination would have an important impact on the community.
>
> Currently, there are two available vaccines to prevent invasive pneumococcal disease in Spain: the 23-valent polysaccharide vaccine (VNP-23v [sic: PPV-23]) and the 7-valent conjugate vaccine (VNC-7v [sic: PVC-7]).
>
> Other conjugate vaccines for serotypes 9, 11 and 13-valent are in a very advanced study phase, although they have not been commercialized yet."

23. De la Pena refers on page 50 to the non-conjugated 23v (Pneumovax) vaccine and to the conjugated 7v Prevenar vaccine. At page 53 in the left-hand column it refers to those two vaccines again, and then to three further conjugated vaccines which it says "have not been marketed and are in a very advanced stage of study". These are:

    i) "The 9-serotype vaccine (it adds 1 and 5)";

    ii) "The 11-serotype vaccine (it adds 3 and 7F)";

    iii) "The 13-serotype vaccine (it adds 6A and 19A)".

24. At page 53 right-hand column there is the following further teaching about the 9-valent vaccine (referring to trials in children in Gambia and South Africa whose details are given on page 53 left-hand column):

> "The study showed that using the PCV-9 vaccine prevents IPD, reduces pneumococcal resistance to antibiotics and decreases

pneumonia in children. The remaining three studies (23, 24, 25) demonstrated the safety and immunogenicity of PCV-9, showing that:

- It is a safe vaccine and produced a good immune response to the 9 serotypes it contains.

- It is a well-tolerated vaccine

- There was a significant reduction in incidence of IPD caused by strains resistant to antibiotics.

- There was a decrease in nasopharyngeal carriers for vaccine pneumococci and an insignificant increase for nonvaccine pneumococci.

- There was a decrease in resistant pneumococcal carriers.

- Simultaneous administration of PCV-9 with routine vaccines in the immunisation programme is safe and immunogenic.

Therefore, we can say that PCV-9 is a safe, effective, and immunogenic vaccine that opens new possibilities in the field of conjugate vaccines."

25. The following passage bridges pages 53-54:

"**The Future of Pneumococcal Vaccination**

The 23-valent polysaccharide vaccine was the first step in fighting pneumococcal disease and the heptavalent conjugate vaccine has allowed us to drastically decrease the disease in younger children. With regard to future pneumococcal vaccination, several aspects must be borne in mind: serotypes and age and geographical distribution, combination with other vaccines, new routes of administration, and other strategies.

The geographical variability of pneumococcal serotypes represents a problem when developing a vaccine with global coverage. There is almost a need to design a specific vaccine for each geographical area, having previously undertaken an epidemiological study of the most common serotypes, something only possible in developed countries. In addition, we know that the spectrum of serotypes broadens with age, which complicates the production of vaccines for age groups other than children, although they are the group at highest risk and in whom the current vaccine is most effective. In this regard, we are working on the incorporation of new serotypes to the PCV-7, and the nonavalent (incorporating serotypes 1 and 5), 11-v (additionally incorporating 3 and 7F) and 13-v (6A and 19A) vaccines are currently in different research phases, which could broaden the spectrum of ages and countries, although coverage

> would remain very diverse. Furthermore, we are trying to incorporate the most antibiotic-resistant pneumococci."

Obviousness

26. At trial Wyeth accepted that, if the skilled formulator was asked to progress the 13v vaccine of de la Pena, it would be obvious to use a siliconized container means, a pH buffered saline solution with a pKa of about 3.5-7.5 if required, and an aluminium salt. The judge found that it would also be obvious to add a surfactant to address aggregation, and there is no challenge by Wyeth to that finding. Thus all the formulation aspects of the claimed invention were obvious.

27. The sole remaining issue on obviousness is whether the 13v vaccine disclosed in de la Pena would have been an obvious choice to progress. The judge held that this would have been the case for the following reasons:

> "332. The law requires that I consider [de la Pena] as if it were read with interest, and in this case that is not a fiction: it reports real practical work being done by a major company in the field with apparent success (to the extent of reaching 'a very advanced phase of study'). The skilled vaccinologist would have had an active desire to progress the work reported. ….
>
> 333. … The following factors are material:
>
> a) The motivation to do so is spelled out on page 54: to broaden the spectrum of ages and countries covered, and deal with antibiotic-resistant pneumococci.
>
> b) The skilled vaccinologist would know from the CGK that there was a strong case that the addition of 19A would give cross-protection and that there was a reasonable case that the addition of 6A could be useful from that perspective.
>
> c) From de la Pena, the skilled vaccinologist would infer that Wyeth had been convinced of the cases for the addition of the 19A and 6A, sufficiently to put a lot of work into it.
>
> 334. The skilled vaccinologist would be aware that the technical issues would increase in difficulty with more valencies, but would have confidence that the 13v could be made to work from the report that Wyeth had successfully reached advanced studies.
>
> 335. However, the skilled vaccinologist would also have to consider the 9v and 11v as candidates for progression.
>
> 336. It was on the last of those points that Wyeth focused. It pointed out that in the period between the publication of de la Pena and the priority date of the Patent, Sanofi and GSK had both

> abandoned their 11v vaccines, with GSK deciding to take forward only a 10v vaccine. It also pointed out, based on the evidence of [Wyeth's vaccinology expert] Prof Eskola, that nothing further would have been heard of the 13v vaccine in the 2004-2006 period.
>
> 337. I have dealt with the Sanofi/GSK matters in connection with the CGK, above. They do not support Wyeth's position, or at least not much, because although those two companies had had difficulties the reader of de la Pena would know that Wyeth had overcome them so as to be able to do trials, and that the difficulties were therefore likely to be for reasons specific to those companies and not innate to the task.
>
> 338. If the skilled vaccinologist had decided to look into progression of the 13v vaccine (e.g. because they were spurred to do so having regard to their knowing of the Sanofi/GSK issue), it transpired from the cross-examination of Prof Eskola that they would have found a variety of references showing that it was being taking forward. So that point also fails on the facts. Mr Hinchliffe for MSD relied on these materials only as a shield to the point that the 13v vaccine might be thought to have been dropped, rather than actively asserting that they would have been found by someone considering what to do with de la Pena. Whether or not he needed to concede that, that is the basis on which I have proceeded.
>
> 339. Overall, it is my clear conclusion that it was obvious to progress the 13v vaccine from de la Pena."

28. Obviousness involves a multi-factorial evaluation and therefore this Court is not justified in intervening in the absence of an error of law or principle on the part of the judge: see *Actavis Group PTC EHF v ICOS Corp* [2019] UKSC 15, [2019] Bus LR 1318 at [78]-[81] (Lord Hodge).

29. Wyeth contends that the judge erred in principle because he misinterpreted de la Pena. In order to put this contention into context, it is necessary first to explain that at trial MSD also contended that the claims were obvious over another item of prior art, referred to as "Chiron". As the judge explained at [350]-[353], Chiron is concerned with vaccine formulation, and contains no teaching about which serotypes to use. As a result, MSD had to make its case on the vaccinology side from common general knowledge alone. The judge held, however, that it was not obvious from the vaccinologist's common general knowledge to develop a 13v vaccine. There is no challenge by MSD to that conclusion.

30. Wyeth's starting point is not what the judge said in the passage quoted in paragraph 27 above, but something he said in the context of discussing the common general knowledge of the vaccinologist. At [134] he explained that certain criticisms of MSD's case on common general knowledge "come home to roost in relation to the attack over Chiron", which contained no pointer to a 13v vaccine. He went on:

> "The position over de la Pena is quite different because, as I will explain, that included the information that a 13v pneumococcal vaccine including 6A and 19A had been put into trials by Wyeth with success."

31. Wyeth also relies upon the judge's statement at [334] that the vaccinologist "would have confidence that the 13v could be made to work from the report that Wyeth had successfully reached advanced studies" and his statement at [337] that "Wyeth had overcome [the difficulties with 11v vaccines] so as to be able to do trials".

32. Wyeth points out that the only trials actually reported in de la Pena are those on the 9v vaccine, and, although reference is made in the abstract and at page 53 to the 9v, 11v and 13v vaccines being "in a very advanced study phase", it is said at page 54 that they are "currently in different research phases". Wyeth argues that that this is very far from a teaching that a 13v vaccine had successfully been conjugated and was the subject of successful trials.

33. So far as the argument that de la Pena does not disclose that the 13v vaccine has been successfully conjugated is concerned, it is true that this is not explicitly stated. MSD contends, however, that this is implicit, in particular from the statement in the abstract that it is "in a very advanced study phase, although [it has] not yet been commercialised" and the similar statement on page 53. I agree with this. Moreover, as MSD points out, both vaccinology experts proceeded on the understanding that de la Pena disclosed that a 13v vaccine had been developed. In any event, it was not suggested by Wyeth at trial that the skilled team would think that there would be any difficulty in preparing and conjugating the 13 serotypes (and any such suggestion would have been inconsistent with the statements in the Patent that this could be done by conventional means).

34. As for the point that de la Pena does not disclose that the 13v vaccine has been the subject of successful trials, it is again true that this is not explicitly stated. MSD contends, however, this is again implicit in the statements quoted above.

35. In approaching this question, one should not read too much into the judge's use of the word "trials". Counsel for Wyeth suggested that the judge had meant clinical (human) trials, but the judge did not say that; and counsel for Wyeth accepted that an animal study could be described as a "trial". If the judge had said "studies" rather than "trials", there could be no objection.

36. The real point is the judge's reference to "success" (in [134]) and "successfully" (in [334]). As to that, MSD contends that the statement that the 13v vaccine was "in a very advanced study phase" necessarily implies success in earlier phases of study. MSD does not suggest that there is any disclosure in de la Pena that the 13v vaccine has demonstrated efficacy or safety (but, as MSD points out, there is no evidence of that in the Patent either, nor do the claims require either efficacy or safety). Rather, MSD argues that the message conveyed by de la Pena was correctly epitomised by the judge when discussing Chiron at [354]:

> "… de la Pena … had a clear focus on pneumococcal disease, a specific teaching of the 13v combination, a rationale for undertaking it, motivation, and a statement that real work had

> been done and real progress had been made by a leading player. Chiron lacks any of these …."

Again, I agree with this.

37. Accordingly, although the last sentence of [134] is perhaps slightly more strongly worded than is warranted, I do not consider that the judge made any material error in his interpretation of de la Pena. In any event, whatever the precise nuances of the statements made about the 13v vaccine in de la Pena, the fact remains that it not only discloses the combination of 13 serotypes claimed in the Patent, but also spells out the motivation for using that combination and gives the clearest possible indication that Wyeth considers it worth pursuing. In those circumstances I consider that the judge was not merely entitled, but correct, to hold that the 13v vaccine would have been an obvious choice to pursue in the light of de la Pena.

38. The only conceivable argument to the contrary is that the skilled vaccinologist would have been put off pursuing the 13v vaccine by the failure of the GSK and Aventis 11v vaccines, but the judge found at [124] that the vaccinologist would have appreciated that the reasons for those failures were specific to the efforts of those companies and would not have considered that they showed that that combination of serotypes could not be successful. Accordingly, he found at [337] that this would not have put the vaccinologist off pursuing the 13v vaccine. There is no challenge by Wyeth to those findings, nor could there be. (Indeed, as counsel for MSD pointed out, it was the evidence of Prof Eskola that the reason for the failure of the Aventis 11v vaccine was not that there was any problem with the 11v vaccine itself, but that it was incompatible with a pertussis vaccine.) Counsel for Wyeth sought instead to argue that the skilled reader of de la Pena would not be motivated to pursue a 13v vaccine given the failures of the 11v vaccines, but de la Pena itself gives the reader ample motivation to do that.

39. Given that the judge was correct to hold that the claims were obvious over de la Pena, it is unnecessary to consider MSD's respondent's notice. Nor is it necessary to consider the infringement issue.

Conclusion

40. For the reasons given above I would dismiss this appeal.

Sir Christopher Floyd:

41. I agree that the appeal on the issue of obviousness should be dismissed for the reasons given by Arnold LJ. The most telling argument advanced by Mr Lykiardopoulos QC, who argued this ground of appeal for Wyeth, was based on the fact that de la Pena was published in 2004, some two years before the priority date. The question for the judge, he argued, had not been what the reaction of the skilled person would have been to de la Pena at the date of its publication in 2004, but what that reaction would have been at the priority date in 2006, in the light of the common general knowledge as it then stood. Mr Lykiardopoulos argued that by 2006 the skilled person would know of the failures in Phase III clinical trials of 11v vaccines by two significant commercial undertakings, Sanofi and GSK. Why, then, would the skilled person think that the more challenging idea of the 13v vaccine disclosed in de la Pena would be worth progressing? De la Pena's teaching that Wyeth had reached advanced studies in 2004 would be discounted

given the failures encountered by these other undertakings. The judge had been wrong to say, as he did in [337], that these difficulties had been overcome as Wyeth had been able to do "trials".

42. Attractively as it was presented, I was not in the end satisfied that this attack on the judge's conclusion of obviousness was made good. I agree that it is not unknown for an obviousness case to be rejected on the basis that, with the passing of time, a prior art document comes to be seen as a dead end as opposed to a useful starting point for further development. Such a treatment of a prior art document must, however, be supported by the evidence that this is how the skilled person would treat the document, based on the common general knowledge.

43. The judge found at [337] that the difficulties encountered by Sanofi and GSK were specific to those companies and not innate to the task. The difficulties would not therefore provide a reasoned disincentive to progress the 13v vaccine which had been disclosed in de la Pena to be in advanced studies by Wyeth. The critical thing for the skilled person was not whether GSK and Sanofi had abandoned 11v for reasons specific to them, but whether there was any evidence that Wyeth had encountered similar difficulties with 13v, so as to cause it to drop its 13v project. Absent such evidence the skilled person would be entitled to assume that Wyeth was still actively pursuing 13v in 2006, just as it said that it had been in 2004.

44. The evidence of Prof Eskola, Wyeth's expert vaccinologist, in his second report, made a number of points about de la Pena. He said that at the priority date the skilled person was not aware of Wyeth's 13v developmental vaccine, and that he did not know of any further information about it which would be part of the common general knowledge. He went on to say that given the time which had elapsed between de la Pena and the priority date, the skilled person would view the brief note in de la Pena "as a record of something which was being considered two years earlier." That evidence falls a long way short of establishing that the skilled person would assume that Wyeth had encountered difficulties with the progression of their project.

45. The judge referred at [338] to the existence of materials which showed that Wyeth was in fact carrying out clinical trials on 13v up to the priority date, but that these were only relied on by MSD to rebut any suggestion that Wyeth's 13v project had been dropped. We were taken to some of these materials, but I think they were beside the point. Unless the common general knowledge supported the notion that Wyeth's 13v vaccine had innate problems of its own, which it did not, de la Pena would still give the skilled person enough motivation to progress to making a formulation within claim 1 of the Patent.

Lord Justice Newey:

46. I agree with both judgments.