Neutral Citation Number: [2016] EWHC 1045 (Ch)

Case No: HP-2015-000002

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
7 Rolls Buildings
Fetter Lane
London
EC4A 1NL

Date: Thursday 12 May 2016

Before :

THE HON MR JUSTICE HENRY CARR

- -

Between :

GLAXOSMITHKLINE UK LIMITED	**Claimant**
- and -	
WYETH HOLDINGS LLC	**Defendant**

- -
- -

Thomas Mitcheson QC and Stuart Baran (instructed by **Rouse Legal**) for the **Claimant**
Michael Tappin QC and William Duncan (instructed by **Marks & Clerk Solicitors LLP**) for the **Defendant**

Hearing dates: 9-11, 14-15.17-18 March 2016

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

.....

MR JUSTICE HENRY CARR

Introduction **1**

The issues **4**

Technical Background **5**

Meningitis *6*
Neisseria meningitidis *8*
Capsular Polysaccharide *10*
Assays *14*

The witnesses **15**

The Microbiologists *15*
The experts on PCR and sequencing *23*
Witnesses of fact *24*

The Skilled Addressee **25**

The common general knowledge **28**

Legal Principles *28*
The serum bactericidal assay *31*
OMVs and PorAs *36*
Attitudes of the skilled addressee to new vaccine candidates *40*
Reverse vaccinology *44*

The Patent **48**

The examples *54*
Example 1 ..... *55*
Example 2 (and Example 6) *58*
Example 3 ..... *59*
Example 5 ..... *60*
Example 8 ..... *61*
Example 9 ..... *65*
Example 10 ..... *66*
The claims alleged to be independently valid *67*

Claim construction **69**

Claim 1 ..... *70*
Claim 3 ..... *72*
Claims 18-20 ..... *81*

Infringement **90**

Plausibility – AgrEvo obviousness/insufficiency **93**

Legal principles *94*
General observations on plausibility *95*
The AgrEvo obviousness allegation *101*
Sequence homology and breadth of claim *102*
Non-lipidated 2086 proteins *105*
At least one PorA protein *109*
Adjuvants *112*

Added Matter **115**

Legal principles *115*
Application to the facts *120*

Priority **128**

Legal principles *128*

The first priority date **129**

The combination of 2086 and PorA(s) *129*
Sequence clusters *133*
Mucosal delivery *137*
Lack of plausibility *140*

The second priority date **142**

Novelty **154**

Legal principles *154*

Novelty over 885 (pre-PD1) **156**

Individualised disclosure *157*

Novelty over the Cuban Vaccine (pre-PD1) **170**

Did the Cuban Vaccine contain fHbp before the priority date? *174*
If fHbp had been present in the Cuban Vaccine, would analysis in 2001 have identified it? *185*
Could the skilled person have identified the presence of fHbp in the Cuban Vaccine before the priority date? *199*
Would the skilled person have been able to reproduce the Cuban Vaccine without undue burden? *205*
In relation to claims 18-20, if fHbp was present, did it make any material contribution to the immune reaction produced by the Cuban Vaccine? *209*
Conclusion in respect of the Cuban Vaccine *211*

Novelty over Andersen (pre-PD1) **212**

Novelty over 869 (between PD1 and PD2) **222**

Novelty/obviousness over Bernfield and Farley posters/abstracts (between PD2 and filing date **232**

Inventive step **240**

Legal principles *240*
Disclosure of 922 ..... *241*

Alleged squeezes **258**

Conclusion **259**

Mr Justice Henry Carr:

Introduction

1. This is a claim by GlaxoSmithKline UK Limited ("GSK") for revocation and a declaration of non-infringement in respect of European Patent (UK) 2,343,308 ("the Patent"). Wyeth Holdings LLC ("Wyeth"), a subsidiary of Pfizer Inc., is the registered proprietor of the Patent. GSK markets a *Neisseria meningitidis B* ("Men B") vaccine product in the United Kingdom under the trade mark Bexsero. Wyeth counterclaims for infringement of the Patent by Bexsero.

2. The Patent claims, amongst other things, a composition comprising a protein which is now known as factor H binding protein ("fHbp"), which is referred to in the Patent as "2086 protein". The claimed composition additionally comprises at least one PorA protein. There are five recombinant Men B antigens in Bexsero, one of which is fHbp. Bexsero also comprises an outer membrane vesicle ("OMV") fraction containing, amongst other proteins, PorA protein.

3. Wyeth has also developed a Men B vaccine known as Trumenba, which has not yet received approval in Europe. In light of the public health requirement for effective vaccines against Men B, Wyeth does not seek injunctive relief if it succeeds in its counterclaim.

The issues

4. There are numerous issues, arising, in particular, from GSK's grounds of invalidity, which may be summarised as follows:

    i) Entitlement to the first claimed priority date of 11 October 2001 ("PD1"). In particular, GSK alleges that there is insufficient basis in US 328101 ("the first priority document") for the claimed invention of 2086 and PorA.

    ii) Entitlement to the second claimed priority date of 30 August 2002 ("PD2"). In particular, GSK relies on the absence of sequence listings from US 406934 ("the second priority document").

    iii) Anticipation by:

        a) WO 01/52885 A1, Outer membrane vesicle comprising N. meningitidis serogroup B outer membrane proteins ("885");

        b) VA-MENGOC-BC, a vaccine developed at the Finlay Institute in Havana, Cuba and administered to patients before PD1 ("the Cuban Vaccine");

        c) Andersen SR, Liang B, Guthrie T, Wong SYC, Hous S, Hyland L (2000), *Immune responses to meningococcal outer membrane vesicles after intranasal immunisation* (the abstract of a poster presented at the Twelfth International Pathogenic Neisseria Conference 12—17 November 2000 in Galveston, Texas) ("Andersen");

        d) If PD1 is lost, WO 03/009869 A1, *Vaccines comprising aluminium adjuvants and histidine* ("869"); and

e) If PD2 is lost, two posters by Wyeth, presented at the Twelfth International Pathogenic Neisseria Conference ("IPNC") in Oslo, Norway in September 2002, which GSK contends amount to a single disclosure ("the Bernfield and Farley posters and abstracts").

iv) Obviousness over:

(a) WO 01/64922 A2, *Heterologous Expression of Neisserial Proteins* ("922");

(b) If PD2 is lost, the Bernfield and Farley posters and abstracts.

v) AgrEvo obviousness – GSK alleges that the Patent claims a mere arbitrary choice from a host of possible solutions which cannot involve an inventive step.

vi) Insufficiency (squeeze) – GSK alleges that any technical contribution which is new and not obvious is not rendered plausible or sufficient by the Patent. It claims that there is a squeeze between the construction of the claims (and what they contribute) and the prior art.

vii) Insufficiency (general) - GSK alleges that the specification does not enable (and/or does not render plausible) the claims, for a variety of reasons which I consider in detail below.

viii) Added Matter – GSK alleges that Wyeth made a series of selections from lists on amending the application as filed, which add subject matter. GSK also relies upon an alleged squeeze between the added matter attack and the disclosure of the prior art.

ix) Infringement – the issue relates to claim 3 of the Patent and its correct construction, which is amongst the claims alleged by Wyeth to be independently valid. This issue has relevance in the event that this is the only valid claim of the Patent.

Technical Background

5. The parties agreed a Technical Primer which was of considerable assistance. This was supplemented by expert evidence. I set out below a summary of certain technical aspects which may be helpful in understanding the issues in this case.

Meningitis

6. Meningitis is a severe and life-threatening disease, often sudden in its onset, where the membranes surrounding the brain and spinal cord become inflamed. For survivors, it can result in long term effects including brain damage, seizures, deafness and paralysis, and may entail the amputation of limbs and digits. One of the major causes of bacterial meningitis is the meningococcus *Neisseria meningitidis*. About two thirds of cases occur in the first five years of life (with peak prevalence in the first year); a second peak is observed in adolescents.

7. Prior to antibiotic treatment becoming available, approximately 70% to 90% of those who contracted bacterial meningitis died from the disease. The overall figure has

fallen over the last 50 years; however, despite the advancement of modern antibiotic treatments, the overall mortality rate for meningococcal disease has remained high: between 5% and 15% of those who contract the disease. In the early 2000s, *Neisseria meningitidis* was still one of the leading causes of childhood deaths from infection in many industrialised countries and has been responsible for a number of devastating epidemics around the world. Despite the availability of effective antibiotics, meningococcal disease to this day remains a substantial health problem in most countries.

Neisseria meningitidis

8. *Neisseria meningitidis* is a Gram-negative bacterium from a genus of bacteria that commonly colonises human mucosal surfaces. The cell envelope of *N. meningitidis* comprises a number of layers as depicted in Figure 1 of the Technical Primer, reproduced below:

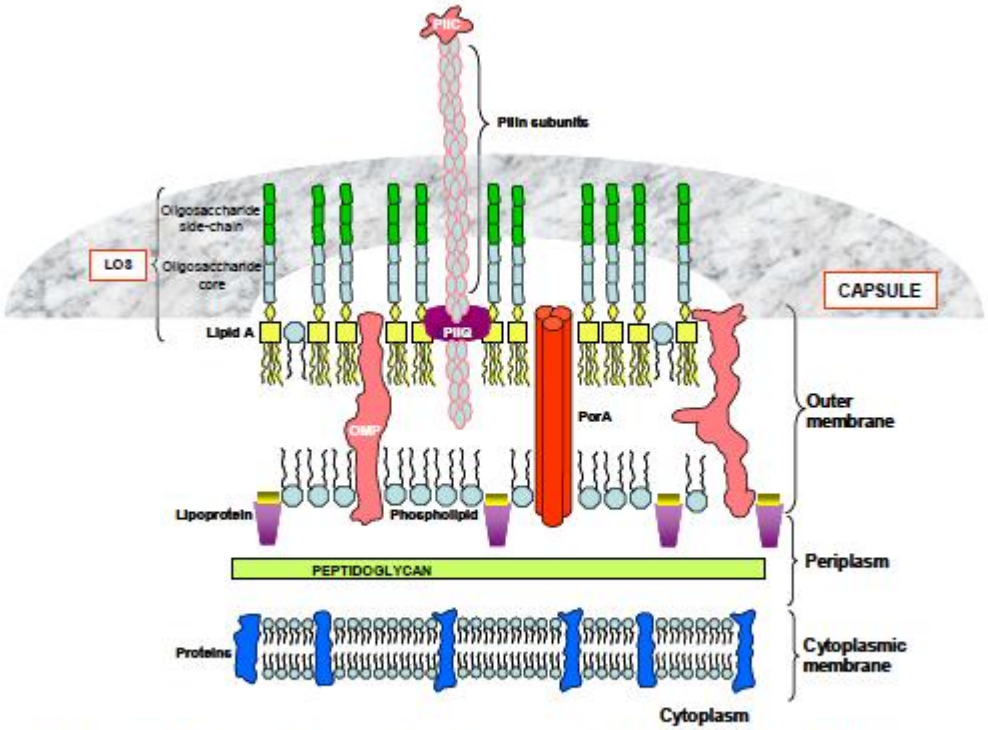


Figure 1: Schematic diagram of the cell envelope of *N. meningitidis* (from Gillespie and Hawkey (2006), *Principles and Practice of Clinical Bacteriology (Second Edition)*, John Wiley & Sons Ltd)

9. It will be seen that there is a layer of lipo-oligosaccharide ("LOS") and outer and inner membranes. The outer membrane has a number of integral outer membrane proteins ("OMPs"). The outer membrane structure of *Neisseria meningitidis* is unstable and this causes the bacteria to produce small "blebs", comprising a lipid bilayer including integral proteins, with fluid enclosed, that are released into the medium around the bacteria. These small vesicles are known as Outer Membrane Vesicles ("OMVs"). OMVs look from the outside like part of the bacterium, but once released are separate and cannot reproduce themselves. Because the OMVs are released from the bacterium's outer membrane, their contents are dependent upon the content of the outer membrane when they are released. As such, changes in bacterial

growth conditions can have an effect on what proteins and lipids are found in the OMVs.

Capsular Polysaccharide

10. Some strains of *N. meningitidis* are non-encapsulated, although capsulated strains are more common and are almost always the cause of invasive meningococcal disease.

11. *N. meningitidis* is classified according to capsular polysaccharide type into a number of serogroups, including serogroups A, B, and C. These different serogroup meningococci are referred to as, for example, Men A, Men B etc.. Within these serogroups the meningococci can be further classified into serotypes and serosubtypes. The serotype is based on the class 2/3 outer membrane proteins (PorB) while the serosubtype is based on the class 1 outer membrane protein (PorA). PorA was known to be a very antigenically diverse protein, and as a result there were a large number of different PorA serosubtypes (about 20).

12. Serosubtyping is a method of measuring "clonal lineage". Clonal lineage is a measure of how unrelated two strains are, and strains with different PorA serosubtypes would be expected to be less related to one another than strains of the same PorA serosubtype. This is not the same as an "isolate", which is a term used to describe a particular sample of Men B that has been isolated from a patient, and does not necessarily imply any difference or heterogeneity from another isolate.

13. Vaccines based on polysaccharides have been successful against some serogroups (but not serogroup B). For example, a tetravalent vaccine containing the A, C, Y and W-135 polysaccharides was licensed in the United States in 1981. Several manufacturers have developed vaccines against serogroup C that have been licensed in the UK.

Assays

14. At the priority date there were a number of standard assays that were used to assess the potential for a protein to be a vaccine candidate for Men B. It was agreed between the experts that the serum bactericidal assay ("SBA") was the best correlate of protection because it was the best available indicator of whether a vaccine candidate will have a protective effect in a human. The SBA is an *in vitro* test for the ability of serum to kill bacteria e.g. *N. meningitidis*. The principle of the assay is that target strains are lysed in the presence of target specific antibodies that are able to activate the complement system. Serial dilutions of sera are incubated with appropriate target strains and a source of complement. The serum bactericidal titre is typically expressed as the reciprocal serum dilution yielding greater than 50% killing.

The witnesses

The Microbiologists

15. Professor John Heckels is an Emeritus Professor of Molecular Microbiology in the Faculty of Medicine at the University of Southampton. He was appointed as a Lecturer at the University of Southampton Medical School in 1974 and became Professor of Molecular Microbiology in 1996. His research work centred on the

structure and immunochemistry of bacterial surface antigens and the molecular basis of their interaction with the human host. Prior to 2001, this included research into meningococci, in order to identify the components responsible for inducing protective immunity and to investigate their potential for vaccines designed to prevent the infection. His group in Southampton was the first to clone the gene for the PorA protein, which was the first protein shown to induce immunity to Men B. He was involved in the design of studies to investigate Men B immunity in university students, and was named as inventor on a number of patent applications in the 1990s relating to PorA.

16. It was accepted that Prof Heckels was well qualified to assist the court in this case and no personal criticism was made of him. I have no doubt that he was anxious to assist the court, and was a very helpful and fair witness. However, there were issues over whether, inadvertently, he exercised hindsight when considering the prior art. I will consider this issue in the context of the prior art, and in particular when considering the question of inventive step.

17. Professor Dlawer Ala'Aldeen was a Professor of Clinical Microbiology at the School of Life Sciences at the University of Nottingham from January 2003 until his retirement in December 2015, when he was awarded Emeritus status. From 1994 to 1998 he was Clinical Lecturer and Honorary Specialist Registrar in Microbiology at the Department of Clinical Laboratory Sciences, University Hospital of Nottingham. In 1998 he was appointed as Reader in Clinical Microbiology at the University of Nottingham, and Honorary Consultant Microbiologist at Nottingham's University Hospitals NHS Trust.

18. In parallel with his work in clinical microbiology, prior to 2001 he ran a research laboratory dedicated to the study of the pathogenesis, molecular epidemiology and vaccine development of various bacterial pathogens, particularly *N. meningitidis*. He established the Meningococcal Research Group at the University Hospital of Nottingham which expanded in 1998 and consisted of a team of 20 researchers. The focus of his research was in defining the role of *N. meningitidis* virulence factors (outer membrane and secreted proteins) in host-pathogenic interaction. His team has established *in vitro* models for the study of meningitis and septicaemia. He has been involved, directly or indirectly, with all stages of pre-clinical research, clinical research and clinical development of vaccines against *N. meningitidis*.

19. Although any personal criticism of Prof Ala'Aldeen was disclaimed on behalf of GSK, it was submitted that his evidence suffered from a number of serious flaws, and that he acted as an advocate rather than an impartial expert. It was suggested that serious inconsistencies emerged in the way that he approached the prior art as compared to the Patent. It is said that he was prepared to give the authors of the Patent the benefit of the doubt, but was highly critical of certain aspects in the prior art, which demonstrated a lack of balance. It was submitted that he was unwilling to answer even the most straightforward questions with a simple yes or no and was sometimes unwilling to answer a question at all.

20. I do not accept that these criticisms (which are undoubtedly personal in that they suggest bias on the part of Prof Ala'Aldeen) are well-founded. He was a highly intelligent and articulate scientist who strongly believed that the opinions expressed in his reports were correct, and he was keen to explain this to the court. At certain times

during his cross examination, he did appear somewhat defensive, but in my judgment, this was because he was very concerned that his evidence should not be misconstrued. He disagreed with GSK's case, but this does not mean that he was partial. I found his evidence very helpful, and he supported his conclusions with compelling reasoning.

21. A number of further criticisms were made of the way in which Prof Ala'Aldeen approached the skills of the notional addressee of the Patent. First, it was suggested that he assumed that the experience of the skilled addressee was limited to that of a 2-3 year post-doctorate student, whereas the skilled team would have greater experience. This reflects a somewhat arid dispute concerning the skill level of the notional team, as to which there was little difference between the experts. Secondly it was suggested that he did not accept the notion that the addressee could be made up of a team. I do not accept this characterisation of his evidence. During his cross examination (at T1/152/2-8) he explained that he agreed with Prof Heckels that a group of people with different experience would work on a project of the nature contemplated in the Patent, including microbiologists, vaccinologists and clinicians.

22. Finally, it was suggested that his analysis of the approach of the skilled team was detached from the reality of teams working in this field. I do not accept this. I consider that Prof Ala'Aldeen was seeking to distinguish between the notional skilled team, which lacks any inventive capacity, and those actually working in the field before the priority date, whom he knew to be inventive. He would have been criticised if he had taken any other approach.

The experts on PCR and sequencing

23. Wyeth performed experiments in these proceedings in connection with its claim to priority from the second priority document. In respect of these experiments GSK relied on expert evidence from Dr Martin Ferguson and Wyeth called evidence from Dr Robert Donald, both of whom had PhDs and postdoctoral experience in biochemistry. Dr Ferguson was not called for cross examination. Dr Donald was cross examined, and I shall consider his evidence in the context of the issue to which it relates.

Witnesses of fact

24. A number of statements of fact were relied upon by the parties, either under Civil Evidence Act Notices or from witnesses who were not called for cross examination. Insofar as it is material, I shall consider this evidence in the context of the issues to which it relates.

The Skilled Addressee

25. There was no dispute on the legal principles. In particular:

    i) A patent specification is addressed to those likely to have a real and practical interest in the subject matter of the invention (which includes making it as well as putting it into practice).

    ii) The skilled addressee has practical knowledge and experience of the field in which the invention is intended to be applied. He/she (hereafter "he") reads the

specification with the common general knowledge of persons skilled in the relevant art, and reads it knowing that its purpose is to disclose and claim an invention.

iii) A patent may be addressed to a team of people with different skills. Each such addressee is unimaginative and has no inventive capacity.

iv) Although the skilled person/team is a hypothetical construct, its composition and mind-set is founded in reality. As Jacob L.J. said in *Schlumberger v. Electromagnetic Geoservices* [2010] EWCA Civ 819; [2010] RPC 33 at §42:

> "… The combined skills (and mindsets) of real research teams in the art is what matters when one is constructing the notional research team to whom the invention must be obvious if the patent is to be found invalid on this ground."

26. In my judgment, the experts were substantially in agreement on this issue. The team would comprise scientists with an interest in *Neisseria* vaccines, including those with experience in microbiology and vaccinology, as well as clinical experience. There was an issue about the extent of bioinformatics expertise that would have been available to the skilled team by 2001. I consider that the team would have access to basic bioinformatics expertise, but not to techniques which were regarded as "cutting edge" at that time.

27. There was a debate about whether the team would be led by a person having more than 10 years' experience, rather than being made up of scientists with 2 to 3 years' postdoctoral experience. Prof Ala'Aldeen explained that the difference would be one of leadership and not of competence. In my judgment, the notional team leader would have at least ten years post-doctoral experience, but the difference between the experts is immaterial to the issues that I have to decide. Prof Heckels did not identify any difference in common general knowledge which was dependent on this distinction.

The common general knowledge

Legal Principles

28. I shall apply the legal principles in respect of common general knowledge set out by Arnold J. in *KCI Licensing v Smith & Nephew* [201] EWHC 1487 (Pat); [2010] FSR 31 at [105]-[115], which was approved by the Court of Appeal at [2010] EWCA Civ 1260; [2011] FSR 8 at [6].

29. GSK relied on the following passage from the judgment of Sales J. in *Teva v Astrazeneca (asthma)* [2014] EWHC 2873 (Pat), (2015) 142 BMLR 94 at [60]:

> "The authorities indicate that CGK includes not just information directly in the mind of the notional skilled person, but such information as he would be able to locate by reference to well-known textbooks. This guidance needs to be adapted and kept appropriately up to date for the procedures for dissemination of scientific knowledge in the age of the internet

> and digital databases of journal articles. Searches of such databases are part and parcel of the routine sharing of information in the scientific community and are an ordinary research technique. In my view, if there is a sufficient basis (as here) in the background CGK relating to a particular issue to make it obvious to the unimaginative and uninventive skilled person that there is likely to be - not merely a speculative possibility that there may be - relevant published material bearing directly on that issue which would be identified by such a search, the relevant CGK will include material that would readily be identified by such a search."

30. I respectfully agree with this analysis. As GSK accepted, this passage does not mean that all material available on-line constitutes common general knowledge. Rather it indicates that material which the skilled addressee knows to be available on-line and which is generally accepted as a good basis for further action (such as material which might be found off-line in a textbook or a key journal article) may constitute common general knowledge.

The serum bactericidal assay

31. The experts agreed that SBA was the main assay used in 2001/2 to establish protective effect of a vaccine candidate in humans, and that it was well established at that date. It was the best test available. However, I find that it was common general knowledge that caution needed to be exercised about drawing conclusions from individual SBA results.

32. In particular, the skilled team would not look for just one or two SBA results but would wish to see a range of information before considering a protein to be a promising vaccine candidate. Prof Ala'Aldeen considered that at least 6 to 12 strains would be required. Prof Heckels considered that six would be a good working number which would then be expanded. Evidence of the level of conservation of the protein across a diverse range of strains, knowledge of the ability to express the protein, and evidence that the protein was surface exposed would also be important. The results of additional tests to support the SBA data, such as ELISA, and/or infant rat assays would be preferable to increase confidence in the SBA results.

33. In 2001/2 there was no standardised assay for Men B. A variety of factors could affect the outcome of an SBA including the reagents, materials and strains, methods of incubation of the antibody / bacteria mix, the sera used, the growth conditions and the source of complement. Accordingly, it was well known that it was not possible to make direct comparisons of the numbers obtained in an SBA in different experiments in different laboratories. It was also important to have correct controls for SBAs in order to avoid false positives.

34. In respect of intra-laboratory experiments, Prof Heckels explained that any lab performing SBAs regularly would have a standard procedure so that comparisons could be made between separate SBA tests carried out in the same laboratory. I accept it is possible to make comparisons of SBA results within the same experiment carried out under the same conditions, as Prof Ala'Aldeen stated. However, even with experiments in the same laboratory it would be important to ensure that different

SBAs were performed under the same conditions using the same reagents etc., before making comparisons of the numbers obtained.

35. In addition, there was a known problem in making extrapolations from mouse SBA data where a strong adjuvant had been used to make a prediction as to its effect in humans, as Prof Heckels explained during his cross examination at T4/616/3-20.

OMVs and PorAs

36. By 2001 there had been many attempts to find an effective vaccine against Men B. which had met with limited success. Effective vaccines had been developed against serogroups A, C, Y and W-135, which comprised polysaccharides from these serogroups. However, serogroup B polysaccharide-based vaccines were not effective, and by the priority date it was no longer thought that a polysaccharide-based vaccine would be developed for Men B. There had been some limited success with OMV based vaccines. However by the priority date it had become clear that OMV vaccines were not effective in infants, which was a key group requiring protection against Men B. Furthermore there was evidence that the OMV vaccines did not give wide geographical protection, for example in regions where there was a more diverse group of serosubtypes than in the location where a particular vaccine had been administered.

37. It was well known that the major immunogenic component of the OMV vaccines was the PorA outer membrane protein. Much of the research and production of meningococcal vaccines at the priority date had centred on OMVs and PorA. Prof Heckels drew attention to a number of such vaccines, which had been used in meningococcal outbreaks or immunisation programs prior to the priority date. These included the Norwegian Vaccine, the Cuban Vaccine, and RIVM's multi-valent Vaccine.

38. However, the majority of the antibodies produced on OMV immunisation were targeted at the particular PorA present in the OMV and thus were specific only to the serosubtype that contained that PorA. PorA was highly antigenically diverse, and thus it was well known that the antibodies against one PorA only protected against a small percentage of the serogroup B meningococci. The RIVM multi-valent PorA vaccine, developed in the early 1990s, attempted to address this problem by including multiple different PorAs. In particular, six different PorAs were included and early clinical data showed that this vaccine conferred protection to those strains with the same serosubtype as one of those expressed PorAs. In order to confer protection against a sufficient variety of strains it would have been necessary to use a large number of different PorAs, resulting in a highly complex vaccine, which was undesirable.

39. The standard view of OMVs and PorAs at the priority date was summarised in Feavers (2001) *Meningococcal Vaccines and Vaccine Developments,* Chapter 1 in *Meningococcal Vaccines: Methods and Protocols* Ed. Pollard and Maiden at pp. 10-11:

> "Together the poor protective efficacy of OMVs in infants and concerns that they would not offer protection against antigenically diverse meningococci raised serious doubts about their suitability for paediatric immunisation programs…Nevertheless, appropriately formulated OMV

> vaccines have considerable potential for the disruption of outbreaks of meningococcal disease caused by a single strain in older children and teenagers.
>
> Reservations over the safety and effectiveness of polysaccharide and OMVs vaccines against serogroup B disease have stimulated the search for the "Holy Grail" vaccine candidate that is antigenically highly conserved and yet elicits a safe and protective immune response."

Attitudes of the skilled addressee to new vaccine candidates

40. Prof Ala'Aldeen explained that the skilled person would be sceptical of new vaccine candidates and would treat them with caution because there had been a lot of work with limited success for many years before the priority date. Candidates would need to be critically assessed on the basis of a series of assays. I accept Prof Ala'Aldeen's evidence on this issue. Prof Heckels was in agreement with this, as he explained during his cross examination at T4/589.

41. Prof Ala'Aldeen considered that in the 1990s the impression of OMVs had changed due to the publication of multiple clinical trial results, and that by the priority date they were no longer on the agenda for new vaccines; their protection was inadequate and they were unable to protect the most vulnerable age group of young children. He also considered that when working on a new vaccine candidate the skilled person would not be thinking of combining it with a PorA in order to improve the overall protection of the vaccine.

42. Prof Heckels had a different view. He considered that there was still interest in OMV vaccines against Men B. He referred to the New Zealand vaccine, which was launched after the priority date. In particular, in 1998 the World Health Organisation approached vaccine manufacturers to develop and design a vaccine specifically against the strain responsible for a long-lasting epidemic of Men B disease in New Zealand. Chiron Vaccines and the National Institute of Public Health (Norway) entered into an agreement with the New Zealand Ministry of Health and the resulting vaccine was offered to all children and teenagers in the country between 2004 and 2008. The vaccine formulation comprised OMVs from the New Zealand Men B strain. He also pointed out that several groups at the priority date were working on identifying new proteins and it was thought that these new proteins could be used with existing vaccine ingredients (for example one or more PorAs) to improve overall protection.

43. Whilst I accept that Prof Ala'Aldeen was no longer interested in pursuing PorAs at the priority date, I consider that Prof Heckels' view is more representative of the common general knowledge on this issue. The limitations of PorAs were well known, but nonetheless it was considered that they could have utility in multicomponent vaccines, in combination with other proteins. I find that the generally accepted view is summarised in Frasch et al. (2003) *Neisseria meningitidis Vaccines*, Chapter 15 in New Bacterial Vaccines. Ed. Ellis and Brodeur pp. 229-243. This was published after the priority date, but shows continuing interest in PorA vaccines, particular in multicomponent vaccines, after 2001:

> "New group B OMP vaccines will have been used in large-scale effectiveness trials in New Zealand and elsewhere, and multivalent PorA vaccines may be in routine use in some European countries. However, two questions will still remain. How do we prevent endemic group B meningococca1 disease caused by diverse populations of strains, and will long-term use of a vaccine that stimulates primarily PorA-based protection result in either antigenic drift of PorA, or an increased occurrence of strains that have a diminished or absent expression of PorA? In light of the tremendous explosion of technologic advances in the area of genomics and proteomics, it is likely that these questions will be addressed by multiple component vaccines, produced either as combination subunit vaccines or as OMV vaccines engineered and produced to enhance the expression of particular surface proteins. These vaccines will utilize both the antigens identified in earlier vaccines, as described above, and novel antigens, perhaps those identified "in-silico"."

Reverse vaccinology

44. Prof Heckels considered that research into Men B was invigorated by the advent of the new ""reverse vaccinology" approach" pioneered by Chiron that accompanied publication of the annotated Men A and Men B genomes. In particular, in the late 1990s the Men A and Men B genomes were sequenced. The annotated Men B genome was published in March 2000 in Tettelin et al. (2000) *Complete genome sequencing of Neisseria meningitidis serogroup B strain MC58* Science, Vol 287, pp. 1809-1815 ("Tettelin 2000"). The experts agreed that this had a considerable impact. The idea of reverse vaccinology was to use the new genome sequence to attempt to express and characterise proteins which might be potential vaccine candidates.

45. Prof Heckels explained that this put into the hands of the skilled team complete information about the genetic sequence of all proteins in the meningococci. His evidence was that reverse vaccinology was a tool which provided a way to identify new vaccine candidates and better to characterise existing candidates. A paper utilising this approach was published by the highly influential Rappuoli group, Pizza et al. (2000) *Identification of vaccine candidates against serogroup B meningococcus by whole genome sequencing* Science, Vol. 287, pp.757-760 ("Pizza 2000"). Whilst not all the detail of this paper was common general knowledge, its general message was widely known and accepted.

46. I accept that the reverse vaccinology approach was an important development which was part of the common general knowledge at the priority date. It meant that many more proteins were available for the skilled person to investigate, but it did not change the criteria for assessment of those proteins as vaccine candidates. Prof Heckels confirmed this in his cross-examination at T4/608/23-609/8:

> "Q. That reverse vaccinology approach was a different approach from the normal approach of skilled people in 2001/2002 which was to work on one protein or class of proteins at a time, I think you say?

> A. Obviously, the difference was because the genome sequence had been available. Reverse vaccinology was not possible before that.
>
> Q. Now the skilled person was given potentially hundreds of proteins which they could investigate?
>
> A. Yes.
>
> Q. So that obviously opened up new possibilities, but it did not mean, did it, Professor, that the skilled person would assess vaccine candidates differently? The same criteria would apply?
>
> A. Yes."

47. I agree that Pizza 2000 was an important publication. It identified "seven representative proteins" and narrowed the options from over 2000 open reading frames ("ORFs") to five vaccine candidates. None of these candidates was 2086 protein.

The Patent

48. The Background of the Invention sets out various facts which I have found to be common general knowledge at the priority date. In particular:

    i) Meningococcal meningitis is a devastating disease that can kill children and young adults within hours despite the availability of antibiotics. Pizza et al., 2000, Science 287: 1816-1820. [0002]

    ii) Serogroup B strains of *N. meningitidis* are a major cause of meningococcal disease throughout the world. For example, it is reported in the medical literature that serogroup B is responsible for about 50% of bacterial meningitis in infants and children residing in the United States and Europe. No vaccine currently exists to prevent meningococcal disease caused by *N. meningitidis* serogroup B. [0003]

    iii) Developing an immunogenic composition for the prevention of serogroup B meningococcal disease has been a challenge to researchers for over thirty years. Unlike serogroup A disease, which virtually disappeared from North America after World War II, disease caused by serogroup B and C organisms remains endemic throughout much of the economically developed world. [0004]

    iv) Vaccines based on polysaccharide conjugates have been developed against *N. meningitidis* serogroups A and C and appear to be effective in preventing disease. However, this immunogenic composition elicits a T-cell independent immune response, is not effective in young children, and provides no coverage for serogroup B strains, which cause upwards of 50% of meningococcal disease. [0005]

v) Studies in humans and animals indicate that the serosubtyping antigen, PorA, elicits bactericidal antibodies. However, the immune response to PorA is generally serosubtype specific. In particular, serosubtyping data indicate that an immunogenic composition made of PorAs may require a PorA for each serosubtype to be covered by such an immunogenic composition. Therefore, 6-9 PorAs will be needed to cover 70-80% of serogroup B strains. Thus, the variable nature of this protein requires a multivalent vaccine composition to protect against a sufficient number of meningococcal serosubtype clinical isolates. [0008]

49. The summary of the invention explains that:

i) To meet this need, the invention provides *Neisseria* ORF2086 proteins ("2086 proteins"), including 2086 Subfamily A proteins and 2086 Subfamily B proteins. Such 2086 proteins include recombinant forms and forms isolated from a natural source, as well as both lipidated and non-lipidated forms. [0014] and [0016]

ii) The present invention unexpectedly and advantageously provides compositions that (amongst other things) elicit bactericidal antibodies to multiple neisserial strains [0017].

50. The invention is explained further at [0026]:

> "The compositions of the present invention have been shown to be highly immunogenic and capable of eliciting the production of bactericidal antibodies. These antibodies are cross-reactive to serogroup, serotype and serosubtype heterologous meningococcal strains. Accordingly, the present compositions overcome the deficiencies of previous *N. meningitidis* vaccine attempts by exhibiting the ability to elicit bactericidal antibodies to heterologous neisserial strains. Thus, among other advantages, the present invention provides immunogenic compositions that can be compounded with fewer components to elicit protection comparable to previously used agents. The compositions or immunogenic agents therein (e.g., polypeptides, immunogenic portions or fragments, and biological equivalents) can be used alone or in combination with other antigens or agents to elicit immunological protection from meningococcal infection and disease, as well as to elicit immunological protection from infection and/or disease caused by other pathogens. This simplifies the design of an immunogenic composition for use against meningococcal infection by reducing the number of antigens required for protection against multiple strains. In fact, purified 2086 protein will dramatically and unexpectedly reduce the number of proteins required to provide adequate immunogenic coverage of the strains responsible for meningococcal disease…"

51. This paragraph emphasises that 2086 protein produces bactericidal antibodies that are cross-reactive against heterologous strains which enables the production of vaccines with fewer components to produce comparable coverage to the multi-component vaccines previously discussed.

52. [0030] is in similar terms:

> "Antibodies to the 2086 protein also passively protect infant rats from challenge with meningococci (see table VII). Recombinant expression of 2086 protein enables the use of 2086 protein as an immunogenic composition for the prevention of meningococcal disease. All of the recent meningococcal immunogenic composition candidates in clinical trials have been complex mixtures or outer membrane protein preparations containing many different proteins. The PorA protein, that provides serosubtype specificity, will require the inclusion of 6 to 9 variants in an immunogenic composition to provide about 70-80% coverage of disease related serosubtypes. In contrast, it is clearly demonstrated herein that antisera to a single 2086 protein alone is able to kill representatives of six serosubtypes responsible for about 65% of the disease isolates in western Europe and the United States. Therefore, purified 2086 protein has the potential to reduce the number of proteins required to provide adequate immunogenic composition coverage of the serosubtypes responsible for meningococcal disease."

53. This paragraph emphasises that antisera to a single 2086 protein is able to kill a range of strains responsible for the majority of the disease isolates in significant geographical areas, and therefore has the potential to reduce the number of components in the vaccine, as compared with the use of PorA proteins, which required 6-9 variants.

The examples

54. I will consider the more important examples set out in the Patent.

Example 1

55. Example 1 sets out the work leading to the identification of 2086 protein as a protein capable of eliciting antibodies which are bactericidal against heterologous strains. Table II shows the inventors' observation that outer membrane preparations from strain 8529 were unusual in that they generated antisera that were bactericidal against several (but not all) heterologous strains. The inventors then identified the agent responsible for this effect by a series of separation and purification steps, tracking the bactericidal effect ([0133] & Table III), and analysed the proteins in the active fraction by various techniques ([0134]). Comparison of the protein sequence information with the sequence of *N. meningitidis* serogroup A (deposited by the Sanger Centre) enabled identification of the protein of interest as that encoded by ORF2086 ([0135]-[0137]).

56. Prof Heckels agreed with Prof Ala'Aldeen that this was an impressive piece of work that was also lucky, because the original observation of cross-reactivity was correlated to a single antigen, whereas it could have been the result of several factors. Prof Heckels was cross examined about this at T4/711/2-11:

> "Q. Again, would you agree with Professor Ala'Aldeen that this was an impressive piece of work that will have taken a long time to undertake?

> A. I do not know how long it would have taken, but it is definitely a good piece of work.
>
> Q. And perhaps lucky, because it turned out the original observation of cross-reactivity in the outer membrane protein preparation from this strain was attributable to a single protein?
>
> A. Yes, that was lucky."

57. [0138]-[0145] describe the methods used in more detail. The immunogenicity methods (preparation of antisera and bactericidal assay) are used throughout the Examples of the Patent. In particular:

    i) The bactericidal assay used in the Patent employs an improved fluorescence-based method of counting the number of live bacteria, eliminating the subjective element which was present in the prior art method of counting;

    ii) It uses human complement rather than baby rabbit complement; and

    iii) It uses normal mouse serum or pre-immunised serum as negative controls to eliminate false positives.

    For these reasons, Prof Heckels considered that it was "a good robust assay"; T4/623/6 – 624/17.

Example 2 (and Example 6)

58. Example 2 describes the amplification by PCR and cloning of the ORF2086 gene from the 8529 strain to produce the recombinant 2086 protein in lipidated form ("rLP2086"). The amino acid sequence produced in part A is SEQ ID NO. 212, while that produced in part B is SEQ ID NO. 214. It refers at [0154] to the SBA results produced by antisera raised against rLP2086 from the 8529 strain, as shown in Table VII at [0189]. The antisera contained antibodies that were bactericidal against 9 out of 10 different serosubtype subfamily B strains tested. These strains are said in [0154] to be representative of strains causing diseases throughout Western Europe, the Americas, Australia and New Zealand.

Example 3

59. Example 3 is concerned with the cloning and expression of the 2086 protein in non-lipidated form (with a T7 tag). The amino-acid sequence of the non-lipidated form of the 2086 protein from the 8529 strain is SEQ ID NO. 216. Table V on p.43 shows the results of SBAs against the heterologous strain H44/76 using rLP2086 (i.e. the lipidated form from Example 2) and rP2086T7 (i.e. the non-lipidated form from Example 3). This gives rise to one of the insufficiency objections, and I will consider these results in that context.

Example 5

60. Example 5 reports on PCR amplification of the ORF2086 genes from 88 strains of *N. meningitidis*. Primers based on the sequence of the ORF2086 gene from the 8529 strain resulted in amplification of the ORF2086 gene for 63 out of the 88 strains –

those were classified as subfamily B and are listed in Table VI-B. Further primers were designed which permitted amplification of the ORF2086 gene for the remaining 25 strains – those were classified as subfamily A and are listed in Table VI-A. The authors report that 2086 proteins from subfamily A were about 75% identical to those from subfamily B. Tables VI-A and VI-B list the various strains used, and their serosubtype, as well as where they were obtained.

Example 8

61. [0204]-[0212] contain data showing the purification and characterisation of various rLP2086 proteins for both Subfamily A and Subfamily B, and the results of WCE and SBA assays against a range of target strains using antisera generated using rLP2086 from the 8529 strain (Table XII); and rLP2086 from the 2996 strain (Table XIII).

62. At [0213]-[0214] it is reported that antiserum to rLP2086 from the 8529 strain and (separately) antisera to each of three PorAs were raised. SBAs were then conducted against a range of strains using (i) a mixture of all the antisera (ii) the antiserum to the rLP2086 protein alone and (iii) in the case of three strains, the homologous PorA antiserum. Table XIV is said in [0213] to show that antisera to rLP2086 and rPorA are complimentary [sic] when mixed.

63. Table XV (and [0215]-[0217]) reports the results of an experiment, in which antisera are raised by immunising mice with (i) a mixture of rLP2086 from strains 8529 and 2996 and (ii) a mixture of those two rLP2086s and two PorAs. Those antisera are tested in SBAs against a range of strains. The antiserum to the mixture of rLP2086s killed 8 out of 10 of the strains (all except NmB and 6557); the antiserum to the mixture of rLP2086s and PorAs killed all 10 strains. The two PorAs used are of the same serosubtypes as strains NmB and 6557. It is said [0218] that "mixtures of P2086 and PorA elicit complimentary [sic] bactericidal antibodies in mice".

64. The results in Tables XII, XIV and XV give rise to certain insufficiency objections, and I will discuss them further in that context.

Example 9

65. This example records the results of SBAs using lipidated and non-lipidated 2086 protein from strain 8529 in Table XVII. They show that higher SBA results were obtained with the lipidated than with the non-lipidated form. Again, this is relevant to an insufficiency objection that the non-lipidated form would not be useful, which I will consider later in this judgment.

Example 10

66. Table XX shows a number of SBA results against various strains using antisera raised against 2086 protein from a variety of subfamily A strains (including 2996). It also shows SBA results for antisera raised against 2086 protein from strain 2996, together with 2086 protein from strain 8529 and, additionally, two PorAs. It also contains various controls, such as antisera raised against PorAs alone.

The claims alleged to be independently valid

67. Wyeth has identified a large number of claims which it says are independently valid. On occasion, the courts have disapproved of such practice, in that it adds to the time and cost of the trial, frequently for little benefit. However, Wyeth submits that because of the large number of different kinds of attack on the Patent, including a number of anticipation-only attacks and a range of "plausibility" points, it has been necessary to specify a large number of claims, certain of which are only relevant if particular objections to validity succeed.

68. I set out below the claims that are said to be independently valid:

> 1. A composition containing at least one protein comprising an amino acid sequence having sequence identity greater than 95% to the amino acid sequence of any one of SEQ ID NOS: 212, 214 and 216, wherein the composition additionally comprises at least one PorA protein.
>
> 2. The composition of claim 1, wherein said at least one protein comprises an amino acid sequence having sequence identity greater than 97% to the amino acid sequence of any one of SEQ ID NOS: 212, 214 and 216.
>
> 3. The composition of claim 1, wherein said at least one protein comprises the comprises the amino acid sequence of any one of SEQ ID NOS: 212, 214 and 216.
>
> 5. The composition of any of claims 1-3, wherein said at least one protein is non-lipidated.
>
> 6. The composition of any of claims 1-5, wherein said at least one protein is a recombinant protein.
>
> 10. The composition of any of claims 1-8, wherein said composition additionally comprises a pharmaceutically acceptable adjuvant, wherein said adjuvant is aluminium hydroxide or aluminium phosphate.
>
> 18. The composition of any of claims 1-16 for use as a vaccine.
>
> 19. The composition of any of claims 1-16 for use in a method of inducing an immune response in a mammal.
>
> 20. The composition of any of claims 1-16 for use in a method of ameliorating or preventing N. meningitidis infection in a human.

Claim construction

69. There is no dispute as to the principles of construction that I should apply. They are set out in *Kirin-Amgen Inc v Hoescht Marion Roussel Ltd* [2005] RPC 9, and in *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2010] RPC 8 at [5]. The essential question for the Court is to determine what the person skilled in the art

would have understood the patentee to have been using the language of the claim to mean.

Claim 1

70. There was some discussion by the experts as to the meaning of "PorA protein". Prof Heckels queried in his first report whether the phrase was limited to a free PorA protein (not associated with a membrane) or whether it could also include a membrane associated PorA. He pointed out that the experimental results for PorA in the Patent were achieved using free PorA. During the course of his cross examination Prof Ala'Aldeen suggested that the phrase was limited to isolated PorA and excluded native PorAs contained within OMVs, because no one would think of using OMVs in a vaccine in 2001.

71. I do not accept either of these implied limitations to the language of the claim. Wyeth submits, and I agree, that there is no reason for the skilled person to think that the patentee was using the term "PorA protein" in the claims to mean only a free PorA protein. The skilled person was familiar, as part of his common general knowledge, with membrane associated PorA proteins being used as antigens to raise bactericidal antibodies, and there was no technical reason to limit the claimed monopoly to a combination of a 2086 protein and a free PorA protein. For similar reasons, I reject the suggestion that the patentee intended to limit himself to isolated PorA, given that I have not accepted that no one would think of using OMVs in a vaccine in 2001. The phrase "at least one PorA protein" is not limited to any particular type of PorA protein.

Claim 3

72. The issue of construction in relation to claim 3 is relevant to the question of infringement and is of importance if Wyeth is obliged to amend down to this claim. The question is whether the skilled person would have understood the patentee to be using the language of claim 3 to limit the claim to sequences which are an exact match to SEQ ID NOS. 212, 214 or 216.

73. Wyeth contends that claim 3 encompasses sequences of, for example, a 99% match. It submits that claims 1 and 2 specify a particular level of sequence identity, whereas claim 3 does not. The sequence is still required to have at least 95% identity to one of the three sequences specified in claim 1, because claim 3 is dependent on claim 1. However there is no requirement for 100% identity.

74. Wyeth relies upon [0051]-[0052] of the Patent, which state:

> "A polypeptide sequence of the invention may be identical to the reference sequence of even numbered SEQ ID NOS. 212, 214, 216, that is, 100% identical, or it may include a number of amino acid alterations as compared to the reference sequence such that the % identity is less than 100%. Such alterations include at least one amino acid deletion, substitution, including conservative or non-conservative substitution, or insertion. The alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere

> between those terminal positions, interspersed either individually among the amino acids in the reference amino acid sequence or in one or more contiguous groups within the reference amino acid sequence.
>
> Thus, the invention also provides proteins having sequence identity to the amino acid sequences contained in the Sequence Listing (i.e. even numbered SEQ IDS NOS: 212, 214, 216). Depending on the particular sequence, the degree of sequence identity is preferably greater than 95% (e.g. 95%, 97%, 99%, 99.9% or more). These homologous proteins include mutants and allelic variants."

75. Wyeth submits that these passages support its case that the skilled person would not understand that the patentee was using the language of claim 3 to confine the claim to proteins which had 100% sequence identity with one of the specified sequences.

76. I do not accept Wyeth's case on this issue, and I consider that claim 3 is limited to proteins with 100% sequence identity to the specified sequences in claim 1. I reach this conclusion for the following reasons.

77. First, the patentee has set out a series of cascading and narrowing claims. Claim 1 is the widest, requiring only 95% identity, claim 2 is somewhat narrower, requiring 97% identity, and claim 3 is the narrowest, requiring precise identity. The purpose, as the skilled reader would understand, is to provide for "back-ups" in case the wider claims are invalid.

78. Secondly, Prof Ala'Aldeen explained that in certain circumstances, a single amino acid change could alter the functionality of a protein. Therefore, the skilled addressee would be aware that precision could be important in the description of any amino acid sequence. Furthermore, he explained that it was the convention in 2001 to define homology or sequence identity in terms of numerical percentage identity. Prof Heckels said at [118] of his second report that "to have the sequence of X" means to contain the exact sequence of X, i.e. 100% identity. I accept this evidence.

79. Thirdly, I do not consider that [0051]-[0052] of the Patent support Wyeth's construction of claim 3. [0052] refers expressly to values of 95%, 97%, 99% and 99.9% identity. Accordingly, where something other than 100% identity is intended by the patentee, the percentage is specified. This is reflected in claims 1 and 2, which refer to thresholds below 100%. Where the patentee has intended to claim less than 100% identity, this is specified in the claims.

80. Fourthly, Wyeth's construction of claim 3 does not provide reasonable certainty to the public, as required by the Protocol to Article 69 of the European Patent Convention, as it is not clear what percentage identity would satisfy claim 3. It may be that this claim would be satisfied by anything more than 95% or 97% identity, or perhaps 99% identity would be required. If claim 3 does not mean 100% identity, then it would be of uncertain scope.

Claims 18-20

81. Claim 1 claims a composition comprising at least a 2086 protein and a PorA protein. Claims 18 to 20 contain functional limitations. In particular claim 18 is directed to a composition "for use as a vaccine"; claim 19 to a composition "for use in a method of inducing an immune response in a mammal"; and claim 20 to a composition "for use in a method of ameliorating or preventing N. meningitidis infection in a human". Attaining the claimed therapeutic effect is a functional technical feature of each of the claims; T 609/02 Salk at [9]; *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] RPC 28 at [56].

82. GSK submits that the functional features require merely that the composition has some clinical technical effect against a single meningococcus strain somewhere. It relies on this submission to suggest that the technical contribution of the Patent is minimal, and the claims set a low hurdle for the prior art.

83. In particular GSK relied on the following arguments:

    i) The natural meaning of the words used in the claims was in accordance with GSK's construction. Some efficacy as a vaccine was required but no more.

    ii) This was supported by the description. For example, [0111] defines "immunologically effective amount" as the administration of an amount "sufficient to at least cause the immune system of the individual treated to generate a response that reduces the clinical impact of the bacterial infection. This may range from a minimal decrease in bacterial burden to prevention of the infection."

    iii) The effect could come from either the 2086 protein or the PorA protein.

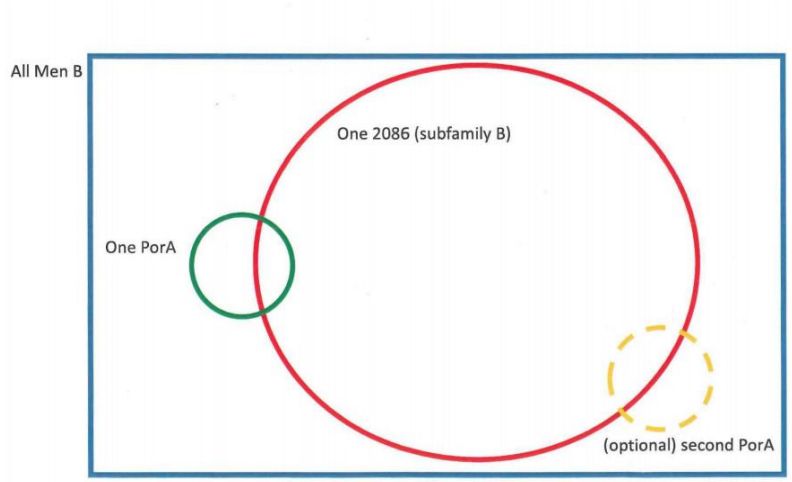
    iv) The effect of 2086 and PorA in the composition varies independently. Accordingly the claims are classic "sausage machine claims". In the words of the EPO Guidelines for Examination at Part G – Chapter VII-16, "the invention consists merely in the juxtaposition or association of known devices or processes functioning in the normal way and not producing any non-obvious working inter-relationship."

    v) If the claims require more than a minimal effect, then their scope is unclear.

84. I accept that the claims do not require more than a discernible effect in the treatment of Men B. As Prof Ala'Aldeen explained, the disclosure of the Patent at e.g. [0111] reflects a clinical spectrum in that some individual patients only get very mild symptoms in the first place. However, I do not accept that it is correct to characterise the technical effect of the Patent in terms of individual patients. This misses the technical contribution of the Patent, namely a composition and vaccine which provides protection for a population of patients against a broad range of diverse strains, as a result of inclusion of the 2086 protein; and strains of the same serosubtype as the PorA(s) that are selected to supplement the protection provided for by 2086.

85. For similar reasons, I do not accept that GSK's "sausage machine" characterisation of the claims is fair, when the claims are interpreted in the light of the description. I refer to my summary of the disclosure of the Patent. The Patent not only identifies 2086 protein for inclusion in a vaccine for the treatment of Men B, but also discloses that it elicits the production of antibodies that are bactericidal against a range of unrelated heterologous Men B strains. This is why it is said to be an improvement over the prior art multi-component vaccines, which required, for example, several PorAs (since individual PorAs were not bactericidal against a range of unrelated heterologous Men B strains). Furthermore the Patent discloses that this bactericidal activity can be complemented by antibodies against one or more PorAs. This is the technical effect which underlies the uses in each of claims 18 to 20, and the claims are to be interpreted accordingly.

86. Mr Tappin handed in a diagrammatic illustration of this concept, which I reproduce below:



87. The red circle illustrates the wider coverage of the 2086 protein against unrelated heterologous Men B strains. The green circle (and optional yellow circle) illustrates the additional (and potentially overlapping) coverage against Men B strains obtained by inclusion of one or more PorA proteins

88. Accordingly, I do not accept GSK's case that the claims cover non-functioning 2086 proteins, where the required efficacy comes from PorA alone. This defeats the object of the claimed combination, and effectively reduces the invention to a single functioning component, which the Patent acknowledges was known and used in the prior art, and on which it seeks to improve. This is not a fair interpretation of the claims, and cannot have been the intention of the patentee, objectively assessed.

89. This does not mean that the 2086 protein has to be effective against every Men B strain. The purpose of inclusion of one or more PorAs is to extend coverage to strains against which the 2086 protein would be ineffective. Furthermore the reference to "complimentary" in the Patent does not mean that the combination of 2086 and PorA has to be synergistic. If, for example, the 2086 protein "is able to kill representatives of six serosubtypes responsible for about 65% of the disease isolates in western Europe and the United States", as stated in [0030] of the Patent, one or more PorAs

will be chosen by the skilled person to kill other strains of the disease, and thereby to extend the coverage of the vaccine.

Infringement

90. The Revised Product Description explains that Bexsero contains fHbp in the form of the C-terminal portion of a fusion protein referred to as 936-741. It also contains OMVs from strain NZ98/254 (which is said to express PorA of serosubtype P1.4) and aluminium hydroxide.

91. An alignment between the C-terminal part of fusion protein 936-741 (starting at amino acid 180) and SEQ ID NOS: 212, 214 and 216 is shown on p.91 of Prof. Ala'Aldeen's first report. The sequence identity between the relevant part of fusion protein 936-741 and SEQ ID NOS 212, 214 and 216 is 99.2%, 98.8% and 99.2% respectively.

92. The only debate at trial in relation to infringement concerned claim 3. I conclude claims 1, 2 and 18-20 are infringed by Bexsero. In addition, it was common ground between the experts that if claim 1 was infringed, then so were claims 5, 6 and 10. Claim 3 is not infringed.

Plausibility – AgrEvo obviousness/insufficiency

93. The parties dealt with these issues together. Lack of plausibility of the Patent is the foundation of many of the pleaded insufficiency allegations, and also of the allegation of AgrEvo-type obviousness, where GSK also contends that the technical contribution is arbitrary.

Legal principles

94. There is no dispute about the principles that I should apply:

i) In relation to sufficiency, the assertion that the invention will work across the scope of the claim must be plausible and in the case of claims involving a medical use, the patent must show that the claimed medical effect is plausible; *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] RPC 28 at [95]-[103].

ii) "Plausible" means that there must be some real reason for supposing that the statement is true; *Human Genome Sciences Inc v Eli Lilly & Co* [2012] RPC 6 at [149]. This excludes speculative patents, based on mere assertion.

iii) Plausibility is a "threshold test" which is satisfied by a disclosure which is "credible", as opposed to speculative; *Actavis Group ptc ehf v Eli Lilly & Co* [2015] EWHC 3294 at [177]-[178].

iv) "Plausibility" is also relevant to AgrEvo-type obviousness, as explained in the cases reviewed by Lord Hoffmann in *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] RPC 8 at [31]-[35], and it is the same threshold test. In particular, Lord Hoffmann stated at [37] that there was:

> "no reason as a matter of principle why, if a specification passes the threshold test of disclosing enough to make the

> invention plausible, the question of obviousness should be subject to a different test according to the amount of evidence which the patentee presents to justify a conclusion that his patent will work."

v) A mere arbitrary selection from a class makes no technical contribution and lacks any inventive step; *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co* [2010] RPC 9 at [40]-[52].

General observations on plausibility

95. A large number of "plausibility" objections were pleaded in support of insufficiency/AgrEvo obviousness, but various allegations did not appear to be pursued by the close of the trial. I will only deal with those referred to in GSK's closing submissions. Before turning to the detail of the "plausibility" objections, it is necessary to observe that Prof Heckels understood that the Patent was promising that there would be a synergistic effect between the 2086 and PorA proteins, in that one would enhance the cross-reactivity of the other, and therefore the combination would be more than the sum of its parts. For example Prof Heckels said at [272] of his first report:

> "The data in the Patent do not support any claim to an effect which is greater than the sum of its parts… The Patent does not therefore make it plausible that all compositions falling within claim 1 would provide an improved breadth of protection."

I have rejected the contention that the patent promises such an effect.

96. Apart from the "synergy" issue, I consider that there was a great deal of agreement between the experts that the disclosure of the Patent was plausible. When Prof Heckels was cross examined about the lack of plausibility concerns in his report, he made clear that this was based on his understanding of the broader, synergistic protection that he considered the Patent was promising. Aside from that confusion, he did not consider that the invention was implausible. At T5/757/6-19 he said:

> "Q. Then, if you turn over the page, you say at the end of the paragraph, 265, "Given the specificity of the response to PorA proteins, it does not make it plausible that such a combination would confer broader protection." I just want to understand what you are saying there, Professor. Broader protection than what?
>
> A. I think that should probably say "broad protection". It is the issue that we have just been discussing.
>
> Q. Right, okay. So what it does make plausible, does it not, Professor, is that you would have the effect of 2086 killing a range of diverse strains and then if you add a PorA, you will add in the ability of that PorA to kill strains of that serosubtype?"

A. Yes, as we have just been discussing."

97. Prof Ala'Aldeen considered that the data in Table VII provide convincing evidence that 2086 protein shows bactericidal effects against a range of unrelated Men B strains and that it was an interesting and serious vaccine candidate. Prof Heckels was cross-examined about this at T4/719/24-720/7, and was in agreement with Prof Ala'Aldeen.

> "Q. So, the skilled person looking at this data in Table VII and having read 154 would understand that this data shows that 2086 elicits bactericidal antibodies against a range of unrelated Men B strains?
>
> A. Yes.
>
> Q. And this data is convincing evidence that 2086 is an interesting and serious vaccine candidate?
>
> A. Yes."

98. Prof Ala'Aldeen and Prof Heckels both recognised that the disclosure of the Patent was very significant. Having expressed his view of the importance of 2086, at [84] of his third report, Prof Ala'Aldeen said that:

> "The pre-clinical work shown in the Patent is exactly the kind of work that was used to make predictions as to likely effects in humans and provides a proof of principle."

99. At T4/715/25-716/6 Prof Heckels fairly acknowledged that the Patent disclosed a vaccine candidate with promise, and of considerable interest:

> "Q. We will come and look at the data in the patent in a moment, but would you agree to the skilled person in 2001 or 2002, the patent would have been an exciting and impressive piece of work?
>
> A. It would be of considerable interest, yes.
>
> Q. It discloses a vaccine candidate with great promise.
>
> A. Yes, certainly with promise, yes. Yes, with promise."

100. None of this evidence supports the pleaded allegations of an arbitrary, implausible selection.

The AgrEvo obviousness allegation

101. GSK submits that if the composition claims cover non-functioning 2086 proteins, then they are arbitrary. This also applies to claims 18 to 20 on GSK's construction – the required efficacy can come from PorA alone, which would mean that the only novelty of the claims lies in the addition of a non-functioning 2086 protein. On this basis, GSK contends that they lack inventive step. I have rejected GSK's construction, and therefore I reject the AgrEvo obviousness allegation.

Sequence homology and breadth of claim

102. GSK contends that the data in the Patent do not support killing of some strains of meningococci by all compositions comprising a 2086 protein having 100% homology with the 2086 protein of the tested bacterial strain. It is submitted that there is even less reason for this to be credible for those proteins having 95% homology. It is alleged that the data in the Patent demonstrate that a 2086 protein from Subfamily A is unlikely to kill Men B from Subfamily B (see Tables XII and XIII), and even within Subfamilies, some strains are not killed. Professor Heckels highlighted an SBA result in Table XII (also shown in Table VII), which indicated that the the 2086 protein target strain had a high homology with 2086 protein but nonetheless there was little or no killing. He thought that this would be of concern to the skilled addressee.

103. I reject this contention which, in my judgment, seeks to read too much into single SBA results. Prof Ala'Aldeen explained that the general impression from, and overall trend in, the data in Tables XII and XIII is what the skilled person would expect i.e. that the killing appears generally to be related to the level of homology between the 2086 protein used to raise the sera and the test strain. He considered that the fact that there were exceptions to this general trend would not surprise the skilled person, as the experiments had been carried out on complex biological systems. Therefore, the skilled person would not expect a direct relationship between homology and SBA data in every case. He mentioned a number of other factors which could affect SBA results, and in his third report at [61]-[63] set out various reasons why killing might not be seen in individual results. I accept Prof Ala'Aldeen's evidence on this issue.

104. GSK further submits that the threshold figure of 95% homology in claim 1 does not arise from any of the data in the specification of the Patent, and is arbitrary. I do not agree. Given that claims 1 and 2 are not limited to 100% homology, there has to be a defined boundary, and 95% is reasonable on the basis of the data in the Patent. Indeed, Prof Ala'Aldeen considered that a lower boundary could have been chosen. He explained that the skilled person would understand from the data prior to Table XII that 2086 protein was a useful antigen that elicits antibodies which are cross-bactericidal, and would expect that effect to be related to the degree of amino acid homology. His view was that a claim to utility based on 95% homology would be entirely credible and well above the level of homology which would cause the skilled person to question it. I accept his evidence on this issue.

Non-lipidated 2086 proteins

105. GSK alleges that the Patent does not enable nor render plausible a composition in which the 2086 protein is other than a lipidated protein. It is said that the data in the Examples do not disclose a technical effect in respect of non-lipidated 2086 proteins. Prof Heckels explained that the removal of lipidation can have a significant deleterious effect on the effectiveness of 2086 as an antigen. He considered that the data in Table V of the Patent did not establish that lipidated and non-lipidated 2086 both worked well. He thought that the test was not a fair one, as the only tested 2086 protein without lipid had substituted in a T7 tag (because the experimenters had not been able to obtain tag-free material). He thought that this could not be said to be representative of non-lipidated 2086. He considered that the notional person skilled in the art would not have added a T7 tag for this purpose.

106. Example 9 also contains data for lipidated and non-lipidated 2086 proteins. However, Prof Heckels considered that there was a huge difference between the results, and that the skilled person would have considered it pointless to use the non-lipidated protein on the basis of this data.

107. On the basis of the data in the Patent, it would be preferable to select a lipidated rather than a non-lipidated 2086 protein. However, that does not mean that it is implausible that the non-lipidated protein would give a bactericidal effect. In particular, Table V shows that it is not necessary for the 2086 protein to be lipidated in order to raise bactericidal antibodies. Prof Ala'Aldeen did not agree that the non-lipidated form without a T7 tag would give no bactericidal effect. The T7 tag may have optimised expression, or it may have had an adverse effect, because T7 does not induce antibodies against *N. meningitidis*. However, the general message of Example 3 is that non-lipidated 2086 has a bactericidal effect. He considered that, having read the Patent, it was plausible that non-lipidated 2086 without a T7 tag would give some bactericidal effect (T4/343-345/5). For example:

> "Q. I suggest to you it is just not credible that a non-lipidated version without a T7 tag would give you any bactericidal effect?
>
> A. Why would you say that? You can remove it or you can just express it in a totally different expression vector that you can find, and there are plenty…"

I accept his evidence on this issue.

108. His view is further supported by Example 9, and in particular Table XVII, which shows bactericidal effect for the non-lipidated form without the T7 tag. Higher SBA results were obtained with the lipidated form, but that does not mean that the non-lipidated form will not work. Prof Heckels made clear at T5/763/7-764/6, that although the bactericidal effect was much greater in the case of the lipidated form, there was also a bactericidal effect in the case of the non-lipidated 2086 protein:

> "Q. Okay. What we are seeing here is that there is a difference in magnitude, but the non-lipidated form raises antibodies which have bactericidal effect against both strains 44/76 and H355. Correct.
>
> A. Yes, but we are comparing 100 with 3,200.
>
> Q. Sure.
>
> A. And 200 with 6,400
>
> Q. Indeed.
>
> A. That is a huge difference.
>
> Q. Right, but you are still getting bactericidal effect with the non-lipidated form
>
> A. There is obviously some detectable bactericidal effect."

At least one PorA protein

109. GSK alleges that there are no data in the Patent relating to compositions comprising only one PorA protein. This refers to the fact that none of Tables XIV, XV, or XX (in Examples 8 and 10) discloses results using one PorA; rather, at least two PorAs are used. Accordingly, it is argued that as the claims extend to use of one PorA, they are not plausible across their full width.

110. I do not accept this argument. It was common general knowledge that PorA raises antibodies that are bactericidal against strains of the same serosubtype. The results in the Patent, before the reader arrives at Examples 8 and 10, show that the 2086 protein is an interesting and serious vaccine candidate, which provides protection against a range of strains, as the experts agreed. It is plausible that a vaccine containing a combination of a 2086 protein with a PorA protein would be useful. The 2086 protein would provide protection against a range of strains and the PorA protein would extend protection to strains of the same serosubtype, which could be used to fill a gap in the protection provided by the 2086 protein. In my judgment, that is evident from the disclosure of the Patent without Tables XIV, XV and XX. The data in those tables provides further support for the technical contribution of the Patent.

111. GSK also alleges that Patent creates the same difficulties for the skilled team that existed with PorA vaccines in the prior art. It would still have to select the correct PorA protein(s) by researching the epidemiological information for the area that it was seeking to manage, and the PorA proteins would need to be tailor-made to fit that epidemiological profile. In my judgment, the selection of PorA proteins to extend the protection of the 2086 protein would have been routine for the skilled team in the light of the disclosure of the Patent. Prof Ala'Aldeen explained that differentiation between strains on the basis of PorAs was the classical method that had been developed in the 1980s and 1990s and people were accustomed to it. I accept this evidence. Prof Heckels' difficulties in this respect arose from his understanding that the Patent was suggesting that 2086 protein would kill all strains, or that the combination of 2086 and PorA would be synergistic. I have rejected this interpretation of the Patent.

Adjuvants

112. GSK submits that the claims are not limited to compositions containing a particular adjuvant. However, the data in the Patent are all obtained while using an adjuvant, which was known to be extremely potent. It is suggested that the claims are not plausible in respect of compositions which do not contain an adjuvant.

113. It was common general knowledge at the priority date that adjuvants boost the response to the administered antigens. Prof Ala'Aldeen explained that an adjuvant has the effect of boosting the immune response, but does not affect cross-protection per se. He stated that the data of the Patent show that the 2086 protein generates cross-bactericidal antibodies and that characteristic remains no matter how much the immune response is boosted or reduced by the presence or absence of an adjuvant. I accept this evidence.

114. Prof Heckels also pointed out that the data in the patent were obtained using adjuvant QS-21, which is a strong adjuvant commonly used in mice. He did not think that it

was possible credibly to extrapolate from that data to compositions with human adjuvants, or no adjuvants. It is correct that the skilled person would need to use common general knowledge to select a suitable adjuvant, if it was considered desirable. This, in my judgment would have been routine trial and error at the priority date. The most commonly used human adjuvants were aluminium hydroxide and aluminium phosphate. Prof Heckels accepted at T5/770/11-19 that it was credible that a 2086 protein with either of these adjuvants would prove to be an effective vaccine in humans, and that would remain the case if a PorA was added. This is sufficient for plausibility:

> "Q. It is entirely credible, is it not, on the basis of the information that we have been looking at, that a 2086 protein with an aluminium hydroxide or phosphate adjuvant would prove to be an effective vaccine in humans?
>
> A. It is certainly possible, yes. It is something that would have to be tested.
>
> Q. And that would remain the case if you added a PorA, of course, as we have discussed?
>
> A. Yes."

Added Matter

Legal principles

115. The principles of relevance to this case may be summarised as follows:

i) The test of added matter is whether a skilled person would, upon looking at the amended specification, learn anything about the invention which he could not learn from the unamended specification; *Vector Corp v Glatt Air Techniques Limited* [2007] EWCA Civ 805; [2008] RPC 10 at [4], approving Jacob J in *Rickardson-Vicks Inc's Patent* [1995] RPC 568 at 576.

ii) One reason for the rule against adding matter is that third parties should be able to look at the application and draw a conclusion as to the subject matter which is available for supporting the claimed monopoly. If subject matter is added subsequently, the patentee could obtain a different monopoly to that which the application originally justified; *AP Racing Ltd v Alcon Components Ltd* [2104] EWCA Civ 40; [2014] RPC 27 at [9]-[10].

iii) The test of whether the skilled person is confronted with new information depends on whether the combination of claimed features in the patent derives directly and unambiguously from the application, read as a whole. It is not necessary for the subject-matter of the amendment to have been explicitly disclosed in the application. Literal support is not required by Article 123(2) (T 667/08 of 20 April 2012, and the EPO Guidelines for Examination Part H, Chapter IV, §2.2).

iv) An intermediate generalisation occurs when "a feature is taken from a specific embodiment, stripped of its context and then introduced into the claim in circumstances where it would not be apparent to the skilled person that it has any general applicability to the invention" (*Nokia v IPCom* [2012] EWCA Civ 805; [2013] RPC 5 at [56]).

v) The question is whether the feature in question would be seen by the skilled person as being generally applicable or only of significance in the context in which it was specifically disclosed. (*Nokia v IPCom* at [59]-[60].

116. GSK relies upon EPO case law concerning selections made from multiple lists. In particular, it submits that where a patent specification comprises a series of lists of variables, but does not point to a particular combination of choices from the respective lists, then an amendment to that particular combination will add matter. The skilled person learns from the amended disclosure that there is something special about that combination; that is not something he could have derived from the application as filed, as the relevant selections had not been made in that document.

117. GSK points out that the Technical Board of Appeal has considered the consequences of selections from lists in a series of decisions, traceable back to T-12/82 *Diastereomers*. In that case, the Board was considering the novelty of a selection from two lists. It stated at [13]:

> "…If on the other hand two classes of starting substances are required to prepare the end products and examples of individual entities in each class are given in two lists of some length, then a substance resulting from the reaction of a specific pair from the two lists can nevertheless be regarded for patent purposes as a selection and hence as new."

118. GSK submits that since a selection from two lists can be novel for the purposes of patentability, then it will also constitute added matter if the selection was not to be found in the application as filed.

119. In my judgment, selections from two or more lists may well amount to impermissible added matter, but this is not a rigid rule. In order to see whether there is a new combination of independent features from two or more lists, the whole contents of the application as filed must be considered, including its general disclosure. It is necessary to avoid a mechanistic approach, and to compare the disclosures of the application as filed and the patent, through the eyes of the skilled person, in order to answer the overall question of whether the skilled person would learn new technical subject matter which was not disclosed in the application.

Application to the facts

120. GSK alleges that Claim 1 of the Patent comprises an impermissible selection from three separate lists in the application as filed. In particular, it claims that (a) SEQ ID NOS 212, 214 and 216 must be selected from many disclosed amino acid sequences; (b) a threshold of 95% sequence identity must be selected from several disclosed threshold percentages; and (c) PorA protein must be selected from numerous disclosed additional components in a combination vaccine.

121. As to the amino acid sequences, the application expressly discloses each of SEQ ID NOS 212, 214 and 216 and that they are all sequences of the 2086 protein from strain 8529, and therefore related to each other (p.25 lines 1-11). More generally, they are the subjects of Examples 2 and 3 and the importance of the 2086 protein from strain 8529 is emphasised by its use in several of the other Examples. Therefore, I do not accept that the disclosure of these amino acid sequences is merely part of a list – the technical information as to their importance is clear from the application as filed.

122. As to the threshold of 95% sequence identity, as indicated above, the utility of the 2086 protein from the 8529 strain is plain from Examples 1-3, 6, and 8-10 of the application as filed. At p.40 lines 23-27 the application discloses that:

> "Thus, the invention also provides proteins having sequence identity to the amino acid sequences contained in the Sequence Listing (i.e., even numbered SEQ ID 25 NOS: 2-252). Depending on the particular sequence, the degree of sequence identity is preferably greater than 60% (e.g., 60%, 70%, 80%, 90%, 95%, 97%, 99%, 99.9% or more)."

123. In one sense, this could be described as a list of preferred levels of sequence identity. However, the disclosure must be read in light of the common general knowledge of the skilled person. He would know that exact sequence identity would not be required, and that a protein with an amino acid homology level of 95% to the specified 2086 sequences would be well above the level at which the protein would be expected to have utility. Furthermore, the claim limitation in the Patent would not be understood as teaching that a sequence identity of less than 95% would not have utility, but rather that the patentee had chosen a reasonable boundary for the claim. Prof. Ala'Aldeen explained this at [65] of his third report, and I accept his evidence.

> "…95% homology is well above the point at which the skilled person would question the usefulness of the class of proteins claimed. I do not believe that the skilled person would understand the Patent to be teaching that a protein with, say, 90% homology would not be useful whereas one with 95% homology would be."

124. As to PorA protein, the application discloses at p.61 lines 5-12 that:

> "…the compositions of the present invention may comprise combinations of two or more 2086 proteins, a combination of 2086 protein with one or more PorA proteins, a combination of 2086 protein with meningococcus serogroup A, C, Y and W135 polysaccharides and/or polysaccharide conjugates, a combination of 2086 protein with meningococcus and pneumococcus combinations, or a combination of any of the foregoing in a form suitable for mucosal delivery. Persons of skill in the art would be readily able to formulate such multi-antigen or multi-valent immunologic compositions."

125. GSK points out that PorA is not accorded any special significance in the application as filed, and that the passage cited above contains other combinations, apart from the express disclosure of "a combination of 2086 protein with one or more PorA proteins". However, this passage contains a general teaching of combining 2086 protein with one or more PorA proteins. The application teaches the importance of

2086 protein and I have found that it was common general knowledge that the major immunogenic component of the OMV vaccines was the PorA outer membrane protein. I have accepted Prof Heckels' evidence that it was well known at the priority date that PorAs could have utility in multi-component vaccines, in combination with other proteins.

126. In summary, I do not consider that claim 1 of the Patent discloses new technical information which was not disclosed in the application as filed. The utility of the 2086 protein from strain 8529 is clear from the Examples of the application. The skilled person would know, and is expressly told, that sequences with 95% homology would also be useful, and it is expressly disclosed that 2086 proteins can be combined with one or more PorAs. In these circumstances I reject the allegation that the amendments to claim 1 have added subject matter.

127. GSK alleges that claim 2, which requires a sequence identity of greater than 97%, and claim 3, which I have interpreted as requiring 100% sequence identity, also add subject matter. I reject this allegation, for essentially the same reasons as I rejected the allegation that the requirement for a sequence identity of greater than 95% in claim 1 adds subject matter. In addition, it is very hard to see how a requirement for exact sequence identity in claim 3 could add subject matter, given that the utility of these amino acid sequences is expressly disclosed in the application.

Priority

Legal principles

128. There was no dispute as to the legal principles that I should apply, which were summarised by Kitchin LJ in *Medimmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234; [2103] RPC 27. In particular:

i) A claim to priority of the "same invention" is referred to in Article 87(1) of the European Patent Convention. Section 5(2)(a) of the Patents Act 1977, which provides for entitlement to priority, is to be interpreted as having the same effect as Article 87(1), pursuant to section 130(7) of the Act; *Medimmune* at [151].

ii) The requirement for the "same invention" means that priority is to be acknowledged only if the skilled person can derive the subject matter of the claim directly and unambiguously, using common general knowledge, from the priority document as a whole; G02/98 *Same Invention* [2001] OJ EPO 413; [2002] EPOR 167.

iii) The approach is not formulaic: priority concerns technical disclosure, explicit or implicit. The question is whether there is enough in the priority document to give the skilled person essentially the same information as forms the subject of the claim and enables him to work the invention in accordance with that claim; *Unilin Beheer v Berry Floor* [2004] EWCA (Civ) 1021; [2005] FSR 6 at [48].

iv) The important thing is not the consistory clause or the claims of the priority document, but whether the disclosure as a whole is enabling and directly and unambiguously gives the skilled person what is in the claim whose priority is

in question. It must "give" this disclosure directly and unambiguously. It is not sufficient that it may be an obvious development from what is disclosed; *Abbot Laboratories Ltd v Evysio Medical Devices plc* [2008] EWHC 800 at [228].

v) Plausibility, as part of the requirement of an enabling disclosure, applies to issues of priority as well as sufficiency; *Hospira UK Ltd v Genentech Inc* [2014] EWCH 1094 at [149].

The first priority date

The combination of 2086 and PorA(s)

129. A difference between the first priority document and the Patent which is relied on by GSK is the absence of Examples 8-11 in the first priority document. It is said that as a result, claim 1 is not supported, in that there is no disclosure of the combination of a 2086 protein with one or more PorAs.

130. I do not accept this submission. The first priority document discloses the combination of a 2086 protein with one or more PorAs at pages 56-7. In particular, it is disclosed at page 57 lines 6-7 that the compositions of the invention may comprise "a combination of 2086 protein with one or more PorA proteins."

131. Prof Ala'Aldeen considered that, as with the Patent, the first priority document discloses data which makes it clear that 2086 is a strong vaccine candidate. I agree, and I have already dealt with the relevant disclosure in the absence of Examples 8-11. For example, the first priority document discloses Table VII in Example 6 at page 88-89, which is the same as the disclosure of the Patent at [0189]. Both experts recognised the significance of this Example to the plausibility of the disclosure, in the evidence to which I have referred above. The skilled person would have known, as a matter of common general knowledge, of the ability of PorAs to raise bactericidal activity against strains of the same serosubtype and thereby to provide protection additional to 2086. On this basis, I accept Prof Ala'Aldeen's evidence that the disclosure in the first priority document of "a combination of 2086 protein with one or more PorA proteins" was plausible.

132. In my judgment, Prof Heckels acknowledged that the disclosure of the first priority document was plausible, and that it was credible that the disclosed combination of a 2086 protein and at least one PorA protein would prove to be a useful vaccine against Men B, when he was cross-examined on Table VII in that document at T4/741/3-12:

> "Q. Then the skilled person would expect, on the basis of this data, you would expect protection against a range of strains from the 2086 and strains of the same serosubtype as the PorA which you added coming from the PorA?
>
> A. Yes.
>
> Q. And it would be entirely credible to the skilled person that such a combination would prove to be a useful vaccine against Men B and subsequent investigations looking at this document?

> A. Against strains of that serosubtype; and the strains that were already covered by the 2086."

Sequence clusters

133. The relevant passage on page 37 of the first priority document discloses that:

> "According to a further implementation, Subfamily B includes Cluster B-1, Cluster B-2, Cluster B-3, Cluster B-4 and Cluster B-5. Cluster B-1 preferably includes polypeptides selected from the group consisting of SEQ ID Nos. 2, 4, 8, 12, 14, 20, 50, 52, 56, 60, 62, 68, 98, 100, 104, 108, 110, 116 and combinations thereof."

The sequences numbered 2, 50 and 98 in PD1 are identified as 212, 214 and 216 in the Patent.

134. GSK alleges that page 37 of the first priority document does not group SEQ IDs 212, 214 and 216 together to form the critical group that is central to the disclosure of the Patent's claims. It submits that the first priority document discloses a different categorisation of clusters within each subfamily of sequences. It is said that page 37 does not make clear how sequences are assigned to these different clusters, or what the clusters signify.

135. I reject this submission for the following reasons. First, each of sequences 212, 214 and 216 are disclosed in the first priority document. The fact that they are assigned different numbers does not matter. These sequences are specified in the alternative in claim 1 of the Patent. Each sequence is unambiguously disclosed and enabled in the first priority document. They are not required to be disclosed without any other sequences in order for priority to be claimed.

136. Secondly, the first priority document discloses that sequences 2, 50 and 98 are all sequences of the 2086 protein from the 8529 strain (p.19 lines 1-2, p.22 lines 22-23 and p.26 line 15). Prof Heckels agreed with Prof Ala'Aldeen that the three sequences form a group. The first priority document focuses on this group, as they are used in Examples 2 and 3 to generate data.

Mucosal delivery

137. GSK alleges that the first priority document does not disclose the claimed compositions for a method of administration other than mucosal delivery. In particular, p. 57 lines 4-12 discloses that:

> "Any multi-antigen or multi-valent immunogenic composition is contemplated by the present invention. For example, the compositions of the present invention may comprise combinations of two or more 2086 proteins, a combination of 2086 protein with one or more PorA proteins, a combination of 2086 protein with meningococcus serogroup A, C, Y and W135 polysaccharides and/or polysaccharide conjugates, a combination of 2086 protein with meningococcus and pneumococcus combinations, *or a combination of any of the foregoing in a form suitable for mucosal delivery*. Persons of skill in the art would be

> readily able to formulate such multi-antigen or multi-valent immunologic compositions." (*emphasis added).*

138. GSK points out that the mucosal method of administration is singled out as being preferred on page 55 line 31 and claimed in claims 207, 210, 225, 228 and 232 of the first priority document. It is suggested that the document is ambiguous as to whether mucosal delivery is the only form of administration.

139. I reject this submission for the following reasons. First, the passage which I have cited is not ambiguous. It discloses that a combination in a form suitable for mucosal delivery is a further alternative to the various combinations referred to in the same passage, which, by implication, do not need to be administered in this form. Secondly, no technical reason was suggested as to why the draftsman of the first priority document would have wished to limit its invention to mucosal delivery. Mucosal delivery was an area of interest in 2001, but was not yet an established approach to vaccine delivery for meningococcal vaccines. The invention of the first priority document is not primarily related to methods of delivery. Prof Heckels' evidence was clear on this issue. The passage at p. 57 lines 4-12 was read to him and the cross examination proceeded as follows at T4/739/4-10:

> "Q. …what I am asking you, Professor, is can you think of any technical reason which would lead the skilled reader to understand that in this passage, the author was intending to restrict all the combinations listed to one suitable for mucosal delivery?
>
> A. (Pause for reading) No."

Lack of plausibility

140. It is alleged that the first priority document does not contain sufficient information to render plausible the alleged invention of the Patent for one or more of the reasons relied on in respect of insufficiency. I have already rejected these plausibility attacks when considering insufficiency. Further, I have referred to the evidence of both experts in relation to the disclosure of the first priority document, which positively supports its credibility. The only additional point that I should mention is that in respect of non-lipidated 2086, the first priority document includes Example 3 with the T7 tag, but not Example 9 without this tag. However, I have accepted Prof Ala'Aldeen's evidence that Example 3 renders it plausible that non-lipidated 2086 has some bactericidal effect, and that the T7 tag would not be regarded as essential to achieve this.

141. For these reasons, I conclude that the Patent is entitled to its first claimed priority date of 11th October 2001.

The second priority date

142. Having decided that the Patent is entitled to it first claimed priority date, it is strictly unnecessary for me to decide whether it is entitled to its second (and later) claimed priority date. This is not a case where either side suggested that, if the Patent was entitled to its earliest priority date, the claim to the second priority date could make a

difference to the result. Nonetheless, in case I am wrong about entitlement to the first priority date, I will deal with this issue.

143. The second priority document is identical to the Patent, save in one respect. While it refers to the sequence listings (including those of SEQ ID NOS. 212, 214 and 216) they are missing. This is surprising, given that the sequence listings are included in the first priority document. The question is whether this is nonetheless an enabling disclosure.

144. Wyeth's case is as follows:

i) Example 2 of the second priority document reports the results of an experiment at p.73 lines 1-6 in which:

"The ORF2086 gene was amplified by PCR from a clinical isolate of a serogroup B Neisseria meningitidis strain designated 8529. … This meningococcal strain was received from The RIVM, Bilthoven, Netherlands. The mature 2086 protein gene sequence from meningococcal strain 8529 is provided herein as SEQ ID NO. 212."

ii) This discloses to the skilled person how to reproduce sequence 212, namely by PCR from strain 8529, which can be obtained from RIVM.

iii) The second priority document also discloses what primers to use in the PCR. P.74 lines 1-6 discloses that ORF 2086 appears to contain a lipoprotein signal sequence and continues:

"In order to recombinantly express P2086 in a more native-like conformation, the oligonucleotide primers were designed to amplify the full-length gene with the lipoprotein signal sequence intact and were based on an analysis of the Sanger sequence for N. meningitidis A ORF 2086."

iv) The primer sequences are then set out and cross-reference is made to Table IV where they are also set out as sequences 303 and 304.

v) Accordingly, the skilled person is told to use primers 303 and 304 to amplify the 2086 gene from the 8529 strain from RIVM to obtain SEQ ID NO. 212. If he carries this out, he will obtain SEQ ID NO. 212.

vi) It was common ground that once the skilled person had SEQ ID NO. 212, he would be able to deduce SEQ ID NOS. 214 and 216 from the information in part (B) of Example 2 and in Example 3 of the second priority document; Ala'Aldeen (2) [54]-[59]; Ferguson (1) [54].

145. In order to demonstrate that following the instructions in Example 2 of the second priority document would yield SEQ ID NO. 212, Wyeth conducted PCR and sequencing experiments on the 8529 strain for the purposes of these proceedings. Wyeth's case is that it was agreed by Dr Ferguson that the experiment does indeed yield SEQ ID NO. 212 and that the experiments are materially the same as those which would have been conducted by the skilled person in 2002.

146. GSK's case is that Wyeth may have demonstrated that it would have been obvious to the skilled person how to perform an experiment to yield SEQ ID NO. 212, but this is not the test. It contends that Wyeth has not shown that the second priority document contains an enabling disclosure of how to do this, which is clear and unambiguous.

147. First, GSK submits that the second priority document merely reports an example of what had been done by the patentee in the course of cloning 2086 for the first time from 8529. It does not direct the skilled person to do any experiment. I do not accept this submission. The question is whether Example 2 is a disclosure from which the skilled person could derive, directly and unambiguously, using common general knowledge, sequence 212. It does not matter that the Example, as a technical disclosure, is not expressed in the imperative, directing the skilled person to carry it out.

148. Secondly, GSK submits that if the skilled team decided to experiment, then there were a number of alternative routes which it could take. Prof Heckels considered that if it wanted to obtain the sequence information for 2086, then the skilled team would be most likely to avoid a wet experiment altogether, and go to the Sanger Sequence, or alternatively to use whatever Men B strain was close to hand and seek to sequence its protein. I do not accept this submission. The question is not whether the skilled person would have chosen to disregard the disclosure of Example 2 of the second priority document, and take a different route. Rather, it is directed at what would be the result if he did follow that disclosure.

149. Thirdly, GSK alleges that Wyeth's experiments would have taken so long to perform that they would have constituted an undue burden to the skilled person. This was based on a number of propositions, which I do not accept:

    i) That it was uncertain whether, and if so how long, it would have taken to obtain the 8529 strain from RIVM. I do not consider that there was anything in this point. Dr Van Alphen was head of the Vaccine Research Laboratory at RIVM between 1997 and 2003. He explained in his witness statement that there would have been no issue with providing a sample of strain 8529 to another laboratory in 2002. There was a rather arid debate about how long it would have taken for the sample to arrive. In my judgment, the evidence established that this would be likely to have taken a few weeks, but this is not an undue burden, as the skilled team would not have had to do anything in the meantime.

    ii) That carrying out the PCR and sequencing in 2002 would have taken too long. Initially, Dr Ferguson estimated that this would have taken five to eight weeks once the 8529 strain had been received. Dr Donald disagreed, and estimated two weeks. Dr Ferguson accepted this at [4]-[5] of his second report. Two weeks is a reasonable estimate, and I do not consider that established any undue burden. The evidence did not establish that the work performed during those two weeks would have been onerous.

    iii) That Dr Donald had ordered the primers over a month before the experiment started, streaking out bacteria even before he received instructions as to which experiment to perform. It does not seem to me that the time at which the

primers were ordered was important, but rather the nature of the work performed after they arrived.

150. Fourthly, GSK submits that Dr Donald had to exercise his own judgment, to some extent, in working out what experiment to perform. During his cross-examination, Dr Donald explained that he had been shown Example 2 of the second priority document, and the protocol prepared by Prof Ala'Aldeen, to which he made certain adjustments. However, the specifics of these adjustments were not pursued by GSK. No example was put forward where it could be said that a choice made by Dr Donald had a material effect on the result of the experiment.

151. Finally, the sequence resulting from Wyeth's experiments has nine errors over the consensus. In other words, there are mismatches between the output sequence from Wyeth's experiment and the consensus sequence for the subfamily B 2086 protein NO. 212 given in the Patent at p.23. However, it is agreed that Wyeth's experiments did in fact produce SEQ ID NO 212, and I do not accept that there would have been any doubt about this, for the reasons set out by Prof Ala'Aldeen at [16]-[25] of his fourth report. Prof Ala'Aladeen explained that there can be a consensus sequence where an amino acid appears in the majority of the contributors but not all of them, and a variety of examples were shown in the literature where a consensus sequence did not mean that 100% of residues at any given position had to be the same.

152. In my judgment, there was no material disagreement between Drs. Ferguson and Donald about the nature or result of the experiments, by the time that reply reports were exchanged. I did not detect any clear suggestion in Dr Ferguson's evidence, when read as a whole, that he (or the skilled person) would have done anything differently, that the experiments would have been onerous to perform, or that they would have resulted in anything other than SEQ ID NO. 212.

153. For these reasons, I conclude that the second priority document contains an enabling disclosure of SEQ ID NOS. 212, 214 and 216, and the claims of the Patent are entitled to the second priority date (as well as the first priority date).

Novelty

Legal principles

154. As was made clear by Lord Hoffmann in *Synthon BV v SmithKline Beecham plc* [2006] RPC 10 at [19]-[33], for prior art to deprive a patent of novelty, two requirements must be met:

i) The prior art must disclose subject matter which, if performed, would necessarily result in infringement of the patent; *Synthon* at [22].

ii) The skilled addressee must be able to perform the claimed invention by using the matter disclosed in the prior art, read and understood together with his common general knowledge. The test for enablement is the same as in the context of sufficiency; *Synthon* at [26]-[32].

155. In the present case, allegations of anticipation based on particular prior art citations raise specific issues of law. I will deal with those issues when considering the relevant prior art.

Novelty over 885 (pre-PD1)

156. 885 is an international patent application published on 26 July 2001. The applicant was Chiron SPA, and the inventors included Pizza. GSK's case of anticipation is as follows:

i) It is disclosed at p.1 line 4 of 885 that the invention relates to vaccines against *Neisseria meningitidis*, serogroup B.

ii) On p.2 of 885, a list is provided of potential antigens (component (b)). It makes reference to a series of other documents, including International Patent Application WO99/57280 ("280"). The list of antigens from 280 is then written out on p.4 of 885.

iii) Among the preferred options for the antigen to be added is SEQ ID No 2536. Prof Heckels explained at [302] of his first report that this is the 741 protein. Its full sequence is given in the 280 specification (pp. 1205-1206) and it comprises an amino acid sequence which is 100% identical to SEQ ID NO. 212.

iv) This is a protein "comprising an amino acid sequence having sequence identity greater than 95% to the amino acid sequence of …SEQ ID No 212…" within the meaning of claim 1.

v) The disclosure of 885 is to add this protein to OMVs (component (a)); the specification states at p.9 lines 12-13 that "A preferred strain from which to extract OMVs is the 44/76 strain". Prof Ala'Aldeen confirmed that this would comprise PorA, and that the skilled team would expect the OMV compositions disclosed in the 885 patent to have an effect as a vaccine.

vi) Accordingly, 885 discloses that; adding certain proteins to OMVs, such as OMVs from strain H44/76, creates an improved Men B vaccine; such proteins may be chosen from a list, preferably from a sub-list which includes 741 protein; and following this teaching yields an effective vaccine composition within at least claims 1, 2, 3 and 18-20.

Individualised disclosure

157. Wyeth submits that anticipation requires a sufficiently individualised disclosure, which is a matter of degree. I agree. This is made clear by the judgment of Jacob LJ in *Dr Reddy's Laboratories Ltd v Eli Lilly & Co* [2009] EWCA 1362; [2010] RPC 92. The Court of Appeal rejected the argument that disclosure of a large class of compounds constitutes a disclosure of each member of the class, and therefore deprives each member of the class of novelty. It held that this was wrong, as a matter of *a priori* reasoning, and because it was inconsistent with settled EPO Board of Appeal case law.

158. Considering the question *a priori*, Jacob LJ said at [26] & [28]:

> "An old question and answer runs as follows: "Where does a wise man hide a leaf? In a forest." It is, at least faintly, ridiculous to say that a particular leaf has been made available to you by telling you that it is in Sherwood Forest. Once identified, you can of course see it. But if not identified, you know only the generality: that Sherwood Forest has millions of leaves
>
> ….
>
> I would add that I would regard the listing out of a great number of compounds as opposed to the use of a Markush formula in the same way. To say a particular book is disclosed by saying "the books in the Bodleian" is no different from saying it is identified by providing access to the catalogue of the Bodleian."

30. As to EPO caselaw, Jacob LJ referred to *Hoescht Enantiomers* T 0296/87 which summed up earlier cases. It said:

> "6.1 Here the Board is guided by the conclusions it reached in its "Spiro compounds" decision T 181/82 (OJ EPO 1984, 401) concerning the novelty of chemical entities within a group of substances of known formula. With regard to products of the reaction of specific spiro compounds with a (C1-C4)-alkyl bromide defined as a group, the Board drew a sharp distinction between the purely intellectual content of an item of information and the material disclosed in the sense of a specific teaching with regard to technical action. Only a technical teaching of this kind can be prejudicial to novelty. If any such teaching is to apply in the case of a chemical substance, *an individualised description is needed*." (*emphasis added*).

159. Wyeth submits that in respect of component (b), 885 contains a list equivalent to a catalogue of the books in the Bodleian, or to the leaves in Sherwood Forest. It contends that the information content of 885 is no different from saying "the books in the Bodleian" or "the leaves in Sherwood Forest". It is therefore not a sufficiently individualised disclosure. In order to assess this submission, it is necessary to analyse the disclosure of 885 in more detail.

160. At p.2 lines 8-24, 885 discloses that:

> "Thus the present invention provides a composition comprising (a) a NmB [N. meningitidis serogroup B] outer membrane preparation and (b) an immunogenic component selected from one or more of the following:
>
> a protein disclosed in WO99/57280, or an immunogenic fragment thereof;

> a protein disclosed in WO99/36544, or an immunogenic fragment thereof;
>
> a protein disclosed in WO99/24578, or an immunogenic fragment thereof;
>
> a protein disclosed in WO00/66791, or an immunogenic fragment thereof;
>
> a protein disclosed in Tettelin et al [Science (2000) 287:1809-1815], or an immunogenic fragment thereof;
>
> a protein disclosed in Parkhill et al [Nature (2000) 404:502-506], or an immunogenic fragment thereof;
>
> a protein disclosed in WO97/28273, or an immunogenic fragment thereof;
>
> a protein disclosed in WO96/29412, or an immunogenic fragment thereof;
>
> a protein disclosed in WO95/03413, or an immunogenic fragment thereof;
>
> a protein disclosed in WO99/31132, or an immunogenic fragment thereof;
>
> a protein disclosed in WO99/58683, or an immunogenic fragment thereof;
>
> a protein disclosed in WO99/55873, or an immunogenic fragment thereof;
>
> Neisseria meningitidis protein PorA, TbpA, TbpB, PilC, OpA or Omp85."

161. There are a very large number of proteins listed in these documents, to which cross-reference is made in 885. P.2 line 25 – p.3 line 21 of 885 states that "if the composition comprises a protein disclosed in WO99/24578, said protein preferably comprises an amino acid selected from the group consisting of…". All even numbered amino acid sequences between 2 and 892 are then listed.

162. P.3 line 29 – p.4 line 2 contemplates a preferred selection of a protein from 2160 genes, or fragments thereof, listed in Tettelin 2000:

> "If the composition comprises a protein disclosed in Tettelin et al. (i.e. a protein encoded by one of the genes disclosed therein), said protein preferably comprises an amino acid sequence selected from the group consisting of An NMB001 to an NMB2160 (or a protein comprising an immunogenic fragment of one or more of these 2160 genes, or a protein comprising a sequence having sequence identity (preferably

> greater than 50% e.g. 60%, 70%, 80%, 90%, 95%, 99% or more) to one of these 2160 genes)."

163. A similar disclosure is given in respect of Parkhill *et al*. at p.4 lines 3-8, where the skilled person is required to select a protein, preferably from "an amino acid sequence selected from the group consisting of the 2121 coding sequences disclosed therein (or a protein comprising an immunogenic fragment of one or more of these 2121 sequences …)".

164. In the case of 280, the protein is preferably selected from the very long list of 1510 sequences set out at p.4 line 9 – p.6 line 31. This includes every even numbered amino acid sequence between 2 and 3020, "(or a protein comprising an immunogenic fragment of one or more of these SEQ IDs, or a protein comprising a sequence having sequence identity (preferably greater than 50% e.g. 60%, 70%, 80%, 90%, 95%, 99% or more) to one of these SEQ IDs).".

165. Nine preferred proteins for component (b) are identified at p.7 line 31 – p.8 line 18. Some of these (in particular ORF1, 287 and 919) are then tested for bactericidal activity against strain 2996, in combination with each other and/or with the Norwegian OMV vaccine – see pp.50-52. These do not include SEQ ID 2536, which is relied on by GSK.

166. The skilled person would be required to pluck out 2536 from the list of 1510 proteins from 280, which comprises all of the proteins in that document. The references to 280 in 885 are no more than a reference to the document as a whole and provide no technical information. Prof Ala'Aldeen pointed out, correctly, that sequence 2536 is not a sequence that the skilled person is directed to by 885. Indeed Prof Heckels had to be directed to it by Rouse Legal. In addition, 280 itself does not direct any attention to 741/2536. Insofar as it singles out any proteins, they are different ones.

167. As to component (a), 885 contemplates that this will be an NmB outer membrane protein. Prof Heckels accepted that there is no direction in 885 that this should contain PorA. He agreed that in 885 an NmB outer membrane protein is not limited to OMVs and certainly is not limited to OMVs from H44/76. He agreed with Prof Ala'Aldeen that PorA deficient Men B are rare, but they do occur, and do cause illness in patients. If such a Men B strain was used to prepare the NmB outer membrane preparation, then it would not contain PorA. Furthermore, at p.10 line 7-17, 885 discloses a way of carrying out the invention (which it exemplifies at page 52) where the OMVs come from a Gram-negative bacterium that does not contain any PorA. Whilst there is no doubt that 885 makes it obvious to select a PorA for component (a), this citation is relied on for anticipation only.

168. In conclusion, I do not consider that there is an individualised disclosure of sequence 2536/741 in 885. Alternatively, I do not consider that there is a clear and unambiguous disclosure of the combination of sequence 2536 with an NmB outer membrane preparation containing PorA, nor is that an inevitable result of carrying out the disclosure of 885.

169. In addition, a variety of subsidiary claims were relied on as independently valid by Wyeth over 885, in the event that claim 1 was anticipated. In particular, claim 5 is limited to non-lipidated proteins. Prof Heckels accepted that 2536 is a sequence, not a

protein, and that, depending on the expression system, the resulting protein might or might not be lipidated. I do not consider that there is a clear and unambiguous direction in 885 that the 2536/741 protein should be non-lipidated. Nor is this an inevitable result of carrying out its disclosure. Therefore claim 5 is not anticipated. Nor is there any disclosure in 885 of any functional technical effect for sequence no. 2536 as a vaccine, and therefore claims 18 to 20 are not anticipated.

Novelty over the Cuban Vaccine (pre-PD1)

170. The Cuban Vaccine was developed at the Finlay Institute in Havana, Cuba, and offered under the designation VA-MENGOC-BC. There is no doubt that it was supplied and administered to patients before the first priority date. Its composition included OMVs, which comprised PorA protein, and was known to do so, before PD1. The issues in respect of the Cuban Vaccine concern the alleged inclusion of fHbp, which is said by GSK to be SEQ ID NO 212, specified in claim 1 of the Patent.

171. GSK's case is that it is clear from work carried out after the priority date – published several years later by Gil J. et al *(*2009) *Proteomic study via non-gel based approach of meningococcal outer membrane vesicle vaccine obtained from strain CU385* Human Vaccine Vol. 5(5) pp. 347-356 ("Gil 2009") that the OMVs of the Cuban Vaccine contained fHbp. GSK submits that there is no basis for concluding that it would not have also contained fHbp in 2001.

172. GSK submits that fHbp is a protein comprising an amino acid sequence having an identical amino acid sequence to 212. It claims that the sequence would have been derivable once the protein spot had been identified by routine sequencing and/or searching of the databases to find 2086 and cloning from that source. Its case is that a comparison of this sequence against those of SEQ ID Nos 212, 214, 216 would have shown that the fHbp in the Cuban Vaccine, as supplied before PD1, had the required sequence identity to fall within the definition of the first protein of claim 1.

173. There are four principal questions which need to be addressed in relation to the Cuban Vaccine:

    i) Did the Cuban Vaccine contain fHbp before the priority date?;

    ii) If so, would the skilled person have been able to discover that fact?;

    iii) Would it have been possible to reproduce the Cuban Vaccine without undue burden; and

    iv) In relation to claims 18-20, if fHbp was present, did it make any material contribution to the immune reaction produced by the Cuban Vaccine?

Did the Cuban Vaccine contain fHbp before the priority date?

174. First, GSK relies on a witness statement of Dr Concepcion Campa Huergo which was served under a Civil Evidence Act Notice. Between 1989 and 2014 Dr Campa was Director-General of the Finlay Institute. She explains that she headed the team that developed the VA-MENGOC-BC vaccine that has been part of the childhood National Immunisation Programme in Cuba since 1991. She states that:

> "VA-MENGOC-BC has had a consistent composition since it was authorised by the Cuban regulatory authority ("CECMED") in 1987. There have been no applications to change the registration in respect of the vaccine's composition (which would have been necessary had there been any such change)."

175. Secondly, GSK relies on a stamped certificate (which appears to have been prepared for the purposes of these proceedings) issued by Dr Pérez, the General Director of the Cuban National Drug Regulatory Authority. This document, also placed under a Civil Evidence Act Notice, says:

> "This is to certify that Finlay Institute from Cuba has been no change (sic) in the composition of the vaccine VA-MENGOC-BC since it was registered in October, 1987, which has had to be notified to CECMED.
>
> I can also confirm that these centers are operating in compliance with Good Manufacturing Practices (GMP) and the vaccine VA-MENGOC-BC has been registered continuously for CECMED in Cuba."

176. Thirdly, GSK contends that the work by the Uli group after the priority date and reported at Uli et al. (2006) *Outer membrane vesicles of the VA-MENGOC-BC® vaccine against serogroup B of Neisseria meningitidis: Analysis of protein components by two dimensional gel electrophoresis and mass spectrometry* Proteomics, Vol. 6, pp. 3389-3399 ("Uli 2006") showed not only that the Cuban Vaccine comprised fHbp but also that it was of consistent composition.

177. Wyeth disputes all of those propositions and offers evidence to the contrary. It contends as follows: First, the registration document for VA-MENGOC-BC permitted a wide variation in the protein composition of the vaccine as it only contained a requirement that it should contain 50 micrograms of protein from the outer membrane of Men B. The evidence of the Cuban witnesses establishes no more than, at the level of detail of the registration, the composition had not been changed. They do not, and cannot, give evidence about a higher level of consistency than that required by the registration document, because they had no reason to look for a higher level of consistency in their process monitoring and because, until the analysis in Gil 2009, most of the proteins in the Cuban Vaccine had not been identified by anyone.

178. Secondly, the earliest evidence of the composition of the Cuban Vaccine is found in Sierra G. V. G. et al., *Vaccine against Group B Neisseria Meningitidis: protection trial and mass vaccination results in Cuba* NIPH Annals Vol. 14 Number 2 December 1991 ("Sierra"). Sierra disclosed at pp.197 and 208-210 that the vaccine comprised proteoliposomes enriched with high molecular weight proteins in the range of 12-18%. By contrast, in Barbera et al. (1996) *Consistency in the large scale production of the outer membrane protein complex of group B Neisseria meningitidis* IPNC '96 (Baltimore), poster 41, there was no mention of adding high molecular weight proteins. This suggests that the composition of the Cuban Vaccine varied before the first priority date.

179. Sierra also discussed the fact that growth media for the Cuban Vaccine had been changed once, and it might be changed again. It was common ground between the experts that changing the growth conditions could affect the composition of an OMV (Heckels T4/647/7-10 and Ala'Aldeen 1 §118).

180. In these circumstances, Prof Ala'Aldeen explained that he had serious doubts over the consistency of the Cuban Vaccine on the basis of the published materials. In particular he explained that there was a world of difference between what was described in the Gil 2009 paper and in the Sierra 1991 paper (T3/513/3-10).

181. Thirdly, Uli 2006 conducted some analyses of the batch-to-batch consistency of the OMVs that were used to make the Cuban Vaccine. Uli looked at three batches of OMVs all produced at the same time, and analysed the consistency of components that made up >0.1% of protein spot volume on the analytical gels. Prof Ala'Aldeen pointed out in his first report at [111], and Prof Heckels accepted, that even between these batches of OMVs, produced at the same time, there were marked changes in the percentages of the five major components, as shown in Table 1. Variation was also seen between the batches in the other more abundant proteins (>0.1% total spot volume), as shown in Figure 3. Uli 2006 did not even try to identify the variation in the minor components (where fHbp would have been if it had been present at that date). These analyses suggest that even when the OMVs were made by the same method at the same time, there were significant variations in their composition.

182. Fourthly, Wyeth contends that further evidence of the variability of the composition of the Cuban Vaccine can be found in a thesis by Quintana of the Finlay Institute dated 2014 *Evaluation of the obtaining process of Outer Membrane Vesicles of serogroup B Neisseria meningitidis*, which considers, amongst other things, the process for manufacture of the Cuban Vaccine in 2006-2009 and in 2011-2013. The site for manufacture for the Cuban Vaccine changed between those date ranges, and there were consequential changes to the equipment used to manufacture the vaccine. The analysis of consistency which was being conducted at the Finlay Institute only checked whether there were bands corresponding to four major protein components (pp.82 and 96). The thesis indicated that high molecular weight proteins were being monitored rather than added, in contrast to the position in Sierra. Prof Ala'Aldeen also pointed out that the extremely high batch rejection rate of OMVs was remarkable, suggesting poor control of the process conditions.

183. I have to decide whether it has been proven by GSK, on the balance of probabilities, that the Cuban Vaccine, as supplied before the priority date of 2001, contained fHbp. I conclude that this has not been proven. In particular, I bear in mind that GSK was unable to produce the Cuban witnesses for cross examination, because of difficulties of travel from and communication with Cuba. Their evidence has not been tested, and is at a level of generality such that it establishes no more than compliance with the registration document, which did not require consistency of minor components. The published evidence, referred to above, shows that the composition of the Cuban Vaccine is more likely than not to have varied over the years, particularly in respect of minor and unidentified components, of which fHbp would have been one.

184. Finally, as this question involves an analysis of various technical documents, I found the evidence of both experts of assistance in resolving it. They both supported the conclusion that I have reached. Prof Ala'Aldeen was clear that, given the high degree

of variation of the product and modifications to the process conditions, it could not be said that it was more likely than not that fHbp was present in the Cuban Vaccine in 2001/2 (T3/551/16-512/14). Prof Heckels evidence at T4/664/22-665/11 was to the same effect:

> "Q. Just stepping back now, we have looked at various documents, would you agree that one cannot say that the Cuban vaccine was consistent in terms of the presence or absence of minor protein components throughout the period between 1987 and ---
>
> A. They were not monitored and therefore it is not possible to say if they were consistent.
>
> Q. So, one cannot say that the fHbp would have been present in the Cuban vaccine before 2002?
>
> A. It is not possible to say that it was present or that it was not present."

If fHbp had been present in the Cuban Vaccine, would analysis in 2001 have identified it?

185. This raises an issue of law in relation to the requirements for an enabling disclosure. Wyeth submits that, in order for the Cuban Vaccine to anticipate as a prior use, the skilled person must have been able to analyse it and identify the presence of fHbp at the priority date. GSK contends that this is not necessary as a matter of law.

186. In particular, GSK relies upon the distinction made by Lord Hoffmann in *Merrell Dow Pharmaceuticals Inc v HN Norton & Co Ltd* [1996] RPC 76, between disclosing enough information to enable a skilled reader to *work* the invention, and disclosing enough that he or she can fully *describe* or understand that invention. Lord Hoffman gave the example of a notional Amazonian Indian who knew of the power of cinchona bark to treat malarial and other fevers, but who could not point to the active ingredient (quinine), and still less to its chemical structure, as being responsible for such activity. He said:

> "The quinine example shows that there are descriptions under which something may in a relevant sense be known without anyone being aware of its chemical composition or even that it has an identifiable molecular structure."

187. Lord Hoffmann continued at p.88:

> "So far I have been considering what it means to know about something in ordinary everyday life. Do the same principles apply in the law of patents? Or does patent law have a specialised epistemology of its own? Mr. Thorley argues that it does. He says that for a substance to be known so as to be part of the state of the art within the meaning of section 2, it must be known (or be readily capable of being known) by its chemical composition. No other description will do. He says that by 1977

> the science of chemistry had advanced so far that the chemical composition of virtually everything was either known or readily ascertainable by analysis. Therefore the legislature assumed that knowledge that something existed could safely be equated with knowledge of its chemical composition. Section 64 would provide a safety net for people like Amazonian Indians who were doing things with substances which did not readily yield to analysis.
>
> My Lords, I think that on this point the Patents Act 1977 is perfectly clear. Section 2(2) does not purport to confine the state of the art about products to knowledge of their chemical composition. It is the invention which must be new and which must therefore not be part of the state of the art. It is therefore part of the state of the art if the information which has been disclosed enables the public to know the product under a description sufficient to work the invention."

188. In GSK's submission, if the Cuban Vaccine, supplied and administered to patients before the priority date, contained fHbp, then this prior use anticipates claims 1-3, 10 and 18-20 of the Patent, whether or not the fHbp protein could have been identified by analysis.

189. In order to evaluate this submission, it is necessary to consider *Merrell Dow* in more detail. The patent in that case ("the acid metabolite patent") related to anti-histamine products. One of the claimed substances was inevitably formed as a metabolite of the known anti-histamine drug terfenadine in the human body. The patentee alleged that the sale of terfenadine for use as an anti-histamine amounted to contributory infringement under section 60(2) of the Patents Act 1977, the invention being put into effect on metabolisation.

190. The chemical composition of terfenadine, and its effect as an anti-histamine, had been published in an earlier patent before the priority date ("the terfenadine patent"). In addition, before the priority date, terfenadine had been administered to participants in clinical trials. On appeal to the House of Lords, the issue was whether, so far as the claim to the metabolite included its manufacture by the action of terfenadine in the human body, the patent in suit was invalid because the invention was not new.

191. In *Merrell Dow*, two allegations of anticipation were relied upon by the Defendants. First, that the invention had been *used* before the priority date since during the clinical trials, volunteers to whom terfenadine had been administered had made the acid metabolite in their livers and experienced its anti-histamine effects. Secondly, that the invention had been *disclosed* before the priority date in the specification of the terfenadine patent, as the inevitable result of following its instructions was to make the acid metabolite. The House of Lords dismissed the argument based on anticipation by use, but accepted the argument based on anticipation by disclosure.

192. At pp.83-84, under the heading "The Intuitive Response" Lord Hoffman noted that a United Kingdom patent lawyer's intuitive response to Merrell Dow's claim was likely to be one of incredulity. There was nothing new about terfenadine at the priority date. Full information about its chemical composition and method of use had been prior

published and participants in clinical trials had actually been taking the drug. The acid metabolite patent gave to the skilled person some information about how the product worked in terms of chemical reactions within the body. But it did not enable anything to be done which had not been done before. Why, therefore, should the later patent confer a right to stop people from doing what they had done before? If Merrell Dow's argument was right, and if someone else had discovered and patented the acid metabolite, then he would have been entitled to stop Merrell Dow from continuing to sell terfenadine.

193. Lord Hoffmann considered the argument of anticipation by use at pp.85-87. He explained why the intuitive response was wrong. In particular, he set out the following principles at p.86:

i) Art. 54 EPC makes it clear that, to be part of the state of the art, the invention must have been made available to the public. An invention is a piece of information.

ii) Making matter available to the public within the meaning of section 2(2) therefore requires the communication of information. The use of a product makes that information part of the state of the art only so far as that use makes available the necessary information.

iii) The 1977 Act therefore introduced a substantial qualification into the old principle that a patent cannot be used to stop someone doing what he has done before. If the previous use was secret or uninformative, then subject to section 64, it can.

iv) Likewise, a gap has opened between the tests for infringement and anticipation. Acts done secretly or without knowledge of the relevant facts, which would amount to infringements after the grant of the patent, will not count as anticipations before.

194. That is why Lord Hoffmann rejected the allegation of prior use in *Merrell Dow*. He concluded on this issue at p.87 by stating that:

> "Mr Thorley is therefore right in saying that his claim cannot be dismissed simply on the ground that making the acid metabolite is something which has been done before. To that extent, the intuitive response is wrong."

195. Lord Hoffmann then turned to anticipation by disclosure, which was the ground upon which the Defendants had succeeded at first instance and in the Court of Appeal. He explained that this was different from the argument on anticipation by prior use, because it did not rely on the mere use of the product by members of the public, but upon the communication of information. The question was whether the prior art specification conveyed sufficient information to enable the skilled reader to work the invention. It did so, because the inevitable consequence of carrying out the disclosure was the manufacture of the acid metabolite in the livers of those who ingested terfenadine. In the context of inevitable result of carrying out the prior disclosure, Lord Hoffman drew the distinction between disclosing enough information to enable

a skilled reader to work the invention, and disclosing enough that he or she can fully describe that invention, and provided the quinine example to illustrate this.

196. He summarised the distinction between anticipation by use, which he rejected, and anticipation by disclosure, which he accepted, at p.91:

> "In both cases no one was aware that the acid metabolite was being made. *In the case of anticipation by use, however, the acts relied upon conveyed no information which would have enabled anyone to work the invention, i.e. to make the acid metabolite.* The anticipation in this form relies solely upon the fact that the acid metabolite was made, as the anticipation in Bristol-Myers Co. (Johnson's) Application relied solely upon the fact that ampicillin trihydrate had been made and sold to the public. It disavows any reliance upon extraneous information, such as the formula for making terfenadine and the instructions to take it for its anti-histamine effect. *Anticipation by disclosure, on the other hand, relies upon the communication to the public of information which enables it to do an act having the inevitable consequence of making the acid metabolite*. The terfenadine specification teaches that the ingestion of terfenadine will produce a chemical reaction in the body and for the purposes of working the invention in this form, this is a sufficient description of the making of the acid metabolite. Under the description the acid metabolite was part of the state of the art." (*emphasis added*).

197. The approach to anticipation by prior use in *Merrell Dow* is consistent with the decision of the Enlarged Board of Appeal in G1/92 at [1.4], which was cited with approval by the House of Lords in *Synthon* at [29]:

> "An essential purpose of any technical teaching is to enable the person skilled in the art to manufacture or use a given product by applying such teaching. Where such teaching results from a product put on the market, the person skilled in the art will have to rely on his general technical knowledge to gather all information enabling him to prepare the said product. *Where it is possible for the skilled person to discover the composition or the internal structure of the product and to reproduce it without undue burden, then both the product and its composition or internal structure become state of the art.*" (*emphasis added*)

198. Therefore, I do not accept GSK's submission that in order for the Cuban Vaccine to anticipate as a prior use, it is not necessary for the skilled person to have been able to analyse it and identify the presence of fHbp at the priority date. If it could not be analysed to identify the presence of fHbp, then the supply of the Cuban Vaccine and its administration to patients conveyed no information which would have enabled anyone to work the invention, i.e. to make a composition which comprised fHbp. In order for this prior use to anticipate, GSK must establish that it was possible for the skilled person to identify the presence of fHbp in the Cuban Vaccine and to reproduce it without undue burden.

Could the skilled person have identified the presence of fHbp in the Cuban Vaccine before the priority date?

199. Prof Heckels expressed the view in his first report at [332]-[324] that in October 2001 it would have been possible for the skilled person to find out what the Cuban Vaccine contained. It appeared that his favoured approach would have been to separate the protein components and then subject them to mass spectrometry analysis. He considered that a two-dimensional gel could be run to separate the proteins and then select the spots. He regarded this analysis as routine, although it would have taken some time, which he estimated as a few weeks.

200. I consider that the analyses contemplated by Prof Heckels to identify fHbp in the Cuban Vaccine would not have been within the capabilities of the ordinary person skilled in the art, for the following reasons:

201. First, Prof Ala'Aldeen explained that the techniques described by Prof Heckels were not routinely used even by specialists to carry out proteomics analyses in 2001/2. He considered that they were at the cutting edge of an already specialised field. Prof Heckels considered that both mass spectrometry and two-dimensional gel analysis were well-known at the priority date, but he accepted that the combination of these techniques was in its infancy at the time. In my view, this combination was beyond the routine work the unimaginative skilled team was capable of undertaking.

202. Secondly, before the priority date, during collaborative work between the Finlay Institute and SmithKline Beecham ("SKB"), SKB analysed the Cuban Vaccine in 1998-9, after desorbing it from an aluminium adjuvant and running 2-DE gels. Spots were excised from the gels and examined using mass spectrometry. It is only necessary for me to summarise the main conclusions to be drawn from SKB's work, as explained by Prof Ala'Aldeen in his fifth report:

    i) The work started in October 1998 and SKB tried to identify conditions which would enable them to desorb the proteins from the adjuvant. Such conditions were not readily available.

    ii) It proved very difficult to desorb the proteins in a manner that would enable them to run properly on a 2-D gel.

    iii) In January 1999 the work on the Cuban Vaccine stopped in favour of work on OMVs from the H44/76 strain which, it was hoped, would be easier to analyse. This work continued until June 1999.

    iv) SKB also attempted a mass spectrometry analysis of the immunoreactive components of the Cuban Vaccine, by analysing spots from all regions of the gels that they were using. They did not find fHbp.

203. Thirdly, the Uli 2006 paper shows that separation and identification of the proteins in the Cuban Vaccine proved to be a considerable challenge for this expert group, several years after the priority date. The authors explain that their first attempt to get a detailed panorama was unsuccessful because lipids on the outer membrane promoted streaking. The Uli group expended considerable effort to find an optimal sample separation procedure, with the additional complication that such procedure tended to

remove hydrophobic proteins from the preparation. The authors of Uli considered that even once that optimisation was complete, it remained a technical challenge to obtain the right conditions to identify most of the protein species. In spite of their efforts, fHbp was not amongst the proteins in the Cuban Vaccine identified in Uli 2006.

204. Fourthly, Gil 2009 was the first publication that identified fHbp in one fragment of the Cuban vaccine. They did so using SCAPE. This was a gel free technique which Prof Ala'Aldeen explained was not available at the priority date and was designed to overcome the problems of the 2DE/mass spectrometry approach. Furthermore, the Gil group did not start with the vaccine product and so they did not need to desorb the proteins from the adjuvant. When this was put to Prof Heckels he accepted, realistically, that the SCAPE technique was not available at the priority date, and he could not say that even with this technique, it would have been possible successfully to desorb the proteins (T4/696/7-24):

> "Q. And of course, you are not able to say whether they would have found fHbp even using this improved SCAPE technique, if they had had to desorb the OMVs from the alum first?
>
> A. No, I am not in a position to comment on that.
>
> Q. I suggest, Professor, looking at the analysis that we have of the Cuban vaccine or indeed OMVs used to make the Cuban vaccine, the only success in finding fHbp was with a technique which would not have been available to the skilled person in 2001/2002, namely, the refined SCAPE technique, and using a product which would not have been available to the skilled person, namely the OMVs; agreed?
>
> A. The skilled person would not have had access to the Cuban OMVs, no.
>
> Q. No, he would have had the vaccine itself?
>
> A. Yes.
>
> Q. And you would not have the SCAPE technique?
>
> A. Certainly, we would not have had the SCAPE technique. As I say, I am not aware that it is used by anybody else."

Would the skilled person have been able to reproduce the Cuban Vaccine without undue burden?

205. Wyeth alleges that even if the Cuban Vaccine contained fHbp, and even if the skilled person could identify, using a technique available in 2001/2, a peptide that matched fHbp, they would not have been enabled to recreate the Cuban Vaccine. This point turns on the availability at the priority date of the strain CU385, which would have

been required to obtain the full length sequence of the protein. The CU385 strain would then have been used to produce OMVs in order to make a vaccine.

206. There is very little evidence on this issue. Wyeth points out that SKB, who were working with the Finlay Institute, did not have access to the CU385 strain, and that the onus is on GSK to establish that the Cuban Vaccine was an enabling disclosure.

207. During his cross examination, Prof Heckels said that he had no idea whether the Cubans would have made the CU385 strain available at the priority date, if anyone had asked them. However, in re-examination, he was taken to a paper included by Wyeth in his cross examination bundle, Masklanka et al *Standardisation and a multilaboratory comparison of Neisseria meningitidis serogroup A and C serum bactericidal assays* Clinical and Diagnostic Laboratory Immunology, Vol. 4 no. 2, 1997 pp. 156-167 ("Maslanka"). The acknowledgements to Maslanka express thanks to the Finlay Institute, Havana, Cuba, for supply of the serogroup B Cuban strain CU385-83.

208. Maslanka, in my judgment, provides some objective evidence that the CU385 strain was available on request before the priority date from the Finlay Institute. On the basis of Maslanka, I conclude that the CU385 strain could have been obtained on request from the Finlay Institute before the priority date. However, in the light of my other conclusions concerning the Cuban Vaccine, this does not mean that it anticipates any of the claims of the Patent.

In relation to claims 18-20, if fHbp was present, did it make any material contribution to the immune reaction produced by the Cuban Vaccine?

209. If fHbp was present in the Cuban Vaccine, it was a very low abundance component (Heckels T4/659/24-660/4). There was no evidence that this very small amount would have made any material contribution to the immune reaction produced by the Cuban Vaccine. Prof Heckels was unaware of any evidence to support such a contribution (T4/642/12-15), and none was provided in the Civil Evidence Act Notices relied on by GSK.

210. Therefore, even if I had concluded that prior use of the Cuban Vaccine anticipated claim 1 of the Patent, I would have concluded that it did not make available to the public the functional technical features of claims 18-20, and therefore, those claims are not anticipated in any event.

Conclusion in respect of the Cuban Vaccine

211. I have concluded that the Cuban Vaccine does not anticipate any of the claims of the Patent, for the following reasons:

    i) On the balance of probabilities, the Cuban Vaccine, as supplied before the priority date, did not contain fHbp.

    ii) In order for this prior use to anticipate, GSK must establish that it was possible for the skilled person to identify the presence of fHbp in the Cuban Vaccine and to reproduce it without undue burden. The skilled person could not have

identified the presence of fHbp in the Cuban Vaccine before the priority date, either at all or without undue burden.

iii) If fHbp was present in the Cuban Vaccine, it was a very low abundance component (Heckels T4/659/24-660/4). There was no evidence that this very small amount would have made any material contribution to the immune reaction produced by the Cuban Vaccine.

Novelty over Andersen (pre-PD1)

212. Andersen is an abstract published before the first priority date which compares the antibody response in different tissues of natural OMVs ("nOMVs") with that of detergent-extracted OMVs ("dOMVs") in mice after mucosal administration of the vaccine. The OMVs were from the "Norwegian strain", H44/76.

213. GSK contends that the composition of natural H44/76 OMVs is now known, from work published some years after the priority date in 2008 by Koeberling et al, to contain fHbp. It is now known that they include a protein comprising an amino acid sequence having sequence identity greater than 95% to the amino acid sequence of any one of each of SEQ ID Nos 212, 214 and 216, within the scope of claim 1 of the Patent.

214. GSK further submits that the skilled person could have found out what was in the OMVs used by Andersen at the first priority date by (a) taking the annotated genome of Men B, published in Tettelin 2000; (b) expressing the proteins encoded by its ORFs and raising antibodies to all those proteins and (c) using those antibodies on a Western blot to identify the proteins present in the OMVs used by Andersen.

215. Finally, GSK submits that H44/76 OMVs were also well known to comprise PorA protein. Accordingly, it contends that the OMV composition disclosed in the Andersen abstract is a composition within claim 1 of the Patent, and the skilled team could have determined that as a matter of course in 2001 using standard techniques of protein sequencing.

216. Prof Heckels characterised this task as "extremely laborious". Prof Ala'Aldeen explained that numerous steps would be required to analyse each of the ORFs and putative proteins in the MC58 annotated genome of which, according to Tettelin 2000, there were 2158. He explained that each of these steps might fail and would, in any event present its own difficulties, which would render the exercise impractical.

217. In particular, not all of the ORFs identified would necessarily produce proteins which had a biological role, and the skilled person could not assume that the predictions in Tettelin 2000 would be accurate. He would be required to design primers from the MC58 genome sequence, which would not necessarily work on the H44/76 strain. Cloning and expression protocols would have to be developed for each single protein to attempt to achieve or enhance expression, which would not be an easy task. Not all of the genes would successfully express a protein: as Pizza 2000 found, only 61% (350) of the ORFs chosen were successfully expressed. If successful expression was achieved, it would not necessarily be the case that the protein had been expressed in a form capable of further use. Of those proteins successfully expressed, the skilled person could not be certain that injecting that protein into an animal would raise

antibodies against the same epitopes as are exposed on the surface of the nOMVs. Therefore he could not assume that he would be able to positively ascertain the presence of all proteins that were successfully expressed.

218. Prof Ala'Aladeen did not believe that the skilled person would even attempt such a project. However, if he did so, he considered that such a project would take a large team of researchers many years to carry out. He explained that it would not have been practically possible in 2001 to take the approach of analysis of the nOMVs that Prof Heckels had suggested. During the cross examination of Prof Heckels (T4/639-640), it became clear that the experts were largely in agreement about this issue:

> "Q. Professor, I think essentially you are agreed with Professor Ala'Aldeen in his conclusion?
>
> A. That it is a lot of work, yes.
>
> Q It is theoretically possible, but not practically; correct?
>
> A. And very unlikely to work; but theoretically possible."

219. After release of this judgment in draft form, Wyeth pointed out that I had omitted to deal with a further allegation by GSK that it was inevitable that the nOMVs which the skilled person would produce, given Andersen, would contain fHbp. There is no disclosure in Andersen about the growth conditions used to produce the nOMVs, nor about the method used to prepare the nOMVs once the bugs had been grown. There were a range of different conditions and isolation methods available to the skilled person when seeking to implement Andersen, and the choices made might vary from laboratory to laboratory. Prof Heckels accepted this at T4/634/6-17. It follows, in my judgment, that it was not inevitable that nOMVs produced by the skilled person, seeking to implement the disclosure of Andersen, would have contained fHbp.

220. GSK contends that it was not in dispute between the experts that the strains used to produce the OMVs for the Norwegian and Cuban Vaccines, H44/76 (the strain used in Andersen) and CU385 respectively, were high expressers of fHbp protein. It relies in particular on a paper published by Masignani et al. after the priority date in 2003 in support of this proposition, and upon the following passages of cross examination; Prof Ala'Aldeen at T3/513/17-514/14; and Prof Heckels at T4/698/17-20. The question that I have to decide relates to the inevitable result of carrying out the disclosure of Andersen. At T4/698/21 to 699/11 Prof Heckels was cross examined about the Masignani paper and reiterated that whether or not fHbp will be present in OMVs will depend on growth conditions and the conditions under which the OMVs are produced. As I have said, these are not disclosed in Andersen.

221. In light of this evidence, I do not accept that Andersen is an enabling disclosure of claim 1, and I do not consider that the skilled team would have considered it practical in 2001 to attempt the project suggested by Prof Heckels. Nor do I accept that it was inevitable, given Andersen, that the skilled person would produce nOMVs which contained fHbp. If I am wrong on this issue, and claim 1 is anticipated by Andersen, then Wyeth accepts that claims 2 and 3 are also anticipated. GSK accepts that claims 5, 6 and 10 are not anticipated by Andersen. As to claims 18-20, I do not accept that

Andersen discloses the functional technical feature of these claims in respect of fHbp, and therefore these claims are not anticipated.

Novelty over 869 (between PD1 and PD2)

222. It is not strictly necessary for me to determine this issue, as I have concluded that the Patent is entitled to its first claimed priority date, and 869 was published after this date. However, in case I am wrong about entitlement to priority, I will set out my conclusions in respect of the allegation of anticipation by 869.

223. 869 is an international patent application published on 6 February 2003. It concerns the formulation of vaccine compositions, and in particular, the discovery that the amino acid histidine enhances the stability of vaccines which contain aluminium salt adjuvants. The examples are intended to demonstrate pH stability and absorption conferred by the use of histidine in formulations of vaccines which contain such aluminium salt adjuvants. There are no data to demonstrate efficacy as vaccines.

224. GSK relies in particular on Example 6 on page 13 of 869 in support of its anticipation attack. This puts forward three vaccine formulations. Each contains 961c protein; ΔG287nz-953 protein and 936-741 hybrid protein; as well as aluminium oxyhydroxide and histidine buffer. The second formulation also had Norwegian strain (H44/76) OMVs, and the third contained New Zealand strain OMVs. GSK alleges that 936-741 is a protein comprising an amino acid sequence at least 95% identical to the sequences 212, 214 and/or 216 of the Patent, and that the OMVs in the Norwegian and New Zealand strain would inevitably have contained PorA. It is alleged that 869 constitutes an enabling disclosure of all of the claims of the Patent.

225. If 869 anticipates, it is on the basis that the inevitable result of carrying out Example 6 will be an infringement of the Patent. As was made clear in *Synthon* at [33] "the invention which must be enabled is the one disclosed by the prior art."

226. 869 does not teach the sequence of any of the proteins in Example 6, and contains no directions as to how to obtain or produce them. GSK alleges that the sequence of 741 and the 741 hybrids could be found by the skilled person from references cited in 869. In particular, in his first report, Prof Heckels cited p.2 lines 8-10 of 869, which discloses that:

> "Specific bacterial antigens for use with the invention include:
> - a protein antigen from N.meningitidis serogroup B, such as those in refs. 9 to 15, with protein '287' (see below) and derivatives (e.g. 'ΔG287') being particularly preferred,"

227. This passage has been extracted from a long list of possible antigens for use in the invention of 869. From references 9-15 in the cited passage, GSK relies on reference 11, which is 280. Amongst the hundreds of sequences that it discloses, 280 lists sequences for a protein numbered "741".

228. The difficulty is that there is no link in 869 between the disclosure of Example 6 and the text on p.2 lines 8-10, much less the text of 280, and it is far from inevitable that the skilled person would find this information when seeking to perform Example 6. Prof Heckels received 280 from GSK's solicitors (together with 885) before any of

the other prior art, and was directed to sequence 741 in that document. Accordingly, when presented with 869 and the problem of finding a "936-741" sequence, it was natural for him to go back to 280, where he knew that sequences for 741 were listed. Furthermore, he inadvertently used hindsight when linking the passage on p.2 lines 8-10 with Example 6, as by this stage, he knew that the formulation in Example 6 was the alleged infringement, Bexsero. This became clear from the following passage of cross examination at T5/833/19 – 834/8:

> "Q. There is nothing, is there, in Example 6 of 869 to direct the reader back to page 2, lines 8-10?
>
> A. No, other than obviously I was aware -- I clearly did not read this only once -- that this formulation was Bexsero.
>
> Q. You were, when you read it?
>
> A. Not immediately, no.
>
> Q. Right.
>
> A. Not when I read it for the first time.
>
> Q. Right.
>
> A. When I then started to look at the numbers and what they meant, then it became clear that it was Bexsero.
>
> Q. That is when you went back to page 2, lines 8-10?
>
> A. Yes."

229. There is a further difficulty with the case that Example 6 of 869 is enabled. The protein relied on by GSK in 869 is a 936-741 hybrid. This hybrid was not disclosed in 280, and Prof Ala'Aldeen explained that the skilled person would not know what it was, nor how to make it. Whilst it would have been possible to make some kind of hybrid of 936 and 741, the sequences for both of which were disclosed in 280, there were a number of choices as to how to do this, and the skilled person would not know if the hybrid that he produced was the same as that used in Example 6. I accept that the skilled person, when attempting to reproduce Example 6, would be free to make a variety of hybrids, without knowing which was used in that example.

230. GSK also relied on reference 92 in 869, referred to in Example 4, which also used 936-741. However, reference 92 discloses a 741 sequence, but does not disclose any 936 sequence. In order to find 936, the skilled person would have to combine the disclosure of reference 92 with 280, which is far from inevitable. Even then, he would be free to make a variety of hybrids, without knowing which was used in Example 6, for the reasons set out above.

231. For those reasons, I reject the case of anticipation of claim 1 in the light of 869. If I had accepted that claim 1 was anticipated, then I would have held that all other claims were anticipated, save for claims 18-20. There is no information as to the efficacy of the formulations disclosed in 869, since its invention is only concerned with improved

stability. In particular, there is no disclosure in 869 that any of its proteins, and in particular 936-741, would give any bactericidal response. Therefore, it contains no disclosure of the functional technical features of claims 18-20.

Novelty/obviousness over Bernfield and Farley posters/abstracts (between PD2 and filing date

232. It is not strictly necessary for me to determine this issue, as I have not concluded that the Patent is entitled to its first and second claimed priority dates. However, in case I am wrong about entitlement to priority at both of these dates, I will set out my conclusions in respect of the Bernfield and Farley posters/abstracts.

233. These four documents were presented by Wyeth at the IPNC meeting in Oslo in 2002. It is common ground that I need only deal with the Bernfield poster. The Bernfield poster discloses the utility of an outer membrane lipoprotein, P2086, in reducing the number of proteins required in a meningococcal vaccine, in contrast to the PorA multi-component vaccines previously required to cover 70-80% of group B strains. It states that:

> "rLP2086 antigens are capable of eliciting bactericidal antibodies against meningococcal strains expressing heterologous PorAs and heterologous P2086 proteins. The P2086 family of antigens may be a useful vaccine either alone or in combination with other neisserial antigens."

234. As to identification of the 2086 protein the Bernfield poster discloses that it is a lipoprotein with a molecular weight of 26,963-27,638 Da. It also states that:

> "The genomic sequence of a group A meningococcal strain was downloaded from the Sanger Center and analyzed by our Bioinformatics group using existing and proprietary algorithms to create a searchable database. The peptide sequence data indicated that ORF2086 was of interest. Primers based on this orf were used to PCR the 2086 gene from strain 8529. Analysis of the gene sequence, the fact that the N-terminus was blocked, and its subcellular location indicated that P2086 is a lipidated outer membrane protein (LP2086). rLP2086-8529 and variants from other meningococcal strains were recombinantly expressed as lipoproteins in E.coli using the *H.influenzae* P4 signal sequence. These recombinant proteins were isolated from *E.coli* membranes by differential detergent extraction, purified using ion exchange chromatography, and used to immunize mice."

235. The issue is whether this disclosure would enable the skilled person to obtain the sequence of 2086, or if not, whether it would have been obvious to do so in light of this disclosure. Prof. Heckels carried out a short, non-laboratory-based experiment to show how the skilled team could have worked out that sequence from the disclosure of the Bernfield poster. In summary, he suggested that the skilled team would have identified the lipoproteins with the molecular weight disclosed in the Bernfield poster

in the annotations to the Men A genome (of which there are 34), and look among those 34 lipoproteins to find those having the correct molecular weights (having deducted the weight of the lipoprotein signal sequence). There was only one such protein. The skilled person would then have found the corresponding protein in the published sequence of MC58, which matches SEQ ID NO 212 exactly.

236. Wyeth disputes that this would have been the course taken by the skilled person when seeking to identify the 2086 protein from the Bernfield poster. Wyeth alleges that the skilled person reading the poster in 2002 would have understood that the authors had been required to use the sequence from the Men A genome that were available at the time, because the Men B genome was not available when the work was done. In contrast, by the priority date, the Men B genome had been published in Tettelin 2000. Wyeth submits that the skilled person, seeking to identify the 2086 Men B protein, would have searched the Men B genome, rather than the Men A genome.

237. At that stage, Wyeth contends that the skilled team would have run into difficulties. Prof. Heckels used a program known as "DOLOP" in his experiment to calculate the molecular weight of the mature protein. Wyeth contends that if the skilled person had used DOLOP on the Men B genome he would not have identified fHbp but, instead, would have identified two different proteins with a lipidation sequence with the right molecular weight range. Given the limited information in the poster, he would not have realised his error, and would not have found fHbp at all.

238. I do not accept Wyeth's submissions on the Bernfield poster for a number of reasons. The Bernfield poster expressly refers to the use of the published Men A genome from the Sanger Centre to identify the 2086 protein. Wyeth's submission assumes, wrongly in my view, that the skilled person would disregard this express disclosure and take an alternative course, which would create difficulties in identifying the correct sequence. Furthermore, it was not necessary to use the DOLOP program to calculate the molecular weight of the mature protein, and a simple word processor would have sufficed to look for the lipoprotein annotations to the sequences in Sanger, which would have been a matter of routine.

239. I do not consider that the simple experiment proposed by Prof Heckels would *inevitably* have been performed by the skilled team in 2002. However, I do accept that it was obvious to take the course suggested by Prof Heckels, in the light of the disclosure of the Bernfield poster. Had I decided that the Patent was not entitled to either of its claimed priority dates, I would have concluded that all claims of the Patent lacked inventive step in light of the Bernfield poster.

Inventive step

Legal principles

240. Legal principles of relevance to the present case are as follows:

i) Obviousness must be considered on the facts of each case, and the Court must consider the weight to be attached to particular facts in the light of all the relevant circumstances. These include the motive to find a solution to the problem that the patent addresses, the number and extent of possible avenues of research and the effort involved in pursuing them; *Generics (UK) Ltd v H*

Lundbeck AS per Kitchin J, approved by the House of Lords in *Conor Medsystems Inc v. Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] 4 All ER 621, [2008] RPC 28 at [42].

ii) If a particular step is obvious in the light of the prior art, it is not rendered any less obvious merely because there are a number, and perhaps a large number, of other obvious routes as well; *Brugger v Medicaid* (No.2) 1996 RPC 635 at 661.

iii) Where it is alleged that a step is obvious to try, the question is whether the skilled person would do so with a fair expectation of success; how much expectation depends on the particular facts of the case. Including something in a research project is not enough to establish lack of inventive step; *Conor v Angiotech* at [42]; *Medimmune v Novartis* at [90]-[91]; *Teva UK Ltd v LEO Pharma AS* [2015] EWCA Civ 779 at [32].

Disclosure of 922

241. 922 is an international patent application from Chiron published on 7th September 2001. GSK submits, and I agree, that the skilled reader would recognise that its inventors come from the same group that published Pizza 2000, which disclosed the Men B meningoccal genome. Given its authors, the skilled team would take its contents seriously.

242. The object of the invention of 922 is apparent from the first paragraphs of the document at p.1 lines 4-15:

> "International patent applications W099/24578, W099/36544, W099/57280 and W000/22430 disclose proteins from Neisseria meningitidis and Neisseria gonorrhoeae. These proteins are typically described as being expressed in E.coli (i.e. heterologous expression) as either N-terminal GST-fusions or C-terminal His-tag fusions, although other expression systems, including expression in native Neisseria, are also disclosed.
>
> It is an object of the present invention to provide alternative and improved approaches for the heterologous expression of these proteins. These approaches will typically affect the level of expression, the ease of purification, the cellular localisation of expression, and/or the immunological properties of the expressed protein."

243. Heterologous expression may be at low levels; or the protein may be transported to a location in the cells which makes it difficult to purify; or the protein may be incorrectly folded which may affect its immunological properties. The aim of 922 is therefore to find approaches to heterologous expression which can be applied generally to any protein to express it at higher levels in a form in which it can be purified and is immunologically active; Heckels T5/844-845.

244. For this purpose, at pages 2-11, 922 discloses thirteen different methods, all aimed at the improvement of heterologous expression in proteins. The first such method is an example which illustrates the general objects of the document:

> "In a first approach to heterologous expression, no fusion partner is used, and the native leader peptide (if present) is used. This will typically prevent any 'interference' from fusion partners and may alter cellular localisation and/or post-translational modification and/or folding in the heterologous host. Thus the invention provides a method for the heterologous expression of a protein of the invention, in which (a) no fusion partner is used, and (b) the protein's native leader peptide (if present) is used."

245. The examples all assess the extent to which the methodologies disclosed in 922 achieve an improvement in heterologous expression of different proteins. For that purpose, it compares the properties of proteins expressed under different conditions. It does not compare the properties of an individual protein with those of another individual protein; the only protein to protein comparisons made are of a series of hybrids. Prof Ala'Aldeen explained, and I accept, that SBA data has been included to test the effect of the different expression methodologies on the immunological properties of the proteins.

246. Wyeth point to four aspects of the SBAs being conducted in 922, which are understandable in view of its overall objectives:

i) They do not contain a normal mouse serum or pre-immune mouse serum negative control; controls which ensure that one does not have non-specific antibodies in the serum which may be responsible for the SBA results;

ii) They are conducted using baby rabbit serum which gives higher, but variable, results compared to human serum. That makes it difficult to correlate results to what would be obtained with human complement.

iii) While some of the examples (such as Example 8) specify the adjuvant used as being FCA, others do not. That makes it difficult to make comparisons between experiments, because the skilled reader does not know whether same adjuvant has been used in each of them.

iv) The experiments are likely to have been done on different occasions and under different conditions. Elimination of such variables would have been unnecessary as the experiments were not designed to provide comparisons between the properties of individual proteins.

247. Prof Heckels collated the data that he considered would have been of interest to the skilled team into a single table at [138] of his first report, which identified proteins 287 and 741 as of particular interest as vaccine candidates. He explained that he had done so because of their good bactericidal titres and breadth of protection. He considered that this gave a "clear steer" towards these two proteins. There are a number of factors which support Prof Heckels' approach. First, the heterologous expression of a protein is one factor to be considered in its usefulness as a vaccine

candidate, as it can affect the immunological responses achieved. Therefore, the methodologies set out in 922, and the results of its experiments are relevant to this particular criterion. Secondly, the data comes from a well respected group. Thirdly, 741 is identified in 922 as a lipoprotein and the Pizza group had targeted such lipoproteins, albeit that 741 was not singled out as a promising vaccine candidate in their previous work.

248. Prof Heckels described the message to be derived from 922 as follows at [143] of his first report:

> "[…] that 287 and 741 both give very good results against other strains in the SBA test and are two proteins which should be followed up as potential antigens to include in a Men B vaccine."

In my judgment, the issue of obviousness in the light of 922 depends on whether I accept this evidence, and whether I consider that the skilled team would consider that there was a fair prospect of success of 741 as a vaccine candidate against Men B.

249. Prof Heckels' evidence on this issue was the subject of a sustained attack, both in the evidence of Prof Ala'Aldeen and during cross examination. Having carefully considered all of the material, I have come to the conclusion that it was not obvious at the priority date from 922 to follow up the 741 protein as a potential antigen to include in a Men B vaccine, with a fair prospect of success. I have reached this conclusion for the following reasons:

250. First, I accept the evidence of Prof Ala'Aldeen that 922 would be used by the skilled team to suggest approaches to improve the expression of proteins on which they were working. 922 was not concerned with vaccine candidate identification, and the information in 922 was not sufficient to conclude that the proteins discussed were promising vaccine candidates. Whilst expression was one potential property of a vaccine candidate, the document is concerned with a variety of general methodologies applicable to any protein. The data that it presents in respect of individual proteins was incomplete and failed to reveal appropriate controls to allow satisfactory analysis.

251. Secondly, the weight that I am able to attach to Prof Heckels' evidence on this issue is limited, because he came to 922 with knowledge of the protein of significance to this case. He was cross-examined about 922 at T5/880/17-24:

> "Q. Professor, also, as far as we can tell, by the time we read this document, you had seen 885 and 280, which identified the 741 protein as being the one of significance in this case.
>
> A. Yes.
>
> Q. So when you read this document, 922, you already knew that 741was one on which we were focusing in this case?
>
> A. I believe so."

252. In my judgment, this is important evidence of hindsight. Given that Prof Heckels knew that protein 741 was the target for the purposes of this case, it is unsurprising that he selected this protein when considering the disclosure of 922. I do not accept that the skilled person would have made the same selection from 922 without knowledge of the invention.

253. Thirdly, Prof Heckels prepared his table by focusing on SBA values for single proteins in 922. This exercise shows that the data for 287 (MC58) and 287 (2996) are identical, even though the proteins are different and one would expect each to give higher SBA results against its homologous strain. That puts in doubt the extent to which these individual results can be regarded as reliable. This highlights the fact that, as Prof Ala'Aldeen said, one cannot compare results across the different experiments conducted in 922, given that the experimental conditions are likely to have been different.

254. Fourthly, Prof Heckels collated data only from SBA values for individual proteins in 922. However, most of the SBA data in 922 is for hybrids. I do not accept that it was justified to ignore the data about hybrids, and to focus only on single proteins. There is a significant amount of SBA data in 922, together with various statements about the bactericidal properties of antisera to various protein constructs, which has not been considered in the preparation of Prof Heckels' table. I have not accepted that the skilled person would analyse the SBA information in 922 with a view to identifying potential vaccine candidates. However, if he did so, then a consideration of all of the information would produce a table as shown in Annex 2 to Prof. Ala'Aldeen's third report, which does not single out 741 as a promising vaccine candidate. The amount of information about 287, 919 and ORF46, and various hybrid proteins, is much greater than that about 741 and, if comparisons are to be made, they appear more promising.

255. Fifthly, I do not consider that the evidence of either expert ultimately supported a conclusion of fair prospect of success in respect of 741. Prof Ala'Aldeen considered that if the skilled team was to take proteins forward as vaccine candidates on the basis of 922, then all of the proteins disclosed in that document would be included, essentially as a research project. He explained his difference of opinion with Prof Heckels on this issue at T3.412/23 -413/17, and I accept Prof Ala'Aldeen's view:

> "A. The difference between us is that I make no list, no shortlisting, no judgment. I take the whole document as it is. I see it as a methodology with a lot of proteins mentioned and I will be interested to know what information is there and how they add up. But Professor Heckels goes straight into shortlisting two most promising, as he calls them, and taking one from a lot of data, taking one from one snapshot of data and says these are the two I have, I am going to take them forward. This is where we disagree. My approach is more cautious than that, because I know the pitfalls, I know the shortcomings, I know the issues that I have to do with such shortlisting.
>
> Q. I suggest to you that your approach is more cautious than the notional skilled person?

> A. My approach, I see it more robust and scientific. The approach that my colleague has chosen, especially when it is implied in that table, is not something that would stand the test of time; or that would not be something that a skilled person would agree with."

256. Prof. Heckels was cross examined about the issue of fair prospect of success at T5/875/4 – 876/15 and I do not consider that he went further than saying that 741 was interesting:

> "Q. Would you agree, Professor, that on the basis of this data about 741 in 922, the skilled person cannot say, "This is a conserved protein which produces antibodies which are bactericidal against a diverse range of Men B strains"?
>
> A. No, I think we have already agreed that. As I say, that data is not there, but it points you towards something that is interesting for further work.
>
> Q. It does not, on the basis of this data, meet the criteria for a promising vaccine candidate?
>
> A. It does not meet all the requirements for something that you are going to start to put into people, but I keep repeating myself, saying that is shows data that is interesting for something that you would take forward.
>
> Q. Right. The skilled person could not say, could he, on the basis of this information, that he would have a fair expectation that 741 would turn out to be useful as a vaccine component for humans?
>
> A. No, I just repeat what I have just said."

257. I do not consider that the identification of 2086 protein as a vaccine candidate for Men B was obvious from 922, when viewed without hindsight. Alternatively, the skilled team would not have tried 2086/741 protein as a vaccine candidate for this purpose in 2001 with a fair expectation of success. Had I concluded that the identification of 2086 protein for this purpose was obvious from 922, I would have considered that the addition of at least one PorA protein was also obvious, given the common general knowledge which I have set out above.

Alleged squeezes

258. I should add that GSK relied upon a number of alleged squeezes between the prior art and insufficiency. The submission was that the Patent, the priority documents and the application as filed are no more enabling than the prior art. Therefore, the Patent must be invalid, as one or other of these objections must succeed. I do not accept this submission. As I have indicated in my judgment, the disclosures of the Patent, the priority documents, and the application as filed, are very different from the disclosure of the prior art relied upon. The former documents disclose that protein 2086 is a

credible and serious candidate for inclusion in a Men B vaccine; that there would be a fair prospect that this antigen would treat a broad range of Men B strains; and that coverage could be increased by inclusion of one or more PorAs. The prior art does not provide this disclosure, nor does it render it obvious.

Conclusion

259. I have rejected all of the challenges to validity of the Patent. Claims 1-2, 5-6, 10 and 18-20 are infringed by GSK's Bexsero vaccine, but claim 3 is not infringed.