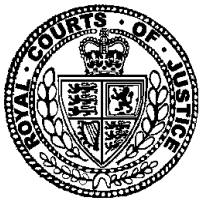

Neutral Citation Number: [2024] EWHC 2672 (Pat)

Case No: HP-2022-000035

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
PATENTS COURT

Royal Courts of Justice, Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 25 October 2024

Before :

HIS HONOUR JUDGE HACON
(Sitting as a Judge of the Patents Court)

- -

Between :

PFIZER INC.	**Claimant**
- and -	
UNIQURE BIOPHARMA B.V.	**Defendant**
And Between :	
(1) UNIQURE BIOPHARMA B.V. **(2) CSL BEHRING LLC**	**Part 20 Claimants**
- and -	
(1) PFIZER INC. **(2) PFIZER LIMITED**	**Part 20 Defendants**

- -
- -

Andrew Lykiardopoulos KC, **Henry Ward** and **Thomas Jones** (instructed by **Taylor Wessing LLP**) for the **Claimant** and **Part 20 Defendants**
Andrew Waugh KC and **Katherine Moggridge** (instructed by **Simmons & Simmons LLP**) for the **Defendant** and **Part 20 Claimants**

Hearing dates: 12, 15, 17-19 and 25-26 July 2024

- -

Approved Judgment

This judgment was handed down remotely at 10.30am on 25 October 2024 by circulation to the parties or their representatives by e-mail and by release to the National Archives.

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HIS HONOUR JUDGE HACON

Judge Hacon :

Introduction

1. The trial in this action was about the validity of European Patent (UK) 3 581 650 ('the Patent') owned by the Defendant. The Claimant alleges that the Patent lacks inventive step over a single item of prior art. There is also a pleaded case of insufficiency which is there as a squeeze on enablement.

2. The Patent is exclusively licensed to the Second Part 20 Claimant. There is a Part 20 Claim. The patentee and the exclusive licensee allege that the Part 20 Defendants (the Second Part 20 Defendant is a UK subsidiary) have infringed the Patent in UK. For the purpose of these proceedings, the Part 20 Defendants admit that they have carried out acts which, if the Patent is valid, infringe.

3. I will refer to the Claimant and Second Part 20 Defendant collectively as 'Pfizer' and will call the patentee Defendant and its exclusive licensee 'the Defendants'.

Technical Background

4. The matters discussed in this section of the judgment were all part of the common general knowledge at the priority date of the Patent, 15 September 2008.

5. Haemophilia is a condition which is inherited from a parent via an X chromosome. The X chromosome in those with haemophilia B carries a defective gene. In a healthy individual, among other things that gene performs an essential role in the functioning of what is known as the 'coagulation cascade'. When an individual suffers injury and there is a need to close up damage to blood vessels and to end bleeding, blood clots form at the site of injury. The coagulation cascade is the name given to a series of reactions culminating in the formation of an insoluble clot at the site of injury.

6. The enzymes which catalyse these reactions are known as 'factors', each identified by a roman numeral. One such is Factor IX, generally abbreviated to FIX. (It was often pronounced 'fix' in the oral evidence.) The gene responsible for the generation of FIX is on the X chromosome. Those suffering from haemophilia B have a defective FIX gene resulting in the failure to produce any or enough FIX. In consequence the coagulation cascade does not work properly and the individual suffers excessive bleeding, which can be fatal.

7. Haemophilia comes in two main types, designated A and B. Haemophilia A arises from another defective gene, also on the X chromosome, which fails to cause the production of any or enough Factor VIII, or FVIII as abbreviated.

8. FIX was first identified in Oxford in 1952 when it was found that a small child with haemophilia named Stephen Christmas did not lack FVIII, as was at first assumed, but that a newly identified protein, given the name Factor IX, was not present. The new protein was at that time alternatively called 'the Christmas Factor' but that seems not to have stuck.

9. Because the FIX gene lies on the X chromosome, women almost never suffer from haemophilia B. All chromosomes come as a pair. Women have two X chromosomes, men one X and one Y. A woman with an X chromosome carrying a defective FIX gene will have another X chromosome which, save in very unusual cases, will have a functional FIX gene. The functional gene compensates, providing enough FIX for the proper working of the coagulation cascade. In men, the partner Y chromosome never includes a FIX gene, so if the FIX gene on their single X chromosome is defective, they will be haemophiliac.

10. The Defendants said that the incidence of haemophilia B is 1 in approximately 25,000 live male births. Pfizer put the figure at 1 in 30,000. It doesn't matter, I assume that on average it is somewhere between the two and that there may be regional variation. In a country such as the United Kingdom the number of men and boys who suffer from haemophilia B runs into the thousands.

11. By the priority date of the Patent some work had been done in an attempt to treat haemophilia B by gene therapy. Gene therapy works as follows. Where an organism has a defective gene, foreign genetic material which includes the relevant functional gene is introduced. In eukaryotes the most effective way of doing this is by using a virus containing the functional gene in its DNA. In the case of humans, the virus selected is one able to enter the host human cell by its usual means when infecting human cells. Recombinant DNA techniques are used to modify the native DNA of the viral vector so that it now contains the functional human gene and to ensure that after infection the native viral DNA does not replicate itself as would normally happen, thereby avoiding the risk of disease and damage to the host.

12. The first human gene therapy trial was in 1989. The first conducted with some limited success was in 1990. Neither concerned the FIX gene.

13. By some years before 2008 haemophilia B was thought to be a promising candidate for gene therapy. This was because (a) it is caused by a single defective gene, (b) the protein sequence of FIX and the nucleotide sequence of the FIX gene were well known, (c) the procedure for introducing the gene into a human cell was well known, (d) there were animal models available for preliminary experimentation, (e) the activity of the FIX gene required to ensure that the coagulation cascade works was relatively low and (f) measuring the activity of the FIX gene experimentally was relatively simple.

14. The idea was to transduce into the cells of patients suffering from haemophilia B 'wild-type' FIX genetic material, i.e. the functioning gene found in people without the condition. One of the challenges was getting sufficient wild-type FIX genetic material into the patient. The more that could be transduced into a patient's cells the more effective the therapy was likely to be.

15. Candidate viral vectors, like all viruses, have a protein coat called a 'capsid'. When the vector infects the patient, the patient's immune system recognises the capsid as foreign protein, causing an immune reaction. The higher the level of infection, the greater the likelihood of a serious immune response, hampering the efficacy of the therapy and restricting the longevity of any successful effect.

16. As of September 2008 the problem of getting enough FIX genetic material into the patient without triggering an excessive immune response had not been solved. There

had been no trial of gene therapy anywhere shown to be effective in alleviating haemophilia B.

The Patent

17. The title of the Patent is "Factor IX polypeptide mutant, its uses and a method for its production". The mutant of the title is the FIX protein with one amino acid substitution relative to wild-type FIX. This is said to have an 8-9 fold increase in activity over wild-type FIX. The principal advantage of such a dramatic increase in activity is that a smaller amount of the variant polypeptide is needed to enable an effective therapeutic effect. Therefore a lower level of transduction of FIX genetic material into the host is required, reducing the risk of a damaging immune response to the vector capsid.

18. The named inventor is Dr Paolo Simioni. His team at Padua University Hospital found that a patient being treated there for deep-vein thrombosis in his right leg had blood containing FIX with very high activity – 776% of wild-type FIX. Analysis of the patient's DNA and that of his immediate family revealed a point mutation in the FIX gene of the patient and his younger brother. Expression of his mutant gene produced FIX with leucine at position 338 of the protein chain instead of arginine. This has since been called the 'Padua variant' form of FIX. The Padua variant is typically much more active than wild-type FIX, variously reported since as being between 8 and 12 times more active.

The description

19. The specification states that attempts had been made to correct the genetic defect causing haemophilia B by gene therapy and that these had been fruitless partly because the expression in plasma of the wild-type FIX gene in man is low and also because side effects had been reported, including hepatitis and myositis (a condition in which the immune system attacks the muscles causing chronic inflammation).

20. The specification identifies a phenomenon sometimes observed known as 'gain-of-function'. Some mutant FIX genes when expressed produce a polypeptide with higher activity than the normal or wild-type FIX protein. There is a reference to a PCT application which disclosed the production of a mutant FIX protein with the arginine at position 338 replaced by alanine. It was reported to have an activity 2-3 times that of wild-type FIX. This PCT application is the cited prior art of the present litigation.

21. The Patent specification says that gain-of-function FIX mutants have not been found to exist in nature and have not been tested in man. Other mutants are referred to. It goes on to discuss the invention which it describes as an improvement on the state of the art as it provides a modified FIX polypeptide which in humans does not cause any adverse side effects, just increased coagulation.

22. There was apparently some confidence about the lack of side effects because, as the specification states, the modified FIX polypeptide of the claims was discovered as the product of a naturally occurring mutant gene, as opposed to a laboratory creation made by recombinant technology. There was disagreement between the parties about how justified this confidence was. Certainly the Patent provides no absolute certainty about safe use of the Padua variant in humans other than the Padua patient and his brother, but an immune reaction to FIX, as opposed to vector capsid, was said to be rare.

23. The principal potential advantage of the claimed invention is the dramatic increase in clotting activity of the Padua variant and the prospect of administering a correspondingly lower dose of vector carrying the gene encoding that variant.

The claims

24. Claim 1 of the Patent is in EPC 2000 form, claiming a nucleic acid encoding at least the necessary minimum amino acid sequence of the mutant FIX, for use in a gene therapy treatment of haemophilia B. The amino acid sequence is set out in the claim. It shows, if one were to compare it with the sequence of wild-type FIX, that the key modification is at position 338: the arginine of the wild-type FIX is replaced by leucine.

25. The claim gives some prominence to a polymorphism at position 148, the claim requiring that alanine is in that position. The polymorphism played no part in the proceedings. It is probably in the claims to avoid an allegation that they are anticipated by the cited prior art.

26. Claim 2 is in similar form but it sets out a specific FIX polypeptide. Claim 3 is to the nucleic acid of claims 1 and 2 where the nucleic acid is in a viral vector. Claim 4 adds that the vector is an adeno-associated virus.

Construction

27. Claim 1 is drafted to cover a nucleic acid 'for use in gene therapy treatment of haemophilia B' encoding the modified FIX. The Defendants' case in opening was that the suitability for use in gene therapy treatment meant that the treatment had to be effective in the long term. Their evidence suggested five years was the right sort of period. This time limitation was dropped in closing, no doubt to avoid the argument of insufficiency raised by Pfizer.

28. I find that the nucleic acid of claim 1 must be suitable for providing gene therapy in the treatment of haemophilia B irrespective of the time over which the therapy lasts. As is apparent from the claim, the nucleic acid must encode a modified FIX polypeptide with an amino acid sequence conforming with the claim.

The Inventive Concept

29. Although the identity of the inventive concept was not central to the issues in the case I will say something about it because it has some limited relevance to further discussion.

30. At the priority date the skilled team would have known that any substitution of any of the amino acids in FIX was possible. The new insight said to be conveyed by the Patent, the inventive concept, is that DNA encoding the mutant FIX of the claim is suitable for use in a gene therapy treatment of haemophilia B. The specification explains and justifies why it is suitable: the FIX of the claim has an 8-9 fold increase in functional activity compared to wild-type FIX.

The Prior Art

31. The single piece of prior art is PCT Application WO 99/0496 published in January 1999, referred to in the evidence as 'Stafford' after the name of the first stated inventor. It is entitled 'Factor IX antihemophilic factor with increased clotting activity'.

32. Stafford introduces its subject-matter this way:

> 'This invention concerns Factor IX in general, and particularly concerns Factor IX containing a mutation that enhances the clotting activity thereof. This invention also concerns DNA constructs encoding such Factor IX, along with vectors containing such constructs.'

33. The FIXs of the inventions disclosed by Stafford are any non-naturally occurring FIX with an amino acid substitution at position 338. More detail is given about possible substitutions:

> 'Substitutions of the inventions are, for example, a substitution of an arginine residue for an amino acid residue selected from the group consisting of alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, glycine, serine, and threonine. In preferred embodiments of the invention, the substitution is a substitution of an arginine residue for an amino acid residue selected from the group consisting of alanine, leucine, and valine'

34. Experiments are discussed in which a nucleotide encoding a FIX mutant was created by recombinant DNA means, introduced into a vector, expressed and tested for clotting activity. The results are set out in which the expressed mutant is shown to have a clotting activity 2.8 times that of FIX taken from human plasma. Strictly, the comparison was between the activated form of each type of FIX protein.

35. The mutant FIX made in the experiments carried out by Stafford and his colleagues had a single substitution at position 338 relative to wild-type FIX, namely arginine to alanine. Nothing else by way of experimental work is reported.

36. Claim 1 of Stafford is:

> 'A non-naturally occurring mammalian Factor IX protein having an amino acid substitution at amino acid position 338'

37. There are 20 amino acids, which means that there are 19 alternatives to arginine at position 338. One is known to occur naturally, namely proline, so this substitution is outside the claim. That leaves 18 alternatives within the claim.

38. FIX with the proline substitution is given a passing mention; the authors say that it gives rise to mild haemophilia B in those individuals who have that gene.

39. These are Stafford's claims 2 to 5:

> '2. A mammalian Factor IX according to claim 1, wherein said substitution of an arginine residue for an amino acid residue selected from the group consisting of alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, glycine, serine and threonine.
>
> 3. A mammalian Factor IX according to claim 1, wherein said substitution is a substitution of an arginine residue for an amino acid residue selected from the group alanine, leucine, and valine.

> 4. A mammalian Factor IX according to claim 1, wherein said substitution is a substitution of an arginine residue for an alanine residue.
>
> 5. A mammalian Factor IX according to claim 1, wherein said substitution is a substitution of an arginine residue for a leucine residue.'

40. No rationale is advanced in Stafford for identifying the group of alanine, leucine and valine or the larger group of alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, glycine, serine and threonine. However, leucine is prominent among the amino acids advanced.

The notation

41. Variant proteins are identified by the letter used as the abbreviation for the amino acid replaced, the numerical position of the replacement and then the letter which stands for the new amino acid in that position. So R338A means that alanine replaces arginine at position 338; R338L means that leucine replaces the arginine and so on. This notation is often hyphenated with the name of the protein concerned, e.g. R338A-FIX or R338L-FIX.

Pfizer's argument in summary

42. Pfizer argued that the substance of the invention claimed in the Patent lies in singling out the Padua variant of FIX, R338L-FIX, as being of significance. That protein is clearly and unambiguously identified in Stafford. It is one of the 3 preferred embodiments referred to in the body of the specification and claim 5 is to R338L-FIX alone. The only difference between that protein and the FIX of the Patent is an alanine at position 148 which is acknowledged to be of no inventive significance. The FIX of the Patent is therefore obvious over that disclosed in Stafford. Claim 1 is obvious.

The skilled team

43. It was common ground that the skilled team consisted of a gene therapist and a structural biologist. The hypothetical task in hand was to find an effective means, or at least a better means, to treat haemophilia B by gene therapy.

44. The Defendants argued that the gene therapist would have required clinical experience since clinical trials would be needed to test any proposed therapy on patients. I do not believe there is much in this. Pfizer's expert gene therapist said that no clinician would be needed for pre-clinical trials and I accept that. The key arguments in this case did not concern clinical trials. When the parties sought and obtained permission to adduce evidence from a gene therapist and a structural biologist at an early stage of the proceedings, nothing was said about the need for clinical evidence and I can see why.

The witnesses

45. Each side called two expert witnesses. Professor Rodney Camire was Pfizer's expert in respect of structural biochemistry and protein engineering, or structural biology for short. He is a Professor of Paediatrics specialising in haematology blood research at the University of Pennsylvania Perelman School of Medicine and is a member of the Division of Hematology and the Raymond G. Perelman Center for Cellular and

Molecular Therapeutics at the Children's Hospital of Philadelphia. Professor Camire's research has focussed on understanding the molecular and cellular processes that contribute to and regulate blood coagulation, in particular the regulation of Factors V, IX and X.

46. Professor Camire was the subject of criticisms from the Defendants in closing, broadly on the ground that he was given to many sweeping generalisations without providing support for them. Though overstated, I think there is something in this. Professor Camire was occasionally given to speculation in his written evidence, speculation presented as if it were hard fact. One or two points in his written evidence were potentially misleading. As with all the witnesses, I will discuss his evidence on specific matters in context below. These shortcomings did not help his credibility which was a pity because his answers in cross-examination were for the most part clear and direct. I am sure he is highly competent with a broad knowledge of his field. This could and should have been allowed to emerge untainted by the occasionally unfortunate drafting of his reports.

47. Pfizer's other witness was Dr Lili Wang who gave evidence on gene therapy. Until her recent retirement Dr Wang was a Research Associate Professor of Medicine at the University of Pennsylvania Perelman School of Medicine, where Dr Wang was also Research Director for Discovery Research and Gene Editing for the Gene Therapy Program.

48. Dr Wang has previously acted as an expert witness for Pfizer. She submitted expert declarations in four proceedings in the United States Patent and Trade Mark Office. She has also provided expert evidence in relation to the Patent (in its undesignated form) in Opposition Proceedings in the EPO and gave expert evidence in the Netherlands in a claim by Pfizer to revoke the Dutch equivalent of the Patent.

49. Dr Wang's evidence was the subject of a sustained attack running to many pages in the Defendants' written closing submissions, where it was described as 'deeply unsatisfactory on so many levels'. I think there is something in the Defendants' view. I am sure that Dr Wang has been a distinguished and respected figure in her field during the course of her career. It would seem that since retirement she has spent quite a lot of her time, presumably lucrative time, as an expert for Pfizer in relation to subject matter with which this litigation is concerned. The written evidence she has given on behalf of Pfizer in the US alone runs to about 1700 pages, quite aside from her oral depositions there.

50. My impression was that at some point during the preparation and delivery of evidence in the US and elsewhere Dr Wang has developed the understanding that the primary duty of an expert witness is not to say anything that may damage Pfizer's case if it can be avoided. I do not say that Dr Wang believed that she was free to mislead the court, just that keeping the court fully informed of all relevant matters, whether helpful to Pfizer or not, was not seen to be her primary duty. Nor do I say that she was responsible for her understanding of an expert's role in court.

51. This impression was initially formed by the way she gave her evidence in cross-examination. There were often sustained pauses after questions were put. Her first answer too frequently did not address the question she had been asked and when asked again she stuck to what seemed to be a stock response. There is nothing necessarily

wrong with a stock response if it answers the question put, but it gives rise to doubt if the question is not addressed. I had to intervene to ask Dr Wang to focus on the question and try to answer what was being asked.

52. Also, Dr Wang was cross-examined on the written evidence she has given in the Netherlands. It emerged that in some of that evidence Dr Wang had omitted relevant material, providing at best an incomplete picture, but it was evidence that she had nonetheless been content to approve.

53. Cumulatively this left me with the impression that in her time as an expert witness for Pfizer, Dr Wang has quite possibly been guided by lawyers as what she should say to an extent that is not consistent with the duty of an expert in this court. It may be that Dr Wang believed that she was thereby doing her job as an expert witness correctly. In the end this did not work in Pfizer's favour. Dr Wang's apparent anxiety to toe the party line left me with the view that although I would consider her evidence as carefully as the evidence from other witnesses, I should treat it with some caution.

54. The Defendants' expert on structural biology was Professor Clint Spiegel. He is Professor and Departmental Chair at the Department of Chemistry at Western Washington University in the United States. He is the primary investigator of a group conducting research into the structural and functional characterisation of blood coagulation factors. Professor Spiegel is the author or co-author of articles and publications concerning the structure and function of clotting factors, primarily Factor VIII but more recently Factor IX.

55. Professor Spiegel was criticised by Pfizer on several grounds, principally that his lack of first-hand experience in the field of FIX research at the priority date was compounded by a lack of consultation with Professor Nathwani. This meant that he did not appreciate the extent to which the skilled team would have wanted to find a way of lowering the dose of the transducing vector to be administered, the consequent desire to find a gain-of-function mutant and the corresponding interest in the potential mutants stated and claimed in Stafford. Pfizer also said that Professor Spiegel was given to exaggeration and avoided giving answers to questions put to him.

56. In my view there is little of substance in these criticisms. It is well established that an expert need not fit the profile of the corresponding skilled person. Professor Spiegel undoubtedly has expertise in research into blood clotting factors. Even though that has only more recently included FIX, I think he was able to put himself into the appropriate mindset of a structural biologist conducting such research at the priority date. As to his alleged lack of appreciation of desire of the skilled team to find a FIX mutant with high gain-of-function, if I were to conclude that an urgent desire of that nature existed, it can be assumed that this would have been communicated to the structural biologist in the skilled team. Professor's Spiegel's opinions about what could and would be done at the priority date can be considered accordingly, as can the evidence of Professor Camire.

57. To my mind Professor Spiegel was a good witness with an impressive knowledge of the relevant field of structural biology. He was careful giving his answers and I think this was because he was keen to be accurate, not because he wanted to stick to a party line.

58. Professor Amit Nathwani was the Defendants' expert on gene therapy. He is a Professor of Haematology at University College London and is a Senior National Institute for Health and Care Research Investigator. Professor Nathwani has conducted an internationally leading gene therapy programme and has coordinated Phase II and III clinical trials in relation to haemophilia B gene therapy. His work has won him several international awards.

59. Pfizer were mild in their criticisms of Professor Nathwani, rightly so. I found him to be an excellent witness. He communicated his considerable knowledge of gene therapy clearly, addressed the questions asked and answered in a direct manner. His manner of prompt and direct answers was consistent with a likelihood that he was stating his genuinely held views without undue reflection as to what he should or should not be saying.

The roles in the skilled team

60. The hypothetical skilled persons in the team are taken to have co-operated in the task of finding an effective means to treat haemophilia B by gene therapy. The evidence from the experts indicated that the gene therapist would have taken the lead. Having carefully read Stafford, he or she would have consulted a structural biologist and together they would have considered whether, and if so how, Stafford provided a way forward.

61. In principle the gene therapist could have read Stafford and rejected the notion that it could provide a way forward without ever consulting the structural biologist, but the evidence did not suggest that the gene therapist knew enough about protein structure, the physicochemical characteristics of each of the amino acids and the likely effect of any particular substitution to have dismissed Stafford out of hand even if they were otherwise minded to. The structural biologist would have been consulted.

The leading teams working in the field at the priority date

62. The evidence identified the leading teams working on the possible treatment of haemophilia B by gene therapy at the priority date. They were:

    (1) Professor Katherine High, who headed a group at the Children's Hospital of Philadelphia. She was probably regarded as the most prominent figure in gene therapy. Her group had a partnership with a US biotech company, Avigen Inc. Professor High's team included Dr Valder Arruda who was a leading researcher in the field. The Journal of Clinical Investigation carried in successive editions a series of interviews under the heading "Conversations with Giants in Medicine". One such was an interview with Professor High published in 2023, giving an idea of her standing in her field, which was in any event not in dispute.

    (2) Professor Roland Herzog, a former member of Professor High's team, who set up his own laboratory at the University of Florida in 2005.

    (3) Professor Mark Kay, who led a team at Stanford University.

    (4) Professor Jim Wilson, a clinical scientist at the University of Pennsylvania, who conducted research into gene therapy until 2005.

(5) Professors Richard Samulski and Darrel Stafford, who worked at the University of North Carolina, Chapel Hill. They collaborated with Professor Herzog and Dr Arruda.

(6) Professor Nathwani, one of the Defendants' expert witnesses in this action, who was the leading figure in gene therapy research in Europe at the priority date. He worked with Professor Edward Tuddenham at UCL.

(7) Professor Thierry VandenDriessche, who led a gene therapy team at the Free University of Brussels and the University of Leuven.

(8) Professor Luigi Naldini at the San Raffaele Telethon Institute for Gene Therapy, Milan.

63. There were other teams in the field around the world. Three of relevance are discussed below.

Common general knowledge

64. The disputes about the common general knowledge concerned not just the usual ones about whether items of information were within the CGK, they also concerned the mindset of the members of the skilled team, especially the prevailing attitude to known techniques of gene therapy and how the structure and function of proteins, specifically FIX, were likely to be affected by modifications to the amino acid sequence.

65. Mindset, of course, depends on the CGK and although it may not be strictly characterised as an issue of CGK, it is convenient to treat it as falling under that head as the parties did.

The CGK of the skilled gene therapist

The motivation to develop effective gene therapy for haemophilia B

66. The treatment for haemophilia B used at the priority date was invasive, it required intravenous administration 2-3 times a week. It was very expensive, costing about $20 million per patient over a lifetime. The potential benefit of using gene therapy to treat haemophilia B to those with the condition and to those funding treatment was known to be considerable.

67. The path to developing such therapy was marked by setbacks and disappointments which I will come to. However, Professor Nathwani said that by 2008 those working in the field of gene therapy were desperate to find a solution and were willing to look at every avenue. This was not disputed evidence. The motivation in the minds of the skilled team to find an effective means of treating haemophilia B by gene therapy would have been very high. The plaudits going to a team that succeeded would have been expected to be correspondingly high.

68. I note here that this broad motivation to develop effective gene therapy for haemophilia B, the overall goal, is not to be confused with the narrower and more specific issue of the scientific motivation to adopt any particular course of action in the search for effective gene therapy.

The likelihood of successfully treating haemophilia B by gene therapy

69. Following the first human gene therapy trial in 1989, well over 1300 clinical trials had been conducted by 2008. They had mixed results.

70. The Defendants argued that as of September 2008 the mood was gloomy among those interested in the possibility of treating haemophilia B by gene therapy, to the point that some were questioning whether it would ever work. Pfizer submitted that this picture of gloom was overstated.

71. I will go through some of the background history which in part supports the Defendants' picture and in part explains why, despite reservations, research did not stop.

72. In 1999 an 18-year-old participant in a trial in the United States, Jesse Gelsinger, died due to a massive immunological response to the capsid of the viral vector. For a while – it was not made clear exactly how long – all gene therapy trials in the United States were halted. An article put in cross-examination to Dr Wang, recalling the impact of Mr Gelsinger's death 20 years after the event, quoted one of the workers in the field:

> "[The death] made the whole field of gene therapy go away, mostly, for at least a decade. Even the term gene therapy became a kind of black label. You didn't want that in your grants."

73. Research did not stop, especially pre-clinical work. On the other hand, after the Gelsinger case there followed a global debate among those in the field as to whether the possible benefit of gene therapy justified the risk to patients. Professor High, discussing this period in an article about her, recalled that there was a dearth of funding for a decade for gene therapy from the late 1990s.

74. The impact of Mr Gelsinger's death may have been more muted in Europe. In 2000 there was some success in France in the treatment of a type of immunodeficiency of infants, although two years later two of the nine infants developed a leukaemia-like condition.

75. In the United States Professor High's team resumed work in the early 2000s, introducing wild-type FIX into the liver of human patients with severe haemophilia B. They used adeno-associated virus (AAV) as a vector, a small virus which infects humans. The work became known as the 'Manno study' after the name of the lead author of a succession of papers published from 2003 to 2006. The Manno paper of 2006 attracted particular attention. It reported that AAV-mediated gene transfer to the liver of human patients led to the expression of the haemophilia B gene for only a short period, accompanied by a rise in the production of liver enzymes. This rise led to a loss of expression of the gene. The work was then halted.

76. A particular problem identified by Manno was one I have already mentioned. Surprisingly it was found that in humans (not in other mammals) there is an immunological response to the capsid of the particular AAV vector used. This led to what was sometimes called the 'Manno dilemma' or 'Manno problem' in the evidence: how to introduce enough genetic material into the host without provoking an immune reaction which would stop the treatment being effective.

77. Possibly influenced by the Manno studies, in 2004 the commercial partner of Professor High's team withdrew funding of haemophilia gene therapy trials on the ground of safety issues.

78. Pfizer referred me to a review article by Dr Michael L. Edelstein of Hemel Hempstead Hospital and others, published in August 2007 as means to gauge the state of play at the time. Dr Edelstein and his colleagues were not leaders in the field but in their review they looked back at over 1340 gene therapy clinical trials that had been conducted so far. The authors' concluding remarks referred to the intense criticism and scepticism of the years before 2007 and said:

> "While the unfortunate occurrence of the serious adverse events has slowed progress and dampened the ardor of some, it has also prompted others to undertake more detailed investigation into the behavior of viral vectors and more careful testing of all approaches, and we can be hopeful that as gene therapy technology is improved and refined the field will make greater steps forward."

79. Professor Nathwani was taken to another review published in 2007 which spoke of the gene therapy field – in general, not specifically relating to haemophilia – as making good progress with some promising results and 'a sense that the tide of public opinion is turning'. Professor Nathwani agreed that it was the sort of article that reflected the feeling in the field.

80. I find that notwithstanding the setbacks of the 10 years leading up to September 2008 and the reduction in funding, work on gene therapy had continued, pursued by at least eleven teams. Optimism improved over that period though there remained a strong awareness of the potential risk to patients in the event that clinical trials were to be conducted.

The potential value of gain-of-function mutants

81. The phenomenon of variant proteins providing greater activity than the equivalent wild-type protein, known as 'gain-of-function', was familiar well before 2008.

82. Relying on the evidence of Professor Nathwani, the Defendants submitted that gain-of-function was not seen as a way forward at the priority date. Professor High co-wrote a review article published in Current Gene Therapy shortly before the priority date, in 2007 ('the Mingozzi Review'), in which the authors listed five possible solutions to the apparent impasse reached in gene therapy. Gain-of-function did not appear in the list. The five were:

(1) The use of alternative AAV serotypes. The hope was that untried serotypes may cause a lower immune reaction.

(2) Using immunosuppression at the time of vector infection to modulate the immune response to the viral capsid.

(3) Using protein capsid engineering or other means to alter the half-life of the capsid antigen to reduce the time over which they would be recognised by the patient's immune system.

(4) Selecting patients with no pre-existing immunity to the AAV serotype used. The level of infection of AAV-8 in humans, for instance, is only about 20%.

(5) Reducing the amount of vector introduced into the patient by using more efficient expression cassettes – a component of vector DNA which directs the expression of the gene transfected.

83. There was at least one other review co-authored by Professor High, specifically on gene therapy for haemophilia, which discusses solutions that also did not include gain-of-function mutants. Professor Nathwani said that in these papers Professor High was providing a comprehensive review of possible options, everything she could think of and that it reflected the prevailing view at the time.

84. Professor Nathwani expanded on this: based on the Manno data the target dose of vector was one twentieth of that which gave rise to elevated production of liver enzymes and that one would have to come up with a formidable answer to the need to boost the effect of FIX expression to be successful at such lower doses.

85. Pfizer argued that once the Manno papers had highlighted the problem of capsid immunogenicity in relation to gene therapy for haemophilia B in 2003-6, there were only two ways to go. They were potentially complementary if progress could be made on both. One was to work on vector delivery to allow a reduced dose of the vector and the other was increase the activity of the FIX protein encoded by the vector. Pfizer said that the first was the route of primary interest to Professor Nathwani at the time, whereas Professor High's team looked more at the second.

86. I agree with this up to a point, but it is clear from the Mingozzi Paper that what Pfizer considered to be the second approach, aiming for increased activity of the expressed FIX protein, did not necessarily involve gain-of-function mutants and that idea was not among the top five considered by the leading team in the field.

87. This notwithstanding, some were looking at gain-of-function variants, including variants that would improve the treatment of haemophilia B. Principal among these were teams that included Professor Stafford, the first named inventor of the cited prior art. The relevant work was published in two important papers, referred to in the evidence as the 'Chang Paper' and the 'Schuettrumpf Paper'. It was common ground between the parties that both papers formed part of the CGK of the skilled team at the priority date and that they would have been in the mind of the team reading Stafford, supplementing the information provided by Stafford itself.

Chang

88. Stafford's priority date is 21 July 1997. About 10 months later in May 1998 the work which forms the basis of the invention claimed in Stafford was published in a paper entitled 'Changing Residue 338 in Human Factor IX from Arginine to Alanine Causes an Increase in Catalytic Activity' in The Journal of Biological Chemistry, the Chang Paper. Dr Jinli Chang is the first-named author of the paper, Professor Stafford is the last-named author and so is conventionally inferred to have been the team leader. Dr Chang is also the second named inventor in Stafford. Both were working in the Department of Biology at the University of North Carolina. This is the beginning of the Chang Paper's abstract:

> 'The study was designed to identify functionally important factor IX (FIX) residues. Using recombinant techniques and cell culture, we produced a mutant FIX with arginine at 338 changed to alanine (R338A-FIX). This molecule had approximately 3 times greater clotting activity than that of wild type FIX (wt-FIX) in the activated partial thromboplastin assay.'

89. The authors did not say that R338A could be used for gene therapy. They did suggest why R338A-FIX has higher activity than wild-type FIX:

> '… we propose that R338A-FIX's increased activity is not due to an allosteric effect on the active site, but that the Arg-338 residue is part of an exosite that binds both factor X and the mucopolysaccharide, heparin.'

90. The authors did not propose any possible substitution at 338 other than alanine. The Defendants submitted that because Chang must have been peer reviewed, such a proposal could never have appeared in the paper. Probably not, because there was no basis for such an idea, but the more significant point is that there is no reason to suppose that the authors even considered a different substitution.

Schuettrumpf

91. In March 2005 a paper entitled 'Factor IX variants improve gene therapy efficacy for hemophilia B' was published in Blood, the Schuettrumpf Paper. The first named author was Dr Joerg Schuettrumpf. There is a relationship not just with the Chang Paper, but also the Stafford prior art and the work done in Padua. Professor Stafford was one of the authors of Schuettrumpf. The team leader was Dr Valder Arruda who was the co-author with Dr Simioni of the paper which disclosed the discovery and properties of the Padua variant. Dr Arruda and Professor Stafford were also part of Professor High's team in Philadelphia.

92. The issue addressed in Schuettrumpf was that intramuscular injection of AAV vector into human muscle, although safe, is hampered by the retention of FIX in the muscle and by the limited capacity of muscle to synthesize fully active FIX at high expression rates. In an attempt to overcome the problem, the authors made two FIX variants, the Chang R338A variant and one in which alanine replaced lysine at position 5, and lysine replaced valine at 10. Using the same system of notation they called it K5A/V10K. Studies using these variants were conducted in mice:

> 'Circulating F.IX levels following intramuscular injection of AAV-F.IX - K5A/V10K, a variant with low affinity to extracellular matrix, were 2-5 fold higher compared with wild-type (WT) F.IX, while the protein specific activities remained similar. Expression of F.IX-R338A generated a protein with 2- or 6-fold higher specific activity than F.IX WT following vector delivery to skeletal muscle or liver, respectively.
>
> …
>
> These studies demonstrate that F.IX variants provided a promising strategy to improve the efficacy for a variety of gene-based therapies for hemophilia B.'

93. The authors concluded that variants such as R338A offered:

> '… an attractive alternative to enhance the efficacy of several distinct strategies to treat hemophilia B'.

94. No alternative variants to wild-type FIX were considered or mentioned. Schuettrumpf shows that gain-of-function was an idea being pursued in 2005 in trying to develop a gene therapy for haemophilia B, but it did not represent a breakthrough that would overcome the Manno problem.

95. The Defendants made four points about Schuettrumpf. The first was that all the subsequent work prompted by the paper used variants with alanine invariably kept at position 338.

96. The second was that a Texas team reported that R338A provided only 2.1-2.2 times the activity when compared to wild-type FIX.

97. Thirdly, at the priority date the hypothetical skilled gene therapist would have known that more than 3 years after the publication of Schuettrumpf no FIX mutant had been found which provided effective treatment of haemophilia B in humans, whether used in combination with other strategies or without.

98. The fourth point concerned animal models. The experts were agreed that such models may not be predictive of what happens when the same recombinant DNA is introduced into humans. The work published in Manno was an example of this: unexpectedly there was an immune reaction in humans to the viral capsid preventing any long-term expression of the encoded FIX even though there had been successful long-term expression in mice with no immune reaction. The Jesse Gelsinger case showed that in the case of human patients receiving gene therapy an immune reaction may be fatal.

99. I accept those four points.

Ways forward other than gain-of-function

100. Professor Nathwani said that his and other teams were looking at other areas which, they felt, would have a much greater impact on the potential for success in gene therapy, such as improved vectors.

101. Not all other teams. Some continued after the publication of Schuettrumpf to look at gain-of-function. Presumably those teams thought that progress on that front could at least make a contribution to overcoming the Manno problem.

Animal models

102. The experts agreed that there would have been an expectation on the part of the skilled gene therapist that there would be a significant and progressive reduction in FIX expression as a study moved from mice to larger animals and from there to humans if the study went that far. These reductions were seen to be associated with a reduced efficiency in transduction by the vector. It was Professor Nathwani's view that this would have led the skilled gene therapist to believe that the results published in Schuettrumpf, even if not downgraded along the lines found by the Texas team referred to above, would not overcome the Manno problem.

Testing alternative FIX variants

103. A point arose about whether making and testing a new FIX variant was a simple thing to do at the priority date. The evidence of Professors Camire and Nathwani was that it would have been routine and taken only a few weeks. In his written evidence Professor Camire estimated two weeks.

104. One might suppose that if making and testing R338L-FIX would have been a routine task of two weeks or so, other replacements at position 338 could have been conducted in parallel. In other words, it would have been routine and straightforward to make and test FIX with each of the 18 candidate amino acids alternative to arginine at position 338 (i.e. excluding proline). The position was never clarified in the evidence.

105. Jumping ahead a little, on the assumption that the skilled team, having read Stafford, would have thought it worthwhile to replace arginine at 338, one possibility is that it would have been routine to try all the alternatives. Another possibility is that this would have strayed into becoming a research project; to qualify as routine the testing would have to be limited to less than 18 amino acids, presumably choosing the most promising on the basis of the skilled team's CGK. If that is right, the evidence did not iron out whether leucine would have made the cut, wherever the cut would have been. The third possibility is that routine testing would never have meant that the test involved more than one alternative amino acid. I doubt that the last is correct. If it were, I think that the Defendants would have been at pains to make it good on the evidence. In any event, this part of the CGK was not resolved.

Teams that followed up on the R338A disclosure

106. Three papers were referred to in evidence which indicated what other teams were doing in the period between the publication of Chang and the priority date by way of following up on the disclosure in Chang, specifically the higher than wild-type activity of the R338A variant.

107. A team in China used a gene encoding R338A-FIX in a different vector. Their paper was published in December 2001 (Lu).

108. A team in Houston published an abstract in Molecular Therapy in May 2008 (Brunetti-Pieri) – the Texas team I have mentioned. Their work used a gene encoding R338A-FIX, another using a gene encoding an epidermal growth factor domain from Factor VII and a third using a gene encoding both. A different vector was used.

109. A team partly in Taiwan and partly in the USA published their research in a paper in Blood in November 2008, just after the priority date but the work will have been done before September 2008 (Lin). The team aimed producing a FIX molecule with higher specific activity. To this end, 7 variants on R338A-FIX were expressed. The most successful had two further substitutions: alanine for arginine at 86 and alanine for glutamic acid at 227, but all had alanine at 338.

110. There is nothing to suggest that any of these teams contemplated changing the alanine at 338.

The CGK of the structural biologist

Grouping the amino acids

111. The main submission made by Pfizer was that the skilled structural biologist would know that alanine, leucine and valine are usually grouped together either because they are all non-polar with aliphatic side chains or because they are hydrophobic. Reference was made to text books, namely Lehninger (Nelson & Cox), Branden & Tooze, Whitford and Elliot & Elliot.

112. This needs to be put into context. Lehninger, for instance, is a well-known undergraduate biochemistry text book. A chapter entitled 'Amino Acids, Peptides, and Proteins' explains what they are and their functions in living beings. A section is headed 'Amino Acids Can Be Classified By R Group'. (Amino acids have a section of their chemical structure which is common to all of them. The part of the structure which is unique to each amino acid is called the 'R group'). In this section the authors say:

> 'Knowledge of the chemical properties of the common amino acids is central to an understanding of biochemistry. The topic can be simplified by grouping the amino acids into five main classes based on the properties of the R groups (Table 3-1). In particular, their polarity or tendency to interact with water at biological pH (near pH 7.0). The polarity of the R groups varies widely, from nonpolar and hydrophobic (water-insoluble) to highly polar and hydrophilic (water-soluble).'

113. This is followed by Table 3-1 which presents the 20 amino acids in 5 groups. One group, headed 'Non-polar, aliphatic R groups', contains alanine, valine and leucine and also glycine, proline, isoleucine and methionine.

114. The authors do not suggest that Table 3-1 sets out the only possible way to group amino acids. The common groupings presented reflect the biochemical properties of their R groups, which affect how they interact with other molecules in a cell, but the groupings of Table 3-1 are not stated to be predictive of anything in relation to the substitution of one amino acid for another in a protein.

115. In his written evidence Professor Camire made much of what he said were similarities between alanine, valine and leucine:

> "… they are all small, nonpolar, hydrophobic, and have aliphatic R groups, though their ability to form α-helices do differ."

116. This evidence was at best incomplete. The three amino acids are not all of a similar size. Alanine is the smallest amino acid but one. The Grantham matrix (discussed further below) gives statistics for volume and polarity. Alanine has a volume of 31, valine 84 and leucine, the second largest amino acid, is stated to have a volume of 111. The polarity of alanine is 8.1, valine 5.9 and leucine 4.9.

117. As to hydrophobicity, Professor Camire accepted in cross-examination that there was known to be a spectrum from isoleucine, the most hydrophobic, given the figure 4.5 on a CGK hydropathy scale, to the most hydrophilic, arginine, at –4.5. Seven amino acids, including alanine, valine and leucine are hydrophobic, but their values differ with alanine at 1.8, valine at 4.2 and leucine at 3.8.

118. Professor Spiegel was cross-examined on this. A table, apparently created by lawyers since it was not part of Professor Camire's evidence, was presented to Professor Spiegel and it was put to him that the figures in the table showed that leucine and valine are the

closest uncharged, nonpolar aromatic amino acids to alanine in terms of surface area and volume. Professor Spiegel was unimpressed and rejected the idea that the table supported this conclusion.

The position of hydrophobic side chains

119. Side chains of amino acids may be hydrophobic or hydrophilic. It was part of the CGK that hydrophobic side chains are not usually positioned on the protein so as to be exposed to an aqueous solvent like blood plasma since it tends to lead to harmful aggregation of the protein. It follows that evolution has rarely led to such an arrangement. Instead hydrophobic side chains are found within the core of the protein.

120. Professor Camire's evidence, which I accept, was that while generally speaking hydrophobic amino acids are not found on the outside of proteins, this is it is not an inviolable rule, exceptions are possible.

121. I find that the skilled structural biologist, if contemplating the substitution of leucine for arginine at position 338 of FIX, would have known that the protein's function tolerated the change from the hydrophilic arginine at that position to the moderately hydrophobic alanine. A switch to the more hydrophobic leucine would have raised a concern but not enough by itself to rule out such a change.

Conservative sequences

122. The term 'conservative' can have an evolutionary meaning in relation to protein structure. Where a protein is found in many species, stretches of DNA in the gene encoding that protein may be identical or substantially identical across all species. This indicates that those stretches are evolutionarily conserved.

123. Professor Camire called this 'sequence alignment' and explained the significance. The principles of natural selection select against the persistence of mutations at sites which are likely to be key to protein structure and function. In other words, taking FIX as an example, across the thousands of years of evolution of each of the species which has FIX, there will have been a range of mutations in the gene encoding FIX which have occurred by chance. If a stretch of the DNA encoding FIX is highly conserved across all the relevant species, none or almost none of those mutations has persisted. One would therefore expect that any kind of mutation in that stretch may well be disadvantageous.

124. A source known as the protein data bank could be consulted to look up known natural mutations of FIX at any amino acid position.

Conservative substitutions

125. Professor Camire's evidence and the Statement of Agreed CGK indicated that 'conservative' can be used in a different sense: the substitution of an amino acid for another is conservative if it is not predicted to have a significant impact on the protein's shape and structure and therefore its stability and function.

Similarity matrices

126. By the priority date structural biologists had developed matrices which showed the differences between the amino acids based on composition, polarity and molecular volume. They graded amino acid substitutions on a range from conservative to non-conservative. Three matrices were discussed in the evidence: Grantham, BLOSUM and PAM.

The structure of FIX

127. The Factors in the coagulation cascade each have an active form denoted by adding 'a', for example FIXa and FVIIIa.

128. It was known that FIX is a serine protease, meaning an enzyme that cleaves peptide bonds in proteins with serine at the active site. Effective clotting depends in part on the interaction between FIXa and FVIIIa. The amino acid sequence of FIXa was well known but that was not true of all aspects of its three-dimensional structure. However, the skilled structural biologist would have known that amino acids 330-338 of FIXa were in the form of an alpha helix, that the alpha helix was involved in the interaction with FVIIIa and that it therefore played a role in the activity of FIXa.

129. It was known that the 330-338 helix is evolutionarily conserved as between all species that have FIX and that the helix is solvent-facing, meaning that the side chains of most of the nine amino acids making up the helix extend into the aqueous solvent.

The mechanism of the binding of FIXa to FVIIIa

130. The FIXa and FVIIIa interface had been computationally modelled and the hypothesis was that the positively charged arginine at 338 of FIXa might interact with the negatively charged aspartate at 560 of a subunit of FVIIIa. The belief was that the 330-338 helix was likely to be an important site for binding to FVIIIa. This was consistent with all known sequences of the helix in different species being identical and by inference highly conserved.

131. A paper published in 1999 (Mathur & Bajaj) proposed that in haemophilia B patients, mutations in the helix led to substantially reduced affinity for FVIIIa, hampering the functioning of the coagulation cascade. The experts were agreed that the skilled structural biologist would have been aware of this paper which would if necessary have been consulted if the skilled structural biologist wished to be reminded of its details.

132. The same was true of a paper published in 2001 (Bajaj 2001). The authors of Bajaj 2001 found among other things that mutation of arginine to glycine or leucine at 330 in the FIX alpha helix causes severe haemophilia B.

The significance of the 330-338 helix being highly conserved and important in binding

133. The expert structural biologists were not agreed as to whether the acknowledged role of the 330-338 helix in the binding of FIXa to FVIIIa and the highly conserved nature of the helix would discourage the substitution of leucine for alanine at 338. Professor Camire pointed out that the change to alanine from the wild-type arginine had had the opposite effect.

134. I found the evidence of Professor Spiegel on this to be more persuasive, more consistent with the other evidence I have mentioned. I find that there would have been an expectation in the skilled team that any substitution in the highly conserved 330-338 helix was likely to make the binding of FIXa to FVIIIa problematic.

Reaction to the publication of the Padua variant

135. In 2023 Professor High gave the Jeremiah Metzger Lecture in New York, published in the Transactions of the American Clinical and Climatological Association. She discussed the hurdles encountered and obstacles overcome in the development of successful AAV vectors for two conditions, the first of which was haemophilia B. She explained the Manno problem and the various ways tried to overcome it. She continued:

> 'This convinced us that the path forward would require a more potent vector that could drive adequate levels of FIX expression at lower vector doses. The solution to our dilemma came from a naturally occurring Factor IX variant, FIX Padua, first described in a kindred in Italy where the proband presented with a deep venous thrombosis in his early 20s.'

136. Professor High went on to describe the studies done by her team with the Padua variant, the data obtained and where they led:

> 'These data led to a marked change in the field – all programs made the switch to a FIX Padua transgene, and those that did not fell by the wayside. The first of these has now achieved regulatory approval in both the United States and Europe and others are expected to follow.'

137. The title of a review article published in Molecular Therapy in 2018 (VandenDriesche and Chuah) indicates the authors' view of the impact made by the Padua variant, discussed in the article: 'Hyperactive Factor IX Padua: A Game-Changer for Hemophilia Gene Therapy'.

138. Even Professor Camire, Pfizer's expert, before his involvement in this litigation thought much the same. He was a co-author of a paper in Blood published in November 2018. The abstract at the start began this way:

> 'Factor IX (FIX) Padua (R338L) has been described as a game changer for hemophilia B (HB) gene therapy. The ~8 fold increased specific activity compared to wild-type FIX (FIX WT) in aPTT-based clotting assay has recently allowed for a lowering of adeno-associated virus (AAV) vector dose compared to earlier gene therapy trials using FIX WT, while still achieving sustained near-curative FIX activity levels.'

139. Other articles in evidence reflected the same view of how the discovery and publication of the Padua variant dramatically changed the field of gene therapy for haemophilia B.

The debate on inventive step

140. The dispute between the parties did not concern whether the skilled team would have understood from Stafford that anything was being said by the authors about the clotting

activity of R338L-FIX. That was not debated or resolved. The dispute was about what, if anything, the skilled team would have understood from the inclusion of leucine in the shortlist of preferred embodiments and, if something was understood, whether that made the invention claimed in the Patent obvious.

The law on inventive step

Pfizer's submissions on the law

141. Pfizer underlined the principle that the determination of whether there is an inventive step is a multifactorial assessment, referring to the statement of Kitchin J in *Generics (UK) Ltd v H. Lundbeck A/S* [2007] EWHC 1040 (Pat), quoted with approval by the House of Lords in *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, at [42]:

> 'The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success.'

142. Pfizer submitted that there was danger in focussing on the last of the examples given, expectation of success. My attention was drawn to the admonishment of Lewison LJ in *Medimmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234, at [181]:

> 'It cannot be said too often that the statutory question is: was *the invention* obvious at the priority date? It is not: was it obvious to try? In my judgment too much elaboration of the statutory question has been attached to it. The questions of the degree of expectation of success and the length of time thought to be needed to undertake a trial have taken on lives of their own. I think that this happened in our case. Insistence on the statutory question is not a novel thought. It is also an obvious one:…'
>
> …
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> 'One of the important points, to my mind, is that all these considerations interact with each other. In short, it all depends. MedImmune's argument proceeded on the basis that Novartis needed to establish (a) a fair prospect of success (b) within a reasonable time, as if these were two independent conditions that had to be satisfied. They are not successive hurdles to be jumped; they are no more than aspects of the statutory question: was the invention obvious? We should stick to the statutory question, which has to be applied in all sorts of circumstances and in all sorts of different fields of endeavour.'

143. I was also referred to other authorities in a similar vein. This is from the judgment of Aldous LJ in *Lilly ICOS Ltd v Pfizer* [2002] EWCA Civ 1, at [57]:

> 'What would have been obvious will depend on all the circumstances. As I said in *Norton Healthcare Ltd v Beecham Group Plc CA* (unreported)19th June 1997:
>
> > "When deciding whether a claimed invention is obvious, it is often necessary to decide whether a particular avenue of research leading to the invention was obvious. In such circumstances the extent of the different avenues of research and the perceived chances of any one of them providing a successful result can be relevant to the decision whether the invention claimed was obvious. Whether the subject matter was obvious may depend upon whether it was obvious to try in the circumstances of that particular case and in those circumstances it will be necessary to take into account the expectation of achieving a good result. But that does not mean that in every case the decision whether a claimed invention was obvious can be determined by deciding whether there was a reasonable expectation that a person might get a good result from trying a particular avenue of research. Each case depends upon the invention and the surrounding facts. No formula should be substituted for the words of the statute. In every case the Court has to weigh up the evidence and decide whether the invention was obvious. This is the statutory task."'

144. Relying on these authorities, Pfizer argued that 'reasonable expectation of success' is a distraction in the present case, where the prior art expressly teaches the reader to take the alleged inventive step. Motivation matters but motivation was plainly there. I quote from Pfizer's skeleton argument:

> 'In the present case, motivation to take the step does not rely on the level of expectation of success, but on the instruction to take that step.'

145. The Defendants' case, Pfizer continued, rests on the skilled person not being able to predict the results of a course of action and therefore not taking that course. But that is not the correct test for obviousness. If it were, a patent protection would be afforded to a party which simply follows the direction of the prior art and ascertains the result of doing so. Expectation of success is bound up with motivation. In the present case, the motivation to undertake the testing does not rely on the outcome, it arises from the fact that Stafford tells the reader to use leucine. The Defendants have fallen into the trap identified by Lewison LJ in that by focussing only on the level of expectation of success that the skilled person would have had in relation to the effective use of R338L-FIX in the gene therapy treatment of haemophilia B.

146. There were two further strands to Pfizer's argument on the law. One was that the patentee is only entitled to a monopoly which is commensurate with his technical contribution to the art. Pfizer relied on Jacob LJ's example of the 5¼-inch plate referred to by Laddie J in *Hoechst Celanese Corp v BP Chemicals Ltd* [1997] FSR 547, at 573-4.

147. That other was that it is important to follow the structured approach to an assessment of obviousness set out in *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588, at [23]. The key *Pozzoli* question is the fourth: does the substitution of leucine for alanine at position 338 constitute a step which would have been obvious to a person skilled in the art, or did it require any degree of invention? In this regard Pfizer emphasised a passage from

a recent judgment given by Meade J in *Modernatx Inc v Pfizer Ltd* [2024] EWHC 1695 (Pat), at [156]:

> 'Pfizer/BioNTech relied on the principle that there can be no invention in doing what is suggested in the prior art unless there is an established prejudice against that idea – the so-called "lion in the path" (see e.g. *Pozzoli v BDMO* [2007] EWCA Civ 588 at [24]-[29]). The principle is an important one, but it applies once a specific suggestion has been identified.'

148. No prejudice, no lion in the path has been identified by the Defendants. It follows that there cannot be invention in doing what is expressly suggested in the prior art.

The Defendants' submissions on the law

149. The Defendants agreed that the starting point was the principle that the assessment of an inventive step is a multi-factorial one. Of the relevant factors, attention must be paid here to motive. The importance of motive to inventive step has been recognized many times. The Defendants cited examples, including this from Laddie J who reviewed the authorities on motive up to that point in *Hoechst Celanese Corp v BP Chemicals Ltd* (cited above) at 572:

> 'All of these passages are consistent with the Object/Solution approach to obviousness adopted by the Technical Board of Appeal of the EPO. Even if the step from the prior art is a small one, to prove obviousness it is necessary to demonstrate that there is some reason for taking it.'

150. This went to the Defendants argument, developed below, that there was no motive to try R338L-FIX.

151. The Defendants' second point on the law was that that it is possible for the skilled person to fail to recognise the potential significance of a cited prior art when it is hypothetically read with care at the priority date. For instance, it may be treated as a 'mere paper proposal' and not given any credence on that ground, see the judgment of Floyd LJ in *E. Mishan & Sons Inc v Hozelock Ltd* [2020] EWCA Civ 871, at [91]-[94]. (This was a dissenting judgment but there was no disagreement on that principle of law).

152. The Defendants' third point was that the reaction of others in the field to the Padua work which underlies the Patent is a strong indication of an inventive step.

153. Finally, the Defendants submitted that secondary evidence can be important, citing the observations of Jacob LJ in *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, at [76]-[85].

Discussion

154. The parties' submissions raise issues concerning whether there may be focus on one factor potentially relevant to the assessment of obviousness permitted in law – specifically expectation of success, the relationship between (a) whether the claimed invention was obvious to try with a reasonable expectation of success, (b) motivation and (c) technical prejudice and the correct application in law of those factors. Also

raised was the weight to be given to secondary evidence. Finally, there is an issue to be considered with regard to the correct approach in law to the content of the specification of a patent or patent application.

155. I begin with Lord Hodge's non-exhaustive list of factors which may be relevant to the assessment of obviousness in *Actavis Group PTC EHF v ICOS Group* [2019] UKSC 15:

> '[65] First, it is relevant to consider whether at the priority date something was "obvious to try", in other words whether it was obvious to undertake a specific piece of research which had a reasonable or fair prospect of success: *Conor v Angiotech* (above) at [42] per Lord Hoffmann; *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234; [2013] R.P.C. 27 , at [90] and [91] per Kitchin L.J. In many cases the consideration that there is a likelihood of success which is sufficient to warrant an actual trial is an important pointer to obviousness. But as Kitchin L.J. said in *Novartis AG v Generics (UK) Ltd* [2012] EWCA Civ 1623, at [55], there is no requirement that it is manifest that a test ought to work; that would impose a straightjacket which would preclude a finding of obviousness in a case where the results of an entirely routine test are unpredictable. As Birss J. observed in this case (at [276]), some experiments which are undertaken without any particular expectation as to result are obvious. The relevance of the "obvious to try" consideration and its weight when balanced against other relevant considerations depend on the particular facts of the case.
>
> [66] Secondly, it follows that the routine nature of the research and any established practice of following such research through to a particular point may be a relevant consideration which is weighed against the consideration that the claimed process or product was not obvious to try at the outset of a research programme. Again, it is only one of several factors to be weighed in the assessment and it has no primacy and certainly no paramount status as a consideration.
>
> [67] Thirdly, the burden and cost of the research programme is relevant. But the weight to be attached to this factor will vary depending on the particular circumstances. This appeal concerns a pharmaceutical patent claiming as an invention a dosage regime. The cost and effort involved in bringing a drug to market through pre-clinical and clinical trials are notorious. Mr Waugh referred to the extrajudicial writing of Sir Hugh Laddie, "Patents - what's invention got to do with it?" (in *Intellectual property in the new millennium: essays in honour of William R Cornish* (2004), p. 91 et seq), in which he stated, at p. 92:
>
> > "In this field it is apparent that, without patents, few new products would be marketed. The expense in producing a new pharmaceutical is in the research and development stage. Normally, once it has been discovered and given regulatory approval, the manufacture of a new pharmaceutical will be comparatively cheap and its replication by competitors easy. Without the protection of patents, there will be no ability to recoup the cost of the research and development, let alone fund such activities in the future. No private company is going to enter this business unless it can see a reasonable prospect of obtaining a return on investment."

The need to facilitate expensive pharmaceutical research is an important policy consideration for legislators and others involved in intellectual property law. It was a factor behind the creation of the Swiss-form claim and the EPC 2000 claim as well as the supplementary protection certificate regime under Regulation (EC) 469/2009, which is available after market authorisation to give the patent owner the protection of the patent for up to 15 years, and the data exclusivity regime which Directive 2001/83/EC (art. 10) and Regulation (EC) 726/2004 (art. 14), which may confer ten years of exclusive marketing protection against competition from generic manufacturers. But the effort involved in research is only one of several factors which may be relevant to the answer to the statutory question of obviousness.

[68] Fourthly, the necessity for and the nature of the value judgments which the skilled team would have in the course of a testing programme are relevant considerations as both the trial judge and the Court of Appeal held.

[69] Fifthly, the existence of alternative or multiple paths of research will often be an indicator that the invention contained in the claim or claims was not obvious. If the notional skilled person is faced with only one avenue of research, a "one way street", it is more likely that the result of his or her research is obvious than if he or she were faced with a multiplicity of different avenues. But it is necessary to bear in mind the possibility that more than one avenue of research may be obvious. In *Brugger v Medic-Aid Ltd (No. 2)* [1996] R.P.C. 635, at p.661, Laddie J. stated:

> "[I]f a particular route is an obvious one to take or try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well."

I agree. As a result, the need to make value judgments on how to proceed in the course of a research programme is not necessarily a pointer against obviousness.

[70] Sixthly, the motive of the skilled person is a relevant consideration. The notional skilled person is not assumed to undertake technical trials for the sake of doing so but rather because he or she has some end in mind. It is not sufficient that a skilled person could undertake a particular trial; one may wish to ask whether in the circumstances he or she would be motivated to do so. The absence of a motive to take the allegedly inventive step makes an argument of obviousness more difficult. In *Agrevo/Triazoles* (above), para 2.4.2, the Technical Board of Appeal of the EPO, having referred to the principle that the extent of the patent monopoly should correspond to and be justified by the technical contribution to the art (see [54] above) made the point in these terms:

> "Moreover, in the Board's judgment, it follows from this same legal principle that the answer to the question what a skilled person would have done in the light of the state of the art depends in large measure on the technical result he had set out to achieve. In other words, the notional 'person skilled in the art' is not to be assumed to seek to perform a particular act without some concrete technical reason: he must, rather, be assumed to act not out of idle curiosity but with some specific technical purpose in mind."

This forms the basis of the EPO's problem-and-solution approach to obviousness which I have quoted in [61] above.

[71] Seventhly, the fact that the results of research which the inventor actually carried out are unexpected or surprising is a relevant consideration as it may point to an inventive step, at least in so far as it suggests that a test was not obvious to try or otherwise the absence of a known target of the research which would make it less likely that the skilled person would conduct a test.

[72] Eighthly, the courts have repeatedly emphasised that one must not use hindsight, which includes knowledge of the invention, in addressing the statutory question of obviousness. That is expressly stated in the fourth of the *Windsurfing / Pozzoli* questions. Where the pattern of the research programme which the notional skilled person would undertake can clearly be foreseen, it may be legitimate to take a step by step analysis. In *Gedeon Richter Plc v Bayer Schering Pharma AG* [2011] EWHC 583 (Pat); [2011] Bus LR D153, Floyd J. stated (at [114]):

> "I think that the guiding principle must be that one has to look at each putative step which the skilled person is required to take and decide whether it was obvious. Even then one has to step back and ask an overall question as to whether the step by step analysis, performed after the event, may not in fact prove to be unrealistic or driven by hindsight."

The obvious danger of a step by step analysis is that the combination of steps by which the inventor arrived at his invention is ascertained by hindsight knowledge of a successful invention. Lord Diplock warned against this in *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] R.P.C. 346, at p.362, a warning which judges have reiterated in later cases. I am not persuaded by Mr Speck's suggestion that *Technograph* is concerned only with a case in which a step by step approach was constructed by counsel on cross-examination in the absence of evidence of routine steps of research. The case contains a wider warning against the use of hindsight and has been interpreted as doing so. I agree with Birss J.'s analysis in *Hospira UK Ltd v Genentech Inc* [2014] EWHC 3857 (Pat), at [240], where he stated:

> "The particular point made in *Technograph* was that it was wrong to find an invention was obvious if it was only arrived at after a series of steps which involve the cumulative application of hindsight. In some circumstances success at each step in a chain is a necessary predicate for the next one and it is only the hindsight knowledge of the invention as the target which could motivate a skilled person to take each step without knowledge about the next one. In a situation like that, *Technograph* is important."

But the Technograph warning has no bearing in a case in which the steps which the notional skilled person would take can readily be ascertained without the taint of hindsight.

[73] Ninthly, it is necessary to consider whether a feature of a claimed invention is an added benefit in a context in which the claimed innovation is

> obvious for another purpose. In *Hallen & Co v Brabantia (UK) Ltd* [1991] R.P.C. 195 the Court of Appeal was concerned with an alleged selection patent for a self-pulling corkscrew which had a helix coated with polytetrafluoroethylene (PTFE) which was a known friction-reducing material. At the priority date PTFE had been used for several years to coat the helix of a twin-lever type corkscrew to aid its penetration into the cork. The PTFE-coated helix had this effect also on the self-pulling corkscrew, a fact which was obvious at the priority date. The PTFE coat when applied to a self-pulling corkscrew also had a non-obvious benefit of making a striking improvement in the extraction of the cork. The trial judge, Aldous J., held that the patent was invalid on the ground of obviousness because it was obvious to select the features of the claim for the first purpose notwithstanding that it was not obvious for the other purpose: [1989] R.P.C. 307, at pp.326-327. The Court of Appeal agreed with the judge, holding (pp. 215-216) that it was self-evident that a PTFE coating would improve the penetration by any corkscrew and that the "golden bonus" or added benefit of the dramatic improvement in extraction of the cork would not found a valid patent as the claimed innovation was obvious for another purpose. Mr Waugh does not challenge this principle but submits that the 181 patent does not involve such an added benefit.'

156. With regard to Lord Hodge's first factor and the passage from *Medimmune* relied on by Pfizer, I respectfully agree with what was said by Lewison LJ in *Medimmune* at [181]. Resolving the statutory question of obviousness potentially invites consideration of many factors, notably those identified by Lord Hodge, and all that are relevant must be borne in mind without undue focus on one or more of them. But as Lewison LJ said, it all depends. On certain facts obviousness could turn on just one factor. In such an instance inevitably the evidence and argument will largely or even wholly concern that factor.

157. In the case of whether the claimed invention was obvious to try with a reasonable expectation of success at the priority date, obviousness may even turn simply on whether there was a reasonable expectation of success since, on certain facts, such an expectation would have made the course of action obvious to try. In that event, the focus of evidence and argument will be directed largely or entirely to whether there was a reasonable expectation of success.

158. There is no need for me to delve into the meaning of 'success' in any particular context. The parties evinced no doubt about what it means in the present case and it is not complicated.

159. Often, the relevant question in the assessment of obviousness is not whether the skilled person at the priority date would have considered the product or process of the claimed invention to be obvious. That is because commonly it cannot be assumed that the claimed invention has entered the mind of the skilled person to begin with. But 'reasonable expectation of success' and 'technical prejudice' are factors which share the inbuilt assumption that the alleged invention has become known to the skilled person as a theoretical way forward. Jacob LJ refers to this characteristic in relation to technical prejudice in *Pozzoli* (cited above) at [25], calling it an 'intellectual oddity'.

160. Technical prejudice and a reasonable expectation of success are largely two sides of the same coin although one could be seen as a subset of the other.

161. As a general principle, if, having read an item of cited prior art, the skilled person would have contemplated the claimed invention, the invention is obvious. The converse also applies. Whether this would have been likely will depend on all or any of the factors identified by Lord Hodge and possibly others. 'Contemplation' in this context means holding the view that it would be worthwhile taking a course of action that constitutes performing the invention.

162. Therefore if the invention would have entered the mind of the skilled person upon reading the prior art but he or she would have dismissed it as an idea not worth taking forward, the invention may not be obvious. It matters why the skilled person would have arrived at the view that going forward with the idea was not worthwhile, if that would have been the case. Where the reason would have been one of technical feasibility – a belief on the part of the skilled person that for technical reasons there was no reasonable expectation of success – there will be a sound basis for an inventive step. On the other hand, reasons solely connected with commercial viability will not found an inventive step, see *Dyson Appliances Ltd v Hoover Ltd* [2001] EWCA Civ 1440, at [56] and [86]-[87] and Lord Hodge's ninth factor.

163. Lord Hodge endorsed the proposition that where the argument on inventive step concerns whether the skilled person would have carried out certain experiments signalled by the cited prior art, it may have been obvious to perform those experiments even though there was no particular expectation as to the result.

164. In other words, no reasonable expectation of success covers the possibility that there is no reasonable expectation one way or the other. It is to be distinguished from a reasonable expectation of no success. Two points arise from this.

165. First, if the skilled person would not have carried out the experiments because on technical grounds he or she would have had a reasonable expectation of no success, a claimed invention based on what would be learned from carrying out the experiments and achieving a successful result will constitute an inventive step. Where those are the facts, motive, Lord Hodge's sixth factor, plays no real role because, self-evidently, if there is an expectation of no success there is no motive to conduct the experiments. Conversely if there is an expectation of success, there must be a motive. (Motive may possibly play an anterior role in assessing whether the claimed invention would have been obvious to try, that is another matter.)

166. Secondly and on the other hand, where there is no expectation one way or the other as to the result of taking the course signalled by the prior art, motive may be important.

167. In this regard I quote Laddie J's observation in *Hoechst Celanese Corp. v BP Chemicals Ltd* [1997] FSR 547, at 572:

> 'Even if the step from the prior art is a small one, to prove obviousness it is necessary to demonstrate that there is some reason for taking it.'

168. In *Hallen Co v Brabantia (UK) Ltd* [1991] RPC 195, Slade LJ, delivering the judgment of the court, said (at 212, relying on a passage from the judgment of Lord Reid in *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346, at 356):

> '… for the purpose of testing obviousness, one cannot assume that the skilled man simply makes technical trials for the sake of so doing.'

169. Connected with a reasonable expectation of success is Floyd LJ's observation about a 'mere paper proposal'. Such a proposal may on the facts give rise to the belief on the part of the skilled person that it offers a reasonable expectation of no success and consequently no motive for pursuing the proposal.

170. On a separate matter, I accept the Defendants' submission that it is possible that a skilled person who is taken to have read and understood the cited prior art would have failed to recognise the significance of its content to the solution of the problem in hand. Such a conclusion could be reached based on the CGK established on the facts.

171. Turning to the law on secondary evidence, it can offer valuable help in the assessment of inventive step although each case will turn very much on its own facts. The facts must be scrutinised to decide whether they genuinely point to an inventive step or whether what was done in the period leading up to the priority date was probably driven by matters which have nothing to do with the obviousness of the patent in suit. In *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819 Jacob LJ, with whom Sullivan and Waller LJJ agreed, looked at the value of secondary evidence:

> '[76] In answering [questions arising on obviousness] it is also important to consider the secondary evidence. I shall go to the details of this in due course, but before I do so I should say something about secondary evidence generally.
>
> [77] It generally only comes into play when one is considering the question "if it was obvious, why was it not done before?" That question itself can have many answers showing it was nothing to do with the invention, for instance that the prior art said to make the invention obvious was only published shortly before the date of the patent, or that the practical implementation of the patent required other technical developments. But once all other reasons have been discounted and the problem is shown to have been long-standing and solved by the invention, secondary evidence can and often does, play an important role. If a useful development was, in hindsight, seemingly obvious for years and the apparently straightforward technical step from the prior art simply was not taken, then there is likely to have been an invention.
>
> [78] As usual Lord Reid had something perspicacious to say on the topic. In *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] R.P.C. 346 he said at 353:
>
> > "Being wise after the event counsel for the appellants pointed out that this was really an easy problem to solve … "
> >
> > "The whole history of this matter shows the falsity of that analysis. Dozens of inventors, and no doubt others as well, had tried and failed to find a satisfactory solution."'

172. I note that in *Actavis v ICOS* Lord Hodge did not suggest any hierarchy among his factors or between the primary and secondary evidence on which each may depend.

173. The manner in which the skilled person is deemed in law to approach the content of a patent or a patent specification in particular circumstances is more easily discussed in context below.

Inventive step in the present case

The Secondary Evidence

174. I will begin with the secondary evidence because I find it compelling.

175. It had been known since the publication of the Chang paper in May 1998 that replacing the arginine with alanine at 338 resulted in a variant FIX with around 3 times the activity of wild-type FIX. In the period of over 10 years between then and the priority date of the patent in suit, none of many teams engaged in looking for a means to provide effective gene therapy for haemophilia B tried a variant with leucine at 338. This included the most prominent team in the field, that led by Professor High, of which Professor Stafford himself became a member. Neither he nor any of his colleagues in the group that carried out the work in Chang, the work underlying Stafford, apparently saw any potential value in making R338L-FIX.

176. It was common ground that making and testing R338L-FIX for clotting activity would have been the routine work of two weeks or so. Yet it was not done by anyone.

177. The evidence left unresolved whether it was routine to try replacing alanine with each of the 17 other candidate amino acids in turn (excluding arginine and proline) to see whether any of the variants created had higher than wild-type clotting activity. However, there is no reason to believe that any team tried varying R338A-FIX by replacing the alanine at 338 with any other amino acid or that they considered doing so.

178. Instead, the teams who worked on other FIX variants all apparently believed that the route to success was to keep the alanine at 338 and instead tried changing amino acids well outside the 330-338 helix. Some teams thought that sticking with R338A but improving the vector was the way forward and some teams tried both.

179. Pfizer offered no plausible reason why there was such a failure on the part of every team in the field to try R338L-FIX in that 10-year period.

180. Pfizer did suggest explanations. One was that Professor Stafford and Dr Chang, the inventors of the Stafford prior art, knew that substituting leucine for alanine at position 338 was an obvious way forward. This was why that possibility is mentioned in the specification of Stafford and features in the claims. But they told no one else about it.

181. I find this unconvincing. Scientists talk to each other, not just at the water cooler but also at scientific gatherings of all kinds. Chang was an important paper, an acknowledged part of the CGK, as was Schuettrumpf. It is hard for Pfizer to argue that Professor Stafford and Dr Chang treated the idea of R338L-FIX as a valuable card to be kept close to their chests because on Pfizer's case the substitution of the biochemically similar leucine was an unremarkable idea. At the very least, Professor Stafford would surely have discussed this with his co-authors of the Chang paper: Drs Jin, Lollar, Bode, Brandstetter, Hamaguchi and Straight and/or the co-authors of the

Schuettrumpf Paper: Drs Schuettrumpf, Herzog, Schlachterman, Kuafhold and Arruda. None of them pursued the idea.

182. Pfizer next suggested that any of the researchers in the field *might* have been taking the idea forward, but it takes time to do this kind of work so it may have been in train without publication during the relevant 10 years. That is not consistent with the undisputed evidence that the work would have been routine and taken a few weeks to provide a result.

183. Quite aside from no one else pursuing the idea of R338L-FIX, neither Professor Stafford nor Dr Chang pursued it even though they continued to conduct research into gene therapy for haemophilia B. In particular, Professor Stafford took part in the work which led to the Schuettrumpf Paper. In his written evidence Professor Camire said that this was because of a reluctance on Dr Schuettrumpf's part to duplicate work done by Professor High's group and/or because Dr Arruda, one of the co-authors of Schuettrumpf, knew of Dr Simioni's work on the Padua variant. These were presented as hard reasons of which Professor Camire was aware. In cross-examination he accepted that they were just speculation. They were not relied on by Pfizer in closing, I can see why, and I place no reliance on them.

184. In fact, Pfizer's experts, who must have had a long time to think about it, were each asked in cross-examination for a plausible reason why Professor Stafford did not try R338L-FIX. Neither could offer any reason.

185. In closing Pfizer was not inhibited by this and came up with alternative possibilities.

186. The first was that nothing was done by Professor Stafford with R338L because of the near moratorium on gene therapy research after the tragedy of Jesse Gelsinger, which followed a year after the publication of Chang. Certainly, gene therapy research became more difficult for a period from 1999, at least in the United States, but it does not explain why Dr Chang and her co-authors, including Professor Stafford, said nothing about a substitution at position 338 of FIX in the Chang Paper if they thought that leucine, valine or anything else would work. Also, it is clear that gene therapy research did not come to a halt as the work of several teams shows.

187. Pfizer's second suggestion was that Professor Stafford lacked financial resources until he started to collaborate with Professor High's group. Yet the evidence was that replacing alanine with leucine was a simple and relatively quick procedure and I infer not unduly expensive. Also, by 2005 Professor Stafford was collaborating with the High team. Pfizer's idea that Professor Stafford was constrained financially came from Professor Camire's second report. It is curious that he did not mention it in cross-examination when asked for a reason why Professor Stafford did not try R338L. He may have forgotten, but if so, his forgetting suggests that it was a reason not at all firmly held in his mind, raising the suspicion that this was just more unreliable speculation in his written evidence.

188. Thirdly, Pfizer said that it was easy to understand why the work in the Schuettrumpf Paper was done instead of trying R338L-FIX because the authors wanted to see whether the increased coagulation effect seen in Chang would translate into expression in mice. This was in part to do with issues of muscle delivery. This suggestion in closing was

not supported by any reference to the evidence and I was not otherwise directed to any evidential support for it.

189. Fourthly, Pfizer pointed out that it was not possible to know what Professor Stafford was interested in at the time. He was a busy man involved in many projects most of which did not concern haemophilia B. A huge amount of his work was devoted to his special interest in developing a new haemophilia B mouse for experimentation. This, too, I find unconvincing. It does not explain why Professor Stafford and Dr Chang ignored the simple project of trying R338L-FIX. There was strong evidence that a breakthrough in gene therapy for haemophilia B was keenly sought and it must be assumed that high credit and plaudits were expected to go to anyone in the field who cracked the problem. Professor Stafford may have been busy, but I do not believe that he would have disdained solving the problem by means of R338L-FIX had he thought of it.

190. Obviousness in this case turns mainly on whether there was a reasonable expectation of success but Lord Hodge's seventh factor, whether the results of research which the inventor carried out were unexpected or surprising, also plays a relevant part. In this regard I think it is telling that when R338L-FIX was discovered by serendipity in the form of the naturally-occurring Padua variant, the leading teams in the field did not respond with an unimpressed shrug. On the contrary, it clearly came as a considerable surprise and was regarded as a breakthrough, a game changer in the long pursuit of an effective means to treat haemophilia B. Even Professor Camire thought so at the time.

191. Pfizer finally argued that what came as a surprise in the real world, even to someone as distinguished as Professor High, would not necessarily have been a surprise to the notional skilled team.

192. It is true that in principle the skilled person, a walking library of CGK but a dullard in imagination, could think of something which real individuals working in the field at the priority date would not consider. But it would require unusual facts. For instance, one could hypothesise there having been a technical fixation held by all the real teams in the field derived from knowledge of which the hypothetical skilled person would have been unaware. Nothing of that nature or anything else to support Pfizer's final suggestion was shown in the present case.

193. In summary, the facts constituting the secondary evidence in the present case were such that they strongly point towards an inventive step.

The Primary Evidence

194. The primary evidence explained the secondary evidence. I will take this in two stages.

195. First, the primary evidence on the question whether, before reading Stafford, the skilled team would have considered it worthwhile making and testing FIX with a substitution for alanine at 338, leucine or any other potential substitution, having the Chang and Schuettrumpf Papers in mind.

196. Secondly, whether reading Stafford would have made a difference and prompted the skilled team into the belief that replacing alanine with leucine was worth trying with a

reasonable expectation of success. This second stage was the principal focus of dispute between the parties.

Before Stafford

197. As to the first, the evidence was that position 338 is in a highly conserved region of FIX, the same in all species with FIX. It is a region which takes the form of an alpha-helix, where the arginine was thought to play an important function in the binding of FIXa to FVIIIa. It seems to me that the skilled team would not, before the publication of Chang, have expected that any change in the conserved 330-338 region would result in improved activity. The team would have expected the opposite.

198. Chang and Schuettrumpf showed that R338A-FIX had increased activity over wild-type FIX. Chang proposed that the change to alanine does not have an allosteric effect – it does not cause a structural change which affects the binding of FIXa to FVIIIa. Rather, the 338 residue is part of a site which binds both FIX and heparin, an anticoagulant, and alanine at 338 thereby improves coagulant activity.

199. The discovery that R338A-FIX had increased activity came as a considerable surprise. But it did not change the fact that the 330-338 helix is highly conserved and important to the binding to FVIII. This is fully consistent with the apparent views of the teams in the field after the publication of Chang: it made sense to them, and would have made sense to the skilled team, to treat R338A-FIX as an extraordinary one-off which did not change their aversion to making changes in that region of the FIX gene. The skilled team would have believed that the substitution of alanine was an unexpected bonus to be built upon, not discarded.

The impact of reading Stafford

200. The hypothesis is that the skilled team would have read Stafford with care. Most of its content would have been familiar since the skilled team already had the content of the Chang and Schuettrumpf papers in mind. But there is the preferred shortlist of alanine, leucine and valine.

201. Professor Camire's position was that the skilled team would have been encouraged by Stafford to replace the alanine at 338 to make R338L-FIX. He said:

> '… Stafford suggests that there may be a number of different possible substitutions for the arginine at 338, and states that the three preferred amino acids for substitution at this position are alanine, leucine and valine. The Skilled Structural Biochemist would understand that alanine had been chosen because it had been shown in the experiments discussed above to result in an increase in activity of the FIX protein. The Skilled Structural Biochemist would consider the suggestion that valine and leucine as preferred alternative substitutions made sense given that these amino acids are similar to alanine (i.e. they are all small amino acids with hydrophobic aliphatic side chains). Of the two, the skilled person would appreciate that leucine is more similar to alanine in its ability to form α-helices than valine.'

202. As noted above, Professor Camire's reliance on similarity of size and hydrophobicity did not stand up to scrutiny in cross-examination and was rejected by Professor Spiegel.

203. It was Professor Camire who introduced the Grantham matrix into the evidence, one of the matrices which ranks amino acids by similarity. He backed away from reliance on it or any other matrix in cross-examination. Grantham pulls together the properties of the 20 amino acids and sets out a table in which the overall differences between them are given D numbers, D for distance so that a high number for a pair of amino acids means that they are dissimilar. The range 0-60 indicates that the substitution would be conservative, 60-100 non-conservative and more than 100 is radical. For the substitution of most relevance in this case, leucine in place of alanine, Grantham gives a D value of 96, just below radical. In cross-examination Professor Camire had to concede that the skilled structural biologist would not have considered such a substitution to be conservative.

204. Professor Camire also conceded that the same non-conservative, almost radical, characterisation for that substitution would have been understood if the skilled structural biologist had consulted BLOSUM or PAM.

205. The evidence showed that, even assuming the skilled team considered replacing alanine at 338, there were positive grounds to for the skilled team to reject leucine as the replacement. Leucine is more hydrophobic than alanine which may have led to an instability in the secondary structure and/or aggregation.

206. Professor Spiegel's evidence was that the skilled structural biologist would not expect the substitution of either leucine or valine at 338 to provide increased clotting activity over wild-type FIX. Even if *in vitro* tests suggested that either did, the skilled structural biologist would have recommended to the skilled gene therapist that neither should be taken for to tests in human patients and therefore it would not have been worthwhile pursuing pre-clinical tests. In an unchallenged passage of his second report he said:

> 'In my view, a strongly hydrophobic amino acid (such as valine or leucine) would not have been taken forward into *in vivo* studies by the Skilled Structural Biologist even if an increased clotting activity were observed *in vitro*. The Skilled Structural Biologist would still be concerned about having a hydrophobic amino acid at the 338 position, which as I have explained would be energetically disfavoured and lead to a risk of instability, misfolding, aggregation, and hence increased immunogenicity of FIX when it is in a natural environment (i.e. in animals and humans). These concerns would not have been put aside, even if elevated clotting activity had been demonstrated in a study from mutants expressed in (for example) HEK293 cells. As such, the Skilled Structural Biologist would be more likely to recommend taking forward into pre-clinical studies a gain-of-function mutant that is not strongly hydrophobic at this position.'

207. Professor Spiegel had no personal experience of *in vivo* trials but his evidence was about the recommendations that the skilled structural biologist would have passed on to the skilled gene therapist about any postulated trial. I accept that evidence.

208. Professor Spiegel's overall view on Stafford was that the skilled team could and would have gleaned nothing from the alternatives to alanine at 338 identified in the preferred shortlists:

> '…there is no unifying thread in Stafford's lists of amino acids and without any data that any of those amino acids (apart from alanine) show improved activity of FIX, the Skilled Structural Biologist would find these lists (both the list of 10 amino acids and the "sublist" of alanine, valine and leucine) to be meaningless.'

209. I find Professor Spiegel's evidence to be more persuasive on this subject than that of Professor Camire.

210. In its closing argument Pfizer advanced a theory which did not come from either of their experts:

> 'Stafford found unexpectedly that substituting the highly hydrophilic arginine with the hydrophobic alanine provided at position 338 increased clotting activity. It is entirely rational and logical then to suggest increasing the hydrophobicity still further (continuing down the same path) using side chains as similar to alanine as is possible. That led Stafford to leucine and valine.'

211. I think that if this theory was well founded in science at least one of the experts in the case would have been prepared to endorse it. None suggested it.

212. In my judgment both Professors Nathwani and Professor Spiegel were right about how the skilled team would have perceived the shortlist of alanine, leucine and valine as presented in Stafford. These two experts thought that the skilled team would have seen the shortlist as a scientifically meaningless bit of patent drafting.

213. The skilled team would have been wise in the ways of patent drafting. This was not just the evidence of Professors Nathwani and Spiegel, it is consistent with the principle of law that the skilled person is deemed to read a patent specification with some knowledge of patent law, see *Virgin Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, at [10]-[15].

214. A task of a patent attorney when drafting a patent is to obtain the maximum protection which the patent examiner might accept. The patent attorney who drafted Stafford apparently thought that it was worth having a go at broadening protection from R338A-FIX to other possible substitutions at 338. A reasonable way to do this would have been to claim on top of R338A-FIX, FIXs with a range of alternative amino acids at 338 each of which has similarities to alanine that a biochemistry undergraduate might identify, such those with non-polar, aliphatic R groups which the authors of Lehninger grouped together.

215. Professor Nathwani put it this way:

> 'Yes, I mean in patents you tend to put a bag of shopping list down, and this is what I think was done by the patent attorneys.'

216. In discussing how amino acids may be classified by their R group, the authors of Lehninger say:

> 'The side chains of alanine, valine, leucine and isoleucine tend to cluster together within proteins, stabilizing protein structure by means of hydrophobic interactions.'

217. I do not imagine that Stafford was drafted with a copy of Lehninger next to the patent attorney's computer, but the sentence quoted and Table 3.1 of that textbook suggest that if one wished to group alanine with other amino acids for patent drafting purposes, grouping it with valine and leucine would be one rational approach, consistent with the well-established knowledge of the biochemical properties of the amino acids. Probably one of alternative rational approaches.

218. I have no idea how patent examiners around the world actually reacted to the shortlist or whether any patents were granted pursuant to the PCT application.

219. In my view, the skilled team would have attached no scientific significance to the notion of substituting leucine at position 338. There were no data at all in relation to R338L-FIX in Stafford and as Professor Nathwani said, scientists are driven by data.

220. The inventive concept of the Patent is that DNA encoding the R338L-FIX (here ignoring the alanine at 148) is suitable for use in a gene therapy treatment of haemophilia B. Stafford does not say that it would be suitable and the skilled team's understanding from Stafford regarding the clotting activity of R338L-FIX was not resolved. However the main point is that I do not think that the skilled team would have believed that anything scientifically useful was being said about leucine in Stafford.

221. If there were any doubt about what the skilled team would have thought, I return to the fact that neither Professor Stafford nor Dr Chang attached any significance to the mention of leucine as a possible substitute in their own patent application, otherwise they would have taken the apparently simple step of trying it out. So would anyone else in the field to whom they mentioned the idea.

222. In my view, the significance of R338L-FIX only dawned on the gene therapy world with the discovery of the Padua variant. It was then hailed as a game changer.

Further points

223. There remain some points of detail raised by Pfizer in their closing argument.

224. Pfizer pointed to Professor Nathwani's evidence in cross-examination in which he was referred to the paper recording the work of a team led by Dr Lin published in Blood two months after the priority date. Professor Nathwani agreed that this team were looking for improvements in the use of R338A-FIX and that this was a reasonable approach. But it is notable that their approach was to *keep* alanine at 338, while exploring the effect of substituting alanine for other amino acids at different positions. This is entirely consistent with the skilled team believing that it there was value in experimenting in the many different possible ways of trying to improve the productivity of R338A-FIX, though never abandoning the surprise benefit of having alanine at 338.

225. Professor Nathwani also said that a reasonable response to the Schuettrumpf paper of 2005 would have been to consider whether there could be improvements on that work with R338A-FIX, but again he was not asked whether and certainly did not say that such consideration would have included replacing alanine at 338. He also said that a reasonable hypothesis would have been that substituting one amino acid for another with similar physicochemical properties would not change the phenotype of the protein.

That very general proposition does not, I think, support the much more specific idea that substituting leucine for arginine at 338 would improve the clotting activity.

226. Professor Nathwani was cross-examined on his evidence in writing that he did not have expertise in the structure and function of amino acids and would not be able to say with confidence whether alanine has similarities with leucine and valine and if so, what they are. It was put to him that one would have to test to find out the effect of substituting another amino acid for alanine. He answered that he would love to see the data, which was emphasised by Pfizer in closing. To my mind this underlines his point that without any data being provided in Stafford the skilled team would have treated the references to leucine or valine at 338 as having no scientific support.

Conclusion on inventive step

227. This is an instance in which obviousness turns very largely on whether the claimed invention would have been perceived by the skilled team at the priority date as being obvious to try with a reasonable expectation of success. Within that, the important question is whether there would have been a reasonable expectation of success.

228. Despite the arguments advanced on motive, I do not think that motive is the real issue here. Had there been a reasonable expectation of success there would have been sufficient motive. A reasonable expectation of no success meant that there was no motive.

229. The notion of R338L-FIX was clearly and unambiguously stated in Stafford. The skilled team would have known that it was possible, quite easy, to make recombinant DNA encoding R338L-FIX and to test the FIX expressed by the gene for clotting activity . It was obvious to try if there was a reasonable expectation of success, but only if there was that reasonable expectation. I note Lord Hoffmann's observation in *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, at [28]:

> 'It is hard to see how the notion that something is worth trying or might have some effect can be described as an invention in respect of which anyone would be entitled to a monopoly. It is therefore perhaps not surprising that the test for obviousness which Pumfrey J. devised for such an "invention" was whether it was obvious to try it without any expectation of success. This oxymoronic concept has, so far as I know, no precedent in the law of patents.'

230. It was not obvious to try using a gene encoding R338L-FIX for gene therapy in the treatment of haemophilia B with any reasonable expectation of success. In fact there would have been a reasonable expectation of no success. Success here would have meant that the clotting activity of R338L-FIX was at a level sufficient to make DNA encoding it suitable for the treatment of haemophilia B.

231. The identification in Stafford of R338-FIXL as a preferred embodiment would have been perceived as a patent attorney's work product. It would not have made any impression on the skilled team.

232. It follows that the inventions of the claims of the Patent constitute an inventive step over Stafford.

Insufficiency

233. Due to the way the Defendants' case was put in closing, Pfizer did not pursue its case on insufficiency.

Final Conclusion

234. The Patent is valid and in consequence it is infringed.