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Case No: HP-2024-000015
HP-2024-000036

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT

The Rolls Building
7 Rolls Buildings
Fetter Lane
London EC4A 1NL
8 October 2025

Before:
MR. JUSTICE MEADE

Between:

HP-2024-000015

(1) FORMYCON AG **(2) KLINGE BIOPHARMA GMBH**	**Claimants**
- and –	
(1) REGENERON PHARMACEUTICALS, INC. **(2) BAYER HEALTHCARE LLC**	**Defendants and Part 20 Claimants**

And Between:

HP-2024-000036

SAMSUNG BIOEPIS (UK) LIMITED	**Claimant**
- and -	
(1) REGENERON PHARMACEUTICALS, INC. **(2) BAYER HEALTHCARE LLC**	**Defendants and Part 20 Claimants**

- -

Hearing dates: 9, 16-20, 23-25 and 30 June and 1 July 2025
Post-trial written submissions 7, 10, 15, 18, and 23 July

APPROVED JUDGMENT

MS CHARLOTTE MAY KC, MR TOM ALKIN AND MR JEREMY HEALD instructed by **Pinsent Masons LLP** for **Formycon/Klinge** and by **Powell Gilbert LLP** for **Samsung Bioepis**

MR ADRIAN SPECK KC, MS ISABEL JAMAL, MR WILLIAM DUNCAN AND MS ALICE HART instructed by **A&O SHEARMAN LLP** for **Regeneron and Bayer**

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Mr Justice Meade:

INTRODUCTION

1. This is the trial of two actions, HP-2024-000015 and HP-2024-000036, concerning European Patent (UK) No. 2 364 691 B1 and European Patent (UK) No. 2 944 306 B1 (respectively "'691" and "'306" and collectively "the Patents"). The Patents are from the same family and have the same claimed priority dates and filing dates.

2. At trial:

    i) Charlotte May KC appeared for Formycon and Klinge in HP-2024-000015, and Samsung in HP-2024-000036, (together, "the Claimants"), leading Tom Alkin and Jeremy Heald. It is occasionally necessary to refer to the sets of Claimants separately because their products are materially different and when I do so I will refer to "Formycon" or "Samsung" as the case may be.

    ii) Adrian Speck KC represented Regeneron and Bayer, leading Isabel Jamal, William Duncan and Alice Hart. I will refer just to "Regeneron" for brevity.

3. The litigation relates to a successful drug called aflibercept, developed by Regeneron, which is used to treat age related or "wet" macular degeneration ("wet AMD", or "wAMD"), by injection into the eye.

4. Formycon and Samsung have each developed and want to commercialise aflibercept biosimilars on the expiry of product protection (the SPC) for aflibercept itself in November 2025. They allege that the Patents are invalid and not infringed. Regeneron counters by alleging infringement.

5. There are parallel proceedings in the Netherlands, Germany, France, Italy and Belgium; and in the US, Canada and South Korea. In the EPO '306 was found invalid by the Opposition Division and Regeneron has appealed ('691 was not opposed). In Germany '691 was found valid in amended form.

OVERVIEW

6. Wet AMD causes progressive blindness, especially in the elderly, and has long been a major health problem. Treatments (mainly photodynamic therapy) were of limited effect and even those that had some efficacy merely slowed disease progression and did not reverse it.

7. Wet AMD is caused by inappropriate growth of blood vessels ("neovascularisation") in the eye. This process depends on a growth factor called VEGF.

8. The first drug targeting VEGF was called Macugen, which was approved in the USA in 2004. It is an aptamer, which is a short sequence of nucleic acids. It too could not restore lost visual acuity.

9. The picture changed greatly with the introduction of two drugs, both developed by Genentech, both antibodies to VEGF.

10. Lucentis (ranibizumab) was in the final stages of phase 3 trials at the date at which I will have to assess obviousness (June 2006), with promising results generally known to have been achieved, though not yet formally published. Regulatory approval was expected in the near future and there was also an expectation that it might restore lost vision. I return to this in more detail below when I address the common general knowledge ("CGK").

11. Avastin (bevacizumab) had been approved as a treatment for cancer some time before the priority date. Cancer also depends on neovascularisation and hence on VEGF. Avastin had successfully been used off-label for wet AMD.

12. Avastin is a full-length antibody whereas Lucentis is an antibody fragment, so while they have the same VEGF-binding regions they are not identical. There has been a long and complex debate about their relative efficacy in wet AMD, why Avastin is much cheaper, and why Avastin has never been authorised for wet AMD. This is not of any direct relevance to the issues before me but was the broader context for some of the evidence.

13. The documents, oral evidence and submissions referred to Avastin and Lucentis both by their brand names and by their non-proprietary names; nothing turns on this and I use both in this judgment, though more frequently the brand names since I find them more memorable.

14. Macugen, Avastin and Lucentis all had to be given by intravitreal injection into the patient's eye. It really goes without saying that this was very unpleasant and presented significant clinical challenges (these are covered further in relation to the CGK). But it was justified given that the alternative was progressive blindness.

15. Injection into the eye can only be given in small volumes, for reasons expanded on below, up to about 0.1 ml.

16. Aflibercept was, as I have mentioned, developed by Regeneron, and also targets VEGF. It is a fusion protein rather than an antibody, which means that although the "stalk" of the protein is the same, being the Fc region of an IgG1 antibody, the binding part is not that of an antibody but rather parts of two VEGF receptors. The details of this are of only limited importance to the issues before me.

17. Aflibercept is also called "VEGF Trap", but one has to be careful about this term because in some contexts (the prior art and the Patents' priority document) "VEGF trap" denotes both aflibercept and closely related variants of it, or is ambiguous. Nonetheless, I refer frequently to VEGF Trap to mean aflibercept specifically because that is how the contemporaneous documents referred to it (as did the experts, often).

18. The Patents are not to aflibercept as such. It was part of the state of the art. In particular, it is disclosed in the only art cited by the Claimants for obviousness,

which is a US patent application by Regeneron referred to as "Wiegand II" (US 2006/0030529 A1, published on 9 February 2006). Wiegand II also teaches pre-clinical experiments with aflibercept in cells and in animals, and a phase 1 trial in humans using intravenous rather than intravitreal administration. Regeneron's written evidence referred to it as "'529" sometimes but it was referred to by both sides at trial as Wiegand II.

19. In Wiegand II, aflibercept specifically is referred to as "VEGFR1R2". I have generally used that name for consistency when dealing with Wiegand II's disclosure and the obviousness arguments.

20. Wiegand II contains a prophetic example (Example 17) about using aflibercept/VEGFR1R2 intravitreally to treat wet AMD. It mentions a dose range of 25-4000µg; Regeneron says that is just boilerplate, and the Claimants say it is a meaningful teaching.

21. The Patents are to formulations of aflibercept for intravitreal use. They specify the concentration of drug, four excipients and their concentrations, and the pH. Because of the limit on injectable volume for the eye there is a close relationship between concentration and dose, to which I will have to return below. Essentially though, at the maximum practical intravitreal volume, the concentration required by the claims of the Patents implies a dose of 4000µg, the top end of what Wiegand II mentions.

22. Wiegand II does not say anything material about formulation.

23. Formycon's and Samsung's products do not have all the formulation features of the claims. The details are set out below but in essence in one or more respects they each (a) use a different excipient from that claimed but of the same general functional purpose, and/or (b) omit one of the claimed excipients and/or (c) use different amounts.

24. Regeneron accepts that there is no infringement as a matter of normal interpretation but says that there is infringement by equivalence in each case. A major theme of the trial was Regeneron's argument that in the exceptionally empirical field of drug formulation patentees have no choice but to advance narrow claims so as to meet the requirements of sufficiency, but that once they have provided a working formulation infringers can get a crucial head start on competing, different formulations, even if the patent in question does not enable them. Regeneron argued that the law of infringement by equivalence should, and does, accommodate this. The Claimants dispute all this and say that the relevant claims of the Patents are deliberately narrow. The key UK authority on infringement by equivalence is the decision of the Supreme Court in *Actavis v Lilly* (discussed further below) and says that it should be assessed by reference to three structured questions. In this judgment I will call them "Actavis Q1", "Actavis Q2" and "Actavis Q3".

25. The Claimants say that the Patents are obvious over Wiegand II. They say it was obvious to take the 4000µg (i.e. 4mg) dose forward and that the formulation of the claims was one of a number of obvious possibilities that

could be identified by routine methods; that each of the excipients used was CGK and is used in the claims merely for its known purpose.

26. Regeneron responds that while the skilled team would have an interest in progressing Wiegand II, (1) it was not obvious to use a 4mg dose at all but rather a significantly lower one would be taken forward and (2) that the formulation of the claims is not obvious either. These two matters are very largely independent; I explain the limited relationship below. Regeneron points out that the obviousness case on the formulation aspects is one of CGK alone, which is true. It relies on the generally extremely high difficulty of protein formulation and points to some specific problems as well.

27. The obviousness arguments depend to some extent on the proper identities of the members of the skilled team and on their interactions with each other.

28. The Claimants also rely on another piece of prior art, another Regeneron patent application called "Dix" (filed on 22 March 2006, published on 5 October 2006). It is said to come in in two ways: as an anticipation by equivalence and as a matter to be taken into account on claim scope, because it is mentioned in the Patents' specifications. As to the former, the Claimants said that they merely want to reserve it for a higher court where they can argue that anticipation by equivalence is possible as a matter of law, so I do not have to decide it, though I will make relevant factual findings. The Claimants dropped what they called a "Formstein extension" or "ensnarement" defence based on Dix during closing submissions following discussion as to where it fitted in and whether it could add anything.

29. I address all aspects of Dix in a single section near the end of this judgment to avoid cluttering it, since I reject all the Claimants' arguments.

30. Separately, there is a dispute about priority entitlement and added matter. The substantive points under the two legal heads are the same, because the disclosure of the priority document and of the application as filed are materially the same and the legal tests are effectively identical for present purposes. Regeneron therefore accepts that if it loses priority the Patents would also be invalid for added matter. The only intervening prior art is Dix, which is novelty-only if priority is maintained. It would come in for obviousness if priority was lost, but in that event the Patents would be invalid for added matter anyway. So I do not need to consider obviousness over Dix; it cannot affect the overall result on validity. Although I am mentioning priority/added matter late on this introduction, it is the first topic I address on validity.

31. Finally, the Claimants rely on insufficiency/lack of technical contribution/*Agrevo* obviousness. These arguments focus on the 4mg dose said to be obvious and its relationship with concentration.

CASE MANAGEMENT AND THE TRIAL

32. At a CMC on 15 October 2024 I made a special order about Regeneron's intention to call a PK/PD expert (see below) and other procedural directions including a Statement of Agreed CGK and a list of CGK issues in dispute.

33. I later held a PTR and other procedural hearings in the immediate run-up to trial to deal with timetabling issues.

34. Formycon and Samsung started their respective actions but Regeneron took the role of claimant at trial because infringement was in issue. The witnesses were called in back-to-back pairs by discipline rather than all of Regeneron's followed by all of the Claimants', and I found this somewhat useful.

35. At trial the junior advocates played a full role and I am grateful to all of them. I will not go into too much detail about which did what, but when I refer to arguments made by "Counsel for the Claimants" I mean Ms May KC except in relation to priority/added matter where Mr Heald made the submissions; when I refer to arguments by "Counsel for Regeneron" I mean Mr Speck KC except on the 4mg dosing issue where Ms Jamal made the submissions, on aspects of Dix where Mr Duncan did the advocacy, and on priority/added matter where it was Ms Hart. Mr Alkin and Ms Jamal also undertook significant parts of the cross-examination of certain of the experts.

36. The trial took 11 days, with four experts on each side who were fully engaged. Every point was taken and nearly all were maintained to the bitter end. Even with what I assume must be an enormous amount of money at stake this was disproportionate. With a will to simplify and economise the parties could have found and used two experts each since the PK/PD material was subsidiary to the clinical evidence and the protein engineering to the formulation. I expect that there are clinicians who could have covered the PK/PD and formulators who could have covered the protein engineering. 11 days should not have been needed for what is in the end effectively a single claim in a formulation patent. This judgment is, largely as a result of this approach, much longer than I would have liked and even then it has not been practical or proportionate to deal with every point in the very long submissions I received, though I have borne them in mind.

THE ISSUES

37. The issues are:

    i) The identity and characteristics of the skilled team;

    ii) The scope of the CGK, where there are many disputes;

    iii) Infringement by equivalence, there being no material dispute about normal interpretation as the starting point for equivalence and no allegation by Regeneron of infringement on a normal interpretation. There is also no live dispute of primary fact. Part of the Claimants'

arguments depends on Dix, also said to be relevant to anticipation (see below);

iv) Whether the Patents are entitled to priority or invalid for added matter. The arguments are subtly but importantly different for '691 and '306;

v) Obviousness over Wiegand II;

vi) Anticipation by equivalence over Dix, reserved for a higher court;

vii) Insufficiency or lack of technical contribution/*Agrevo* obviousness.

38. An additional procedural issue is that the Claimants applied at the end of trial to amend their Grounds of Invalidity to add two documents. The deployment of the documents was contingent on whether or not I accepted certain evidence of Regeneron's PK/PD expert.

OTHER TECHNICAL DOCUMENTS

39. In addition to the cited prior art, I was referred to a number of technical documents. Many dozens of documents were referred to in the experts' reports (I make no criticism of this), in three agreed volumes. Following trial I was given a consolidated index indicating in chronological order which had been referred to in the oral evidence or submissions, which was also very helpful. In the course of this judgment I will be referring to some, which it is helpful to explain and identify now:

i) Akers (2002) "Formulation Development of Protein Dosage Forms" and Gokarn (2006) "Chapter 17 – Excipients for Protein Drugs" were both texts relied on as showing formulation CGK. I refer to them below as "Akers" and "Gokarn"; similar was Carpenter (2002), "Rational Design of Stable Protein Formulations" (chapter authors Chang and Herschenson) put in by Dr Daugherty as evidence of CGK ("Carpenter") and Wang (1999) "Instability, stabilization, and formulation of liquid protein pharmaceuticals" ("Wang").

ii) Nguyen (2006) "Results of a Phase I, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreous VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration" is a meeting abstract concerning Regeneron's work with VEGF Trap. The Claimants contingently alleged that in certain circumstances it would be found by routine research. I refer to it below as "Nguyen 2006".

iii) A 2006 press release by Regeneron entitled "Regeneron Reports Positive Phase 1 Data for the VEGF Trap in Age-Related Macular Degeneration". Similarly, it was said that this would be found by routine research. I will refer to it as "the Regeneron Press Release".

iv) Nguyen (2009) "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" is a later publication about aflibercept, post-

priority which the Claimant said was secondary evidence of obviousness. I refer to it below as "Nguyen 2009".

v) Various publications having as an author Dr Philip Rosenfeld, a leading researcher in the field, including on Lucentis and Avastin. I have not in general found it necessary to refer to individual of the publications but refer below to work by this group. One of the publications reported on the PrONTO study (see below in the section dealing with the CGK of the skilled clinician).

vi) Various publications having as an author Dr Jeffrey Heier, another leading researcher and who was the lead author on the MARINA study (again, see the clinician CGK section).

40. Nguyen 2006 and the Regeneron Press Release are the two documents which the Claimants applied to add to their Grounds of Invalidity.

THE WITNESSES

41. Each side called four experts. They were in the following disciplines:

i) Formulation;

ii) The clinical aspects of AMD;

iii) Protein engineering;

iv) Pharmacokinetics/pharmacodynamics ("PK/PD").

42. No fact witnesses were called.

43. The parties made only limited criticisms of each other's witnesses. I address each witness in turn below. Where I do not mention any criticisms of a particular witness that is because there were none. In general I thought all eight witnesses were extremely good, clear at explaining, and honest and straightforward. All were competent and appropriately experienced to give their evidence. Such few criticisms as I have accepted to any degree were sufficiently minor as to not affect this overall assessment.

Regeneron's witnesses

44. I will describe Regeneron's witnesses first and then the Claimants'.

Regeneron's formulation expert, Prof Gukasyan

45. Professor Hovhannes Gukasyan is an Associate Professor at the University of Southern California School of Pharmacy. Prior to that he was in industry for over 15 years. His work included projects on pharmaceutical formulations and in particular some intravitreal formulations. Quite a lot of that work was post-priority but I am satisfied it was relevant and took place in circumstances not materially different from those at the priority date.

Regeneron's clinician expert, Prof Kodjikian

46. Professor Laurent Kodjikian is a Professor of Ophthalmology and Chair of the University of Lyon and Associate Chair of the Ophthalmology Department at Croix-Rousse Teaching Hospital in Lyon, France. He has extensive experience of wet AMD (among other retinal diseases) and of clinical trials, including as a principal investigator.

47. Prof Kodjikian gave evidence with the help of an interpreter. His English is extremely good and he needed help only with the translation of occasional questions, giving his replies in English. These arrangements caused no problems and I am sure that there was a full understanding in both directions and that I am able satisfactorily to assess his evidence.

48. While not criticising his expertise, and noting (correctly) that his manner of giving evidence was due to his passionate views, the Claimants made a number of criticisms of Prof Kodjikian's evidence:

    i) That he came up with some ill-thought through answers. Of the three examples given the only one that I thought had substance was in relation to his evidence that giving 4mg of a drug in the eye could result in a higher systemic exposure than 1mg/kg given intravenously. I must say that I could not understand his position, but it is a trivial point in the context of the very extensive evidence he gave.

    ii) That he had a propensity to approach documents which did not help Regeneron's case "with an unduly critical eye". I do not accept this. Of course there were many areas where his answers aligned with Regeneron's case but that cannot in itself be a criticism. In general he was open minded and willing to accept propositions that favoured the Claimants where he agreed with them.

    iii) That he relied on commercial rather than technical reasons (in particular in relation to targeting minimum efficacy for minimum duration of action). But this was an area where the commercial and technical cannot be readily separated: a more ambitious target for a clinical trial is likely to be missed, which is both a commercial problem because regulatory authorisation will not be obtained and a technical problem because the result of the trial will be a null and the opportunity to learn important information about a more modest target will be lost. In any event, this cannot be a personal criticism of Prof Kodjikian.

49. The Claimants pointed out that CGK is local and that Prof MacLaren was better placed to give evidence on the situation in the UK. This is true but irrelevant: the field was highly international and I was not directed to any relevant UK-only CGK that was different from the international position.

Regeneron's protein engineering expert, Prof Leatherbarrow

50. Professor Robin Leatherbarrow had a very distinguished career in academia working on protein engineering, at Imperial College and later at Liverpool John Moores University. He also worked with industry during his career.

51. The Claimants submitted that Prof Leatherbarrow was over skilled in some areas and under skilled in others. I can understand the former submission but not the latter, of which no cogent examples were given. It is obvious that in general he was far more skilled that the notional skilled protein engineer but this had no relevance to what he was giving evidence about and anyway I am confident he understood and sought to apply the relevant legal standard.

52. The real dispute on the protein engineering side of the case was about the notional skilled person's general scope of skill and experience, i.e. about identifying in an objective sense the relevant person. I deal with this below; it has nothing to do with the individual characteristics of Prof Leatherbarrow, or Dr Esposito.

Regeneron's PK/PD expert, Dr Ward

53. Dr Keith Ward is a pharmacokineticist with pre-clinical and clinical experience, including in particular in relation to ocular PK/PD and ophthalmic drug development.

The Claimants' witnesses

54. I move on to the Claimants' witnesses.

The Claimants' formulation expert, Dr Daugherty

55. Dr Ann Daugherty worked in formulation at Genentech for many years until her retirement in 2023. She mainly worked on the formulation of large molecules, including therapeutic proteins.

56. Regeneron submitted that Dr Daugherty was too highly skilled – more so than the ordinary skilled person – and that that led her to see things as easy when they were not. Relatedly, Regeneron submitted that she thought things were easy because the individual experiments involved were routine. I agree she was more highly skilled than the ordinary scientist in her field but I reject the other submissions. She readily agreed that protein formulation was difficult; her view was that the skilled person would nevertheless try persistently to solve the tasks they were given, which is entirely consistent with the legal construct of the skilled person.

57. Regeneron also submitted that Dr Daugherty was too focused on antibodies and that this led her astray because she should have drawn on or considered broader materials when considering aflibercept, which is not an antibody but a fusion protein. I do not think Regeneron made good that this distinction made a relevant difference, however. I will take into account what excipients were

used for antibodies and for fusion proteins as appropriate when I come to the merits below, but the details do not impact on Dr Daugherty as a witness.

The Claimants' clinician expert, Prof MacLaren

58. Professor Robert MacLaren is a Professor of Ophthalmology at the University of Oxford and an Honorary Consultant Ophthalmologist. He has about 30 years' experience in retinal eye diseases including deep involvement with international clinical trials.

59. Regeneron submitted that Prof MacLaren had personal experience of the cynomolgus monkey model and that this made him over-skilled. I reject this. Both he and Prof Kodjikian gave evidence about the model and clearly the skilled team would need to understand it. The fact of personal experience cannot be a relevant criticism, indeed it was an advantage, to a modest degree.

60. Regeneron nibbled away at Prof MacLaren's experience of clinical trials, where his involvement as principal investigator has been in relation to gene therapy. I reject this because his general understanding of trials remained highly relevant and anyway he had worked on trials of therapeutic proteins as a sub-investigator.

61. Lastly, Regeneron said that Prof MacLaren erred in assuming that statements in patents can be taken to be supported by evidence even if none is presented. This is an important point on the dose range in Example 17 of Wiegand II which I consider below, concluding that Prof MacLaren was indeed wrong in his assumption. But that is hardly his fault since he cannot have been expected to know this point of patent law and practice. I am able to assess his evidence on that point taking into account the standard he was applying, since he was transparent about it, and this matter has no wider impact on the force of his evidence.

The Claimants' protein engineering expert, Dr Esposito

62. Dr Dominic Esposito is Director of the Protein Expression Laboratory (PEL) at the Frederick National Laboratory for Cancer Research, USA.

63. The main point taken by Regeneron about Dr Esposito's evidence was that he envisaged the skilled protein engineer purely as someone who could *make* a protein (this notional person came to be referred to at trial as the "fermentation technician") and not someone who could *analyse* a protein so as to provide input to a formulation project. This is a material point on the nature of the skilled team, which I deal with below and conclude by agreeing with Regeneron. But it is not a point that can be laid at the door of Dr Esposito, who was following his instructions.

64. Regeneron also pointed out that Dr Esposito made a bad point in criticism of Prof Leatherbarrow's pI calculations. It was indeed a bad point – the details do not matter - but experts make mistakes sometimes and I do not think this isolated incident revealed any personal shortcoming on the part of Dr Esposito in terms of his independence or integrity. It did reflect Prof Leatherbarrow's

overall greater experience, however, which I take into account where the experts clashed on details of the calculations.

The Claimants' PK/PD expert, Dr Wensel

65. Dr Theodore Wensel is a Professor of Biochemistry and Molecular Pharmacology, Professor of Ophthalmology and Professor of Neuroscience at Baylor College of Medicine (I have to say I remain rather unsure why he is styled as "Dr" Wensel). He has decades of experience in pharmacokinetics including in relation to retinal disease.

66. Regeneron submitted that Dr Ward had, relatively speaking, more practical experience of hands-on drug development and of the monkey CNV model. I agree with that but it is merely the usual and unhelpful comparison of which expert more closely in fact approximates to the notional skilled person and has no bearing on my assessment of Dr Wensel.

THE SKILLED PERSON OR TEAM

67. It was common ground that the main principles about identifying the skilled person or team are set out in *Illumina v Latvia* [2021] EWHC 57 (Pat) (Birss J, as he then was).

Does the skilled team have a "leader"?

68. There has been discussion in a number of authorities about whether the skilled team has a leader or "boss" and if so what that means. Any suggestion that there was previously an inconsistency in the case law has been dispelled, however, and the parties both cited decisions to the same effect: it is wrong to envisage a team in which one member is the head, directing all the others as if they were subordinates; each team member is assumed to play their own part; the nature of each member's role is fact-specific, as are the relationships between them. The team may have a leader if the facts make it appropriate, but not in the head/subordinate style and not so as to cut across each member playing their part. See e.g. Arnold J (as he then was) in *Generics v Warner-Lambert* [2015] EWHC 2548 at [118] and then Arnold LJ in *Alcon v Aspire* [2022] EWCA Civ 845 at [56]-[57], in each case addressing and rejecting the submission that the decision of the Court of Appeal in *Halliburton v Smith* [2006] EWCA Civ 1715 had any different effect.

69. The reason this matters is because of the Claimants' case that the clinician would tell the formulator what dose and volume were required and that because of that, the expectation of success of the formulator was irrelevant because they would just have to do as they were told. In its fullest force that argument seems to me to be inconsistent with the law as I have just identified it to be, but I will return to this below. To be fair, the Claimants retreated significantly and explicitly from the extreme form of this argument in their closing submissions.

"Reverse *Schlumberger*"

70. The Claimants argued that the skilled team is limited to those people with the skills and knowledge needed to implement the Patents. Since, the Claimants say, the Patents do not need any analysis of the fusion protein but only the ability to make it, and since the concentration and hence effectively the dose are given in the Patent, the skilled team for the purposes of obviousness would only include the Claimants' stripped-down "fermentation technician" and no PK/PD expertise at all.

71. Counsel for Regeneron aptly described this as "reverse *Schlumberger*": in *Schlumberger v EMGS* [2010] EWCA Civ 819 the Court of Appeal said (I paraphrase) that the skilled team may *expand* for the purposes of sufficiency, with the patent in hand, compared with the position for obviousness, in cases where a fundamental invention is made which transforms the perspective of the art by drawing on two fields which were previously not brought to bear on a problem together. By contrast, the Claimants' point in this case was that the skilled team *shrinks* because once the patent provides the solution some members are no longer needed, compared with the team who would have worked on the prior art.

72. I reject the Claimants' case on this. Looking at what a patent expects or needs the reader to be able to do is informative about the skilled team but not the only part of the picture and certainly not automatically limiting in the way that the Claimants say. The Claimants' argument is also inconsistent with the approach – common ground – that the identification of the skilled team starts with the problem that the patent aims to solve.

73. The Claimants' argument is entirely artificial, too: real teams in the field were not so limited, and a team which wanted to progress Wiegand II would, in actuality, include the members for which Regeneron argued. Counsel for Regeneron pointed out that if the skilled team were analysed as the Claimants said it would not even need to include a clinician, just someone to make the protein and someone to mix up the formulation, yet the Claimants certainly argued for a clinician to be in the notional team. There is truth in this but it is really a rhetorical flourish and not necessary to my rejection of the Claimants' argument.

74. The importance of this dispute faded rather since the Claimants accepted in their written opening that because of the nature of real teams there would be a PK/PD expert in the notional team (this seemed inconsistent with the Claimants' position on the law, but it does not matter); a potentially important dispute remained about their relationship with the clinician, and I address that below. But the point remained live in relation to whether the protein engineer would have skills to analyse a candidate protein, or just be the fermentation technician able to make it. I address this below.

The skilled team in the present case

75. There were two disputes about the characteristics of individual members of the skilled team; only the first matters.

The protein engineer

76. As I have mentioned, Regeneron said that the protein engineer would be someone who was both able to make the protein, and to analyse its characteristics so as to pass on to the formulator an understanding of its potential instabilities that might be predicted from its structure.

77. The Claimants on the other hand said that the protein engineer would be the fermentation technician, as I have explained it above.

78. This argument is tied in to the reverse *Schlumberger* point of law, on which I have rejected the Claimants' position.

79. In my view Regeneron is right about this:

    i) Real teams included persons with the analysis skills in question, as I conclude from the evidence both of Prof Leatherbarrow and of Dr Daugherty.

    ii) Given that it is accepted that the formulator would know that certain physical characteristics were associated with the risk of various kinds of instability, it would be irrational not to find out if they were present in the protein under consideration.

    iii) The tools needed for the analyses were not obscure, difficult to access, or hard to use. On the contrary they were simple to obtain and easy to use.

    iv) Dr Esposito said that while he envisaged the fermentation technician not knowing about how to analyse the protein, the formulator would be able, and would expect, to ask someone else about stability risks, who would know what to do.

The formulation scientist

80. It was of course accepted that this discipline would be represented in the skilled team. There was a trivial and inconsequential dispute about how many years' experience they would have. I do not need to decide it and decline to do so.

Interactions between members of the skilled team

81. There was also a major dispute about how the skilled team's members would interact. The Claimants said that the clinician would take the lead, decide that 4mg was the necessary and appropriate dose, and tell the formulator to do it. The Claimants said that this made the formulator's assessment of the prospects of success irrelevant. This is why the argument of law over whether the skilled team has a "leader" was made. I will deal with it below when I come to obviousness since it makes more sense once the disclosure of Wiegand II and the arguments from it have been explained. In the end it matters little, if at all.

THE COMMON GENERAL KNOWLEDGE

82. The CGK was dealt with by the parties in four separate parts, one for each discipline for which they had an expert witness.

83. For each such part, the parties agreed a joint document which identified the CGK that was agreed (the "ASCGK") and another identifying what was in dispute. This led to quite a degree of overlap between the clinician and PK/PD CGK and the formulator and protein engineering CGK, respectively. I have edited the documents down considerably to try to focus on that which matters, but the number of arguments run means that a lot of CGK still needs setting out, even if of limited relevance to the central issues. My cutting material out does not remove its agreed status. The use of tenses in the documents supplied to me was not completely consistent and I have not spent the time to make it uniform but even when the present tense is used the position at the priority date is what is being referred to (except in a few cases where the position today is expressly mentioned). There is also some variability in the way in which the members of the skilled team are referred to, but this has no significance and it is obvious from the context what is meant.

84. There was no general dispute about the law applicable to CGK. To be CGK, something must be generally known and accepted as a good basis for further action.

Agreed CGK - formulation

Protein physical and chemical instability

85. A key objective in protein formulation development is to stabilize the protein so that it remains safe and effective following manufacture, transportation, storage, and administration.

86. A formulation for a phase 1 clinical trial only requires stability for a matter of months. Ideally this would be for around 6 months or so to allow for a single batch to be used for a whole trial but in some cases this would not be achieved. The Formulation Scientist would aim from the outset to develop a formulation that would have the potential to be used as a commercial formulation.

87. Stability studies to test the long-term stability of the formulation used in the phase 1 clinical trial would typically be run in parallel to the clinical trial itself. The formulations are tested at specific time points and analysed for degradation products.

88. Achieving long-term stability is generally more challenging for proteins than for small molecules because proteins usually have more stability issues due to their larger size and increased structural complexity. This is particularly the case in aqueous solutions.

89. Protein instability issues can be divided into two major categories: those caused by physical instability and those caused by chemical instability. The following would be known to the Formulation Scientist, but to the extent they

did not know this information, it would be provided to them by the Protein Engineer.

90. Physical instability arises as a result of non-covalent changes that disrupt the structure of the protein. These instabilities include:

i) **Aggregation**: this is covered in the agreed CGK protein engineering section.

ii) **Adsorption**: this is where the proteins associate with the surface of the container, for example if the surface of the container is hydrophobic. If hydrophobic residues on the surface of the protein come into contact with the hydrophobic residues on the surface of the container, it can result in the protein adhering to the surface of the container and coming out of solution.

iii) **Denaturation**: This is the term for proteins losing their native three-dimensional structure due to external stressors such as heat, pH extremes, or shear and surface interaction through mechanical agitation. Denaturation results in the loss of biological activity and may lead to aggregation.

91. Chemical instabilities can result from the following chemical reactions which occur in the presence of water, dependent on pH, which lead to changes in the protein's chemical structure:

i) **Deamidation** – see the agreed CGK protein engineering section.

ii) **Deamination** – this is the removal or modification of an amino group of any amino acid. It can result in a change in the protein sequence. In practice, it occurred rarely.

iii) **Oxidation / loss of electrons** – see the agreed CGK protein engineering section.

iv) **Hydrolysis of peptide bonds / fragmentation** – the peptide bonds between amino acid residues in the protein backbone can break.

v) **Reduction of disulfide bonds** see the agreed CGK protein engineering section.

vi) **Isomerization** – the side chain of aspartic acid can undergo rearrangement via a cyclic intermediate from aspartate to isoaspartate.

vii) **De-glycosylation** – see the agreed CGK protein engineering section for further details about glycosylation.

92. The functionality of a protein drug is linked to its structure and the above structural changes can risk a loss of activity. These chemical reactions can also lead to physical instabilities if the chemical changes destabilize the folded protein structure.

Stability requirements

93. In order to obtain regulatory approval for a therapeutic product, the protein needs to satisfy certain guidelines which include requirements to conduct certain stability studies and meet certain acceptance criteria. The International Council for Harmonization (ICH) issued guidelines on stability testing of biological products which were adopted by a number of regulatory agencies, including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). These guidelines specify that a stability-indicating profile of the drug product should be provided with the regulatory submissions, including:

    i) Potency studies.

    ii) Purity and molecular characterization, including size, charge and hydrophobicity to monitor for the occurrence of degradation products.

    iii) Other product characteristics including visual appearance and pH.

94. Certain excipients and/or the container itself might negatively affect the stability of the product. As a result, the product should be monitored in an environment that is consistent with its final intended presentation.

Liquid and lyophilized formulations

95. Proteins are not typically suitable for oral administration, primarily because they are degraded in the digestive tract.

96. A liquid protein formulation must keep the protein in solution, protect it from physical and chemical degradation, and be physiologically suitable for its route of administration.

97. A number of stability issues associated with proteins arise as a consequence of interactions with water and a protein may not be stable enough to be handled as a liquid formulation for the required period. Therefore, lyophilized formulations, also known as freeze-dried formulations, were also considered.

98. Lyophilized formulations are created by removing water from the protein solution under low temperature and pressure, leaving a dry powder that must be reconstituted with a suitable diluent before administration. This process generally enhances the stability of the formulation and therefore allows for longer storage times, as the rate of protein degradation is reduced. Table IV of Akers 2002 shows that out of 36 U.S. marketed protein dosage forms approved by the FDA through 2000, 18 were stored in lyophilized form. However, the Formulation Scientist would be aware that, although lyophilization could achieve good long-term stability, the reconstitution step was considered an additional procedural step, there were stability issues associated with the lyophilization and reconstitution process itself, and lyophilization was also an expensive procedure to carry out, compared to liquid formulations.

99. Liquid formulations are generally considered preferable to lyophilized formulations as there is no need for reconstitution, and dose administration of a liquid formulation may have better accuracy. Additional reasons include:

    i) **Inconvenience and human error** with lyophilized products.

    ii) **Time and cost of manufacturing** with lyophilisation.

    iii) **Protein aggregation**: The swirling involved in reconstituting lyophilized proteins can lead to the formation of protein aggregates.

    iv) **Particulates**: A lyophilized formulation may contain more particles than a liquid formulation due to the lyophilization process.

Influence of concentration of protein on the formulation task

100. The Skilled Formulator would have been aware that the desired concentration of protein within a formulation may give rise to certain formulation challenges.

101. For example, at low concentrations of protein, it is particularly important to ensure that there is minimal adsorption onto a contact surface because this would further reduce the effective concentration below an already low starting point leading to inconsistent and inaccurate dose accuracy.

102. It would have been appreciated that formulating proteins at high concentrations could pose different formulation challenges. In general, aggregation has a tendency to occur at higher concentrations of a protein because there can be higher incidence of random protein:protein interactions. It was also understood to be dependent on other factors such as temperature, pH and the presence (or absence) of stabilising excipients.

103. In addition, protein concentration will also change the viscosity of the solution, with the solution generally becoming more viscous as protein concentration increases, which is generally undesirable for proteins to be administered intravitreally and through a small gauge needle.

Influence of pH on protein formulations

104. This is covered, in particular the relationship between pH and pI (the isoelectric point), in more detail in the agreed CGK of the Protein Engineer.

105. The physical stability of a protein at different pHs is influenced by its specific pI. At pHs far from the pI of a protein, electrostatic repulsions between like charges in the protein increase, resulting in a tendency to unfold. On the other hand, a pH too close to the pI can increase the propensity for aggregation and reduce the solubility of the protein. The pI varies between proteins as it depends on the specific number and type of amino acids a protein has. This means that different proteins have different levels of stability and solubility at different pHs. The need to find a pH which struck a balance between solubility and stability was well recognized.

106. Additionally, the pH of the solution can affect differently the rate of the different chemical reactions, which can lead to degradation of the protein. For example, Figure 1 of Akers 2002 (reproduced below) shows that peptide cleavage reactions and Asp transpeptidations occur fastest at acidic pHs, whereas deamidation and various oxidation reactions occur faster at basic pHs:

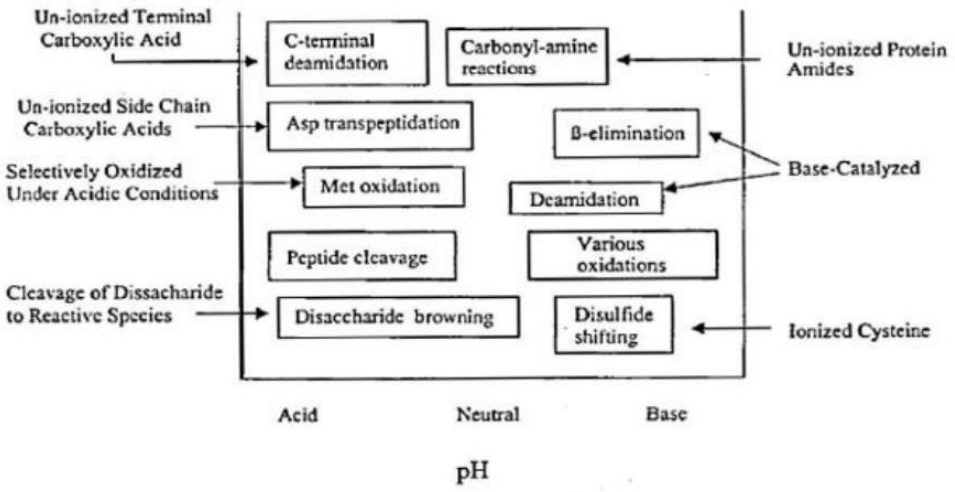


Figure 1. Protein reactions as a function of pH. Figure courtesy of Dr. Lee Kirsch.

Tonicity

107. Tonicity refers to the ability of an extracellular solution to cause water to move into or out of cells by osmosis across the semi-permeable cell membrane. A solution may be hypotonic, hypertonic or isotonic.

    i) A hypotonic solution causes water to enter the surrounding cells, which can lead to swelling, cell lysis and tissue destruction.

    ii) A hypertonic solution causes water to leave the surrounding cells, which can lead to cell shrinkage and dehydration.

    iii) An isotonic solution causes no net movement of water.

108. Tonicity can be quantitated as either osmolarity or osmolality. Osmolarity is stated in osmoles or milliosmoles per litre of solvent (Osm/L or mOsm/L). Osmolality is expressed in osmoles or milliosmoles per kilogram of solvent (Osm/kg or mOsm/kg). For most liquid formulations, the values of osmolarity and osmolality are very close to each other. Formulators can carry out relatively simple calculations to estimate the osmolarity of a proposed formulation, which can be verified empirically.

Intravitreal administration

109. In addition to the stability of the protein the Formulation Scientist must consider the intended method and route of administration. In the case of products intended for intravitreal administration, this requires that the product must be suitable for injection directly into the vitreous of the eye.

110. The Formulation Scientist would know (from the skilled clinician if they did not know themselves to begin with) that limited volumes of 50 µl to 100 µl can be injected intravitreally.

111. The Formulation Scientist would have understood that the standard for approval of formulations intended for intravitreal use were very stringent. A formulation containing a protein which has undergone some chemical or physical degradation including the formation of aggregates can trigger adverse events and these can cause serious safety issues in the eye.

112. In 2006 there was comparatively little information available on excipients and the concentrations of those excipients which could be safely administered into the vitreous. The excipients used, and their amounts, may therefore also need to be tested and established to be suitable for intravitreal administration.

113. The osmolality and pH of the formulation must also be compatible with the eye. It was known that the biological pH of the vitreous was 7.0-7.5 and that this would have been a safe pH for a formulation for intravitreal use. In addition, in light of Macugen, the Formulation Scientist would have known a pH of 6-7 could also be used for a drug administered regularly. This was also supported by the off-label use of Avastin (also discussed below), which has a pH of 6.2. The safety and suitability of regular administration of formulations with pHs outside of the pH range of 6-7.5 was not known.

Formulation development

114. Commercial drug products typically contain at least one active pharmaceutical ingredient ("API"), also known as the "drug substance" or "active", plus a number of excipients.

115. Common examples of biologics include antibodies as well as hormones, growth factors, enzymes and vaccines. The Formulation Scientist would also have been aware of fusion proteins and antibody fragments.

116. An excipient is a therapeutically inactive substance included in the formulation of drug product. Although excipients have no therapeutic activity of their own, they can modify the therapeutic effect of the API(s) and are typically included to stabilize or to provide a convenient dosage form.

117. A protein's amino acid sequence can be assessed to identify the pI.

118. The Formulation Scientist has the volume of administration (within the clinical restraints), physical conditions (such as pH and temperature), state (such as liquid or lyophilized) and excipients at their disposal which they can use as 'tools' in their formulation project.

pH

119. The pH of the solution can affect the rate of different chemical reactions. The pH of the formulation can therefore be varied to influence the stability of the

formulation while maintaining adequate solubility. However, the pH must also be tolerable to the human eye – see above.

Excipients

120. Excipients are divided into different classes depending on their function in the formulation. A single excipient can fall into several classes and have several different functions.

121. Since different proteins display different levels of stability, the type, amount and combination of excipient functionalities which may achieve a stable formulation will depend on the specific protein, as well as the pH, temperature, and concentration of protein in the formulation.

122. The Formulation Scientist would expect that, for any given excipient, there was not necessarily a precise amount which would be required to improve the stability of the protein in the formulation, but there might be a range of concentrations over which a beneficial effect could be achieved.

123. With respect to a formulation intended for use intravitreally, the Formulation Scientist would consider that the functional classes of excipients available to them as possibilities for use in their formulation would include the following (but this list is given here without prejudging the dispute between the parties dealt with below about which classes would be included in a formulation of aflibercept at the initial stage of a formulation project):

Buffers

124. A buffer included in a formulation can be used to set the pH to the desired target pH and to maintain it. Akers 2002 includes a table setting out the typical buffers used in protein formulations, their pKa values, and the range of pH over which that buffer is typically used and this table is reproduced below.

Table V
Buffers Used in Protein Formulations

Buffer system	pK_a	pH range of use
Acetate	4.76	2.5–6.5
Citrate	3.14, 4.8, 5.2	2.5–6.0
Glutamate	9.67(pK_{a3})	8.2–10.2
Glycinate	2.4,9.8	6.5–7.5
Histidine	1.8, 6.0, 9.2	6.2–7.8
Lactate	3.8	3.0–6.0
Maleate	1.92, 6.23	2.5–5.0
Phosphate	7.2 (pK_{a2})	6.0–8.2
Succinate	4.2, 5.64	4.8–6.3
Tartrate	2.93, 4.23	3.0–5.0
Tris	6.2 (pK_b 7.8)	6.8–7.7

Figure 3*. Table V from Akers 2002.*

125. Buffers consist of a mixture of one or more acid(s) and their conjugate base(s). For example, citric acid buffer consists of citric acid (a weak acid) and monosodium and disodium citrate (the conjugate bases).

126. The ability of a buffer to maintain a particular pH is determined by the ratio of the concentrations of the weak acid and its conjugate base components in the buffer and the pKa of the buffer. The pKa is an intrinsic property of a buffer reflecting the equilibrium pH between the acid and base components in the buffer.

127. Phosphate buffer can consist of phosphoric acid (H3PO4), dihydrogen phosphate ($H2PO4^-$, otherwise known as phosphate monobasic), hydrogen phosphate ($HPO4^{2-}$, otherwise known as phosphate dibasic), and phosphate ($PO4^{3-}$, otherwise known as phosphate tribasic). For this reason, there are three pKa values associated with a phosphate buffer: 2.15, 7.20, and 12.35, and the target pH will drive the choice between them.

128. The phosphate buffer also will include a counter-ion, most typically sodium. Potassium cations (alone and in combination with sodium) were also used.

129. The buffer maintains the target pH by preventing changes in pH which can affect protein stability. pH is a measure of the concentration of hydrogen ions (H^+) in a solution and buffers work by releasing or capturing hydrogen ions, which helps maintain a consistent pH level. Over time and because of chemical degradation reactions, a protein can release small amounts of H^+ into the formulation. The conjugate base component of the buffer will capture the H^+ to maintain the pH. Conversely, over time a protein can also release bases such as ammonia which react with water to form basic ions (OH-). The weak acid component of the buffer will react with these basic ions by releasing H+ to neutralize them to maintain the pH.

130. A buffer's capacity is defined as the amount (as in, number of moles) of acid or base that one litre of buffer can neutralize before its pH changes by 1 unit.

131. The buffering capacity of a buffer in a formulation depends on the proximity of the pH of the formulation to the pKa of the buffer and the concentration of the buffer. The closer the pKa of the buffer to the target pH of the formulation, the better its buffering capacity. The greater the concentration of the buffer in the formulation, the more molecules available to neutralize the acidic or basic ions and therefore the better its buffering capacity.

132. Where a buffer is added to a formulation, the amount of buffer to add would typically be measured experimentally by selecting for example three or four concentrations of buffer and measuring pH over time.

133. High concentrations of buffer increase the risk that the buffer might have other impacts on the formulation. For example, in certain cases it has been shown that the choice of buffer can affect deamidation rates. In general, these effects are not commonly observed and/or even if observed, can be minimized by appropriate choice of concentration.

Stabilizers

134. Stabilizing agents act to stabilize the folded and active conformation of the protein. The mechanism(s) by which this occurs varies based on both the

stabilizer and the characteristics of the protein being stabilized. The same stabilizer can have different interactions with different parts of the protein. The effect of a stabilizer is not always positive and in some cases a stabilizer could stabilize an unfolded or inactive conformation of the protein over the active, folded configuration. As a result, whether or not a stabilizing agent has a beneficial effect needs to be tested for each protein.

135. One class of stabilizing agent are carbohydrates including sugars such as sucrose and trehalose, and polyols. The following mechanisms were thought to operate:

    i) By forming a protective shell around the protein comprising of sugar and water.

    ii) By changing the interactions at the surface of the protein, a mechanism referred to as preferential interaction. The protein exists in solution in an equilibrium between the folded, active state and one or more unfolded, inactive states. The carbohydrate alters the interactions at the surface of the protein. If the effect of this change in interactions is that the active folded form of the protein is stabilized to a greater extent or destabilized to a lesser extent, than the unfolded, inactive forms of the protein, the net result is that the energy required for the protein to change from the active to inactive state increases and the folded, active protein becomes more thermodynamically favoured than the inactive, unfolded protein.

136. When using sugars, the Formulation Scientist would be aware that sugars can also react with certain side chains on the protein. So the Formulation Scientist would select a non-reducing sugar. In addition, sugars also can contribute significantly to the osmolality of the formulation. In the case of formulations for intravitreal administration, this limits the amount that can be added.

137. In addition to carbohydrates, there were also examples of certain amino acids being used before the Priority Date as stabilizing agents for proteins in solution.

Co-solvents

138. A protein in solution will be surrounded by water molecules (referred to as solvation). Co-solvents increase the solubility of the protein. One mechanism by which this can occur is through interactions with the protein and displacing water molecules to solvate the protein. Co-solvents can also act by disrupting water-water interactions and by doing so reduce the polarity of the water molecules in solution. This reduction in polarity can increase the favourability of interactions between the water and the protein, increasing the solubility of the protein.

139. There are a number of different types of compounds which can act as co-solvents, which include glycerin, propylene glycol, polyethylene glycol, ethanol, cyclodextrin derivatives and polysorbates.

140. Some co-solvents (e.g. polysorbates) are also surfactants.

Surfactants

141. Surfactants are compounds which reduce the surface tension of protein solutions and decrease the adsorption and/or aggregation of proteins at the surface of solutions.

142. Surfactants:

    i) reduce aggregation;

    ii) reduce adsorption onto the walls of the formulated liquid protein's container; and

    iii) provide protection at air-liquid interfaces.

143. Surfactants can be ionic (charged) or nonionic (not charged). In general, ionic surfactants were considered harsh and, in many cases, would denature the protein. However, there were examples of ionic surfactants having a stabilizing effect on certain proteins. In contrast, nonionic surfactants, such as polysorbate (which can act as a surfactant in addition to a cosolvent), were generally considered to be milder.

144. Polysorbates comprise an ethoxylated sorbitol (a sugar group) attached to a fatty acid chain by an ester bond. The number after polysorbate indicates the length of the fatty acid chain and the higher the number, the longer the fatty acid chain.

145. Structurally surfactants contain hydrophobic and hydrophilic groups. Their hydrophobic phase binds to a similarly hydrophobic pocket on the protein, preventing undesirable interactions with another protein, and leaving the hydrophilic tail of the surfactant free in solution to interact with water.

146. The amount of surfactants and cosolvents used needs to be suitable for the intended route of administration. For example, the Formulation Scientist would be aware that polysorbate at high concentrations may be toxic. In June 2006, there were no products authorized for intravitreal administration which contained polysorbate, and therefore, the Formulation Scientist would not be aware that the ocular safety and toxicity had yet been properly studied. The fact that Avastin, which contained polysorbate 20, had been administered intravitreally off-label would provide some reassurance to the Formulation Scientist, but they would still want to investigate the safety of polysorbate before using it in a formulation intended for intravitreal administration, given that Avastin was not approved for intravitreal use. Details following on from this paragraph are disputed and I deal with that below.

Tonicity agents

147. A tonicity agent, also known as a tonicifier, is an excipient used to adjust the tonicity of a solution so as to achieve the appropriate level of

osmolarity/osmolality. At the Priority Date, salts and sugars were typically used as tonicity agents, with sodium chloride being most common.

Formulations of VEGF Antagonists

Macugen

148. The Formulation Scientist could have obtained the Macugen label and what it states with respect to the formulation is set out below:

    i) "MACUGEN® (pegaptanib sodium injection) is a sterile, aqueous solution containing pegaptanib sodium for intravitreous injection. Macugen is supplied in a single-dose, pre-filled syringe and is formulated as a 3.47 mg/mL solution, measured as the free acid form of the oligonucleotide. The active ingredient is 0.3 mg of the free acid form of the oligonucleotide without polyethylene glycol, in a nominal volume of 90 µL. This dose is equivalent to 1.6 mg of pegaptanib sodium (pegylated oligonucleotide) or 0.32 mg when expressed as the sodium salt form of the oligonucleotide moiety. The product is a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide to adjust the pH and water for injection"

    ii) "Macugen is formulated to have an osmolality of 280-360 mOsm/Kg, and a pH of 6–7."

    iii) "Store in the refrigerator at 2° to 8°C (36° to 46°F). Do not freeze or shake vigorously."

149. If the Formulation Scientist wished to find information on the amounts of the excipients included in the formulation of Macugen in order to check which excipients had been shown to be suitable for intravitreal use, the Formulation Scientist could search the literature and identify from its FDA drug approval package that it contained 9.0 mg/ml sodium chloride, 0.77 mg/ml monobasic sodium phosphate monohydrate and 1.2 mg/ml dibasic sodium phosphate heptahydrate.

Avastin

150. The Formulation Scientist could have obtained the Avastin label. It states with respect to the formulation:

    i) "AVASTIN is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion. AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose

dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection"

ii) "AVASTIN vials must be refrigerated at 2−8°C (36−46°F). AVASTIN vials should be protected from light. Store in the original carton until time of use. DO NOT FREEZE. DO NOT SHAKE."

iii) "AVASTIN is supplied as 4 mL and 16 mL of a sterile solution in single-use glass vials to deliver 100 and 400 mg of Bevacizumab per vial, respectively. Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN (25 mg/mL). NDC 50242-060-01 Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN (25 mg/mL). NDC 50242-061-01"

Agreed CGK - clinical

Biology of eye

151. The human eye's primary physiological process is photoreception, the process by which light energy is converted into electrical signals through specialized photoreceptor cells in the retina. These cells cannot regenerate and what is dead is lost forever.

152. In summary the structures of the eye include:

i) the sclera – the opaque, white layer that covers most of the surface of the eyeball;

ii) the choroid – a layer of vascular tissue which sits between the sclera and the retina. It consists mainly of blood vessels which supply nutrients and oxygen to the retina, macula and optic nerve;

iii) the retina – a transparent layer at the back of the eye which contains millions of light sensitive, photoreceptor cells (rods and cones) and other nerve cells that organize and transmit nerve impulses from the photoreceptors to the brain;

iv) the macula – a small area, near the middle of the retina, at the back of the eye. It is responsible for most of our "straight ahead" vision. In the centre of the macula is a depression known as the fovea; and

v) the vitreous or vitreous humor – a jelly-like substance of around 4 to 5 ml in volume that fills the cavity of the eye between the lens and the retina.

153. The eye contains two main fluid compartments:

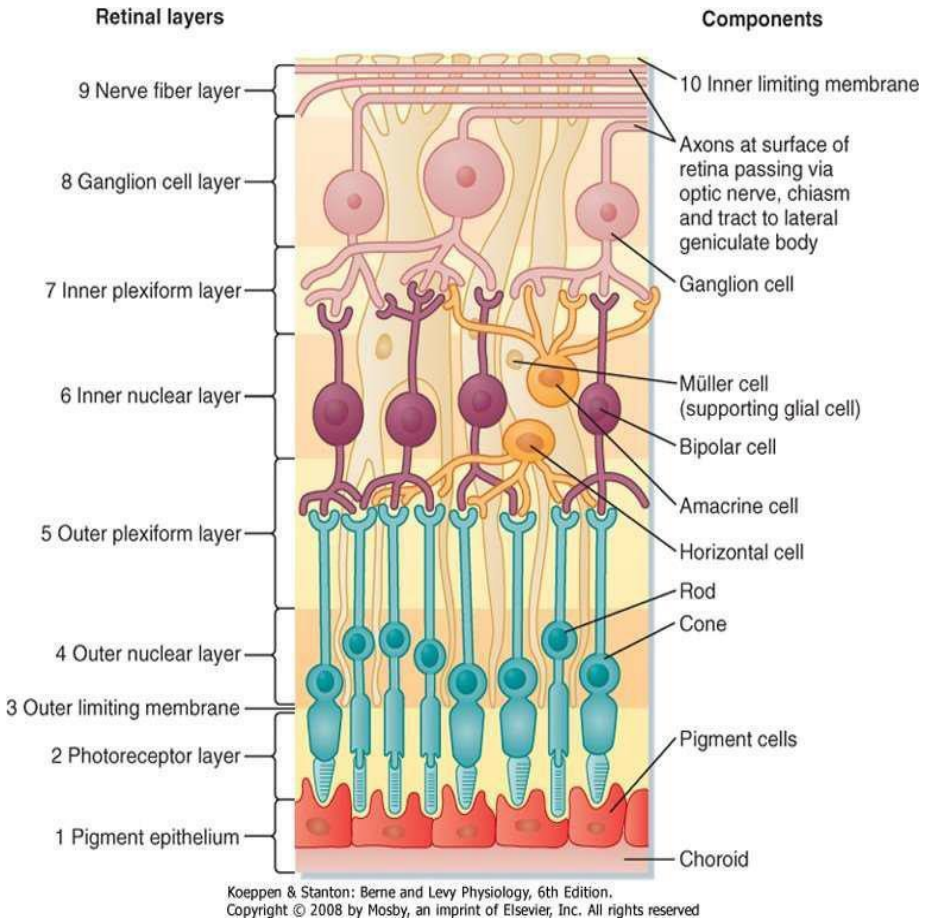
i) The anterior segment, located between the cornea and the lens with a volume of around 0.5 ml and containing aqueous humor.

ii) The vitreous cavity, in the posterior segment, comprising the central region of the eyeball beneath the lens and in front of the optic nerve. This contains the vitreous humor.

154. The retina is one of the most metabolically active tissues in the human body and therefore requires a constant blood supply. There are two distinct vascular networks which supply blood to the retina:

i) The retinal vasculature supplies oxygen and nutrients to the cells of the inner retina. The blood vessels of the retinal vasculature branch out from the central retinal artery which brings oxygenated blood into the eye and are dispersed over the inner surface of the retina. Deoxygenated blood from the retinal venules collects into the central retinal vein which carries it out of the eye. Although the blood vessels of the retinal vasculature extend over most of the inner surface of the retina, they do not cover the macula, where they would obstruct the passage of light and disrupt the detailed vision provided by the photoreceptors in this region. The macula is therefore exclusively supported by the choroidal vasculature.

ii) The choroid forms a vascular bed surrounding the outside of the retina, which supplies oxygen and nutrients to cells of the retina, including photoreceptor cells as illustrated in Figure 6. The choroid contains the basement membrane (Bruch's membrane) and blood vessels that support the RPE, which collectively form the 'choriocapillaris'.



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

The choroid comprises of multiple components:

iii) Bruch's membrane, the innermost layer of the choroid sitting beneath the RPE and acting as a barrier between the retina and choroid. It acts as a physical and biochemical barrier between the retina and the choroid.

iv) The choriocapillaris, a layer of densely filled capillaries that provides nutritional support for the retina, particularly the photoreceptors in the neurosensory retina.

v) The vascular layer, a highly vascularized layer that sits beneath the choriocapillaris and consists of intermediate-sized vessels, major arteries and veins.

vi) The suprachoroid, a thin space, called suprachoroidal space, located between the choroid and sclera.

Drug delivery to the eye

155. There were several forms of known drug delivery for drugs to reach the eye at the Priority Date:

i) Topical administration: this administers the drug to the cornea or the conjunctiva and is usually in the form of eye drops.

ii) Subconjunctival injection: this involves injections of the medication underneath the conjunctiva into the tenon and episcleral tissue of the eye (the outermost layer of the sclera).

iii) Intravitreal administration: this involves injections directly into the vitreous humor (as described further below). This is suitable for drugs which must reach a site of action behind the lens.

iv) Systemic administration: drugs can be introduced into the systemic system (i.e. blood) for example by oral or intravenous administration. Much smaller quantities of the drug reach the eye than if the drug is introduced directly into the eye, often due to the 'liver filter', and so generally larger doses of the drug are required. There is also a greater potential for systemic side effects.

156. The mode of administration primarily depends on the site of action for the drug in question. For example, topically administered drugs are generally only suitable where the site of action is the anterior segment of the eye.

Disorders Treated by Intravitreal Administration

157. Intravitreal administration is primarily used where a drug's site of action is behind the lens, i.e. the vitreous, the retina and/or the choroid, and therefore introducing the drug into the vitreous brings it closer to its site of action. One of the major uses of intravitreal administration in 2006 was to administer drugs for the treatment of retinal disorders such as wet AMD and diabetic retinopathy.

AMD

158. AMD is the leading cause of blindness in developed countries. The risk of AMD rises significantly with age, with the majority of patients being over 60. There are two main forms of AMD: non-neovascular AMD ("dry AMD") and neovascular AMD ("wet AMD").

Wet AMD

159. At the Priority Date and today, wet AMD was the disease with the largest market for anti-VEGF treatments and was the primary focus of clinical research.

160. It is known as "wet" because it is characterized by the abnormal growth and leakage of blood vessels from the choroid into the retina. This abnormal growth of blood vessels from the choroid is called choroidal neovascularization or "CNV". Patients with wet AMD typically present with sudden-onset vision loss, visual distortion and blind or blurry spots in the centre of their vision. The major clinical signs of wet AMD include a thickening of the retina caused by sub- and/or intraretinal fluid and/or haemorrhage, and the appearance of subretinal lesions which may be pigmented. This can lead to detachment of the RPE or retina, or intraretinal fluid, leading to vision loss. Chronic wet AMD is also characterized by the presence of subretinal fibrosis, i.e. scar tissue formed as a result of a wound healing response to CNV, or secondary atrophy.

161. CNV may be further categorised as "classic" or "occult". In classic CNV the blood vessels grow through the RPE and into the subretinal space. In occult CNV the blood vessels grow below the RPE.

162. If left untreated, the natural progression of wet AMD is a worsening and loss of central vision as photoreceptors are irreversibly damaged, and blood vessels are replaced by a fibrovascular scar, eventually potentially leading to legal blindness (corrected visual acuity of less than 1:20).

Diabetic retinopathy (DR) and diabetic macular edema (DME)

163. In patients with diabetes, blood vessels and capillaries throughout the body are affected. Small capillaries are affected more than other types of blood vessel. Over time, hyperglycemia can cause hyperpermeability (excess blood vessel leakage, potentially responsible for the development of DME) and ischemia (a restriction of blood supply). When this occurs in the small blood vessels in the eye, there may be leakage of fluid and/or haemorrhage into the retina. Patients with more serious forms of DR can also see the development of new blood vessels on the surface of the whole retina which is known as 'proliferative' DR. This is in contrast to wet AMD where neovascularization is subretinal and limited to the macula. Around one-third of patients with diabetes develop DR.

Role of VEGF in Angiogenesis

164. Angiogenesis is the process by which new blood vessels grow ("neovascularisation"). It is a normal process, but abnormal angiogenesis is involved in several retinal disorders including wet AMD and proliferative DR.

165. In the 1990s, one particular growth factor termed vascular endothelial growth factor ("VEGF") had been identified, which was found to play a critical role initiating and controlling angiogenesis. VEGF had also been identified as a controlling factor in vascular permeability.

166. Molecules of VEGF bind to VEGF receptors which are located on the surface of endothelial cells (these cells form the walls of capillaries, as well as lining all larger blood vessels). There are a number of different VEGF receptors, namely:

    i) VEGFR1 (also called "FLT1" in humans);

    ii) VEGFR2 (also called "KDR" in humans, "Flk-1" in mice); and

    iii) VEGFR3 (also called "FLT4").

167. In the early 2000s, VEGF blockade had been established as a successful strategy in cancer treatment (see further below with regard to Avastin). However, it was also well established that VEGF played a principal role in a number of non-neoplastic diseases (e.g. diseases which do not cause tumour growth), including eye diseases characterised by neovascularisation and vascular permeability, such as wet AMD and diabetic retinopathy. From at least the early 2000s it was anticipated that a similar "anti-VEGF" approach may also be effective in the treatment of these diseases.

168. In animal models of eye disease, VEGF had been shown to induce the ocular neovascularisation associated with diseases including proliferative DR and wet AMD.

169. In human studies, elevated concentrations of VEGF were found to be present in the vitreous of patients with DR and in surgically excised choroidal neovascular membranes from patients with wet AMD.

170. By June 2006, the strong evidence for the critical role of VEGF in eye diseases characterised by neovascularisation and vascular permeability had led to a number of VEGF inhibitors being studied in clinical trials. One had been approved (Macugen/pegaptanib sodium) and another was in the final stages of development (Lucentis/ranibizumab). Avastin/bevacizumab had also been administered intravitreally ("off-label") by that time for the treatment of wet AMD. Each of these is discussed further below.

Intravitreal and Intravenous Administration

171. An advantage of intravitreal administration is that it produces a high localized concentration of the drug in the eye close to the site of action and therefore a lower dose can be used. The drug will still be cleared from the eye into the

systemic circulation, but as less of the drug is given via this route, it leads to relatively low systemic concentrations compared to systemic administration. Systemic side effects would be expected to be lessened compared to systemic administration. However, intravitreal administration could still lead to systemic side effects.

172. Intravitreal administration had to be done by a trained clinician. It is also unpleasant for the patient and both of these issues lead to problems with patient compliance. Frequent intravitreal injections can be challenging for elderly patients and are also a burden on healthcare providers. There is also a risk of complications due to, for example, a rise in intraocular pressure following injection as a result of the volume administered, which can cause irreversible damage to the eye and also infection from penetrating the eye. Other complications include eye pain, inflammation, bleeding, and, rarely, retinal detachment or damage to the lens during injection.

173. Intravenous injections are less of a burden but higher doses need to be given than if the drug is injected directly into the eye to obtain similar intravitreal concentration, which can cause relatively high systemic drug concentration.

Assessing Progress of Retinal Diseases in Patients

Visual Acuity

174. The standard measure of eyesight is visual acuity. This is assessed using "best corrected visual acuity" (BCVA) which measures a patient's vision with the best possible correction using glasses or contact lenses. The standard clinical method was to use a visual acuity chart, including the standardized Early Treatment Diabetic Retinopathy (ETDRS) chart adopted for clinical trials, which contains five-letter lines with the size of the letters in each row decreasing down the chart in a logarithmic progression. The BCVA is recorded as the total number of letters (or lines) read at the specified distance.

175. Visual acuity is scored in one of two ways:

    i) reference to a number of lines; or

    ii) if the acuity chart has the same number of letters in each row (such as the ETDRS chart), the total number of letters correctly identified by the patient.

176. Since patients with wet AMD or DME typically experience compromised visual acuity as central vision generally worsens over time, one of the primary markers for efficacy of any treatment at the Priority Date was stabilization in visual acuity. This was also because at the Priority Date the only authorized treatment available for wet AMD only delayed the loss of vision. For the purpose of clinical trials, 'stabilization' of visual acuity was generally considered to be a loss of fewer than 15 ETDRS letters over a specified period.

Monitoring Anatomical Changes

177. It was also common practice at the Priority Date to supplement visual acuity with more objective techniques: optical coherence tomography ("OCT") and fluorescent angiography ("FA"). These are not direct measurements of eyesight but provide evidence of the anatomical features associated with wet AMD, DR and/or DME.

178. Patients with wet AMD or DME commonly experience a thickening of the retina. The efficacy of treatments can therefore be measured by the reduction in the central retinal thickness, presence and quantity of fluids, and how long this reduction is maintained.

179. In day-to-day clinical practice, the Clinical Ophthalmologist would be more focused on OCT and FA measurements on the basis that anatomical changes usually occur before visual acuity is affected. However, when measuring the efficacy of any treatment, in particular in the context of clinical trials, the key indicator of efficacy would have been on the visual acuity results.

History of treatments for AMD and diabetic retinopathy

180. In the early 2000s there were no effective treatments for dry AMD and only very limited treatment options for wet AMD. The treatment options available could only be used in a minority of cases and their efficacy was limited to slowing progression of the disease. There were no treatments that could reverse sight loss that had already occurred. Typically, clinicians would diagnose AMD and then discuss dietary and lifestyle advice with the patient, which might help to reduce the rate of disease progression. Most patients were then discharged because there was no suitable treatment available to them.

181. For DR, treatment of early-stage disease was typically limited to improving patients' blood glucose control and blood pressure control, which had been established in trials in the 1990s to reduce the risk of progression to more severe disease. Other treatments were only available when non-proliferative DR became particularly severe, progressed to proliferative DR, or where complications such as DME were experienced.

Focal laser treatment

182. Focal laser treatment had been used since the 1960s to treat ophthalmic disease. In the most common type of focal laser treatment used in the early 2000s, laser energy was used to induce photocoagulation of the retinal blood vessels. Scarring caused by the laser permanently damaged the area of the retina which is targeted.

183. This meant that it was not suitable for patients (the majority) who had neovascularisation in the region of the fovea because damage to this sensitive region of the retina would result in immediate vision loss.

Photodynamic therapy

184. In the early 2000s, photodynamic therapy ("PDT") was introduced as an alternative to traditional laser focal treatment. Verteporfin, a light-activated photosensitizer, is injected intravenously, and then activated by an illumination at a specific wavelength to occlude abnormal vessels and prevent continued growth into the retina. PDT was administered to patients potentially every three months.

185. Although PDT represented a substantial improvement over traditional laser photocoagulation, a number of limitations and drawbacks remained. There remained a risk of severe, possibly permanent vision loss following treatment. PDT did not restore previously lost vision, and it was only effective in delaying worsening visual acuity in around one-third of patients with wet AMD, so there remained a significant need for more effective treatments even for patients who were eligible for PDT.

Treatment for DME and diabetic retinopathy

186. At the Priority Date, the typical approach to treating patients with DME was, excluding laser treatment, to first try to treat the underlying diabetes, for instance through dietary and lifestyle changes and monitoring medication for diabetes and blood pressure. For the later stages of DR, laser photocoagulation was performed. There was some off-label use of steroids.

Intravitreally Administered Treatments

187. At the Priority Date, some antibiotics and antiviral drugs were being routinely administered intravitreally but all off-label. Only one authorized intravitreal drug for the treatment of wet AMD, an anti-VEGF aptamer called pegaptanib sodium (marketed as Macugen), was being used. Pegaptanib sodium inhibited the activity of VEGF and therefore decreased the angiogenic activity in the eye. In addition to pegaptanib sodium, two other VEGF antagonists were being used or developed for the treatment of retinal disease.

Treatment for Wet AMD

188. Prior to the authorization of pegaptanib sodium the standard treatment for wet AMD was PDT.

Pegaptanib sodium (Macugen)

189. Pegaptanib sodium is an anti-VEGF aptamer. It was first authorized for the treatment of wet AMD by the FDA in December 2004 and the EMA in January 2006. It was not approved for DR or DME. It was given by intravitreal injection with a fixed regimen, once every 6 weeks. It was supplied in a pre-filled syringe which delivered a dose in a volume of 90 μL.

190. The Phase 3 studies for pegaptanib sodium (the "VISION") studies were reported in December 2004. The primary endpoint was the proportion of

patients losing fewer than 15 letters of visual acuity (which was the definition of 'stabilization' at the Priority Date) at 54 weeks compared to those receiving "sham" injections. 70% of treated eyes lost fewer than 15 letters of visual acuity compared to 55% receiving "sham" injections. In addition, the risk of severe loss of visual acuity (30 letters or more) was only 10% for the pegaptanib group compared to 22% in the control.

191. Following the EMA authorisation, Macugen was privately available to patients in the UK.

Bevacizumab (Avastin)

192. Bevacizumab (marketed as Avastin) is a full-length humanized monoclonal antibody which binds to and blocks VEGF. Bevacizumab was approved by the EMA in January 2005 and the FDA in February 2004 as a treatment for metastatic colon cancer. It was not authorized for the treatment of wet AMD or for intravitreal administration. However, by the Priority Date it had been administered intravitreally off-label for the treatment of wet AMD in a dose of 1.25 mg in a 50 µL injection following several case reports. There was not a formal dosage regimen for intravitreal administration of bevacizumab. In the literature it had been reported that it had been administered monthly for a limited period of time.

Ranibizumab (Lucentis)

193. Ranibizumab (marketed as Lucentis after the Priority Date) is a modified version of the fragment antigen-binding region (the "Fab" region) of bevacizumab and therefore is much smaller than bevacizumab. In June 2006 it was in the final stage of development by Genentech which is described in more detail below. As with bevacizumab, it was known that ranibizumab was a VEGF antagonist which bound all isoforms of VEGF-A.

Lucentis clinical trials

194. At the Priority Date, Lucentis's development was a significant ongoing event in the field and there was much anticipation of its approval and launch. The Clinical Ophthalmologist would have been following its development and the positive results of the clinical trials.

195. The results of a Phase 1/2 trial of Lucentis in which patients were randomised to receive either 0.3 or 0.5 mg of Lucentis by intravitreal administration every 4 weeks or "usual care" was published in Ophthalmology in April 2006 (Heier 2006).

196. The results of a Phase 1 study were published in Ophthalmology in 2005 (Rosenfeld 2005), patients were assigned to different dose groups and were administered a single intravitreal injection.

197. In a second Phase 1 study published in Ophthalmology in April 2006 (Rosenfeld 2006), patients were assigned to one of three escalating dose groups.

198. Two Phase 3 clinical trials, MARINA and ANCHOR, were commenced before the Priority Date.

199. In the MARINA trial, patients with minimally classic or occult wet AMD were randomised to receive monthly 300 or 500 µg doses of Lucentis, or a sham injection, for a period of 24 months. In the ANCHOR trial, patients with predominantly classic wet AMD were randomised to receive monthly 300 or 500 µg doses of Lucentis, or PDT, for 24 months.

200. The full reports of the MARINA and ANCHOR trials were not published at the Priority Date. However, preliminary results from both trials had previously been presented at meetings.

201. It was known that Lucentis had met its primary efficacy endpoint in the MARINA trial after 12 months.

Volume of administration

202. It was known that only limited volumes could be injected intravitreally, otherwise there could be a dangerous rise in intraocular pressure. Volumes up to 100 µL / 0.1 mL had been administered intravitreally: Lucentis (50 µL / 0.05 mL), Avastin (50 µL / 0.05 mL), Macugen (90 µL / 0.09 mL) and triamcinolone (100 µL / 0.1 mL).

Efficacy

203. The natural history for patients with wet AMD, DR and DME was a worsening of central vision over time and eventual loss. The authorized treatments at the Priority Date (PDT and pegaptanib sodium for wet AMD only) had been shown to be effective in delaying vision loss but for most patients with wet AMD, these treatments did not improve visual acuity.

204. However, it was well known that the Phase 3 trials with Lucentis had led to an improvement in vision. There were also some positive reports of the off-label use of Avastin.

205. At the Priority Date, Lucentis was not authorized, therefore, Macugen was still the only authorized drug and would have been the comparator for the design of a clinical trial with a new potential VEGF antagonist.

Duration of action/durability/interval between two injections

206. The Clinical Ophthalmologist would have been aware that a drug would need a sufficient duration of action so that injections into the eye were not too frequent due to the logistical challenges of repeated injections, their unpleasant

nature for the patient, and the potential complications as a result of the injection procedure.

207. The Clinical Ophthalmologist would have been aware that Macugen was dosed 6-weekly.

208. The Clinical Ophthalmologist would have been aware that Lucentis was dosed monthly in the MARINA and ANCHOR Phase 3 studies.

Toxicity/Side Effects

209. When developing or testing any VEGF antagonist therapeutic the Clinical Ophthalmologist would also consider any adverse effect of the treatment locally on the eye, such as ocular inflammation, immunogenic reactions or signs of toxicity in patients and also for systemic toxicity.

210. At the Priority Date, the primary systemic side effects that the Clinical Ophthalmologist would look for were infarction and stroke caused as a result of the drug itself because of systemic thromboembolic side effects seen following systemic administration of Avastin for cancer. Products administered intravitreally will also enter the systemic circulation. The risk of adverse events will depend on the dose administered although the dose administered intravitreally is relatively small.

Dose

211. The efficacy, duration of action and toxicity will be influenced by the administered dose. The commercial dose selected will be the result of careful consideration of toxicology studies and Phase 1, 2 and 3 clinical trials.

212. As regards safety, the Clinical Ophthalmologist would understand that generally higher doses increased the risk of toxicity and adverse effects, both local, and systemic side effects, including the chance for rarer side effects to arise once patient numbers increased.

Stages of drug development

213. The Clinical Ophthalmologist would have an understanding of the key stages of drug development, i.e. the process of bringing a new pharmaceutical drug to the market and the considerations and criteria the skilled team would have in mind during clinical trials.

Phase 1 studies

214. The first-in-human studies are called Phase 1 clinical trials. Based on the pre-clinical and animal efficacy and toxicity studies a number of doses would be selected to take into Phase 1 clinical trials. The first Phase 1 study conducted with a candidate intravitreal drug will normally be a single-dose, dose escalation study in which small groups of patients (usually around 3 to 5 per dose level) are administered the drug at a given dosage level. The patients are

monitored primarily for adverse events, although as phase 1 studies for intravitreal drugs were conducted in patients not healthy volunteers some measures of efficacy may also be monitored and reported. The primary objective of Phase 1 trials is to study the safety of the treatment.

Phase 2 studies

215. If the results from Phase 1 are positive the study would progress to a Phase 2 clinical trial to study both efficacy and safety over a longer period of time and in a larger number of patients, usually between around 50 to 200 in total. The trial will typically employ two or three different dose levels.

Phase 3 studies

216. The final stage of clinical development before applying for regulatory approval for the drug is to conduct Phase 3 trials.

217. A clinical Phase 3 study would test the product in around 300 patients per group. They would typically be multi-centre studies and would be randomized, controlled and double-blind.

218. To secure approval from relevant regulatory bodies, such as the FDA in the USA and the EMA in the European Union, typically a drug must successfully complete at least two similar Phase 3 trials.

Regulatory Approval

219. If the regulatory agencies are satisfied that the data from the Phase 3 trials establishes that the drug is safe and effective, they will grant a marketing authorisation which permits the company to begin selling the drug for clinical use.

Agreed CGK – protein engineering

Proteins

220. Proteins are biological molecules comprised of chains of amino acids linked by peptide bonds. There are 20 different naturally occurring amino acids. Each amino acid can be referred to by its full name, a three-letter code or a single letter code. For example, Alanine is Ala or A, and Arginine is Arg or R.

221. Amino acids share a common structure with an amino group (-NH2), a carboxylic acid group (-COOH), a single hydrogen and a variant (R) side-chain group branching from a central carbon atom (the α-carbon).

222. Amino acids may be classified on the basis of the properties of their R-group into one of four groups: (I) non-polar; (II) polar; uncharged; (III) acidic; and (IV) basic. Other systems of classification based on the structure or chemical characteristics of the amino acid side chains may also be used. The amino acids can also be categorised as hydrophilic and hydrophobic, with the hydrophobic

amino acids being those that are non-polar and the remainder being hydrophilic.

223. Neighbouring amino acids in a protein molecule are linked through covalent peptide bonds (proteins may also be referred to as polypeptides). The properties of the specific amino acids of a given protein will affect the structure and function of that protein.

Protein Structure and Folding

224. Protein folding is the process by which a linear polypeptide chain folds into a specific three-dimensional structure necessary for its biological function. There are four levels of structural organisation to a protein:

    i) The primary structure is simply the sequence of the amino acids in the polypeptide that is produced by the process of translation.

    ii) The secondary structure is defined by the conformation of the polypeptide backbone, which generally forms a regular arrangement of amino acids.

    iii) The tertiary structure is the three-dimensional structure of the protein. It is formed by the folding of the secondary structural elements of a protein and is determined by the properties of the side chains of the amino acids that make up the primary structure. The tertiary structure is formed largely due to the hydrophobic (non-polar) side chains being buried in the core (where water is largely excluded) and the majority of the hydrophilic (polar) side chains being exposed on the surface (where they can interact with water).

    iv) The quaternary structure is the binding together of multiple proteins to form larger protein complexes. For example, two proteins can associate together to form a dimer, or multiple proteins can associate together to form a multimer.

225. The structure of a protein is also influenced by the formation of disulfide bonds. Disulfide bonds are covalent bonds formed between the sulfur atoms of cysteine residues on the same (intra-chain) or a different (inter-chain) polypeptide chain. Intrachain disulfide bonds stabilise a protein's secondary and tertiary structure, whereas inter-chain disulfide bonds stabilise a protein's quaternary structure.

226. The process by which a protein undergoes folding varies across eukaryotic and prokaryotic cells due to differences in their cellular environment, chaperone systems (i.e., systems that use specialized proteins to assist in translocation and folding of proteins) and post-translational modifications.

Protein expression

227. Protein expression is a fundamental process of biology and is the mechanism by which proteins are synthesised based on instructions encoded for within deoxyribonucleic acid (DNA).

228. All cells – eukaryotes (mammalian, insect, plant, yeast and fungi) and prokaryotes (such as bacteria) – produce proteins as part of their natural processes. Protein expression varies in prokaryotic and eukaryotic cells. Prokaryotes are single celled organisms; their cells are simpler and lack a nucleus.

229. In the first step of protein expression, DNA is transcribed into mRNA. In eukaryotic cells this happens within the nucleus of the cell and in the cytoplasm of the prokaryotic cell. The mRNA undergoes several post-processing steps, and (in the case of eukaryotic cells) is then transported out of the nucleus to the cytoplasm.

230. The open reading frame (ORF), or coding region, of an mRNA encodes the protein and is translated into protein by ribosomes.

231. After translation, the newly formed polypeptide chain may undergo various post-translational modifications to become a functional protein. The type and nature of such post-translational processes will vary depending on the type of cell in which the protein is produced.

Post-translational modifications

Signal peptide cleavage

232. Secretory proteins are proteins that are actively transported out of the cell following production. Secretory proteins possess an amino acid sequence known as a signal peptide sequence. Enzymes called ‘signal peptidases’ cleave the signal peptide.

233. Both prokaryotic and eukaryotic proteins can include signal peptides. Signal peptides generally consist of between 15 to 30 amino acids. These sequences are most commonly located at the N-terminus of the peptide sequence.

234. Signal peptides can often be identified due to the high proportion of hydrophobic residues they contain and cleavage sites are often indicated by small uncharged residues one residue before in the sequence and small or larger aliphatic residues three residues before.

Glycosylation

235. Proteins produced in eukaryotic cells are commonly glycosylated, a process which involves the attachment of carbohydrate residues, also referred to as glycans, to specific amino acid residues on the protein. By contrast, it was known that proteins are typically not glycosylated when produced in prokaryotic cells.

236. Eukaryotic glycosylation was known at the Priority Date to play a role in improving protein stability and increasing protein half-life.

237. N-glycosylation, the most common form of glycosylation for secreted and membrane-bound proteins, occurs at the side-chain amino group on asparagine (Asn) residues and occurs where the following sequence motif is present: Asn-Xaa-Ser/Thr, where Xaa can be any amino acid except proline. Where this sequence is present, the asparagine may be glycosylated. The size of the glycan attached at a specific N-linked glycosylation site varies and in the majority of cases is made up of approximately 7 to 19 monosaccharide units.

238. O-linked glycosylation can occur at the oxygen of the hydroxyl group on serine or threonine residues. Unlike for N-linked glycosylation, it is not possible to predict, based on the sequence, where O-linked glycosylation will take place. The structure of both N-linked glycans and O-linked glycans will differ between eukaryotic species in terms of size and complexity.

239. Complex oligosaccharides can have 2, 3 or 4 branches. The sugar structures on each branch are built up in such a way that it is common to have incomplete additions, but if glycosylation runs to completion, then each branch can be terminated via a sialic acid residue. The terminal residues are typically present in fractional amounts, resulting in a large mixture of different possible lengths within the same structural families.

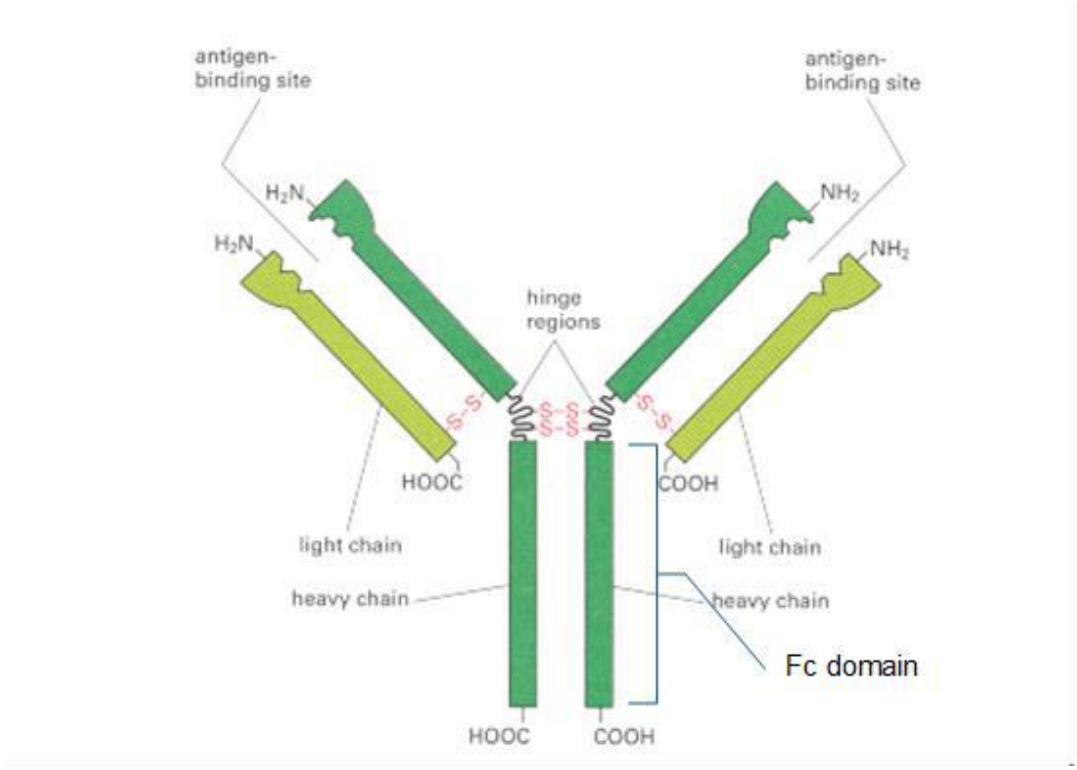
240. Whilst all other sugar residues that can be part of the glycan are neutral, sialic acids have a carboxylate group that can ionise and contribute to the overall protein charge. This impacts the isoelectric point of proteins.

Therapeutic Proteins

Antibodies

241. Antibodies were the most common therapeutic proteins produced recombinantly. Antibodies are a type of protein that are produced by the immune system to recognise and bind to specific antigens, which are typically foreign molecules that elicit an immune response. Antibodies (or immunoglobulins (Ig)) are classified into five major classes based on their structure and function: IgA, IgD, IgE, IgG and IgM. The classes are related in structure, though IgA has two linked structures and IgM has five.

242. An antibody has a Y-shaped structure, with the two arms of the Y being the Fab (fragment antigen-binding) region and the stem of the Y being the Fc (fragment crystallisable) region. The Fab region is highly specific and diverse, being responsible for binding to the antigen. The Fc region is responsible for interacting with other immune cells and molecules.



Structure of the basic functional unit of an antibody (disulfide bonds in C region of FC, not shown).2 "-S-S-" indicates a disulfide bond.

243. Monoclonal antibodies or mAbs are synthetic therapeutic antibodies that are designed to bind to an antigen on a specific protein, cell or pathogen as a means to treat disease by neutralizing or modulating the activity of the target. Antibody fragments are typically fragments of the binding portion of a mAb (and are thus smaller than the full-length mAb).

Fusion proteins

244. Fusion proteins are artificial proteins that are made by joining together different proteins (or protein domains) to make a new molecule, typically in order to enhance stability, increase the half-life of the protein, reduce immunogenicity, improve targeting and / or modify the function of the original protein. Therapeutic fusion proteins typically comprise a biologically active protein (such as a cytokine, receptor or enzyme) and a stabilizing component (such as the Fc region of an antibody), with the latter intended to prolong circulation time and / or reduce degradation of the protein. Each part of the fusion protein would typically be expected to behave as they would naturally.

Online resources for protein analysis

245. Two online tools that were routinely used at the Priority Date were:

    i) SignalP 3.0: a platform which could assess an amino acid sequence and predict: (i) the presence of a signal peptide sequence; and (ii) the location of its cleavage site (at a single amino acid position, or over a short range of amino acids). The algorithm allowed for predictions in the context of

different organisms (prokaryotes and eukaryotes). The platform required an amino acid sequence of the protein. Different methods for the analysis could be chosen ("neural networks", "Hidden Markov models", or both). SignalP 3.0 can predict the presence (or absence) of a signal peptide with a high degree of certainty and estimate (with a lower degree of certainty) the likely cleavage site(s) for that signal peptide.

ii) Compute pI/Mw: a tool for calculating the theoretical isoelectric point of a protein, and its molecular weight, based on its amino acid sequence.

Manufacture of recombinant therapeutic proteins

246. Proteins can be produced by chemical synthesis or in cellular expression systems. The most common method to produce large therapeutic proteins is using a cell-based expression system.

247. Recombinant protein expression is a biotechnological process that involves the production of proteins by genetically engineered cells. This technique is widely used in the manufacture of therapeutic proteins to produce proteins in large quantities.

248. This involves creating a DNA construct for the target protein, inserting it into an expression vector, introducing it into a host cell, and ensuring its expression.

Expression in the host cell

249. The necessary DNA is introduced into the host cells in which the protein of interest is to be expressed. These host cells can be eukaryotic – mammalian, insect, plant, yeast or fungi – or prokaryotic (bacterial).

250. The cellular machinery of the host cell transcribes the DNA and translates that mRNA into the protein of interest.

251. When the protein is expressed in a cellular system each domain needs to be correctly folded and retain its native structure, as this is essential for maintaining the function and biological activity of the protein.

Cell systems

252. There were established eukaryotic and prokaryotic cell lines which were commonly used as host cells for recombinant protein expression. The Protein Engineer would have been aware, in particular, that *E. coli* and CHO cell lines had been used to produce therapeutic proteins that had received regulatory approval.

253. The prokaryotic cells relevant for the purposes of recombinant protein production are bacterial cells. Prokaryotic cells can be advantageous due to the ease with which culture can be grown and the high yields that can be produced, however they are less-equipped to carry out the post-translational modifications that are found in many large proteins that are in clinical use. *E. coli* was a commonly used prokaryotic expression system.

254. Eukaryotic cells, such as mammalian, yeast, and insect cells, may be used to produce glycosylated proteins. The CHO (Chinese hamster ovarian) cell expression system is a standard expression system for the expression of recombinant therapeutic proteins.

255. It was well known at the Priority Date how eukaryotic cells (particularly mammalian, yeast and insect) could be effectively cultured and the conditions in which expression could be maximized.

256. **Mammalian cells**: at the Priority Date, mammalian cell expression systems were used routinely for the production of recombinant proteins for use as therapeutics in humans. Various established cell lines were in use at the Priority Date for different applications. These included Human Embryonic Kidney (HEK) 293 cells, cells derived from African green monkey kidney (COS), baby hamster kidney (BHK) cells, various murine cell lines and CHO cells. CHO cells were routinely used for stable protein expression and / or when high yields were required, and were the preferred system for synthesis of therapeutic proteins

257. At the Priority Date it was known that mammalian cells had the following advantages as expression cell lines for recombinant proteins for human therapeutic use:

    i) they produce proteins that have characteristics that more closely resemble naturally occurring human proteins;

    ii) in particular, they typically produce recombinant proteins with the full complement of post-translational modifications, and complete folding;

    iii) for secreted proteins, yields were generally much higher compared to other expression systems; and

    iv) as addressed above, the mammalian CHO cell line was known to have been used to produce therapeutic proteins that had received regulatory approval.

258. The key limitations of mammalian cell lines at the Priority Date were that their use for the industrial production of recombinant proteins was costly and typically slower.

Protein characteristics

259. Based on their specific amino acid sequence and structure, proteins can have varying levels of stability.

Molecular weight

260. The molecular weight of a protein is the average weight of one mole of the protein. It is generally expressed in Daltons (Da) or kiloDaltons (kDa).

261. The molecular weight of a protein can be approximated using an electrophoresis technique, such as SDS-PAGE (gel electrophoresis) or measured more accurately using a mass spectrometry technique.

262. It is also possible to estimate the molecular weight of a protein based on its amino acid sequence with online tools such as ExPASY. To calculate the molecular weight, ExPASY adds together the weight of each individual amino acid residue within the sequence. If the protein is glycosylated, the weight of the N-linked glycans attached to the protein has to be accounted for separately, since ExPASY will only calculate the weight of the primary amino acid sequence.

263. As the weight of the glycans added by glycosylation is variable and as a glycosylation site may not always be glycosylated, the additional molecular weight for each molecule will not be known precisely and there will be a spectrum of molecular weights for the variously glycosylated forms. The presence of O-linked glycosylation is more difficult to predict than N-linked glycosylation, and the mass of any O-linked glycans is less due to their reduced size. Unless it was known that O-linked glycosylation was present, it would be usual to calculate the protein molecular weight (and other physical characteristics) on the assumption that O-linked glycosylation was absent.

Isoelectric point (pI)

264. Five amino acid side chains contain ionisable groups that are able to accept or lose hydrogen ions under physiological conditions. The side chains of aspartic acid and glutamic acid are acidic, meaning that they can lose hydrogen ions and become negatively charged. In comparison, the side chains of histidine, lysine and arginine are basic, meaning they can gain hydrogen ions and become positively charged. The N-terminus of the protein is also positively charged while the C-terminus is negative. The charge state depends on the ionisation constant (pKa) of the residue in question, which is the pH value at which half of the species in a solution will be in their ionised form. A residue's pKa value is primarily due to its chemistry but can also be influenced by the spatial location of the residue within the protein structure. Certain protein modifications, for example glycosylation, can also result in additional charged groups on the protein. At any given pH there will therefore be a net charge that is either positive or negative depending on the protein's sequence and pattern of post-translational modification. The pH at which the net charge balances out to zero is the isoelectric point, or pI.

265. ExPASY can also be used to calculate theoretical pI values for proteins based on the intrinsic pKa value for each ionisable group in the protein. ExPASY uses the pKa values of ionizable groups on the amino acids of the protein (side chains plus the N- and C-termini) to determine the pH at which the net charge is zero.

266. Glycosylation is inherently heterogeneous. In addition, the calculated pI value assumes that the ionisation of each group is independent and unaffected by protein folding when in reality protein folding does affect the ionization of

buried residues. The 3D structure of the protein may well cause the calculated pI to differ from the measured pI. ExPASY does not account for folding of a protein, multimerization or post-translational modifications such as glycosylation.

267. The isoelectric point of a protein can also be measured experimentally, for example by using isoelectric focussing (which gives a range of results for glycosylated proteins including sialic acid residues).

Physical instabilities

268. Physical instability arises as a result of non-covalent changes that disrupt the structure of the protein over time. Aggregation is an example of physical instability, and is the clumping together of protein molecules. This occurs when the exposed hydrophobic residues in one protein interact with the exposed hydrophobic residues on an adjacent protein. Protein aggregation can lead to precipitation, which is when the aggregates are of a sufficiently large size that they fall out of solution. Based purely on its amino acid sequence, it was not possible to predict the level of solubility of a protein or its propensity to aggregate. However, it would be expected that proteins would be least likely to be soluble if the pH of the solution was at their pI, where the protein would be uncharged.

Chemical instabilities

269. Any change that is a result of a chemical modification in the protein sequence can have direct and indirect influences on the protein's biological properties. If close to the binding site then this could directly influence the protein's ability to bind to its target and hence its biological activity through that binding. However, any chemical modification to the protein can also impact on its solubility and its propensity to aggregate, resulting in insoluble or aggregated proteins with no or reduced biological activity.

Deamidation

270. Deamidation is a spontaneous chemical reaction where an amide in the side chain of asparagine or glutamine is hydrolysed.

271. The deamidation reaction involves water and therefore there is a greater risk of deamidation where the asparagine is solvent exposed, and a lesser risk when the residue is buried inside the protein.

Oxidation

272. Oxidation is a chemical reaction where amino acid side chains, especially those that contain sulfur or nitrogen atoms, are modified by oxidising agents, which includes molecular oxygen.

273. Methionine residues carry the greatest risk of oxidation, because of the inherent susceptibility of their sulfur atom. Methionine oxidation occurs when the sulfur atom in methionine attacks the electrophilic oxygen of the oxidising agent.

274. Cysteine residues also contain a sulfur atom and are therefore at risk of oxidation, however this risk is significantly decreased if the cysteine residue is connected to another cysteine residue through a disulfide bond.

Glycosylation changes

275. Lack of a glycan attached to a site (i.e., N-linked and O-linked glycosylation sites) that is usually glycosylated can cause changes in the protein's hydrophilicity and charge distribution.

Disulfide bond cleavage

276. Cleavage and/or rearrangement of disulfide bonds can significantly alter the conformation of the protein and lead to loss of function.

Agreed CGK – PK/PD

Structures of the eye relevant to intravitreal administration

277. The Ocular PK/PD Scientist would have a good general understanding of the biology and structure of the eye.

278. Following intravitreal administration, drugs move within the vitreous humor via diffusion, a process which can sometimes be affected by the location of the needle tip, the composition of the vitreous humor, and the physicochemical properties of the drug. It is expected that the distribution of most drugs within the vitreous humor itself would be unhindered.

Ocular PK

279. The overall field of PK and PD was well-developed in 2006 but the same cannot be said for ocular PK and PD, which would have been regarded as a more specialist area in the wider field. Concepts of ocular PK/PD are different from PK/PD principles following systemic administration.

280. PK, which is considered to encapsulate the effect of the body on a drug, can be split into four main PK concepts that are commonly referred to by the acronym 'ADME'; absorption, distribution, metabolism, and excretion. ADME can be applied in the intravitreal administration context but the considerations for each may differ compared to other forms of administration.

Absorption

281. Absorption is typically defined as the process by which a drug enters the systemic circulation. For drugs administered intravitreally, absorption into systemic circulation is not a consideration for therapeutic efficacy because the

drug is directly administered into the vitreous and the site of action is located in the eye.

Distribution

282. Distribution is the movement of the drug within the body. Following intravitreal administration, it is the movement of the drug within the vitreous and into neighbouring tissues and compartments of the eye. The properties of a drug, such as its size, may influence its diffusion within the vitreous and subsequent passage into neighbouring ocular tissues and compartments.

Metabolism

283. Metabolism is the breakdown of the drug within the body. The primary site of metabolism is the liver which is of less relevance for drugs administered intravitreally in terms of its therapeutic effect where the drug is injected directly into the eye. Even so, it was understood in 2006 that there may be limited metabolic activity in the eye that can cause drug breakdown.

Excretion

284. Excretion is the removal of the drug from the body. For an intravitreally administered drug, the drug passes from the eye into the systemic circulation via two routes; the 'anterior route' and the 'posterior route'. Once it is in the systemic circulation it will be broken down and eliminated via the usual pathways.

285. In the anterior route the drug diffuses through the vitreous to the front of the eye into the aqueous humor. The drug is then eliminated from the front of the eye and into the systemic circulation. The posterior route requires the drug to penetrate from the vitreous humor into the retina crossing the various layers before finally crossing the RPE, Bruch's membrane, and then into the choroid. The choroid contains blood vessels, which the drug can enter and pass into the systemic circulation.

286. Smaller molecules tend to be eliminated at a faster rate than larger molecules.

287. Within ADME, there are certain key pharmacokinetic parameters. These are as follows:

    i) Half-life is defined as the time taken for the concentration of a drug in a particular compartment or tissue to decrease by 50%. For drugs administered intravitreally, the half-life can theoretically be assessed in each of the vitreous humor, aqueous humor, retina, choroid, and the plasma.

    ii) C_{max} is the measured maximum concentration of a drug in a particular compartment or tissue following administration. As for half-life, the C_{max} may vary between different compartments or tissues. Following intravitreal administration, theoretically, and assuming a well-mixed

sample has been obtained, the maximum concentration in the vitreous is the dose of drug administered divided by the volume of the vitreous (including any injection volume).

iii) T_{max} is the time taken for a drug to reach C_{max} in a particular compartment or tissue following administration. As above, the T_{max} may vary between different compartments or tissues.

iv) AUC (area under the curve) is an expression of concentration over time of a drug and characterizes distribution and elimination following intravitreal administration. AUC is a useful measure that can be used to compare the exposure of the body or eye to two different drugs over time.

288. There are difficulties in assessing pharmacokinetic parameters in the human eye. The primary difficulty is sampling. Even for the vitreous and aqueous humors, liquid bodies that can theoretically be aspirated, insertion of a needle into the eye is required to extract a sample, and this can lead to a risk of infection for the patient. It therefore has ethical barriers if it is conducted just for scientific research.

Use of animals in ocular pharmacokinetic studies

289. As a result of the difficulties in sampling the human eye to obtain pharmacokinetic information it is standard practice to use animals to carry out ocular PK/PD studies. Rabbits are commonly used in pharmacokinetic studies of ocular drugs because they are relatively inexpensive and have relatively large eyes which facilitate dosing and sampling. However, there are significant anatomical and physiological differences between rabbits and humans. Other animals that are commonly used in ocular pharmacokinetic studies are mice, rats, pigs, dogs, and non-human primates (including monkeys). Monkeys are the gold standard model as they are closest anatomically and physiologically to humans. However, monkey studies are expensive, and their use poses ethical challenges, so they would usually only be conducted later in the pre-clinical drug development process.

290. In addition to the differences between the human and animal eye, sampling in animals also raises (different) problems.

Pharmacokinetic modelling

291. Unlike for systemically administered drugs, in 2006 there were no well-established methods, models, or algorithms for accurately predicting the human PK of drugs administered by intravitreal injection based on animal data that the Ocular PK/PD Scientist would routinely use. The Ocular PK/PD Scientist would have been aware of early attempts to develop such models or one-off descriptive 'modelling' of agents administered intravitreally but none of these would have been sufficiently validated or established to be relied upon routinely in drug development.

Efficacy

Potency for target

292. Potency is a measure of the strength of a drug to achieve a certain outcome or measured parameter at a particular dose or concentration. The more potent a drug the less that needs to be administered to achieve the desired effect. The potency of a drug can be visualized by plotting concentration, amount, or dose against response on a dose-response curve.

293. The potency of a drug is linked to its binding affinity for the target, with a higher affinity generally resulting in greater potency. A further measure of potency of a drug is its EC50, which is the concentration of drug required to achieve 50% of its maximum effect. For an antagonist, potency can also be represented as an IC50, which is the concentration of drug required to achieve 50% of maximum inhibition of the target. Both EC50 and IC50 are often given as a molar concentration.

294. Generally speaking, a drug with a greater potency for a given target will require a lower amount of drug to achieve the same effect as compared to another drug with a lesser potency. More potent drugs are generally preferred as less can be administered to achieve the same effect which can have advantages in terms of reduced adverse effects, cost of drug, ease of formulation, etc. This is not always the case though as highly potent drugs can have more severe adverse effects if these are caused by its mechanism of action on the target. A greater potency generally also results in a longer duration of action as the drug is able to produce the required therapeutic effect when present at lower levels. Therefore, at the same dose, a more potent drug will take longer to fall back down to these levels and its effect will generally last longer.

295. Potency (particularly in the context of binding affinity) is, however, only one part of what makes a drug efficacious. Another important aspect is the stoichiometry of a drug, that is, the ratio of the number of molecules, or binding sites (for macromolecular drugs) of the drug to the number of molecules of the target in the relevant cells. Over time, the concentration of drug available to bind a ligand will reduce (by virtue of degradation / clearance of the drug). The amount of ligand may also increase over time, through secretion or transport from other sites.

296. *In vitro* assays, which can measure the affinity of a drug for its target and therefore potency, may provide a general indication of potency.

297. It was known that a drug can behave differently in a cell-based or non-cell-based *in vitro* system as opposed to *in vivo*.

Half-life

298. Small molecule drugs were known to generally have relatively short half-lives in the vitreous humor (ie, hours). Larger biologics like proteins were known to have a half-life in the vitreous of several days following intravitreal

administration. Whether this equates to a longer duration of action or efficacy is also dependent on whether the size of the molecule (or other properties of the molecule) affects whether, or how fast, it reaches the site of action in the retina (as discussed below).

Biological effect

299. Cell culture models, sometimes referred to as functional assays, are widely used in pharmaceutical drug development to study the effects of potential drugs on different types of cells, tissues, and organs *in vitro*. Their purpose is to assess the effect of the drug on a particular cell parameter and infer drug activity based on the magnitude of the effect and the potency of the drug in that model.

300. *In vivo* animal models can also be used to imitate human pathologies and assess the efficacy of a drug in a disease state. As with the use of animals in PK studies, disease state models in small animals such as mice and rats are commonly used, and the use of larger, more physiologically and anatomically relevant animal models, including non-human primates, are usually reserved for later in the pre-clinical drug development process due to their expense. There is a wide range of animal models that can imitate the pathology of retinal disease, described below.

Adverse effects

301. The overriding maxim is that all agents produce toxicity at some dose, and it is just a question of when or at what dose this toxicity appears. It is a widely accepted principle in the field that as the dose increases so generally does the risk of adverse effects.

302. Some adverse effects are more serious than others and some may be reversible and others may not. Some individuals are more susceptible to adverse effects than others and some adverse effects may not appear (or may become more frequent) until the drug has been administered to thousands of individuals.

303. Adverse effects in the eye are described in more detail in the section dealing with the CGK of the clinician.

Pre-clinical and clinical intravitreal drug development

304. The Ocular PK/PD Scientist will investigate the PK/PD properties of potential drug candidates and an evaluation of these will be used to select, with input from the skilled team, a candidate(s) to progress to pre-clinical toxicity studies to consider adverse effects in animals. If successful, the drug would then be moved into clinical trials in humans.

Pre-clinical toxicity studies

305. Due to the risk of adverse effects, pre-clinical toxicity studies in animals are carried out following *in vitro* and efficacy studies in animals, and prior to first

use of the drug in humans. The purpose is to identify at what dose adverse effects appear in animals and the type and severity of these adverse effects.

306. A wide dose range will be administered because the aim of the toxicity studies is to identify doses at which adverse effects appear and characterize the nature of those adverse effects. The dose range will expand upward from the dose range that the Ocular PK/PD Scientist expects would achieve the desired efficacy for the desired duration of action based on the *in vitro* and animal efficacy studies which have already been conducted.

307. A range of doses will be administered to the animals via the intended clinical mode of administration and the animals will be observed for any adverse effects, both systemic and ocular, such as ocular inflammation. The occurrence of any observable adverse effects while the animal is alive will be recorded and these effects are referred to as 'monitorable'. Upon completion of the study, the animals will be sacrificed, and their tissues, including the eye, are assessed for any damage and anatomical changes that resulted from adverse effects that were not noticed while the animal was alive, ie, not monitorable. Adverse effects that are not monitorable are particularly concerning as it may mean that they would not be readily identified if they occurred in humans. The adverse effects are also assessed to see whether they can be reversed or not. The most serious adverse effect is one that is not monitorable and cannot be reversed.

308. Based on the above adverse effect assessment a no-observed-adverse-effect-level ('NOAEL') is identified for the drug. The NOAEL is the highest dose tested at which no adverse effects were observed. Once a NOAEL has been established, it can be compared to the doses recommended by the Ocular PK/PD Scientist that they consider would achieve the desired efficacy for the desired duration of action on administration to patients based on the pre-clinical efficacy assessment.

"Maximum tolerated dose"

309. In the pre-clinical toxicity studies, if a dose of a drug is causing severe adverse effects such that the animal is in observable pain, distress, or dies, then in the pre-clinical toxicity study context that dose can be referred to having exceeded the "maximum tolerated dose" and the animal is sacrificed. It is not the aim usually to try to find the maximum tolerated dose in animal toxicity studies as this would raise ethical barriers.

310. The terminology of "maximum tolerated dose" can sometimes be used more loosely in other contexts, for example, in human Phase 1 and 2 studies. In clinical trial reports the term is for example sometimes used to refer to the highest dose administered to patients in that study which did not cause adverse effects or to the highest dose administered to patients in that study which did not meet the pre-defined safety stopping criteria. The dose would not be deliberately increased in human studies to find the maximum that was tolerated. It should be noted that although this and the previous two paragraphs are agreed CGK, there was a significant dispute about closely related points which I deal with in connection with the Ting publication, below.

Phase 1 clinical studies

311. The CGK relating to phase 1 clinical studies set out in the section dealing with the CGK of the clinician would also be CGK of the Ocular PK/PD Scientist.

Use of animal models in retinal disease drug development

312. Animal models are used to assess the potential efficacy and safety of a drug prior to clinical administration. Results from the testing of the drug in disease effect animal models are considered, for example, when recommending a dose for progression to first-in-human clinical studies.

313. Animal models are an artificial representation of human disease due to physiological and anatomical differences, for example intravitreal administration can be difficult in animals particularly when they have small eyes and therefore systemic administration was often used to consider efficacy. Animals models that used systemic methods of administration such as intravenous, subcutaneous, or intraperitoneal, would though be of limited relevance to decisions regarding the dosage regimen of intravitreal administration given the differences in the mode of administration, which would mean for example that a much smaller dose would be needed for the eye due to the proximity to the site of action, as well as the relatively unconstrained doses that can be administered systemically. Such systemic models are though still useful to see if the drug has an effect and as a proof of concept prior to testing intravitreal administration.

314. The animal model used to assess efficacy depends on the type of disease being targeted. For retinal diseases such as wAMD and diabetic retinopathy in 2006, there were certain animal models that could be used within the field to test the effect of drugs that were being developed for intravitreal administration.

315. Animal models for retinal diseases at the Priority Date included the following:

    i) Chemically induced diabetic mouse/rat models of diabetic retinopathy

    ii) The oxygen-induced retinopathy model

    iii) Laser-induced CNV model. The neovascularization that is typical in conditions such as wAMD can be simulated, in rodents, rabbits, and non-human primates, using a laser to damage tissues in the eye such as the Bruch's membrane and RPE. Breaking the blood-ocular barrier in the choroid with such a laser injury stimulates new vessel growth into the retina, in a manner similar to the pathologic new vessel growth observed in patients with wAMD. In such a model, it is typical for the animal to receive multiple laser burns in a grid patten. The damage results in the formation of lesions around the burn site, resulting in choroidal neovascularization that is similar in character to that seen in conditions such as wAMD, which can be visualised and graded based on their severity. It was known that these animal models are not without differences to the disease state in humans.

316. The drug can be administered before or after laser injury and the effect of the drug on lesion incidence can be assessed using fluorescein angiography. Administration of the drug after injury, and therefore the development of lesions, is more representative of the real-life clinical situation where the drug is administered to treat an existing condition and is therefore a higher bar for the drug to overcome in terms of efficacy.

317. This model can be used in animals such as mice, rats, and rabbits. The larger size of rabbit eyes as compared to mice and rats provides practical benefits, including that intravitreal administration can more easily be tested in rabbits. Due to the small size of the vitreous cavity compared to the lens in rodents, candidate drugs are typically administered intravenously or intraperitoneally in these animals.

318. Non-human primate ("NHP") eyes are similar in structure to the human eye. In contrast to many other species (including rodents and rabbits), NHP eyes have a macula and fovea, which means that they much more closely replicate the physiological conditions relevant to wet AMD and diabetic retinopathy in humans. It was understood that the monkey eye was both anatomically and physiologically closest to humans. NHP studies are expensive to run, however, and companies developing new drugs will typically only take forward promising candidates into NHP studies.

319. The use of the CNV model in monkeys ("Monkey CNV Model") to assess the performance of a drug administered intravitreally was understood to be the leading animal model to assess the performance of a drug for the treatment of wAMD.

320. Even though the Monkey CNV Model was the leading one in the field, it was still imperfect and not a true representation of the pathology of wAMD in humans. For example, laser-induced injury is much more acute and aggressive than the relatively slow progressive degeneration and resultant neovascularization that typifies wAMD in humans. Further, the physical laser damage that initiates neovascularization in this model is not the same insult that elicits the damage in humans, and differences in the underlying cause of the vessel growth could limit the ability to extrapolate from this model. Another limitation of the Monkey CNV Model (and laser injury models in any animal) is that unlike human wAMD, the laser-damaged tissue eventually heals over time, approximately over a period of 8-12 weeks, potentially affecting the results of the study and therefore limiting the assessment period. It should be noted that although this paragraph remained in the agreed statement of CGK there was a significant dispute about the ability to translate monkey results to the human situation. So I am not confident that this paragraph was in fact truly agreed. In any event, I deal with the dispute below.

321. In addition to the above, the Ocular PK/PD Scientist would know that the Monkey CNV Model is not a perfect model for translation of how the administered drug and dose will impact wAMD in humans. The monkey eye does not have identical anatomy to the human eye. For example, the volume of the vitreous is different. There is therefore a physical limit on the amount of

volume and concentration of drug that can be injected into the monkey vitreous that is not the same for the human vitreous.

Disputed CGK

322. Following discussions between the parties at the start of trial, and in the light of the written submissions at the end of trial, there remained 20 disputed issues of CGK for me to resolve; number 3 fell away and some of the issues were addressed by the parties under the heading of obviousness rather than CGK, which I have also done where appropriate, while bearing in mind that the legal issues are distinct even if the subject matter is closely related. The parties organised the disputed issues into groups depending on which expert discipline they each concerned. A number of the issues concerned both the clinician and the PK/PD expert, or both the formulator and the protein engineer.

323. During the oral evidence, the Claimants put a number of questions to Dr Ward on PK/PD issues based on a 2006 publication edited and partially written by Dr Naitee Ting of Pfizer, "Dose Finding in Drug Development", ("Ting"). Ting was only supplied as part of the cross-examination materials for Dr Ward; its CGK status and its support for CGK propositions were not addressed by the Claimants' witnesses.

324. Dr Ward expressed a considerable number of disagreements with what Ting said. He also said he did not accept that it evidenced CGK, pointing to its nature as a collection of separate chapters rather than as a true textbook, some points which he said were clearly errors, and what he said were internal inconsistencies on contents that were put to him. I found Dr Ward's points convincing; I found him a good witness in general, as I have said above. I also am faced with a situation where he was the only witness who spoke to the quality of the contents of Ting.

325. In those circumstances I would not accept Ting as evidence of CGK unless and to the extent that Dr Ward agreed with what it said, and agreed that it was CGK. I expressed my reservations about Ting during the closing oral submissions and asked the Claimants to identify propositions from Ting with which Dr Ward agreed. The Claimants produced a document after trial which sought to do this. Regeneron complained that rather than just listing propositions with which Dr Ward agreed, the document also identified propositions with which Dr Ward partially agreed and partially disagreed, and it said that the Claimants would rely on the propositions subject to Dr Ward's caveats. Regeneron said that was not what I had directed. I agree that it was not, and that I had expected that the Claimants would take the simpler course of listing statements with which Dr Ward just agreed. But although more fiddly, the Claimants' approach is not out of keeping with the spirit of what I said. Where Ting said X and Dr Ward said that the CGK position was X subject to Y then it would be unfair not to allow the Claimants to rely on X subject to Y just because it started from Ting. This is theoretical though, since there was nothing with which he agreed that helps the Claimants.

Disputed CGK – Clinician and PK/PD

326. I group these together because the evidence on them came from the experts in both disciplines to some extent in some instances.

Issue 1 – awareness of the ongoing MARINA, ANCHOR and PrONTO and PIER clinical trials

327. It was common ground that the skilled clinician was aware as a matter of CGK of MARINA and ANCHOR. Both were trials of Lucentis. MARINA was a phase 3 trial with a 4-week dosing interval. ANCHOR compared Lucentis with photodynamic therapy. The results had just come out by the priority date and were not in a peer-reviewed journal but had been presented at the ARVO meeting and were well known. An important feature which was known from in advance of detailed results was that Lucentis could reverse loss of vision.

328. PrONTO was a trial, also of Lucentis, intended to explore extending the dosing interval by giving three doses at monthly intervals and then switching to "as needed". The Claimants accepted that the results were not CGK, but said that the existence of the study and its purpose were CGK. Regeneron did not materially dispute that and it was supported by the evidence. More broadly, it was CGK that extending the dosing interval was an important consideration for the future if possible.

329. The Claimants did not put PIER in cross-examination so that falls away as CGK, but it does not matter.

Issue 2 – goal of the skilled clinical ophthalmologist

330. The competing positions are as follows:

    i) The Claimants argued that the skilled clinician would want to get more visual improvement than Lucentis and to get a longer duration of action than the 4 week dosing interval for which it was expected to be approved.

    ii) Regeneron on the other hand said that the skilled clinician would design their studies with the goal of proving the minimum visual improvement that allowed confidence that it was real and not down to chance or patient variability; the skilled clinician would start with a four weekly interval as a goal but with the willingness and desire to extend it longer once that was achieved.

331. This issue bridges CGK and obviousness.

332. It is not in dispute that it was CGK that Lucentis had shown potential for visual improvement (not just halting progression of vision loss) with VEGF antagonism. I accept that it would be an obviously desirable goal to increase the degree of visual improvement in due course. It would not be the goal of a phase 1 trial to show that, since phase 1 trials are for safety (see below); this is a question of looking forward to the future, thinking about doses and goals for phase 2 and phase 3.

333. It was CGK that Lucentis was being taken forward to assess a dosing regime of three four weekly intervals followed by "as needed" (the PrONTO trial – see above). I accept it would be an obvious desideratum to think about VEGF Trap ultimately being used with a longer dosing interval than 4 weeks.

334. The fact that these were long term ambitions, as a matter of CGK or just obviousness, does not automatically mean that the skilled clinician would set a high(er) dose for a phase 1 trial, though. Having in mind proving an improvement in vision e.g. twice as big as with Lucentis in later efficacy trials could just turn out to be too ambitious, resulting in the drug failing to meet its endpoint when it would have succeeded. This is a scientific as well as a commercial consideration.

335. In terms of the evidence, Prof Kodjikian was very clear that the natural approach was to aim for the minimum improvement in vision that could confidently be said to be real: 5 or more letters. Prof MacLaren said he would prefer to think in terms of a percentage of patients who achieved an improvement of 10 or more letters. I agree with the Claimants that this turned out to be a difference in opinion about how better to define the goal of a definite improvement. Prof MacLaren, in his second report, replying to Prof Kodjikian on this, said that the typical distribution curve for a mean improvement of 5 letters (if the sample size was statistically meaningful) could likely include a notable proportion of patients with an improvement of 10 letters.

336. Prof Kodjikian was challenged in cross examination on the basis that it would be aiming low, too unambitious, to aim for 5 letters. I reject this. He had in mind setting a realistic goal, just characterised in a different way from Prof MacLaren.

337. A better point, in one way at least, was that Prof Kodjikian advocated his 5 letter goal and the objective of matching Lucentis when the skilled person would not know specifically what Lucentis had achieved, the results for it not yet having been published (though it was known they were good, and that there was recovery of vision). I do not see this as a positive inconsistency, though: whatever target might be set at the priority date would be in ignorance of the details of the Lucentis results.

338. Prof Kodjikian said that the formal comparator for any later phase trial of VEGF Trap would be Macugen, as the only authorised VEGF inhibitor. Prof MacLaren agreed, but in his reply report said that the skilled clinician would also have in mind Lucentis and would want to "show at least the same performance as, or benefit over" the positive initial results from the phase 3 trials of it. He said that an improvement could be either a greater visual improvement or an increased dosing interval. Prof MacLaren was not saying that an improvement over Lucentis in both visual acuity gain and dosing interval would necessarily be sought at the same time.

339. Proving efficacy with monthly dosing and then trying to extend was what had happened with Lucentis. It was also essentially what had been done with Avastin, although the situation there is more complicated because it was off

label, and there were considerations of the different molecule sizes between it and Lucentis, and the like.

340. Prof Kodjikian also made the point, which I found persuasive, that it would be risky to go to a longer dosing interval when the comparator would be Macugen: there would be two differences between the comparator and the test arm, because the drug would be different and the dosing interval, too. If the goal was not met then it would not be clear whether that was because of the interval or the drug. Again, this is both a commercial and a scientific problem.

341. In addition there would be some clinical risk going to a longer dosing interval because if vision was lost in the "extra" two weeks it would not be recovered. This has some relevance, but the risk would be taken at some stage when extending the interval was tried, and the countervailing benefit of fewer treatments has to be taken into account.

342. Overall my conclusion is that the skilled clinician would think the most straightforward and least risky approach would be to aim for what Prof Kodjikian said for the reasons he gave, but it would also be reasonable and scientifically justifiable to be a bit more ambitious. It was not, however, CGK or supported by the CGK that the clear way to go was to aim for significant improvement in visual acuity and a longer dosing interval all at once, and concrete decisions for a greater improvement than ranibizumab would be hindered by not knowing specifically what it had achieved in phase 3.

343. There was some discussion at trial about more general targets such as "the best improvement possible" but it faded and was not really where the arguments focused. In any event I reject it: the CGK was that concrete and specific, measurable goals and plans were needed.

Issue 3 – preclinical development of intravitreal drugs

344. The parties agreed that this issue fell away.

Issue 4 – adjusting the dose used in non-human primates to reach an equivalent dose in humans

345. This goes with issue 6 (the monkey CNV model). The dose adjustment for the difference between the monkey and human was, as a matter of CGK, based on the fact that the monkey eye is about half the volume of the human. So a scaling factor of about 2:1 would be the first order assumption to make. However, when a physiological effect was seen in a monkey at some specific dose it could be that that dose was above the minimum needed to get the effect. This is relevant to analysing the skilled team's thinking from Example 9 of Wiegand II.

Issue 5 – the relative importance of biochemical features including potency and stoichiometry as indicators of efficacy

346. This issue went to any detailed assessment of Dr Ward's calculations of the potency of VEGF Trap based on the characteristics of Lucentis and Avastin.

Dr Wensel maintained that efficacy does not follow inexorably from potency because of other factors such as stoichiometry, clearance and penetration. I accept this was CGK and would potentially limit the usefulness of Dr Ward's analyses, at least in quantitative terms, but since I hold that the skilled person would not do the searches on other drugs that Dr Ward started with, this issue does not matter. For what it is worth, Dr Ward accepted that potency was not the only factor, and the difference between the experts was therefore, at most, a matter of degree or of emphasis.

Issue 6 - the monkey CNV model

347. The monkey CNV model was, it was common ground, CGK and recognised to be the best there was, the "gold standard". But that is not to say that it was a perfect model of actual wet AMD in a human patient, and indeed the CGK was that it differed. The main differences were:

    i) Nature of the injury: the laser-induced damage was more sudden and more severe than wet AMD.

    ii) Immediate healing: the monkey eye starts to heal immediately whereas wet AMD is a chronic disease.

    iii) Differences in vitreous: human vitreous is more fluid than the monkey.

    iv) Differences in clearance: there were clinical reasons why clearance in wet AMD patients differed from the monkey, including in relation to patients with cataracts as well as AMD.

    v) The "superficial" nature of the lesions in the monkey model.

348. The last of those – superficiality - is a complicated point and the most significant and contentious so I will go into it in a little more detail.

349. Physiologically, the laser treatment breaks the RPE and Bruch's membrane, so is not really superficial, but more so than the blood vessel damage and leakage in occult wet AMD. Prof MacLaren was the best placed to speak to this having done the monkey procedure and having treated patients, and he said the CNVs in wet AMD were larger. But Prof Kodjikian also had a relevant perspective and pointed out that larger CNVs in wet AMD might be beyond treatment anyway, and the ones of clinical interest would therefore be smaller ones. The PK/PD experts said that the injury in the monkey model was acute and aggressive, and Dr Wensel agreed that it was a reasonable theory, although no more than that, that there would be more VEGF produced with the laser injury.

350. There are factors pointing in different directions here and their individual magnitudes are not knowable and were not CGK. I was not shown anything to evidence it being CGK that the monkey model consistently gave such lesser injury (or healed sufficiently quickly) that a scaling was appropriate, let alone how much, by contrast with the fact that the CGK comparative volume difference was agreed to be well understood enough to scale. It was no more

than a plausible theory that the factors other than volume were such as to justify an increased dose.

Issue 7 - the goal of phase 1b clinical trials and factors going to the choice of a dose range for it

351. This is the issue that I have mentioned above where the Claimants relied on the Ting publication. My findings are as follows.

352. First, what is under consideration is a trial with patients rather than healthy volunteers. This was common ground.

353. Second, a phase 1 trial is a safety trial. Observations of efficacy are welcome if they happen, but secondary. Their utility will be limited because of the small sample size. This too was common ground.

354. Third, a phase 1 trial of the kind under discussion is a single-dose, dose escalation study (this sounds odd, but what it means is that each patient gets only one dose, but successive groups of different patients get higher doses). One dose at a time is given starting with the lowest, and the next is only given if the adverse effects (if any) seen are tolerable. The study design will set out what level/kind of adverse event(s) is/are acceptable for the next dose to be given. If the adverse events are sufficiently bad, the next dose is not given and the trial stops. The dose below the one at which the terminal adverse events occurred is then the Maximum Tolerated Dose. I think that all this was agreed to be CGK, with the possible exception of the expression "Maximum Tolerated Dose" and the desirability of reaching it, to which I return below.

355. A phase 1 trial design requires the identification of the lower end of the range to be tested. This has to be decided based on pre-clinical animal models. There is a concept called the NOAEL (mentioned above in the agreed CGK), which is the highest level at which no adverse events are observed. I accept the evidence of Dr Ward as to this, and the concept is in any event defined by the FDA, in 2005 guidance written for other contexts but applicable to IVT drugs, and to which Dr Wensel assented as representing CGK. It remains unclear to me whether the Claimants disputed that, but if they did I reject their contention.

356. From there, the Maximum Recommended Starting Dose is identified. It bears emphasising that this is the highest dose at which human dosing in the phase 1 trial can begin, not the highest dose to which escalation may take one. The Maximum Recommended Starting Dose is, in general, the NOAEL, scaled from the animal to the human (e.g. based on size – this gives the Human Equivalent Dose, "HED") and then divided by at least around 10, as a safety factor. It is the maximum: the skilled team might start even lower, because another concept is the PAD, pharmaceutically active dose, which is the lowest level at which the desired pharmacological activity was seen in the animal. If the PAD (also scaled to a human equivalent) was lower then consideration was encouraged to be given to using it instead of the Maximum Recommended Starting Dose. Again, this was supported by the FDA guidance and the expert evidence.

357. One of the problems with Ting, I note in passing, is that it uses a different definition of PAD from the FDA Guidance. Significant points in it to which Dr Ward also objected were its suggestion that the NOAEL is only used to set the starting point (he said it was also used to assess higher doses suggested for the phase 1 trial) and the way it described using animal NOAELs to set human doses. He was challenged in cross-examination that he had not produced documents to justify this, but of course when he wrote his reports he did not know Ting would be put to him, and furthermore his evidence about using NOAEL to assess the appropriateness of higher doses was considered and not contradicted (subject only to a minor terminological clarification) by Dr Wensel in his first report.

358. The approach underpinned by the above concepts in the way they are explained in the FDA Guidance (and by Dr Ward and Dr Wensel) is a cautious one in which the phase 1 trial is designed to assess safety across a dose range which is aimed, based on the animal data, to encompass the lowest level at which efficacy is hoped to be found in humans.

359. This brings me to the first really hotly debated issue, which is whether phase 1 trials are intended to "explore the therapeutic window" and, relatedly, with the goal of identifying the Maximum Tolerated Dose.

360. I reject the Claimants' argument on this. There is no general desire to "explore" in phase 1 trials. It is perfectly possible that such a trial will conclude with all the planned doses given and no material adverse effects. There is no need, given the overall goal, to aim for higher and higher doses until adverse effects kick in, and it would not be efficient or ethical to do that. Finding a lack of adverse effects at doses hoped to be efficacious would be a completely acceptable result.

361. I think the apparent disputes on this topic, such as they are, are either triggered by the Claimants' reliance on Ting, or terminological. So far I have referred to Dr Ward and Dr Wensel, but the clinicians also commented.

362. I understood Prof MacLaren to agree that possible identification of the Maximum Tolerated Dose is constrained by the rules about the adverse effects at which the trial stops, which may never happen. When Prof MacLaren referred to identifying the Maximum Tolerated Dose as a goal of a phase 1 trial he was not precluding the possibility that all planned doses might be given with no significant side effects noted and he certainly was not saying that a plan would be made with the specific intention of observing side effects. He also agreed that the overall approach was conservative, as I have described above.

363. Prof MacLaren disagreed with Prof Kodjikian over the latter's statement that a phase 1 trial should be designed to "determine the lowest dose that gives the desired efficacy". His disagreement, though, was because the primary purpose of a phase 1 trial is assessment of safety, as I have said. I do not think Prof Kodjikian intended to say otherwise; he meant that the dose range over which safety is assessed is set with an eye to the best assessment of the lower end of a dose range at which efficacy is hoped to be seen in due course.

364. Against this background, I return to Ting and its use by the Claimants. I have said that they ought to be allowed to rely on things that Dr Ward accepted in the context of being asked about it, whether that was a clear acceptance of something that Ting said, or an acceptance subject to caveats. Having reread his evidence, I do not think that the questions based on Ting led him to say anything contrary to what I have set out above as the CGK. His caveats on the critical parts of Ting (figure 1.2 and figure 3.3) were major ones. He said Figure 1.2 was not representative of how a phase 1 trial would be designed; he said that seeking the Maximum Tolerated Dose was not an objective; he only said that if a trial were desired to operate in accordance with Figure 3.3 (which I reproduce below) it could be done, and not that Figure 3.3 is a road map for the way to go. Again, the debate is partly terminological, but if Ting were to be using "MTD" and "PAD" in the way those terms are used conventionally, as by the FDA, then figure 3.3 is clearly not how phase 1 trials are set up. They escalate to the maximum planned dose unless the defined adverse events for stopping occur. Figure 3.3 seemed to be put to Dr Ward on the basis that it shows the conduct of a phase 1 trial which carries on until one of two possible ending points happens: the MTD or the PAD. I found this very confusing; figure 3.3 is expressed as being two different ways to choose the doses for phase 1 trials, not the steps or decision points to be taken when the trial is being run. I also do not see how the Claimants' case on figure 3.3 is supported by the evidence of Prof MacLaren or Dr Wensel. So I reject the Claimant's reliance on Ting entirely, on the facts.

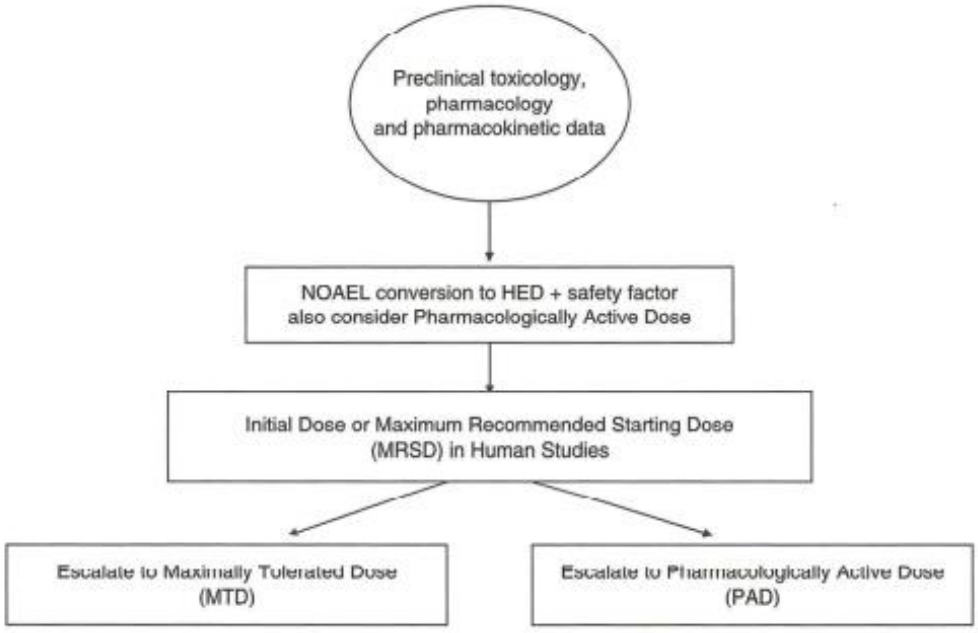


Figure 3.3. Overview of dose selection for FIH studies.

365. Lastly, the Claimants submitted that setting the phase 1 doses too low ran the risk of not enabling the taking of higher and more effective doses forward into phase 2. They illustrated this by reference to Nguyen 2009 from which one can see (but, importantly, only with hindsight) that if Regeneron had limited themselves to 0.5 or 1mg they would never have identified greater efficacy at higher doses. This is true and Prof Kodjikian accepted as much, but it is just

the nature of the situation. The Claimants did not explain how the issue could be avoided consistently with what was agreed to be a CGK conservative approach. Because phase 1 trials are not primarily intended to obtain efficacy data but just present the possibility of getting it adventitiously they are not declared a failure if they do not show good efficacy.

366. There was a somewhat related point folded into the parties' submissions on this issue, which was whether it was CGK to decide to take doses into phase 1 trials which were materially higher than the scaled maximum dose from animal toxicity studies already to hand. It was put to Dr Ward that some publications from the Rosenfeld group showed that they had done so. Dr Ward said that it was likely that those groups had additional unpublished toxicology data, and Dr Wensel confirmed that it was normal to have additional materials like that. There is some indication in other Rosenfeld work that that might be the case. So while this was sometimes done there is not enough evidence to conclude that it was CGK. I do not think it matters much, though, because it was common ground that the skilled person would be likely to do another animal toxicology study immediately prior to the phase 1 trial anyway.

Formulation and protein engineering disputed CGK issues

367. Again, I group these together because the evidence from the two disciplines overlapped.

Issue 8: C-terminal lysine cleavage/clipping

368. Following the evidence the Claimants accepted that this was CGK. It follows that it was also CGK that it happened in eukaryotic cells but not prokaryotic cells. This issue is primarily relevant to priority/added matter. What it means is that in eukaryotic cells a last, lysine amino acid is cleaved off by enzymes in the cell.

Issue 9: How the skilled Protein Engineer would calculate the theoretical pI of a protein

369. I cover this in the context of obviousness, as did the Claimants. Regeneron organised its submissions on the topic in a separate annex to its written closing submissions which dealt with CGK and obviousness together.

Issue 10: "soft spots" analysis

370. This is about the skilled protein engineer analysing the sequence of a protein to consider features which might cause problems with formulation. Again, the parties dealt with it in the context of and/or together with obviousness. I will again deal with it in the context of obviousness.

Issue 11: which buffers were commonly used for liquid protein formulations and the factors which affect the choice

371. It was common ground that the skilled formulator would test a couple of buffers at a couple of pHs; I find that that was the CGK. I say a little more about it in the context of obviousness.

372. A number of buffers were CGK. They included sodium phosphate and for the purposes of the obviousness issues it is enough to observe that that would have been regarded as a stand-out possibility. Its specific choice was not said by Regeneron to be inventive in itself or even really to contribute to inventiveness alongside other choices. For the purposes of the infringement issues, it is relevant that there were other CGK choices that could cope with a pH of 6.2-6.3, including histidine (I mention this first only because it has a particular relevance to the infringement arguments) acetate, citrate (though this might cause injection pain so would not be a likely choice), phosphate or carbonate.

Issue 12: whether ionic interactions of buffers and/or salts with the protein were thought potentially to have an effect on stability

373. This issue about CGK goes to the infringement arguments and most particularly to Actavis Q2. In the end there was a large measure of agreement.

374. The phenomenon involves ionic interaction between the charged ions of a salt and charged amino acids of the protein being formulated. It can stabilise a protein by shielding attractive or repulsive interactions between protein molecules that would otherwise destabilise the overall formulation. This is called Debeye screening or Debeye Huckel screening. The same kinds of effects can also lead to destabilisation, or they may have no impact. It is covered in a number of practical, CGK-style textbooks.

375. Buffers include salts, and I agree with the Claimants that for this reason they are covered by descriptions of the phenomenon even if not separately mentioned, and the skilled person would appreciate that.

376. So far what I have said was either common ground or not seriously disputed.

377. The main difference of opinion between the experts was whether the phenomenon was of practical importance. Thus, as the Claimants pointed out, Prof Gukasyan said that while buffers of similar pKa could have different effects on protein stability because of different ionic interactions, he had not seen it happen in his experience. He said much the same about salts' possible stabilising effects. But he was a little inconsistent in his views and differed somewhat from his written evidence. He said that the texts said that the interactions could take place at isotonic concentrations, that he knew that, and it was CGK. But he repeated that he had not seen it in practice.

378. Dr Daugherty disagreed and said that addition of salt would be thought by the skilled person to "have quite a bearing" on stability because of the ionic strength of a formulation.

379. I prefer Dr Daugherty's evidence. I found it more convincing and consistent and I think objectively speaking that it is significant that the effect is mentioned in practical CGK texts, not merely as a theoretical matter.

380. Regeneron said that the Patents describe the primary functions of the excipients and that this would tell the skilled reader that there were no secondary effects like ionic interactions going on. This shades into claim scope arguments, but so far as the CGK is concerned, there is no inconsistency between e.g. having a stabiliser for the primary stabilising effect and calling it such, while knowing that a salt in the formulation might also be contributing.

Issue 13: candidate surfactants

381. This is an important issue because the choice of polysorbate 20 was one of the individual decisions which Regeneron said was not obvious. The matters in dispute bridge CGK and obviousness; unlike some of the earlier issues I will say something here and more when I come to obviousness.

382. I note at the outset that it was not CGK that all protein formulations had a surfactant. Some did not, and contrary to the Claimants' implications, there were some successful and notable formulations that did not: the 100mg formulation of Synagis (which also had no sugar), and a drug called Etanercept.

383. There were only a relatively small number of surfactants that might be candidates for the sort of formulation exercise I am considering. The ones I heard about were polysorbate 20 and 80, tyloxapol (trade name Triton), and Poloxamer 188.

384. As I mention when I come to obviousness, there were only a relatively small number of protein/antibody drugs around, and once one subdivides according to injection route, whether they were authorised and so on, the data points are still fewer. I did not find this categorisation very helpful, though.

385. As to polysorbate 20, it clearly was CGK as a possibility for use as a surfactant. Numerically speaking it was not used in that many products, but it was used in Avastin which would certainly have been on the skilled team's radar.

386. I also find that tyloxapol was CGK as a possibility; it was in the CGK texts. It was one of the ones that was not approved as an injectable so its adoption for VEGF Trap would involve regulatory effort but that would not have impacted on the skilled formulator's assessment of its technical merit in terms of stability. And anyway, none of the candidates under discussion was approved for intraocular administration so approval is something of a non-factor (it should be recalled that Avastin's intraocular use was off-label).

387. Poloxamers were also CGK, Dr Daugherty accepted ("part of the toolkit"). The Claimants pointed out that they were only introduced into the case in cross-examination and not raised by Prof Gukasyan in his written evidence. The Claimants may be right that this was possibly a counter by Regeneron because Poloxamer 188 was in an approved formulation while tyloxapol was not, but the important point of substance was that Dr Daugherty accepted poloxamers

were CGK. Had she not done so, it would have been important that Prof Gukasyan had not mentioned it. When asked if it would be obvious to choose Triton as an alternative to polysorbate 20 she said "They might consider an alternative, not necessarily Triton, but one of the others we have discussed, such as poloxamers".

388. My conclusion therefore is that polysorbates 20 and 80, Triton and poloxamers were all CGK possibilities. There were some minor points about the relationship between polysorbate 20 and polysorbate 80 but they do not matter enough to go into.

Issue 14: which authorised formulations of antibody products were CGK?

389. The title of this issue became a bit misleading because the Claimants did not limit themselves to relying on authorised formulations.

390. I find that on the evidence there were four intravitreal formulations that would be CGK: Macugen, Avastin, Lucentis and Kenalog. Only Macugen was approved. Avastin was used intravitreally only off-label, as was Kenalog; Lucentis' approval was imminent. The formulation details would be CGK if the skilled person would know that they were available and would be able to find them.

391. The CGK status of the Lucentis formulation was marginal: Prof Gukasyan had looked for but not found it for his report and Dr Daugherty had not done a search. A different search of patent literature by the Claimants was put to Prof Gukasyan in cross-examination and he accepted that it could be done. The positive for the Claimants from Lucentis is that it had polysorbate 20, but on the other hand its pH was 5.5 so it would show that that pH is possible in the eye. Kenalog (off label) had a pH of 5-7.5 so that might found a similar argument anyway.

392. Not without some hesitation I find as a specific point that the Lucentis formulation was CGK, as the Claimants contend. Lucentis was very topical and the motivation for the skilled formulator to find out about it would be very high. The reason Prof Gukasyan did not find it was because of a lack of familiarity in looking for patent documents, but in industry it is common to use them as a source of information and I conclude that the search the Claimants put forward would have been routine.

393. Other formulations, including a number of other antibodies, were also CGK and could be looked up. They were less material to the issues than the intravitreal ones and so I will not list them. They could be found in CGK publications such as Gokarn and Akers.

Issue 15: the extent to which other protein formulations would assist the skilled formulator

394. This issue faded in importance. The skilled formulator could use this information to work out what excipients were authorised/tolerated in the eye, for what that is worth. But neither side said that the skilled formulator would

use another formulation as a template, and the candidate excipients that I have to consider in relation to obviousness are clear enough without the need to go into this CGK issue separately.

Issue 16: perceived difficulty of formulating proteins stably at higher concentrations

395. It is inherently impossible to give a hard cut-off for the protein concentration at which formulating a protein stably becomes "difficult" or "risky"; the proteins vary as do the contexts of the formulation tasks. In extremely rough terms the evidence was that up to 10mg/ml was very comfortable, the difficulty and risk started to mount at around 25 mg/ml, and became a lot more pronounced at 50mg/ml or so. But there were CGK formulations at 50 mg/ml or even 100 mg/ml (Humira and Synagis respectively, both monoclonal antibodies).

396. What this means in the context of obviousness is that the skilled formulator would not refuse to attempt to formulate at 40mg/ml and would attempt to do so if the clinical desire was sufficiently pressing, a matter I consider in the context of the skilled team and the interactions between its members.

Issue 17: soft spot analysis from the perspective of the formulator

397. I deal with this, as with issue 10, when I come to obviousness.

Issue 18: pHs

398. Again, I deal with this when I come to obviousness and it is closely related to the CGK on pI calculation debated with the protein engineering experts.

Issue 19: what excipients to test and approach to stability testing

399. I deal with this below when I come to obviousness, under the heading "The formulator's approach to the initial formulation".

Issue 20: whether and to what extent the skilled formulator would expect interdependency between excipients

400. This is an important issue both to obviousness and to infringement. I do not think, however, that there was any dispute at the end of the day. A formulation is a totality in which all the excipients work together to achieve stability. Each excipient can change the overall stability by improving it, making it worse, or doing nothing. Adding or changing an excipient or its quantity can move the optimum pH, as well. The ways in which these changes happen is at best poorly understood and when something goes wrong it is a challenge even to understand why. The general understanding of the primary function of each excipient category does not detract from these points.

THE PATENT SPECIFICATION

401. The trial was argued by reference to '691. There was no suggestion that there is any material difference in the specification of '306, although the claims are somewhat different.

402. The Patent is entitled "VEGF Antagonist formulations suitable for intravitreal administration".

403. Although the correct priority date is disputed, Regeneron accepts, as I have already mentioned, that if priority is lost then the same reasons will mean that the Patents are invalid for added matter. So for the purposes of obviousness I only need to consider matters at the priority date of 16 June 2006.

404. In the "Field of the Invention" section, [0001] states:

> [0001] The present invention is directed to pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations. The invention includes liquid pharmaceutical formulations having increased stability, as well as formulations that may be lyophilized and reconstituted for intravitreal administration.

405. Prof Gukasyan was cross-examined on this paragraph but I think it is too general to have any impact either way on the issues I have to decide.

406. In the "Statement of Related Art" section, [0002] to [0005] state:

> [0002] Vascular endothelial growth factor (VEGF) expression is nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis. Blockade of VEGF function, by binding to the molecule or its VEGFR-2 receptor, inhibits growth of implanted tumor cells in multiple different xenograft models (see, for example, Gerber et al. (2000) Cancer Res. 60:6253-6258). A soluble VEGF-specific fusion protein antagonist, termed a "VEGF trap" has been described (Kim et al. (2002) Proc. Natl. Acad. Sci. USA 99:11399-404; Holash et al. (2002) Proc. Natl. Acad.Sci. USA 99: 11393-8).
>
> [0003] Ophthalmic formulations are known, see for example, U.S. 7,033,604 and 6,777,429. An ophthalmic formulation of a VEGF antibody is described in US 6,676,941.
>
> [0004] Lyophilization (freeze drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state (see, for example, U.S. 6,436,897).
>
> [0005] WO 2006/047325 is concerned with a method for treating intraocular neovascular diseases. WO 2005/020972 is concerned with

> combination therapy for the treatment of ocular neovascular disorders. WO 2006/104852 and US 2006/0217311 A1 are concerned with VEGF antagonist formulations.

407. WO 2006/104852 is Dix.

408. In the "BRIEF SUMMARY OF INVENTION" section, [0012] to [0015] describe some preferred embodiments:

> [0012] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 50 mM sodium chloride, 0.1 % polysorbate, and 5% sucrose, pH about 6.2-6.3.
>
> [0013] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 50 mM sodium chloride, 3% PEG, and 5% sucrose, pH about 6.2-6.3.
>
> [0014] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 40 mM sodium chloride, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.
>
> [0015] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 135 mM sodium chloride, and 0.03% polysorbate, pH about 6.2-6.3.

409. [0012] maps to Example 1, [0013] to Example 2, [0014] to Examples 3 and 4, and [0015] to Examples 5 and 6. Examples 5 and 6 do not have sucrose and that is a point relied on by the Claimants in relation to the skilled person's understanding of how the various formulations work.

410. [0024] to [0027] provide some further details of possible formulations "in various embodiments", as "specific embodiments" and the like:

> [0024] In another aspect, a stable liquid ophthalmic formulation is provided that comprises about 10 to about 80 mg/ml VEGF antagonist, about 10 mM sodium phosphate buffer, about 0.03% polysorbate, and about 135 mM sodium chloride, pH of 6.2 to 6.3.
>
> [0025] In various embodiments, the VEGF antagonist is present at a concentration of about 10 to about 80 mg/ml. In various embodiments, the VEGF antagonist is present at a concentration of about 10, about 20, about 30, about 40, about 50, about 60, about 70, or about 80 mg/ml. In a specific embodiment, the VEGF antagonist is present at a concentration of about 40 mg/ml.
>
> [0026] In one embodiment, the stable liquid ophthalmic formulation comprises 40 mg/ml of VEGF antagonist, 10 mM sodium phosphate

> buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3. In a specific embodiment, the stable liquid ophthalmic formulation consists essentially of 40 mg/ml of VEGF antagonist, 10 mM sodium phosphate buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3.
>
> [0027] In another aspect, a lyophilizable formulation of a VEGF antagonist is provided, wherein upon lyophilization followed by reconstitution, a stable liquid ophthalmic formulation as described herein is obtained.

411. I was taken to these paragraphs by Counsel for Regeneron in opening but really just to show that again (second half of [0026]) there are options without sucrose, and that while [0027] introduces lyophilizable options, they are not claimed.

412. [0041] discusses the problems of protein formulation and the kinds of chemical and physical instability that can arise:

> [0041] Safe handling and administration of formulations comprising proteins represent significant challenges to pharmaceutical formulators. Proteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation and/or precipitation.

413. This is no more than CGK but it serves to make clear, if it was not already, some of the problems that the formulations of the Patents seek to solve.

414. [0049] is a consistory clause; it refers to a VEGF antagonist. I have not so far mentioned that [0007], [0008] and other paragraphs refer to this "consisting of aminos acids 27-547 of SEQ-ID No: 4 which is glycosylated at Asn residues 62, 94, 149, 222 and 308". This definition is not problematic in the context of the Patents but is important in relation to the priority/added matter issues.

415. The Examples begin at [0057]. As I have said, these map back to [0012] to [0015]. Some relatively minor points arise on whether the formulation is in a glass vial or a prefilled syringe (hereafter, "PFS"), and also for how long stability was tested (and found to be stable):

> Example 1 at [0059], maps to [0012], glass vial, stability tested to 24 months.
>
> Example 2 at [0060], maps to [0013], glass vial, stability tested to 24 months.
>
> Example 3 at [0061], maps to [0014], glass vial, stability tested to 4 months. This is the formulation that corresponds to claim 5 of '691.

Example 4 at [0062]: also maps to [0014] same as Example 3 except in a PFS.

Example 5 at [0063], maps to [0015], glass vial, stability tested to 5 months. No sucrose.

Example 6 at [0064], also maps to [0015], same as Example 5 except in a PFS.

416. SEQ ID No: 4 appears at pages 13-14. It gives the full amino acid sequence from residue 1 to residue 458 but as already mentioned the claims require a VEGF antagonist which consists of amino acids 27-457, so residues 1-26 and 458 must be absent.

Claims in issue

417. Claim 5 of '691 as unconditionally proposed to be amended is:

5. An ophthalmic formulation according to claim 1 comprising:

(a) ~~10 mg/ml or~~ 40 mg/ml of a VEGF antagonist consisting of amino acids 27-457 of SEQ ID No: 4, which is glycosylated at Asn residues 62, 94, 149, 222 and 308;

(b) 0.03% of polysorbate 20;

(c) about 40 mM of sodium chloride;

(d) 10 mM of sodium phosphate buffer; and

(e) 5% sucrose,

wherein the pH of the formulation is pH 6.2-6.3.

418. Although not relied on by Regeneron, claim 1, on which claim 5 is dependent, is of some relevance to the equivalence arguments:

1. An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising:

(a) 40-50~~1-100~~ mg/ml of a VEGF antagonist consisting of amino acids 27-457 of SEQ ID No: 4, which is glycosylated at Asn residues 62, 94, 149, 222 and 308;

(b) 0.01-5% of one or more organic co-solvent(s) which is one or more of polysorbate, polyethylene glycol (PEG), and propylene glycol;

(c) 30-150 mM of a tonicity agent selected from sodium chloride or potassium chloride;

(d) 5-40 mM of sodium phosphate buffer; and

> (e) 1.0-7.5% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol, pH between about 5.8-7.0, wherein the formulation is suitable for intravitreal administration.

419. Claim 11 is to a PFS suitable for intravitreal administration comprising the formulation of claim 5.

420. I need not set out the claims of '306, but the points to note are that:

i) Claim 1 is to a PFS comprising the formulation, whose parameters are the same as claim 1 of '691;

ii) Claim 2 matches the formulation requirements of claim 5 of '691 and explicitly refers to "liquid stable";

iii) The VEGF-specific fusion protein "comprises" certain amino acids of SEQ ID NO:4 compared with the claims of '691 where "consist" is used.

421. Points i) and ii) do not make any difference to my analysis or the overall result. Point iii) is material when it comes to priority/added matter, however.

CLAIM SCOPE

422. As I have already said, Regeneron does not allege infringement on a normal interpretation, only by equivalence.

Legal principles on infringement by equivalence

423. The key principles are to be found in the decision of the Supreme Court in Actavis *v Lilly* [2017] UKSC 48. The arguments in the present case engage all three of the questions applicable to equivalents and to the way that the Supreme Court drew the overall balance, so it is useful to quote extensively from the decision. So, see at [53]-[66]:

> **The proper approach to infringement claims**
>
> 53. Any patent system must strike a balance between the two competing factors referred to at the end of article 1 of the Protocol, namely "a fair protection for the patent proprietor [and] a reasonable degree of legal certainty for third parties". The balance cannot be struck on an ad hoc case-by-case basis without any guiding principles, as that would mean that there was no legal certainty. On the other hand, striking the balance by adopting a normal approach to interpretation would risk depriving patentees of a proper measure of protection; as explained in paras 37 to 39 and 52 above, that is clear from the approach of all the courts which considered the "Epilady" patent, where it could not seriously have been suggested that, as a matter of language, a slotted rubber rod falls within the expression "helical metal spring", even if one was construing those words in the context of the claim in the patent in suit. But, if one departs from ordinary language, it is necessary to have some guidance or to draw

some lines, as Lord Hoffmann implied in *Kirin-Amgen* [2005] RPC 9, para 37. That is why he promulgated his three questions in *Improver* [1990] FSR 181, 189. By means of an extended version of the ordinary concept of "construction" or "interpretation", Hoffmann J explained how our domestic law, as laid down in *Catnic* [1982] RPC 183 , implements article 2 of the Protocol and thus, as I see it, how it gives effect to the doctrine of equivalents. That approach was (perhaps unsurprisingly) then adopted in *Kirin-Amgen* [2005] RPC 9 .

54. In my view, notwithstanding what Lord Diplock said in *Catnic* [1982] RPC 183, 242, a problem of infringement is best approached by addressing two issues, each of which is to be considered through the eyes of the notional addressee of the patent in suit, ie the person skilled in the relevant art. Those issues are: (i) does the variant infringe any of the claims as a matter of normal interpretation; and, if not, (ii) does the variant nonetheless infringe because it varies from the invention in a way or ways which is or are immaterial? If the answer to either issue is "yes", there is an infringement; otherwise, there is not. Such an approach complies with article 2 of the Protocol, as issue (ii) squarely raises the principle of equivalents, but limits its ambit to those variants which contain immaterial variations from the invention. It is also apparent that the two issues comply with article 1 of the Protocol in that they involve balancing the competing interests of the patentee and of clarity, just as much as they seek to balance the encouragement of inventions and their disclosure with the need for a competitive market. In my view, issue (i) self-evidently raises a question of interpretation, whereas issue (ii) raises a question which would normally have to be answered by reference to the facts and expert evidence.

55. In *Kirin-Amgen* [2005] RPC 9 , Lord Hoffmann, following his approach in *Improver* [1990] FSR 181 (which itself had followed Lord Diplock's analysis in *Catnic* [1982] RPC 183) effectively conflated the two issues, and indicated that the conflated issue involved a question of interpretation. I have considerable difficulties with the notion that there is a single conflated, or compound, issue, and, even if that notion is correct, that that issue raises a question of interpretation. Indeed, in my view, to characterise the issue as a single question of interpretation is wrong in principle, and unsurprisingly, therefore, can lead to error. While normal principles of interpretation could, I think, accommodate the notion that "vertically" extended to an item which was not at precisely 90° to another item, I do not see how such principles could possibly lead to the conclusion that a slotted rubber rod was within the expression "helical metal spring". As Hoffmann J said in *Improver* [1990] FSR 181, 197, "the angle of the support member [in the allegedly infringing product in *Catnic* [1982] RPC 183] can be regarded as an approximation to the vertical", but "[t]he rubber rod is not an approximation to a helical spring". The problem with treating the issue as one of normal interpretation is thus that that point alone may be thought to have been sufficient to put an end to the patentee's infringement argument on facts

such as those in *Improver* [1990] FSR 181 , and there would seem to have been little purpose in going through the three questions in that case.

56. I had wondered whether the question whether issue (ii) truly involves a question of interpretation raised what was merely an arid issue of categorisation. However, I have concluded that that nettle needs to be grasped, because, so long as the issue is treated as one of interpretation, it will lead to a risk of wrong results in patent infringement cases and it will also lead to a risk of confusing the law relating to the interpretation of documents. In my opinion, issue (ii) involves not merely identifying what the words of a claim would mean in their context to the notional addressee, but also considering the extent if any to which the scope of protection afforded by the claim should extend beyond that meaning. As Sir Hugh Laddie wrote in his instructive article *Kirin-Amgen - The End of Equivalents in England?* (2009) 40 IIC 3, para 68, "[t]he Protocol is not concerned with the rules of construction of claims" but with "determining the scope of protection."

57. I might add that the notion of a product or process which infringes despite an immaterial variation from the invention as claimed is by no means new to domestic patent law. That point is convincingly demonstrated by Sir Hugh in his article at paras 33 to 39. Thus, in *Walton v Potter & Horsfall* (1843) 1 WPC 585, Tindal CJ told the jury that they had to decide whether the defendant's product was "perfectly distinct" from the patented product, or whether it varied "only in certain circumstances, which are not material to the principle and substance of the invention". And Lord Cairns LC in *Clark v Adie* (1877) 2 App Cas 315, 320, referred to the alleged infringer having "really taken and adopted the substance of the instrument patented", and having "taken in substance the pith and marrow of the invention". The patents in these cases included relatively primitive forms of claim, but that does not undermine the fact that our domestic law has long recognised that an immaterial variation does not get an infringer off the hook. Particularly in the light of what he said in *Catnic* [1983] RPC 183, 242, it is worth mentioning that Lord Diplock himself in *Beecham Group Ltd v Bristol Laboratories Ltd* [1978] RPC 153, 200 rejected a submission that "[t]he increasing particularity with which claims are drafted … has made the doctrine [of pith and marrow] obsolete", and said that the doctrine "still remains a part of patent law."

58. Turning to the two issues identified in para 54 above, issue (i), as already mentioned, involves solving a problem of interpretation, which is familiar to all lawyers concerned with construing documents. While the answer in a particular case is by no means always easy to work out, the applicable principles are tolerably clear, and were recently affirmed by Lord Hodge in *Wood v Capita Insurance Services Ltd* [2017] 2 WLR 1095 , paras 8 to 15. In the present case, there is no doubt that, according to normal principles of interpreting documents, the Actavis products do not infringe the Patent, as in no sensible way can pemetrexed free acid, pemetrexed ditromethamine, or pemetrexed dipotassium mean, ie be said

to fall within the expression, "pemetrexed disodium" in claim 1 of the Patent, any more than a slotted rubber rod can be said to be within the expression "a helical metal spring" in the claim in the Improver patent. According to normal principles of interpreting documents, then, this would be the end of the matter.

59. However, the second issue poses more difficulties of principle: what is it that makes a variation "immaterial"? In that connection, I consider that Hoffmann J's three questions in *Improver* [1990] FSR 181 provide helpful assistance, a view supported by the fact explained in paras 44 to 52 above that similar but not identical tests have been adopted in other EPC jurisdictions. However, each of the three questions requires some exegesis, and, particularly the second question, some reformulation.

60. The first *Improver* question, which asks whether the variant has a material effect on the way in which the invention works, seems generally satisfactory. It is a question which was framed in the context of a mechanical patent, and is not wholly aptly expressed for every type of case. However, in practice, the question as framed by Hoffmann J, with its emphasis on how "the invention" works, should correctly involve the court focussing on the "the problem underlying the invention", "the inventive core", or "the inventive concept" as it has been variously termed in other jurisdictions. In effect, the question is whether the variant achieves the same result in substantially the same way as the invention. If the answer to that question is no, then it would plainly be inappropriate to conclude that it could infringe. If, by contrast, the answer is yes, then it provides a sound initial basis for concluding that the variant may infringe, but the answer should not be the end of the matter.

61. The second *Improver* question is more problematic. In my view, it imposes too high a burden on the patentee to ask whether it would have been obvious to the notional addressee that the variant would have no material effect on the way in which the invention works, given that it requires the addressee to figure out for himself whether the variant would work. The facts of the present case serve to make that proposition good. As Floyd LJ explained in para 65 of his judgment below, because a chemist "would not be able to predict the effect of [a] substitution [for the sodium counter-ion] without testing at least the solubility of the [active ingredient in the Actavis products]", it followed that "predicting in advance whether any particular counter-ion would work was not possible", and therefore that the second Improver test could not be answered yes. However, as mentioned in para 25(i) above, salt screening is a routine exercise in determining suitability, and as Floyd LJ said, "the chemist would be reasonably confident that he would come up with a substitute for the sodium counter-ion". In those circumstances, given that the inventive concept of the patent is the manufacture of a medicament which enables the pemetrexed anion to be administered with vitamin B12, it appears to me that application of the second Improver question fails to accord "a fair protection for the patent proprietor" as required by article 1 of the Protocol.

62. In my opinion, the second question is better expressed as asking whether, on being told what the variant does, the notional addressee would consider it obvious that it achieved substantially the same result in substantially the same way as the invention. In other words, it seems to me that the second *Improver* question should be asked on the assumption that the notional addressee knows that the variant works to the extent that it actually does work. That, I think, would be a fair basis on which to proceed in terms of balancing the factors identified in article 1 of the Protocol, and it is, I think, consistent with the approach of the German, Italian and Dutch courts. It is also consistent with the fact that the notional addressee is told (in the patent itself) what the invention does.

63. This reformulated second question should also apply to variants which rely on, or are based on, developments which have occurred since the priority date, even though the notional addressee is treated as considering the second question as at the priority date. Such an approach is supported by the desirability of both consistency of approach and pragmatic justice. It seems right in principle to have the same question, including the same assumption (ie that the variant works) for all cases. As to pragmatism, the point is touched on by Judge Kalden in the passage quoted at the end of para 51 above: while the notional addressee may answer the reformulated second question affirmatively even where the variant was unforeseeable at the priority date, he is less likely to do so than in relation to a variant which was unforeseeable as at that date.

64. The second test applied by the German courts, as I understand it, at least sometimes appears to require the variation not to be inventive, but I am not sure that that is an appropriate requirement, although it is unnecessary to decide that point on this appeal. If the variation represents an inventive step, while it may render it less likely that the patentee will succeed on the second reformulated question, I find it hard to see why that alone should prevent the resultant variant from infringing the original invention. It may entitle the infringer to a new patent, in the same way as the invention of a novel use for a patented invention can itself be patented, but like such a novel use I see no reason why the variant should not infringe the original patent. Having said that, it should be added that the German version of the second test will, I suspect, usually produce the same result as the reformulated second question.

65. The third *Improver* question as expressed by Hoffmann J is whether the notional addressee would have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention. That is in my view an acceptable test, provided that it is properly applied. In that connection, I would make four points. First, although "the language of the claim" is important, consideration of the third question certainly does not exclude the specification of the patent and all the knowledge and expertise which the notional addressee is assumed to have. Secondly, the fact that the language of the claim does not on any sensible reading cover the variant is certainly not enough to justify holding that the patentee does

not satisfy the third question. Hence, the fact that the rubber rod in *Improver* [1990] FSR 181 could not possibly be said to be "an approximation to a helical spring" (to quote from p 197) was not the end of the infringement issue even in Hoffmann J's view: indeed, as I have already pointed out, it was because the rubber rod could not possibly be said to be a helical spring that the allegedly infringing product was a variant and the patentee needed to invoke the three Improver questions. Thirdly, when considering the third question, it is appropriate to ask whether the component at issue is an "essential" part of the invention, but that is not the same thing as asking if it is an "essential" part of the overall product or process of which the inventive concept is part. So, in *Improver* [1990] FSR 181 , 197, Hoffmann J may have been (and I mean "may have been") wrong to reject the notion that "the spring could be regarded as an 'inessential'": while it was undoubtedly essential to the functioning of the "Epilady", the correct question was whether the spring would have been regarded by the addressee as essential to the inventive concept, or inventive core, of the patent in suit. Fourthly, when one is considering a variant which would have been obvious at the date of infringement rather than at the priority date, it is, as explained in para 63 above, necessary to imbue the notional addressee with rather more information than he might have had at the priority date.

66. In these circumstances, given the weight that has been given by courts in this jurisdiction (and indeed in some other jurisdictions) to the three " Improver questions", I think it must be right for this court to express in our own words our reformulated version of those questions. In doing so, it is right to emphasise, as Lord Hoffmann did in *Kirin-Amgen* [2005] RPC 9, para 52, that these questions are guidelines, not strict rules (as indeed the Oberlandesgericht indicated in Case No 6 U 3039/16, when saying that it was "generally" true that "three requirements must be met"). While the language of some or all of the questions may sometimes have to be adapted to apply more aptly to the specific facts of a particular case, the three reformulated questions are as follows:

> i) Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, ie the inventive concept revealed by the patent?
>
> ii) Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?
>
> iii) Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?

In order to establish infringement in a case where there is no literal infringement, a patentee would have to establish that the answer to the

> first two questions was "yes" and that the answer to the third question was "no."

424. Important aspects of *Actavis v Lilly* were considered by the Court of Appeal in *Ice-Scape v Ice-World* [2018] EWCA Civ 2219. At [60] Kitchin LJ (as he then was) made clear that the starting point for the *Actavis* questions is the normal, purposive interpretation.

425. He referred to the way the invention works at [62] (and although this was in the context of question 1 it is important throughout):

> 62. The first *Improver* question, whether the variant has a material effect on the way the invention works, was addressed by Lord Neuberger at [60]. He thought this was generally satisfactory but the court must focus on "the problem underlying the invention", "the inventive core", or the "inventive concept". In effect the question is whether the variant achieves the same result in substantially the same way as the invention.

426. He summarised the approach to question 3 at [64]:

> 64. The third *Improver* question, namely whether the notional addressee would have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention, was considered by Lord Neuberger at [65]. He thought this was acceptable provided it was properly applied. Here he made four points:
>
> i) Although "the language of the claim is important", consideration of this question does not exclude the specification of the patent and all the knowledge and expertise which the notional addressee is assumed to have.
>
> ii) The fact that the language of the claim does not on any sensible reading cover the variant is certainly not enough to justify holding that the patentee does not satisfy the third question.
>
> iii) It is appropriate to ask whether the component at issue is an "essential" part of the invention, but that that is not the same thing as asking if it is an "essential" part of the overall product or process of which the inventive concept is part. Here regard must be had to the inventive concept or the inventive core of the patent.
>
> iv) When one is considering a variant which would have been obvious at the date of infringement rather than at the priority date, it is necessary to imbue the notional addressee with rather more information than he might have had at the priority date. Here Lord Neuberger had in mind the assumption that the notional addressee knows that the variant works.

427. And he summarised the overall approach at [66]-[67]. In the circumstances of the case he found it significant to identifying the inventive concept or core that

many of the claim features were common general knowledge, which threw the focus on the one that was not.

428. The doctrine of equivalents has been applied in relation to numerical ranges in two first instance cases in this jurisdiction: *Regen v Estar* [2019] EWHC 63 (Pat) at [212]-[218] and *Teva v Novartis* [2022] EWHC 2847 (Pat) at [218]-[222]. I will proceed accordingly.

429. A further principle is that where a specification discloses a number of possibilities but claims (as a matter of normal interpretation) only some of them, that is a factor against the doctrine of equivalents resulting in protection for the unclaimed possibilities. An example is *Akebia v Fibrogen* [2020] EWHC 866 (Pat) at [453]-[454], based in part on the decision of the German Bundesgerichtshof in *Okklusionsvorrichtung*, Case X ZR 16/09. It is not necessarily a decisive consideration where it arises, though: see e.g. *Sandoz v Biogen* [2024] EWHC 2567 for a case where it failed.

Question 2

430. I have set out what Lord Neuberger said about question 2 above.

Are experiments allowed for question 2?

431. As I have mentioned above, the Claimants raised as a possibility that stability for the relevant formulations might be achieved by ionic interaction and not just the primary action of the excipients, in particular the sucrose stabiliser. Given the lateness with which the point came in, a procedural compromise arrived at was such that the Claimants accepted that in the alleged infringements ionic interaction in this way is not in fact at work, that there are routine experiments which could be done to show as much, and that if the experiments were done on the alleged infringements they would show no ionic interaction at play.

432. Nonetheless the Claimants say that Actavis Q2 is not satisfied because, once told that the variant does work, as Lord Neuberger explained at [61] and [62] ought to be assumed, it must still be obvious that the variant works in the same way. They say it cannot be "obvious" if experiments are necessary and/or that as a matter of policy experiments ought not to be allowed because Actavis Q2 is there to provide certainty for the public. Regeneron said that experiments are allowed for Actavis Q2.

433. It was my recollection that there were cases prior to *Actavis v Lilly* where the issue of experiments for what was then question 2 of the "Protocol questions" (another name for the *Improver* questions) was considered. The parties kindly researched that and indeed there are two cases which said that experiments were not allowed for Actavis Q2 because the public ought to be able to assess the impact of a monopoly on them before going to the trouble of doing experiments and/or building a product only to later find out that it infringed. The cases were *Sara Lee v Johnson Wax* [2001] EWCA Civ 1609 per Aldous LJ at [35]-[36] and *Merck v Generics* [2003] EWHC 2842 (Pat), Laddie J at

[40]. So on Actavis Q2 they put the greatest weight, in terms of the Protocol, on certainty for third parties.

434. Counsel for Regeneron said that *Actavis v Lilly* had wrought a sea change because it decided that equivalence could not be elided with interpretation and had to be the subject of a separate conceptual approach starting from normal interpretation. I agree that it did make that change, but it still left in place the three questions. It did not say that they should be abandoned, but it did revise Actavis Q2. The critical point for the purposes of this case is not that the Supreme Court said there had to be a doctrine of equivalence as well as normal claim interpretation, but how it reframed Actavis Q2.

435. Lord Neuberger at [61] was explicit that the existing Actavis Q2 did not give fair protection for the patentee (the other limb of the Protocol) and so he was certainly rebalancing it in favour of the patentee and away from third parties. Although he did not mention *Sara Lee* or *Merck v Generics* (I doubt if they were cited in the Supreme Court) it is clear that he would not have agreed with them on this point. In fact I note that the key submission by counsel for the patentee in *Sara Lee*, rejected by the Court of Appeal, was that the skilled person should be told that the variant worked (see [35]). Lord Neuberger plainly said that that submission was, after all, correct.

436. The rebalancing that Lord Neuberger undertook does, in a way, let in experiments to some extent. The assumption is that the variant works and there will be some cases where that can only be found out to be true by trying it. So third parties cannot know in advance of trying where they will stand. But at a practical level third parties take the risk of failure on board at a commercial level anyway. I can see that it is not too problematic to put third parties in a position where they say to themselves: "I would like to try X. It may not work and if it does not then I have wasted time and effort. But if it does work then the very fact of it working will tell me that it does so by means Y, in which case, obviously, it will be working the same way as the patentee's invention".

437. It would be a step further to allow experiments to work out how the variant works, given it does work. Lord Neuberger did not say anything about that. He did not have to turn his mind to it because he was addressing a factual situation where, given that the variant worked, it was plain how it worked. That has turned out to be the situation for essentially all cases in the UK where Actavis Q2 has come up since the Supreme Court's decision: the patentee wins because once one knows the variant works there is no doubt about how. Allowing experiments on Actavis Q2 would put third parties in a situation where, on top of taking the risk that their product would not work at all, they would have the uncertainty that if it did work and it was not thereby self-evident how, they would not know if they infringed or not without more experiments.

438. Fundamentally, I think that allowing experiments for Actavis Q2 would abolish it completely. It is already often said, with considerable justification, that Actavis Q2 will only ever avail a defendant when their product is a "black box". Allowing experiments to determine how it works would leave nothing to Actavis Q2 at all.

439. Regeneron said that it was only routine tests that should be let in in this way. That does not affect the points I have just made. It also said that there should be no difference between the contents of CGK texts (the information in which could be used for Actavis Q2) and the results of routine experiments. I disagree for two reasons. First, all aspects of the CGK come into play in all stages of the consideration of these issues because they condition the nature and knowledge of the skilled person. Experiments which have not been done are conceptually completely different. Second, third parties can identify and access the CGK before they undertake the development of a product, but they can only do the kind of experiments relied on by Regeneron, to find out if they infringe, much later.

Level of generality

440. An issue which has been considered on many occasions in this jurisdiction is at what level of generality the question of infringement, either by "normal" purposive claim interpretation or by equivalence, should be considered. It is built into the approach to normal claim interpretation as it has been developed and as is now summarised in *Saab Seaeye v. Atlas Elektronik* [2017] EWCA Civ 2175 at [18]-[19], point (v) in particular, and it was long a facet of the *Improver/Protocol* questions, when equivalence was seen as part of the process of interpretation, before *Actavis v Lilly*.

441. The need to assess the level of generality was not considered by the Supreme Court in *Actavis v Lilly* because it was not live: Actavis accepted that the first question was to be answered in the patentee's favour, and the Supreme Court clearly thought that the invention was the use of the pemetrexed ion together with the antifolate (i.e. not referable to the counterion) and that is how the argument proceeded, without contradiction from Actavis, whose defence was based on questions 2 and 3.

442. It is worth quoting the relevant sub-paragraph of *Saab Seaeye,* [18(v)]:

> (v) When ascertaining the inventor's purpose, it must be remembered that he may have several purposes depending on the level of generality of his invention. Typically, for instance, an inventor may have one, generally more than one, specific embodiment as well as a generalised concept. But there is no presumption that the patentee necessarily intended the widest possible meaning consistent with his purpose be given to the words that he used: purpose and meaning are different.

443. That is of course about normal interpretation rather than equivalence, but the point that the patentee may disclose more than one invention at multiple levels of generality is of wider importance.

444. Actavis Q1 involves a comparison of the result achieved, and the way of achieving it, between the invention and the variant. The comparison itself is a factual exercise, but identifying the invention in order to make the comparison is a question of interpreting and assessing the patent specification in the light of the CGK. I return to the question of the level of generality at which this should be done. In my view it should be done at the level of generality of the

claims. I believe this is consistent with the pre- and post- *Actavis v Lilly* case law, and it was the conclusion reached by Mellor J in the specific context of equivalence and Actavis Q1 in *Pfizer v GlaxoSmithKline* [2024] EWHC 2523 (Pat) at [497]-[508] after consideration of one of my own decisions.

445. I make four further observations about this.

446. The first is that the Court should not be misled by the level of generality being that of the claims into a conclusion that the words of the claims themselves and without more answer Actavis Q1 or Actavis Q3 against the patentee. Lord Neuberger was quite clear on Actavis Q3 that the claims in isolation are not a reason to find that strict compliance is necessary. Similarly, identifying the relevant invention by considering matters at the level of the claims does not preclude the conclusion that some claim features are merely peripheral (as happened in *Ice-Scape*, for example).

447. The second is that a paradigm example of there being, at least potentially, more than one invention is where there are some very general ideas in the specification but also some specific preferred embodiments. These may be – usually will be – different inventions. It would be a mistake to take one of the general ideas as "the invention" and then use it to answer the Actavis questions in respect of a claim drafted at the detailed level of the specific embodiments.

448. Third, assessing the relevant invention at the level of the claims ensures the claims remain a central part of the analysis, as Article 69 and the Protocol require.

449. Fourth, and last, I think it may be a relevant factor when assessing the right level of generality that the claim under consideration is a dependent claim, particularly when it is a dependent claim directed to a preferred embodiment, which would be a recognised and narrow invention in its own right. But I agree with Regeneron that this cannot be carried too far and that it cannot be a rule, by the backdoor, that equivalence does not apply to dependent claims (as appeared to be the consequence of some of the Claimants' arguments).

450. This focus on the claims and the specification in the course of answering Actavis Q1 is consistent with a number judgments which have said that the same answer can be obtained in a given case by application of either Actavis Q1 or Actavis Q3: see *Facebook v Voxer* [2021] EWHC 1377 (Pat) at [210] (which was, I recognise, in the specific and rather different context of disclosed-but-not claimed and which I followed in *Shenzhen Carku v NOCO* [2022] EWHC 2034 (Pat) at 112) and the decision of HHJ Hacon sitting as a High Court judge in *Teva v Novartis* [2023] EWHC 2847 (Pat) at 233-243. It will depend on the facts of the case but speaking for myself I think it will usually be preferable actually to answer Actavis Q1 first and in its own terms and then to bear in mind possible relevant effects of the analysis later, on Actavis Q3. Textual or drafting points which are not relevant to Actavis Q1 may come in only, or more naturally, at Actavis Q3 (for example, disclosed-but-not-claimed, not reading onto acknowledged prior art).

Law on reference to the file history

451. I recently summarised the law as to when the court may have regard to the history of the patent's prosecution in *Alexion v Samsung Bioepis* [2025] EWHC 1240 (Pat), where I cited *Actavis UK Limited and ors v Eli Lilly & Co* [2017] UKSC 48 at [81] – [88] and my own decision in *Siemens Gamesa v GE Energy* [2022] EWHC 3034 (Pat). I do not need to repeat any of that here.

Law of sufficiency

452. Apart from the narrow point on the relationship of concentration to dose, which I deal with at the end of this judgment, there is no allegation that the Patents are invalid for insufficiency. But it is necessary to identify what the law of sufficiency requires to assess Regeneron's broad point that formulation inventions will not get fair protection unless the law of infringement by equivalence is adapted for them.

453. The law of sufficiency requires that a patent is enabled across the scope of the claims and the claims must correspond to the technical contribution. This means (simplifying greatly for brevity) that a relevant effect which represents the technical contribution has to be plausible for the whole scope of the claims (*Warner-Lambert v Generics* [2018] UKSC 56) and it has to be possible to make that which is claimed across the whole scope of the claims (*Regeneron v Kymab* [2020] RPC 22).

Infringement by equivalence – analysis and discussion

454. I will deal with the prosecution history separately, since it is a minor part of the picture and only applies to '691.

Regeneron's basic argument

455. I have identified Regeneron's basic point at a very high level in the Overview section of this judgment.

456. Regeneron relies on the very empirical nature of the formulation exercise, which I do not think was ever in doubt. It says that when faced with the task of formulating a new protein for the first time the skilled team has a vast envelope of possibilities across which to search for a stable formulation. But, it says, if such a formulation is found, the picture changes completely. Someone who comes along to make another formulation still has an empirical task to do, but they know it is possible and they have a starting point. This was referred to by Counsel for Regeneron as the "game changer" and it was supported by some evidence from Prof Gukasyan. I accept that it would provide some degree of encouragement to later workers that the patentee had been able to make a successful formulation because it would be known that the task was not inherently impossible, and I accept that narrow predictions could be made about other possible formulations, starting from the patent. But "game changer" is hyperbole.

424. Regeneron accepts and indeed relies on the fact that the family of possible further stable formulations which draw on such an initial invention cannot be predicted. They have to be conceived, made and tested. Regeneron accepts that the law of sufficiency would prevent the maker of such an invention from drafting a valid claim to, effectively, "all the formulations that take advantage of my formulation".

457. Regeneron's central point is that this situation does not provide the inventor of an empirical formulation invention with fair protection. However, it says, that can be remedied by a sufficiently generous approach by the law to infringement by equivalence: the inventor should be able to draft a claim which is very narrow on its ordinary interpretation and hence not vulnerable to insufficiency attacks, and then call on the law of infringement by equivalence to bring within the scope of the monopoly the full range of further formulations which are inspired or helped along in their development.

458. Regeneron further conceptualises its contribution as follows: the excipients required by the claims of the Patents work at two levels. The first level is that each component performs its primary function: the surfactant prevents aggregation, the buffer maintains pH, and so on. The second level is that the components all together interact so that the total formulation is stable. It will be apparent that the first level is easy to understand and explain (and if the first level was all that there was to it the formulation aspects of the claims could well be obvious as just the unrelated use of CGK components for their individual CGK purposes – Regeneron meets such an attack by relying on the second level). By contrast the second is unpredictable and is where the empirical nature of the work comes in. Even after the skilled team knows the total formulation is stable they will not understand this second level and how the excipients, at the molecular level of extremely fine detail, are interacting to allow stability to be maintained. I agree that these two levels reflect scientific reality and were CGK: see "disputed" CGK issue 20 above (not in fact disputed).

459. A fundamental fallacy with Regeneron's basic argument is its premise that there is something wrong with the law of sufficiency that needs remedying (by expanding the scope of the law of infringement by equivalence). I do not accept that that is so for reasons I will return to in a moment, but the law of sufficiency which Regeneron argues leads to its inability to claim more broadly has been set by the Supreme Court in *Warner Lambert v Generics* and *Regeneron v Kymab* and by the Court of Appeal in a number of other judgments, including in particular *Fibrogen v Akebia* [2021] EWCA Civ 1279. Those decisions are all binding on me. I agree with Counsel for Regeneron that *Regeneron v Kymab* is a case where the insufficiency was about inability to make the products, not about the difficulty of prediction, but it is nonetheless binding authority about the scope of the monopoly having to correspond to the technical contribution to the art.

460. I said I would deal with whether there is a defect in the law of sufficiency in the way that Regeneron argues. The reason that I do not think there is, is that the technical contribution in formulation cases such as the present will often be a very narrow one. It exists at the second level of Regeneron's argument:

the interaction of the excipients which the skilled team does not understand but which works for a specific combination of excipients in specific amounts at specific conditions such as pH. This is not a principle of general application, let alone one that can meaningfully be said to be used by someone who comes along later and does their own empirical work, even if they get some comfort from the fact that they know a solution is possible.

461. This is not to say that formulation science is one in which broad, general inventions can never be made. A new family of excipients or an explanation of how stability at Regeneron's second level is achieved that could be put to practical effect might justify broad protection, but that is not the situation in the present case.

462. I also do not accept that patentees in the position of Regeneron are as helpless to draft and maintain somewhat broader claims as Regeneron argued. Counsel for Regeneron maintained that there was a narrow range across which predictions could be made and the requirements of sufficiency satisfied. One example was a modest change in a concentration, and another was that it was reasonably predictable that histidine could be used as a buffer instead of sodium phosphate (the submissions did not seem entirely consistent on the latter, but I take it as an example nonetheless).

463. There is nothing to stop a patentee drafting claims of still modest scope which list two or three alternatives in an excipient class if they think a prediction is possible. Indeed an example is claim 1 of '691 as granted which has a short list of choices for e.g. the co-solvent and tonicity agent, and ranges for the concentrations. Regeneron has chosen to abandon that claim. I do not know the reasons although I suspect it is more to do with the prior art than sufficiency. In any case, the fact that Regeneron was able to have a broader claim granted and then drop down to a narrower one illustrates that a patentee with a narrow invention is not prevented from trying to generalise and then retreating if necessary. I appreciate that scientific and legal thought and analysis is needed when working out how far to generalise, but that is the work that is required of patentees and their highly-skilled advisers in many areas of patent law.

464. Finally, I should note that "fair protection" comes into these arguments in two ways. One is a general value judgment about whether the law of insufficiency strikes a fair balance, which I have addressed. The other is the reference to "fair protection for the patent proprietor" in the Protocol to Article 69 of the EPC (balancing with certainty for third parties). These are different things. The Protocol is not a general licence to adjust other parts of substantive patent law.

<u>The inventive concept in this case</u>

465. In setting out the applicable legal principles I identified that *Ice-Scape*, following *Actavis v Lilly*, requires identification of the inventive concept. This is of general importance but also specifically allows the Court to pick out those claim features that are key, or central and those that are merely CGK and/or implementation details. It is possible that a variant in a feature which is not

key will lead to a conclusion of non-infringement, especially under Actavis Q3, but less likely.

466. The parties pleaded out what they said the relevant inventive concept is.

467. The Claimants essentially said that the inventive concept of claim 5 of '691 is exactly what the claim says, with no feature to be regarded as peripheral. They also identified suitability for intravitreal administration and a clinically useful degree of stability as part of the concept (the latter, stability, is not expressly required by the claims of '691 but the parties agreed that it was to be treated as part of the inventive concept and I agree).

468. The Claimants did not say that this was the inventive concept merely and only because it is what the claim says. They said it was identifiably so because it was a narrowing down from the broader classes of excipients allowed by claim 1 and because the skilled person would see that it was a claim directed to two of the preferred embodiments (Examples 3 and 4).

469. The Claimants had a fallback inventive concept by which they brought in ionic interactions.

470. Regeneron pleaded (Consolidated Re-Amended Defence and Counterclaim paragraph 5.2) that each of the claims of both patents comprised "at least the following inventive concept: the provision of 40mg/ml of aflibercept in stable liquid formulations of the claims at pH 6.2-6.3 suitable for intravitreal administration, including in the light of the characteristics of aflibercept … " and they went on to define further what was meant by stable and by the characteristics of aflibercept, which I do not need to spell out. This was essentially the inventive concept for which Regeneron argued, and it makes no reference to specific excipients.

471. The next paragraph in Regeneron's pleading said this:

> "5.2.3 The skilled person would understand that the aforesaid stability and suitability for intravitreal administration of the claimed formulations is achieved by the functionalities provided by the following components:
>
> 5.2.3.1. The "0.03% polysorbate 20" or "0.03% polysorbate" which is an organic co-solvent which protects aflibercept when dissolved in water, minimising protein aggregation and precipitation out of solution;
>
> 5.2.3.2. The "about 40mM NaCl" or "40mM NaCl" which is a tonicity agent which brings the osmotic pressure of the formulation within the acceptable range for intravitreal administration;
>
> 5.2.3.3. The "10mM sodium phosphate" which is a buffering agent which maintains the pH of the formulation within the claimed pH range which is necessary for the stability of aflibercept by releasing or capturing hydrogen ions; and

> 5.2.3.4. The "5% sucrose" which is a stabilizing agent which forms a protective environment for aflibercept to stabilize it and to maintain its conformation."

472. This does deal with the specific excipients and in the amounts required by the claims in issue. But it does not say they are part of the inventive concept; rather it says how the skilled person would understand that the individual excipients achieve their primary functions in the formulation; what Counsel for Regeneron called the first level. It was by reference to this explanation of how the excipients work at the first level that Regeneron sought to meet the inevitable objection that its inventive concept was too broad and would extend to any excipient which did the same thing at the first level as those claimed.

473. I agree that based on CGK and the teaching in the Patents the skilled person would understand that the excipients would achieve that set out in the parts of paragraph 5.2.3. But while the CGK is necessary background to identifying the inventive concept, that does not mean that everything at every level of detail that the skilled person would deduce with CGK is the inventive concept, or part of it.

474. Regeneron never really settled to any one position. It skipped between saying the inventive concept was the broad one identified above when arguing the specifics of infringement by Formycon's and Samsung's products, and saying that the inventive concept did include the specific excipients when it came to obviousness.

475. I do not think it is particularly hard to identify the inventive concept in this case: it is the Claimants' primary one. The Patent identifies the very broad idea of a stable liquid ophthalmic formulation of aflibercept e.g. at [0007] and the idea of high concentration with a range of excipients in succeeding paragraphs e.g. [0009] – [0011]. But then in [0012]-[0015] it sets out some very specific formulations which the skilled person would see were directed to the Examples that had actually been tested. It would be the stuff of angels dancing on the head of a pin to say exactly how many inventions there are disclosed, but clearly there are multiple inventions of differing degrees of specificity and that disclosed in e.g. [0014] is narrower than the broader ones set out earlier.

476. The skilled person would understand this at a technical level. They would understand that the specific formulations of the Examples had actually been tested and shown to be stable: they worked at the first and second levels referred to by Counsel for Regeneron in that each individual excipient worked according to the well understood CGK but also in that the specific combinations of excipients did not interact together in some way to disrupt stability. The skilled person would also understand that there was the broader idea of high concentration aflibercept associated with categories or choices of excipients in ranges of quantities but that these had not been tested in the same way.

477. In some cases, *Ice-Scape* is an example (at [72]), the fact that claim features are CGK has been a reason to exclude them from the inventive concept. But

that cannot be regarded as an absolute rule and in that case the one feature that was not CGK was identified as key to the inventive concept while the CGK features merely served their own CGK purposes. In the present case there is the presence of different levels of inventions plus the fact that while the excipients are individually CGK they interact in a very important way (at the second level).

478. Although not necessary to my conclusion this all makes sense from a patent point of view. It is rational for a patentee to describe and claim a narrow invention even if broader ones are also identified in the specification: for example to provide the smallest target for the prior art, or to be confident of enablement. This may be reflected in the cascade of claims and is in the present case, although as I have made clear above, the mere structure of the claim dependencies cannot be conclusive and is mainly a matter at Actavis Q3. It may not be apparent from a patent or from the prosecution file what thinking went into drafting a narrower claim, and it is not necessary for the skilled person to have to speculate about that (see e.g. Birss J in *Illumina v Latvia* at [396]) but is a welcome reassurance that my conclusion makes sense in this way.

479. I do not think ionic interaction is part of the inventive concept since it is not mentioned in the Patents. But it may still play a part at Actavis Q2 as an instance of whether it would be obvious how the infringement works.

Infringement facts

480. The Formycon product varies from claim 5 because it has 10mM histidine buffer instead of 10mM sodium phosphate.

481. There is no dispute but that effective buffering at pH 6.2-6.3 takes place. Additionally, there is no dispute that histidine buffers the same way as sodium phosphate in the sense that both take in and release hydrogen ions, i.e. at a general level. This was all in accordance with the CGK.

482. There is no dispute that the Formycon product is stable to the relevant degree (this is not a requirement of the claims of '691, only later claims of '306, but it is relevant to equivalence in any event, the parties agreed).

483. There is no dispute that the Formycon product is suitable for intravitreal administration.

484. The Samsung product varies from claim 5 in two ways:

    i) It has 7.78mM sodium phosphate buffer not 10mM.

    ii) It does not have any NaCl at all but has more sucrose (8%).

485. As with the Formycon product, there is no dispute but that effective buffering is still provided, in the same general way as identified above. Regeneron said that this was because 10mM is in fact excess of what is needed.

486. There is again no dispute about stability or suitability for intravitreal administration. The reason that the Samsung product remains suitable for intravitreal administration is that the higher level of sucrose means that no NaCl is needed to make the formulation isotonic. I do not believe there was any dispute about this.

Formycon product – Actavis Q1

487. I have set out my conclusions about the appropriate level of generality and the inventive concept above.

488. Given those conclusions, I consider it follows that Regeneron fails on Actavis Q1 in relation to the Formycon product. The Formycon product achieves stability but it does so in a different way from the invention at the relevant level of generality. Stability results at Regeneron's second level from a very particular combination of excipients and the way in which they do or do not interact and that is not the same for the claimed formulations as for the Formycon product. This was supported by evidence Dr Daugherty gave that histidine would be expected to behave differently from phosphate in some ways, being chemically different; she specifically pointed out that it is not known exactly how stability would be achieved with histidine. This is not inconsistent with its providing buffering in the general sense of maintaining pH as described above: that is at Regeneron's first level.

Formycon product – Actavis Q2

489. Given my conclusion on Actavis Q1 this does not arise for decision. However, I reiterate my conclusions above that the skilled person would not understand how stability at Regeneron's second level was achieved, just that it was (Dr Daugherty's evidence again supports this), and specifically would not be able to assess what role was played by ionic interactions without experiments (or indeed generally why the formulation was stable), which I have held are not permissible for Actavis Q2. I note in passing that the inability of the skilled person to understand what provides stability in the context of the Patents is emphasised by Examples 5 and 6 where there is no sucrose yet significant stability is achieved. Regeneron pointed out that the stability is lower than in some examples which do have sucrose, but the Claimants said, and I accept, that what would be surprising and ill-understood was that there was good stability at all.

Formycon product – Actavis Q3

490. Again this does not arise for decision given my decision on Actavis Q1, but I address relevant points in the next section.

Formycon product - if I were wrong about the inventive concept

491. My main conclusion is that Regeneron fails on the Actavis questions starting with Actavis Q1 because the inventive concept of the claims is a narrow one, indeed a very narrow one. In turn that depends on my view of the appropriate

level of generality. I think I should go on to consider what would be the answer to the Actavis questions if Regeneron were right about the inventive concept.

492. This all turns on Actavis Q3 because Formycon accepts that on Regeneron's inventive concept Actavis Q1 should be answered in its, Regeneron's, favour (the Claimants did not address Actavis Q2 separately on the parties' different inventive concepts but since Regeneron's inventive concept does not include ionic interactions, that only being a fallback part of the inventive concept for the Claimants, I do not see that Actavis Q2 can help the Claimants in this scenario).

493. If the skilled reader thought the inventive concept was Regeneron's broad one then they would still see that:

    i) Despite the inventive concept being broad, the patentee had drafted a claim that was consistently very narrow for all the excipients (only one excipient, quantities precisely specified);

    ii) Claim 5 was a dependent claim which was therefore intended to have a narrower scope;

    iii) Claim 5 corresponds to Examples 3 and 4. In fact as the Claimants point out, it is more than that because claim 5 does not, as written, cover other examples such as Example 1 and 2.

494. All of these matters point to a deliberately narrow claim, i.e. that strict compliance was intended. I recognise that the fact that claim 5 is a dependent claim cannot be conclusive and I do not treat it as such, but it is nonetheless a material factor. Taking these matters in the round I would have answered Actavis Q3 against Regeneron even on its inventive concept. It is fair to say that the points leading to this conclusion overlap with some of the considerations for Actavis Q1, but there is a greater stress on the way the specification and claims are written and structured.

495. The specification does not spell out why the patentee had gone for narrow claim scope. As I already mentioned, I do not think it is necessary for the reader to have to speculate about that but there would be obvious rational possibilities (prior art, sufficiency concerns). The skilled reader certainly would have no reason to think that it was irrational or accidental that the patentee had chosen a narrow scope; the broader ideas disclosed might also be in a divisional application.

496. The Claimants also relied on Dix in connection with Actavis Q3 (because it mentioned histidine). I reject such reliance for reasons given when I deal with Dix.

497. Relatedly, the Claimants also said that histidine was a CGK buffer and that therefore the skilled person would conclude that the patentee had consciously decided not to claim it. This approach has no support in the authorities that I can see and is conceptually nowhere close to the situation where the specification discloses something which is then not claimed. The Claimants

sought to bolster this with a slight variant: that the skilled reader would think that as part of the screening exercise the patentee must have tested other buffers yet had claimed only one. I found this speculative and unconvincing and there is no reason to think that the patentee had tried histidine, specifically, so as to not want to have protection for it (there were multiple CGK buffers that could maintain a pH of 6.2-6.3).

498. My rejection of these two specific points about histidine in Dix and/or the CGK does not undermine the matters which led me to my conclusion on Actavis Q3 on Regeneron's inventive concept. They are just bad points which did not go anywhere.

Prosecution history

499. In a communication with the EPO of 9 March 2012 in the course of prosecuting '691, Regeneron distinguished a piece of prior art "D1" partly on the basis that it used histidine as a buffer, rather than phosphate as required by what was then claim 1. Regeneron said this was "an important distinction" and relied on the fact that histidine tended to discolour.

500. Formycon relies on this as being an instance of the second, public policy, situation from *Actavis v Lilly* (at [88]).

501. Regeneron's responses were that:

    i) Histidine's tendency to discolour is not relevant to the invention, which is about stability.

    ii) The statement was made in the context of a much broader claim with wider concentrations of excipients, where there were multiple bases for distinguishing D1.

    iii) The point only applies to '691.

502. I think the first point is correct, although it is rather to the effect that Regeneron was in fact making an irrelevant point to the EPO.

503. As to the second point, the Claimants said that although the claim at the time had wider concentrations of excipients, D1 in fact discloses 10mM histidine, which is what Formycon now uses. That is not stated in the communication to the EPO, however, although it was mentioned in the IPRP (raised for the parent application) to which Regeneron was effectively responding.

504. As to the third point, the Claimants said it was "artificial" and that the file history should also be considered for '306. I do not agree. The practical effect of the Claimants' submission if accepted would be that parties trying to understand whether there were relevant statements in the prosecution history would have to study all the histories of all applications in the same family, at least, and then additionally analyse if statements made in one were relevant to others. It is conceivable that that might be different if a submission in one

application was clearly cross-referenced to another application in the same family, but that is not the situation before me.

505. I reject the reliance on the prosecution history, primarily because of the point about lack of clarity. Many different points were in play and the Claimants' argument requires an artificial focus on one among them, and an appreciation about the relevant concentration which could only be gleaned by going back to much earlier in the file of the parent application. There is no sufficiently clear statement of a limitation as is required by *Actavis v Lilly*.

506. Had I thought the point had any merit, its effect would have been confined to '691.

Samsung product – Actavis Q1

507. The Samsung product has two differences from the claim, which I have identified above (more sucrose balancing the omission of NaCl, and 7.78mM sodium phosphate buffer instead of 10mM). Because of the differences, I need to consider both how the Samsung product achieves an osmolality suitable for intravitreal administration, and how it achieves stability. The Claimants' written submissions tended to run them together, but Regeneron clearly understood that both were relevant, and addressed them fully.

508. I will deal with the sucrose/NaCl point first.

509. Regeneron's main arguments were that:

    i) On osmolality, there was just a difference of degree in having 40mM of NaCl and no NaCl at all. Having no NaCl at all was the same as setting its level at 0mM rather than 40 or 20 or 0.1mM.

    ii) The skilled person would understand that what was really going on was using some amount of NaCl to adjust the osmolality in the light of whatever amount of sucrose there was, and if there was enough sucrose then there would be no need for any NaCl.

    iii) The sucrose achieved stability by the same mechanism at 8% as at 5%: by preferential exclusion. So that was the same "way".

510. Given my view on the right level of generality, these arguments fail for reasons which parallel those for the Formycon product. The claims are to a very particular formulation.

511. The "way" in which an osmolality appropriate for intravitreal administration is achieved is by balancing a particular amount of sucrose with a particular amount of NaCl. Having no NaCl at all is not just a question of degree. I reach this conclusion without relying on a very semantic point which the Claimants made, that sucrose is referred to in the Patents as a stabilising agent but not as a tonicity agent: that just reflects what the skilled person would understand to be the primary function of sucrose, the one with which it is most commonly

associated. That would not cut across the skilled person also understanding that with enough sucrose no NaCl would be needed for osmolality.

512. Although the sucrose would achieve its stabilising effect by the same primary mechanism whether at 5% or 8%, that is at Regeneron's first level, and does not affect the arguments about overall stability given the whole formulation with quantities and specific excipients and their interactions, at Regeneron's second level. Those apply to the Samsung product just as they did to the Formycon product. This aspect of the argument is also relevant to the buffer concentration point, to which I now turn.

513. The claimed buffer concentration is 10mM; there was evidence about whether the skilled person would think that this was an excess. My assessment of that evidence is that the skilled person would understand that the patentee probably had not done the considerable work of identifying the absolute minimum amount of buffer needed and I accept Prof Gukasyan's evidence to the effect (which was very largely consistent with Dr Daugherty's on this topic) that if 10mM was the absolute minimum there would be at least some slight sign of a stability "drift" after two years. But this does not mean that the skilled person would think that 10mM was in significant excess: the specification does not say so and there was no way of calculating it. I conclude that the skilled person would think that it was probably a slight excess and that the patentee had pitched the claim at that level with that expectation.

514. This point does not, though, change my assessment of the relevant "way": the claim is at a very granular level of detail and the "way" that stability is achieved, including as it relates to pH, is by a very particular combination of excipients in specific concentrations. Dr Daugherty said that, in the context of the 7.78mM buffer used in the Samsung product "It is the entire formulation working together that would be how does that all work."

Samsung product – Actavis Q2

515. What I have said above in relation to Actavis Q2 for the Formycon product applies equally here. I note that Dr Daugherty gave specific evidence that she was surprised the Samsung product was stable (and that she would not know if it was without testing); given the law on Actavis Q2 this is not directly an answer to Regeneron's case, because the skilled person is taken to know that the variant does work. But Dr Daugherty's evidence also supported the fact that the skilled person would not understand, when they did observe, or were told about, stability, how it came about at Regeneron's second level. The role of sucrose is a particular conundrum given the point about Examples 5 and 6 to which I have referred above.

Samsung product – Actavis Q3 and if I were wrong about the inventive concept

516. Again, the same logic as applies to the Formycon product which I set out above applies to the Samsung product and I will not repeat myself.

517. There are however some additional points arising from the specification which could have been relevant to Actavis Q3 on Regeneron's inventive concept:

i) The point that sucrose is not described as a tonicity agent in the Patents: I reject this purely semantic point for reasons already given. Armed with the CGK the reader would understand that it was just described by reference to its most commonly understood function.

ii) The point that the Patents e.g. at [0010] say the "stabilizing agent is sucrose … and the tonicity agent is sodium chloride" (see also "aspect" 1 of [0067]). This is a similar but potentially slightly better point since the text indicates that there is a separate (from the sucrose) tonicity agent and that it is NaCl. But it does not really go further than the claim itself, which, as Actavis says, is not enough on its own for Actavis Q3.

iii) That claim 6 of '691 (and "aspect" 5 of [0066] of '306) provide for "optionally … 1-10% of a stabilizing agent [which may be sucrose] …or 20-150 mM of a tonicity agent [which may be NaCl] or [both]" (emphasis added). This a more powerful point since it emphasises that the patentee turned its mind to the possibility of having just sucrose in an amount above 5% as an alternative to having both, but did not claim it. This point reinforces my conclusion about Actavis Q3 significantly but I would have reached it anyway.

VALIDITY

518. I will deal with the points on priority and added matter, and then with the prior art attack from Wiegand II.

Priority and added matter

519. As mentioned above, these points go together; if there is no priority entitlement then Regeneron accepts there is also added matter. The issue was argued before me on the basis of and in the context of priority and the priority document but the result would have been the same if it had been argued under added matter and the application as filed.

Legal test for priority

520. There was no dispute about the legal test, although the parties cited different cases. A convenient and fairly recent statement can be found in *Ice Scape v Ice-World* [2018] EWCA Civ 2219 at [33]-[42], citing the key EPO case G2/98, and especially at [42], referring to the decision of the Court of Appeal in *HTC v Gemalto* [2014] EWCA Civ 1335: the skilled person must be able to derive the subject matter of the claim directly and unambiguously, explicitly or implicitly, from the disclosure of the priority document; the priority document must be read through the eyes of the skilled person or team and they will have the CGK; but the CGK is for the purposes of understanding the disclosure, not supplementing or adding to it, and the test is what is the disclosure of, not what was obvious from, the priority document.

521. It was not in dispute that the priority document must be read as a whole, but in practical terms the priority issue turns on a few key paragraphs.

Disclosure of the priority document

522. The priority document is US/60/814,484 and its title is "VEGF Antagonist formulations suitable for intravitreal administration".

523. [0010] and [0011] say:

> [0010] In a specific preferred embodiment, the ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 50 mM NaCl, 3% PEG, and 5% sucrose, pH about 6.2-6.3.
>
> [0011] In a specific preferred embodiment, the ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.

524. Under the heading "VEGF Antagonists", [0030] says:

> [0030] An VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO:2 or 4; more preferably, SEQ ID NO:4. In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308. Preferably, the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO:4

525. Example 3 is as follows:

> **Example 3. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.**
>
> [0044] A liquid formulation containing 40 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 3. Turbidity, percent recovered protein and purity was determined as described above.
>
> [Nothing turns on the results so they are not reproduced here, likewise with Example 4].

526. Example 4 is as follows:

> **Example 4. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in Pre-filled Glass Syringe.**

> [0045] A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C in 1 ml prefilled luer glass syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 4. Turbidity, percent recovered protein and purity was determined as described above.

527. The only difference between Examples 3 and 4 is that the former uses a glass vial and the latter a prefilled syringe (and there are minor differences in the results).

528. Regeneron said that the formulation details given in [0011] map to Examples 3 and 4. In point of detail, [0011] says "pH about 6.2 to 6.3" and Examples 3 and 4 say pH 6.3 in the text, with the results ranging from 6.2 to 6.4. The Claimants acknowledged that [0011] "aligns somewhat" with Examples 3 and 4.

529. SEQ ID NO:4 appears later in the document and is 458 amino acids long. Position 458 is a lysine.

The points

530. The two major points on priority are:

    i) Does [0030] contain an adequate disclosure of the particular VEGF antagonist specified by the claims of '691 as "consisting of amino acids 27-457 of SEQ ID No: 4, which is glycosylated at Asn residues 62, 94, 149, 222 and 308", noting that [0030] says "comprises" not "consisting of "?

    ii) If so (i.e. if Regeneron survives the first point), is there an adequate disclosure of that VEGF antagonist in combination with the excipients specified in Examples 3 and 4 (or in [0011])? The point being, the Claimants say, that references to "VEGF antagonist (SEQ ID NO: 4)" in [0011] or "VEGF Trap (SEQ ID NO:4)" in Examples 3 and 4 are to a range of possibilities and the claims of the Patents require specifically the version with stipulated start and end points and with identified glycosylation.

531. I will call these the "specific antagonist" point and the "combination" point (my terms, not the parties').

532. A third point is that the claims of '306 have "comprises" rather than "consisting of" prior to the specification of the amino acids. The Claimants say that even if the priority document taken as a whole identifies the specific antagonist in combination with the necessary excipients, the claims of '306 are to the excipients with a range of antagonists (the range introduced by the "comprises") and that is an intermediate generalisation. I will call this "the '306 intermediate generalisation point".

533. There were the following more minor points:

    i) [0011] and earlier claims of '691 requires pH "about" 6.2-6.3 whereas claim 5 requires just "pH 6.2-6.3" with no "about";

    ii) Claim 5 of '691 requires "about" 40mM NaCl.

534. But in their written closings Claimants said that I need only consider "the VEGF antagonist feature of the claims", by which they meant the specific antagonist point and the combination point and not these two minor points (they also maintained the '306 intermediate generalisation point). This was a sensible approach as the "about" points were trivial. The Claimants also effectively, and sensibly, accepted that Examples 3 and 4 gave the other, excipient features of the claims.

535. The priority/added matter points are intricate and detailed. The time for oral argument on them was compressed because of the very large number of other points in the case. As a result I received a number of written submissions after trial, including, at my request and after I had started writing this judgment, a final round of submissions on the '306 intermediate generalisation point. I found these all very helpful.

Analysis – the specific antagonist point

536. [0030] talks of the possibility of expression in a mammalian cell line such as CHO "in specific embodiments" and it refers to post-translation modification. It goes on to "a specific embodiment" (singular) in which the fusion protein "comprises" the specified amino acids with the specified glycosylation.

537. The Claimants say that:

    i) The two sentences ("In specific embodiments …" and "In a specific embodiment") are independent though not mutually exclusive. The main implication of this would be that the second is not limited to CHO cells.

    ii) On the evidence, while the skilled person would appreciate that with CHO cells the whole of the signal peptide (amino acids 1-26) and the C-terminal lysine at amino acid 458 would be cleaved, the skilled person would also appreciate that with other expression systems some of the signal peptide and/or the C-terminal lysine might, or at least could, be retained. So "comprises" makes sense.

538. The points are somewhat related.

539. As to the first point, the overall thrust is that the teaching is becoming more specific ("In specific embodiments [plural] …" and "*such as* a CHO cell" versus "In *a* specific embodiment [singular]" …). Regeneron pointed out that the paragraph starts yet more generally, then narrows from two possible SEQ IDs to SEQ ID NO: 4, and this is also part of the picture, although a modest one.

540. At a strictly textual, literal level it is not altogether clear that the "In a specific …." sentence narrows the previous one as would be the case with a dependent claim, because it does not say anything along the lines of "*is* made in a CHO cell" and because of "comprises", to which I return below.

541. On the second point the propositions put by the Claimants were rather messy, primarily based on the cross-examination of Prof Leatherbarrow, and were not completely supported by the examples deployed. *E. Coli* could be used but is not a mammalian cell line and would not glycosylate, while insect cells could cleave the protein at different positions and would glycosylate, but not at the specified positions (where CHO cells would).

542. On the other hand Regeneron said on the basis of Dr Esposito's evidence that in eukaryotic systems the signal peptide would be expected to be cleaved between positions 26 and 27, but I do not think that went so far as to show that that was invariably the case. In oral closing submissions Counsel for the Claimants submitted on the basis of the same evidence that CHO cells specifically might not cleave between positions 26 and 27, arguing that if they always cleaved there Prof Leatherbarrow would have said so. This was not, as far as I can tell, put directly to Prof Leatherbarrow and the thrust of his written evidence was that CHO cells characteristically cleave off the signal peptide; he clearly meant all of it. So I do not accept the skilled person would have in mind CHO cells which left part of the signal peptide in place.

543. Regeneron submitted that it was not shown at trial that there was a specific system which would lead to glycosylation at the specific residues required but not be precisely amino acids 27-457. I think that is correct but the variety of possibilities mean that the reader would understand that the patentee was leaving the door open to other possible systems even if no specific one came to mind. And if CHO was "the only game in town" and uniquely led to the specified glycosylation in a sequence which was specifically 27-457 then "comprises" was not the right word to use, at least in its normal, conventional patent meaning.

544. So there is rather a tension between the narrowing sequence of the sentences of [0030] and the later focus on CHO as a system on the one hand, and "comprises" on the other. The tension introduced by "comprises" is however ultimately a very linguistic one. I do not have any difficulty, and I do not think the skilled person would have any difficulty, with the main thrust of the teaching being towards something very specific, with the patentee including a let-out by way of "comprises", just in case.

545. Following on from this, and in any event, the submissions of the Claimants did not grapple with the question of whether, among what it says is a range of possibilities in [0030], there is the necessary clear and unambiguous disclosure of the relevant features of the claims of '691 and hence of the invention of that Patent: the fusion protein having precisely amino acids 27-257 and the glycosylation specified. In my view there is: on the Claimants' case, and according to its conventional meaning in patents, "comprises" means that the *minimum* amino acids that can be present are 27-457; that minimum is clearly disclosed (along with the specified glycosylation pattern) even if other

possibilities are open. It is also plain as a matter of substance: even if, as the Claimants submit, the requirements of the two sentences are independent and so do not necessarily go together – are not necessarily cumulative – they may do so, and it stands out a mile that one thing being disclosed is using CHO cells to remove the whole signal peptide and C-terminal lysine and result in the glycosylation stipulated. So even to the extent the Claimants are right and the two key sentences allow for a range of things, one thing from that range that is clearly and unambiguously disclosed as a matter of substance is the "consisting of" possibility, the specific antagonist.

546. Two other tribunals have considered this same point, under the headings of priority or added matter or both. The parties did not initially address them in closing in any detail and I asked for and received helpful written submissions after the end of the trial.

547. By a decision of 8 January 2025, with reasons given on 13 January 2025, the Opposition Division of the EPO revoked '306. The main analysis was in relation to priority of the main request. The OD said there was no priority because it was not permissible to "mentally replace" SEQ ID NO: 4 (with the specific antagonist of the claims) every time it appeared in the priority document.

548. In reaching that conclusion the OD referred to two earlier TBA decisions (by coincidence considering the disclosure about SEQ ID NO: 4 in the Alexion patent family I dealt with in *Alexion v Samsung (supra)* which, it reasoned, said that sequences in patent documents mean what they say and cannot be subjectively reimagined based on how they might be made.

549. Although agreeing in the result, the Claimants did not adopt this reasoning "given the differences in evidence and arguments". I think the Claimants were right about that: Regeneron's argument to me is not that SEQ ID NO: 4 should be mentally replaced everywhere it is mentioned, but rather that the specific antagonist of the claims of '691 is disclosed.

550. The Claimants did draw support from the OD's statement at the top of page 23 of the decision that what is written at the end of paragraph [0030] "cannot be interpreted as the most preferred embodiment, let alone as the only method for preparing SEQ ID NO: 4 according to the invention". I agree that it is not explicitly stated there to be the most preferred, but it is the only specific one exemplified. I will return to this when I consider the combination point.

551. In any event, the Claimants do not say that I should just adopt the OD analysis but should make my decision afresh. That is what I have done.

552. The other tribunal that has considered these points is the German Federal Patent Court, which on 26 June 2025 rejected apparently very similar attacks (made on the basis of added matter, and against '691 rather than '306). No reasons are available, although in the post-trial written submissions I was given the preliminary opinion. In this situation I cannot get real assistance from the decision, although the likelihood is that the court accepted broadly similar submissions to those made to me on behalf of Regeneron. I do note from the

preliminary opinion that it seems that at that stage the Court thought that "comprises" in [0030] (it was dealing with [0045] of the application as filed but the text is identical) means "consists of". If so, I disagree. Regeneron did not argue before me that "comprises" means "consists of"; in its post-trial written submissions it expressly disclaimed that and said that "comprises" (in [0030] and in the claims of '306) denotes a class of proteins.

553. Finally on the specific antagonist point I record that Regeneron relied on the fact that Dr Daugherty, when dealing with validity over Dix, treated a part of its teaching essentially the same as [0030] of the priority document as if it disclosed what Regeneron says (i.e. the specific antagonist). That is consistent with Regeneron's position on priority but does not compel me to accept it and is not of any direct relevance since disclosure is a matter for the court, once properly able to put itself in the position of the skilled person.

554. I conclude that the specific antagonist point fails. The specific antagonist is disclosed albeit that there is also disclosure of other possibilities – in practice not very likely ones - as a result of "comprises".

The combination point

555. I turn to the combination point.

556. Examples 3 and 4 are real examples which give actual results for something that the priority document says was, as a historical fact, done. This is not a case of taking a part of a specification which is a recommendation, or a general teaching, or a prophetic example, and combining it with another part of the teaching.

557. However, the Examples do not expressly say what they mean by "VEGF Trap (SEQ ID NO: 4)". The Claimants rightly did not say that that phrase specifically and only means the whole of SEQ ID NO:4; their point, harking back to the specific antagonist point, was that there is a range of possibilities in [0030] and no disclosure to the rigorous standard required for priority that Examples 3 and 4 use a protein with specifically amino acids 27-457 and the specified glycosylation.

558. In this context I think it is especially important not to slip into tacitly applying an obviousness approach. If the question was what protein the skilled team would consider to pick to follow up on Examples 3 and 4 there can be no doubt that an obvious choice would be the CHO approach from [0030] with exactly amino acids 27-457 and the glycosylation pattern mentioned, but that is not the test.

559. I think the critical point is that the two key sentences of [0030] are about specific embodiment(s). They are also the only place in the document where an actual VEGF Trap protein is fully specified in terms of its physical characteristics of sequence and glycosylation. [0030] is in the section entitled "VEGF Antagonists" so there can be no doubt that is where the skilled person would go from Example 3 or 4 to understand what had been done. So the skilled person would be clear, to the necessary standard, that the specific thing

that had been done was to test the stability of the formulation of Examples 3 and 4 using the specific antagonist disclosed in [0030].

560. I therefore conclude that the combination point does not give rise to a lack of priority, either, given Regeneron's defence to it, which I hold succeeds, that the specific antagonist disclosed in [0030] is disclosed, to the relevant standard, in combination with the formulation taught in Examples 3 and 4.

561. That means that the claims of '691, with their "consisting" form, are entitled to priority.

The '306 intermediate generalisation point

562. As I have said, the Claimants also argued on '306 that there was an intermediate generalisation: that Regeneron was taking the very specific teaching of the formulation components of Examples 3 and 4 and applying it to the more general context of a range of proteins in [0030] that come in as a result of the word "comprises". I have said above that I think that "comprises" does disclose a range because it means that some of the leader sequence and/or amino acid 458 can be retained, as well as amino acids 27-457. It is not very likely that that would be done and the means to do so are not apparent, but it is, nonetheless, disclosed.

563. I have found in favour of Regeneron on '691 because "consisting" in the claims identifies one very specific VEGF antagonist which is adequately disclosed as going with the detailed formulation of Examples 3 and 4. The fact that [0030], via "comprises" discloses a range of possibilities as well does not stand in the way of that conclusion. But nor does it, in itself, justify a claim, as in '306, which says that the VEGF antagonist "comprises" amino acids 27-457. Unless "comprises" in the claims does not mean what it says (which I reject), that is a range of antagonists and there is no disclosure to support the very specific formulation of Examples 3 and 4 being used for any other antagonist. It is indeed an intermediate generalisation because it takes the extremely specific formulation details of Examples 3 and 4 and generalises the fusion protein.

564. As I have said above, Regeneron accepts that "comprises", in [0030] and in the claims of '306, denotes a class of proteins. So it cannot defend '306 simply on the basis that it is correct on '691. It has to grapple with whether there is an adequate disclosure supporting a combination of the specific excipients of Examples 3 and 4 with the class of proteins disclosed by "comprises". The final round of written submissions were directed to specifically this point, at my direction.

565. Regeneron's final written submissions did not seem to me to address the intermediate generalisation. The key point made was that the specified antagonist was the "paradigm" of the class disclosed. I think that is true, but it is the problem, not the solution. It is because the specified antagonist stands out that the skilled reader would conclude that that was what was used in the context of Examples 3 and 4. That is why the first two added matter points fail: there is a very narrow disclosure supporting the exact combination of "consisting" and the excipient requirements. There is no disclosure of the

excipients of Examples 3 and 4 with anything else and not the class introduced by "comprises".

566. So, unlike '691, '306 lacks priority and is invalid for added matter. This is not an important conclusion in the overall scheme of things since neither Patent is infringed and '691 is valid over the prior art.

Obviousness – the law

567. There was no disagreement about the basic approach, which may be found in the decision of the Supreme Court in *Actavis v. ICOS* [2019] UKSC 15 at [52] – [73]. I also bear in mind the statement of Kitchin J, as he then was, in *Generics v. Lundbeck* [2007] EWHC 1040 (Pat) at [72], approved in *Actavis v ICOS*.

568. *Pozzoli v. BDMO* [2007] EWCA Civ 58 provides a well-known structured approach to obviousness. The parties did not expressly articulate their arguments by reference to it, but effectively it underlay them, since they dealt sequentially with the skilled team, the CGK, the differences between Wiegand II and the claims (concentration, choice of pH, choice of other excipients), and the reason why those differences did or did not represent an inventive step. I have borne it in mind.

General obviousness considerations for formulations

569. The Claimants drew my attention to the dicta of Floyd LJ in *Hospira v Genentech* [2017] R.P.C. 13 at [50]-[51]:

> 50. Next, I must deal with the could/would debate. I have already explained why I do not accept that it is necessary in every case for the court to conclude that the skilled person acting only on the basis of the prior art and his common general knowledge would arrive without invention at the precise combination claimed. Given that the screening methods were part of the common general knowledge, that the tests involved were routine, that the excipients were common general knowledge excipients and that there was no a priori reason why a successful lyophilised formulation could not be made, it seems to me that it was beyond argument that the claimed combination in this case was one that could be made by the skilled team. The question is whether this is the type of case where it is necessary to go further and ask whether the skilled person would necessarily have made the precise combination claimed.
>
> 51. In an empirical field it will be seldom be possible to predict in advance that any individual experiment will work. In many cases, the fact that a routine screening exercise could be carried out will be inadequate to establish obviousness. Nevertheless, on the facts of an individual case such as the present, the team may have a reasonable degree of confidence that a series of experiments will produce some which will work. To impose a requirement that the skilled team must be able to predict in advance which would be the successful combinations

> is wholly unrealistic. It would lead to the grant of patents for a whole variety of combinations which in fact involved no inventive effort.

570. On the other hand, Regeneron relied on the following passage from the judgment of Lord Hodge in *Actavis v ICOS*:

> 103. The UK BioIndustry Association asked for guidance on the relevance in the assessment of obviousness of (a) the reasonable expectation of success as a factor and (b) the problem-and-solution approach of the EPO. It expressed concern that the judgment of the Court of Appeal might support the view that empirical research in the field of bioscience would not be seen as inventive in so far as the methods of research were well-established. The IP Federation similarly expressed concern about a perceived risk that people might extrapolate from statements in the Court of Appeal's judgments that the result of routine investigations cannot lead to a valid patent claim. It expressed a particular concern about the breadth of the statement by Lewison LJ (in para 180): "in a case which involves routine pre-clinical and clinical trials, what would be undertaken as part of that routine is unlikely to be innovative". Its concern was that a simplistic adoption of this phrase as a blanket test without regard to the facts of the specific case would be contrary to the fundamental principles of patent law. I do not interpret the Court of Appeal's judgments, including Lewison LJ's statement which I have quoted, as supporting such an extrapolation. Kitchin LJ gave the leading judgment, in which he adopted a fact specific assessment based on the facts of this case and involving the weighing up of several factors, and Floyd and Lewison LJJ agreed with his reasoning and conclusions. I do not construe the judgments of the Court of Appeal as supporting any general proposition that the product of well-established or routine enquiries cannot be inventive. If that had been what the experienced judges had said, I would have respectfully disagreed. But it is not. As Jacob LJ stated in Actavis v Merck (above) para 29, there is no policy reason why a novel and inventive dosage regime should not be rewarded by a patent. A fortiori, efficacious drugs discovered by research involving standard pre-clinical and clinical tests should be rewarded with a patent if they meet the statutory tests (para 54 above).
>
> 104. Mr Waugh in his reply attacks Mr Speck's proposition that nothing which was already within the skilled person's repertoire could be inventive. He suggests that such a proposition would undermine the so-called selection patents and improvement patents. But because I do not accept Mr Speck's submission on the skilled person's repertoire in this broad formulation, this judgment does not militate against selection patents or improvement patents. Selection patents are patentable as involving an inventive step if the selection is not arbitrary and is justified by a hitherto unknown technical effect (*Agrevo/Triazoles* (above) para 2.5.3) or, in other words, when they make a real, novel and non-obvious technical advance (*Dr Reddy's Laboratories* (above) para 50 per Jacob LJ; para 104 per Lord Neuberger MR). "Improvement" in

> the context of the law of patents is "in the most technical sense … an invention which comes within the claims of an earlier patent but contains a further inventive step": *Buchanan v Alba Diagnostics Ltd* [2004] UKHL 5; 2004 SC (HL) 9; [2004] RPC 34 , para 32 per Lord Hoffmann. The use of well-known research tests of itself does not render such selections and improvements obvious.

571. Two extreme propositions lurked in the parties' submissions: that nothing is obvious in the formulation field because predictions can never be made for individual experiments, or that everything is obvious because the methods used are all routine. These propositions are both wrong, as the above dicta make clear. Obviousness remains a multifactorial question in which the empirical nature of the field and the routine nature of the methods are factors but not determinative. It is clear that the court has to look at the overall expectation of success in a project as well as the expectation of success for individual experiments.

572. There can be cases where there is no expectation of success; *Teva v Leo* [2015] EWCA Civ 779 was an unusual case of that kind, and Regeneron relied on it. But there is a difference between a lack of any expectation of success for a particular route and a general difficulty of operating in a particular field. Regeneron relied on various strong statements about the high level of difficulty in formulating proteins/antibodies. This general high level of difficulty, which was accepted by Dr Daugherty, is a factor to take into account, but it would be wrong to elevate it to an overwhelming consideration such that nothing is obvious because it is always very difficult. To some extent the unusually high level of difficulty may be matched by a high level of skill (but, of course, not inventiveness) on the part of the skilled person. And the significance of the general difficulty of formulating proteins/antibodies in a given case must depend on context and whether the matters known to the skilled team at the start of the task indicate that the protein might be particularly hard to deal with.

Lions in the path

573. The Claimants relied on the line of cases, which includes *Pozzoli* itself, where the Courts have said that a prejudice against taking the step said to be inventive cannot be relied on unless the patent dispels the prejudice. The analytical basis for this approach in *Pozzoli* was explained by Jacob LJ at [25]-[28] as being that the idea of the invention and the prejudice are both part of the state of the art, and the inventive step lies in changing that position by making the technical contribution of dispelling the prejudice. If the prejudice is not dispelled then there is no technical contribution.

574. Although perhaps not stated entirely explicitly in *Pozzoli* because of the context and the nature of the arguments, although I think it is clearly part of the reasoning, this principle really bites when the patent is suit is otherwise already obvious and the patentee tries to rely on the deterrent effect of the prejudice. This is explicit in the decision of the Court of Appeal in *Koninklijke Philips v Asustek* [2019] EWCA Civ 2230 at [73]-[74], per Floyd LJ:

> 73. Finally, the defendants contend that the issues which the judge held would have deterred the skilled person from proceeding to implement Shad at the base station remained issues for the implementation of the 525 patent, in the sense that the patent did not teach the skilled person how to overcome them. This is the point based on the passage from *Pozzoli* which I have cited above. The principle is that you cannot have a patent for doing something which the skilled person would regard as old or obvious but difficult or impossible to do, if it remains equally difficult or impossible to do when you have read the patent. To put it another way, the perceived problem must be solved by the patent.
>
> 74. I do not think this principle avails the defendants in the present case. On my reading of his judgment, the judge did not accept that the idea of implementing Shad at the base station was, on its face, obvious. The judge concluded that the skilled person would follow up Shad's proposal to optimise his algorithm, and would not be prompted to think of alternative ways of implementing it. The argument, therefore, does not get off the ground. Secondly, the judge deployed the difficulties involved in implementing Shad at the base station as a legitimate means of testing Mr Gould's evidence that the idea of implementing it there would readily occur to the skilled person. He did not fall into the trap of placing imaginary lions (some call them paper tigers) in what was otherwise an obvious path.

575. The Claimants particularly cited [73], but [74] provides an important explanation of the point I have mentioned: there is a difference between an idea which is otherwise obvious but which the patentee seeks to meet with an alleged prejudice on the one hand, and testing the route to obviousness in the first place.

576. Another case which makes the same point is *Teva v Astellas* [2023] EWCA Civ 880 at [72]-[78], drawing together *Pozzoli* and *Philips v Asustek* (this was not cited to me at trial; it does not change the position either way, it just articulates matters clearly in the light of the two previous cases).

577. In the present case, the issue characterised as a prejudice by the Claimants related to the safety of aflibercept. They said, correctly, that the Patent does not contain any safety data so could not dispel any prejudice based on the fear of side effects from too high a dose. Regeneron disclaimed relying on any such prejudice as a remedy to obviousness, and insofar as the situation might be that a dose of 4mg was otherwise or prima facie obvious, for example for cogent efficacy reasons, then indeed Regeneron could not rely on such a prejudice.

578. But the situation is more complex than that, because the Claimants' obviousness case is positively based on taking aflibercept into a phase 1 trial, whose primary goal is to explore side effects and in which observations about efficacy are useful if they can be made but not the key output. I do not see that the lions in the path line of cases prevents Regeneron from testing the Claimants' case for getting to obviousness in the first place and I think the cases, in particular *Philips v Asustek*, confirm this. It would be just unreal for the Claimants to make assertions about safety en route to obviousness and for

them to have to be accepted unquestioningly by the Court and the patentee because of the data which is and is not in the patent.

579. Regeneron's main argument was in any case based around it not being obvious, in pursuit of efficacy, to go to a dose of 4 mg. It engaged with safety only as the surrounding context for the dose selection.

Disclosure of Wiegand II

580. The important parts of Wiegand II for the purposes of obviousness are the Examples, but two paragraphs of the more general description are significant to the arguments on how the skilled team would interpret the dose range in Example 17. Thus:

> [0006] In a second aspect, the invention features a method for the treatment of a human subject diagnosed with an eye disorder, comprising administering an effective amount of a vascular endothelial growth factor (VEGF) inhibitor to the human subject, the method comprising administering to the subject an initial dose of at least approximately 25-4000 ug VEGF inhibitor protein to an affected eye, and administering to the subject a plurality of subsequent doses of the VEGF inhibitor protein in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks. The eye disorder is one of age-related macular degeneration or diabetic retinopathy. In various embodiments, the initial dose is at least approximately 25 to 4000 ug of VEGF inhibitor protein. In various embodiments, the subsequent doses are separated in time from each other by at least two weeks to 12 months; more preferably, the subsequent doses are separated in time from each other by at least 3-6 months. The VEGF inhibitor protein is administered directly to the affected eye, including by use of eye drops or intravitreal injection. Preferably, the VEGF inhibitor is a dimer having two fusion polypeptides consisting essentially of an immunoglobulin-like (Ig) domain 2 of Flt1 and Ig domain 3 of Flk1 or Flt4, and a multimerizing component. In specific embodiments, the VEGF inhibitor is a dimer comprising the fusion polypeptide of SEQ ID NO:2,

581. And:

> [0036] In one embodiment of the method of the invention, a human subject with at least one visually impaired eye is treated with 25-4000 ug of a VEGF inhibitor protein via intravitreal injection. Improvement of clinical symptoms are monitored by one or more methods known to the art, for example, indirect ophthalmoscopy, fundus photography, fluorescein angiopathy, electroretinography, external eye examination, slit lamp biomicroscopy, applanation tonometry, pachymetry, and autorefaction. Subsequent doses may be administered weekly or monthly, e.g., with a frequency of 2-8 weeks or 1-12 months apart.

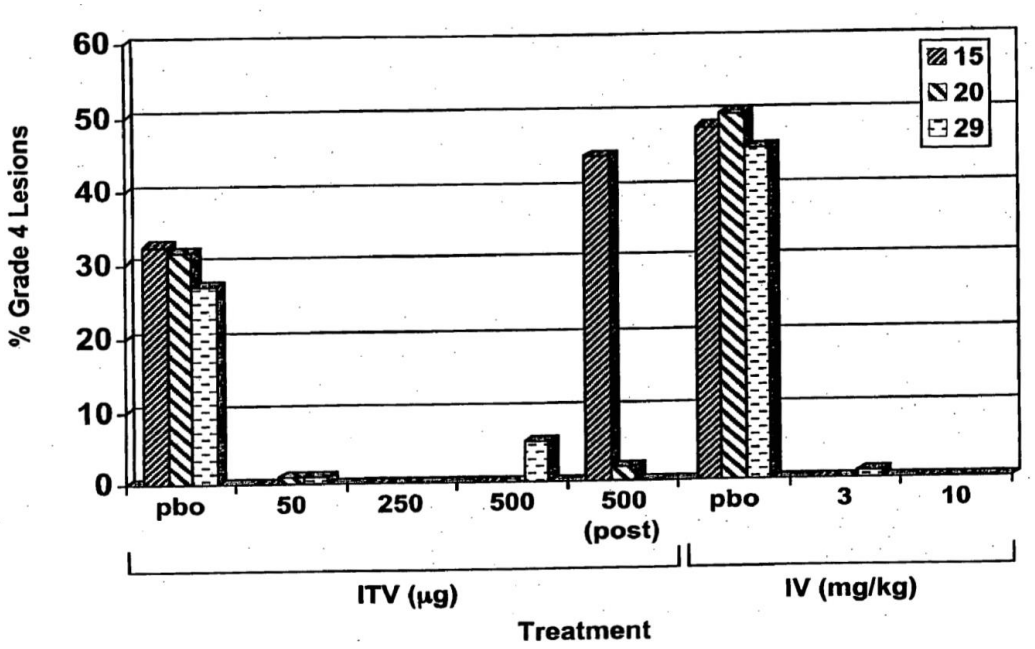
582. These paragraphs both reference the dose range of 25-4000 µg. They are not limited to age-related (i.e. wet) AMD although [0006] mentions it, they have a wide range of dosing intervals, and [0006] includes administration by eye drops or intravitreal injection; [0036] discusses only injection. They are not limited to any particular VEGF inhibitor.

Example 9

583. I turn to the Examples. I will narrate the important ones. Apart from Example 17 there is no real dispute about their disclosure in the sense of what they mean, but in this section I will also indicate some of my findings about the skilled team's reaction to the teaching of the individual examples. I come to the obviousness analysis in terms of what they would or would not consider it obvious to do, later.

584. Example 9 is a test in the monkey CNV model of "VEGFR1 R2-FcAC1(a)". This is also referred to as SEQ ID No: 6. It corresponds to SEQ ID No: 4 in the Patents and is aflibercept (once properly truncated and glycosylated). It is also referred to as VEGFR1R2, as I have mentioned above.

585. The results of Example 9 can be seen in Figure 9:



586. I take the following (undisputed) description of Figure 9 from the Claimants' written opening:

> For each regimen a cluster of three bars is shown (although some are indistinguishable from zero) showing results at 15, 20 and 29 days post injury (from left to right). From left to right the clusters of bars relate to:
>
> i) ITV pbo: intravitreal placebo;

ii) 50, 250, 500: Intravitreal VEGFR1R2 once every two weeks, starting one week before laser injury at a doses of 50, 250, or 500 µg/eye;

iii) 500 (post): a single intravitreal 500 µg dose of VEGFR1R2 two weeks after the laser;

iv) IV pbo: Intravenous placebo; and

v) 3, 10: Intravenous VEGFR1R2 once per week, starting one week before laser injury at a dose of 3 mg/kg or 10 mg/kg.

587. The "500 (post)" results are especially significant as in that instance the animal receives the drug only after the laser injury.

588. Example 9 says nothing explicit about toxicity. There was quite a lot of detailed evidence about what inferences, if any, could be drawn from the Example about toxicity in this light. In my view the only reliable upshot, which was close to common ground is that (1) the Example was not designed or intended to test toxicity, and (2) despite that, if there had been serious systemic or toxicity issues they would have been mentioned, so the skilled person would infer that there were not any (but could not draw any inference one way or another about more minor toxicity). The absence of serious toxicity issues is supported by the fact that it was possible to anesthetise the animals and take ocular measurements.

589. The doses used in Example 9 achieved good results: that was common ground. Dr Wensel accepted that the results were good enough that it could be inferred that a lower dose might have also achieved a therapeutic effect, including in humans (if the data translated well to humans). Given the differences in size between monkey and human eyes, the 500µg used in Example 9 would scale to about 1mg in a human. I return to the dose issue below once I have reviewed the other examples.

Examples 14 and 15

590. Examples 14 and 15 concern a cell based assay. Example 14 describes the assay and Example 15 gives some results, comparing Avastin and VEGFR1R2. It was common ground that VEGFR1R2 was a lot more potent. The disagreement was over the consequences of this. Regeneron through Dr Ward said that this higher potency would lead to the expectation of a lower dose relative to Avastin and Dr Wensel disagreed. Regeneron through Dr Ward and Prof Kodjikian said that the results supported efficacy for 28 days but did not allow an inference of efficacy for a longer period while the Claimants said that higher potency could in general be assumed to lead to longer duration of action.

Example 18

591. Example 18 is a phase 1 study of the intravenous administration of VEGFR1R2 in wet AMD patients. The details are sufficiently important for me to set out the whole of the three main paragraphs, and the conclusion:

Example 18

A Double-Masked, Placebo-Controlled, Dose

Escalation, Phase I Study of Intravenous VEGF

Trap in Patients with Neovascular Age-Related

Macular Degeneration

[0085] A study was conducted to obtain preliminary assessments of the safety, pharmacokinetics (PK), and biological activity of single and repeated intravenous (IV) doses of the VEGF trap antagonist (SEQ ID NO:6) in patients with neovascular age-related macular degeneration (AMD).

[0086] Methods. Successive cohorts of patients with neovascular AMD (≤12 disc areas, ≥50% active choroidal neovascularization (CNV), ETDRS best-corrected visual acuity (BCVA) s 20/40) were randomized (3:1) to receive either VEGF trap or placebo at dose levels of 0.3, 1.0, or 3.0 mg/kg. Patients received a single IV dose, followed by a 4-week safety observation/PK evaluation period, followed by 3 biweekly IV doses. Safety assessments included laboratory assessments (hematology, chemistry, urinalysis, anti-VEGF trap antibody measurements), vital signs, and ophthalmic exams. Measures of biological activity included mean percent change in excess retinal thickness (ERT) as assessed by optical coherence tomography (OCT), and ETDRS BCVA. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v. 3.0). Dose-limiting toxicity (DLT) was defined as Grade 2 or 3 ocular AEs, or Grade 3 or 4 systemic AEs with modified criteria for hypertension and proteinuria. The maximum tolerated dose (MTD) was defined as the dose level below that at which ≥2 patients experienced DLT.

[0087] Results. Twenty-five patients were enrolled (11 male, 14 female; mean age 76 years). Nineteen patients received VEGF trap (7 at 0.3 mg/kg; 7 at 1.0 mg/kg; 5 at 3.0 mg/kg), and 6 patients received placebo. The majority of AEs encountered on VEGF Trap treatment were mild to moderate in severity. Two of 5 patients encountered protocol-defined DLT at the 3.0 mg/kg dose level: Grade 4 hypertension (n=1); Grade 2 proteinuria (n=1). Therefore, all of the patients in the 3.0 mg/kg dose group were prematurely withdrawn from study. None of the patients in

> the study developed anti-VEGF trap antibodies. The mean percent changes in ERT were: —12%, —10%, -66%, -60% for the placebo, 0.3, 1.0, and 3.0 mg/kg dose groups at Day 15 (ANOVA $p<0.02$), and -5.6%, +47.1%, -63.3% for the placebo, 0.3, and 1.0 mg/kg dose groups at Day 71 (ANOVA $p<0.02$). The changes in BCVA were: +1.9, +1.8, +3.4, and +4.6, for the placebo, 0.3, 1.0, and 3.0 mg/kg dose groups at Day 15 and were: +2.8, +3.9, and +3.9 for the placebo, 0.3, and 1.0 mg/kg dose groups at Day 71. The BCVA results were not statistically significant.
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> [0090] Conclusions: The maximum tolerated dose of intravenous VEGF trap in this study of neovascular AMD patients was 1.0 mg/kg. A dose-dependent improvement in ERT as evaluated by OCT was suggested in this small number of patients, with a longer initial duration in improvement at the 3.0 mg/kg as compared to the 1.0 mg/kg dose level. A trend towards a dose-related improvement in BCVA was also suggested.

592. Thus at 3.0mg/kg there were two patients with dose-limiting toxicity and all patients in that group were prematurely withdrawn. By the definition adopted, 1mg/kg was the maximum tolerated dose, but caution is needed in interpreting that because the definition of MTD was two or more patients with dose limiting toxicity, so it is possible that one patient in the 1mg/kg group experienced DLT.

593. As summarised in the conclusions in [0090], some efficacy was observed but the small size of the trial limits the weight that can be put on it.

594. The clinician experts agreed that Example 18 would motivate them to want to explore VEGFR1R2 further, in an intravitreal setting.

595. I agree with the Claimants that the overall effect of the evidence on Example 18 is that it is reassuring about systemic side effects, because the systemic level following intravitreal administration would be much lower. Dr Ward's cross-examination supported that view, and as I have said in my assessment of him as a witness, I could not understand Prof Kodjikian's different view. I do not think Example 18 gives any material comfort about ocular toxicity; Prof MacLaren pointed out that there was no ocular toxicity leading to actual loss of vision in Example 18 but this is extremely remote from the concerns that could arise with intravitreal administration.

Example 17

596. I take Example 17 out of numerical sequence because unlike the other Examples that I have to consider it is prophetic rather than presenting experimental results.

597. Given its importance I will set it out in full:

Example 17

Treatment of Age-Related Macular Degeneration

> [0083] A patient manifesting age-related macular degeneration is treated with an intravitreal injection of the VEGF trap protein of SEQ ID NO:6 or 23. The purpose of this treatment is to reduce or prevent the development of neovascularization, macular disease, and retinal damage. Once a patient reaches the age of 60, increased ophthalmic surveillance is performed to detect the presence of AMD. This increased surveillance should include periodic retinal examinations and fluorescein angiograms to monitor for the presence of subretinal fluid, blood, exudates, RPE detachment, cystic retinal changes, or the presence of grayish green subretinal neovascular membrane. When AMD is diagnosed, a regime of VEGF trap protein treatment is commenced coupled with or without other treatments such as photocoagulation. As the first step of treatment, the patient is to receive a full ophthalmic examination to establish a baseline of ocular health. The ophthalmic examination includes indirect ophthalmoscopy, slit-lamp biomicroscopy peripheral retinal examination, intraocular pressure measurements, visual acuity (unaided and best corrected) symptomatology, fund us photography, fluorescein angiography electroretinography and A-scan measurements. Following the preliminary examination, an intravitreal injection of VEGF trap protein is given to the patient's affected eye manifesting AMD. If both eyes are affected, they may be treated separately. The eye to be treated is injected with 25-4000 ug of VEGF trap protein in an ophthalmic solution
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> [0084] After treatment, the patients' eyes are to be examined on days one (1), two (2), seven (7), fifteen (15), thirty (30) and sixty (60). Because of the possibility of reoccurrence, the patient should return for periodic examinations on a monthly basis thereafter. On each examination day the patient is monitored for vitreous liquefaction. Additionally the patient is monitored for posterior vitreous detachments using indirect ophthalmoscopy with scleral depression Finally, the extent of AMD presented by the patient is continuously monitored through periodic retinal examinations and fluorescein angiograms to monitor for the presence of subretinal fluid, blood, exudates, RPE detachment, cystic retinal changes, or the presence of grayish green subretinal neovascular membrane. Additional VEGF trap protein treatments may be required if indicia of reoccurring neovascularization are observed. Additional treatments may be given on weekly or monthly basis. In a preferred embodiment, an initial treatment is followed by subsequent treatments between 1-6 months apart.

598. A first and key issue is what the skilled team would make of the 25-4000 µg dose suggestion. In my view they would consider this against the background that Example 17 is merely prophetic, and clearly relates back to the earlier references in [0006] and [0036] to the same dose range, where it is mentioned in the context of a wider range of possibilities. They would see that Example 17, while narrower, also refers to a range of possibilities, both as to the very drug substance to be used (SEQ ID NO:23 is the mini-VEGF Trap) and as to the later dosing intervals. They would see that there was no data on the face of the specification in Example 17.

599. Prof MacLaren's written evidence about Example 17 was given on the basis of his assumption that the patentee must have had some scientific basis for the dose range that is not stated in the document. I do not think this assumption was justified in fact and it is not correct as a matter of law: see Henry Carr J in *Actavis v Lilly* [2015] EWHC 3294 (Pat) at [183]-[184]. In relation to the factual position, I agree with the Claimants that the authors of Wiegand II would have had at least some underlying data that is not in the document, one example being the images of the eyes of the monkeys used in Example 9 and another being regulatory materials underlying Example 18. But that does not mean that that additional information would provide a sound basis for the dose range in Example 17 and I do not think Prof MacLaren's evidence was that it might.

600. The parties argued the approach to Example 17 partly on the basis of the extent to which the skilled person is taken to know patent law. I do not think it matters one way or another and the fact that prophetic examples often have no support is more a matter of practice than law; whatever the skilled person's exposure to patent law I think it is plain that the 25-4000 µg range in Example 17 is boilerplate picked up from earlier in the specification and carried through into the narrower scope of prediction of Example 17. This does not mean that the skilled team would completely ignore it, but they would not give it serious credence as a scientifically-based proposal. I should make it clear that I am not saying that including this sort of prophetic example is wrong or improper in any way, I am merely commenting on its value as a disclosure.

601. As well as Prof MacLaren having proceeded on a wrong assumption (which is no criticism of him personally), the Claimants' initial case on Example 17 suffered from treating the dose range of 25-4000mg as a proposal for the dose range to be explored in a phase 1 (intravitreal) trial. It is not; it is just a wide suggested range of doses to use in actual treatment at some time in the future following hoped-for success in appropriate trials. By the oral closing submissions the Claimants had largely given up on this and more or less said that it had always been agreed that it was not a proposal for the dose range of a phase 1 trial. I reject any argument that that had always been the position: there are clear indications in the Claimants' evidence and opening skeleton that it was a dose range for a phase 1 trial. In the light of my main conclusion about the boilerplate nature of the dose range the skilled team would have to work out appropriate doses for a phase 1 trial from the data that they had, and the Claimants still say that 4mg would be arrived at. But it is another example of significantly overinterpreting Example 17, and part of the obviousness picture. It affects my assessment of the Claimants' evidence, which proceeded on the wrong basis.

602. During his oral evidence Prod Kodjikian repeatedly said that he thought that Example 17's dose range was obviously not sustainable and offered to explain why. The cross-examiner did not take him up on that; Regeneron's Counsel did not re-examine. In closing oral submissions I asked about this and Counsel for the Claimants said there was no need to cross-examine in the light of the Professor's written evidence. I agree that that evidence only says that there is no data for Example 17, that the range is a wide one and that work would be

needed to decide the dose range to use. It did not contain any statement that the dose range of Example 17 is not sustainable on its face for some reason and it therefore was not necessary to dig into such a proposition with him. Regeneron could have re-examined if it wanted to.

Next steps from Wiegand II

603. The Claimants' case was based on the skilled team deciding a dose range for a phase 1 clinical trial of VEGFR1R2; it was not disputed that for the purposes of such a trial it would be necessary to formulate the fusion protein in a complete formulation which it would be intended would be the final formulation for clinical use if later trials went well and regulatory approval was obtained.

604. The *Pozzoli* differences between Wiegand II and the claims of the Patents are the dose/concentration (on the clinical/PK and PD side) and the pH and excipients (on the formulation/protein engineering side). It is necessary to be alert to the degree to which these might interact. However, for reasons given in relation to CGK, above, and the skilled team's interactions, below, I reach the conclusion that while 40mg/ml is on the high side it would not be considered so difficult that clinical desires should yield to formulation concerns, and the skilled formulator would agree to try at that concentration if asked. So the skilled clinician and PK/PD expert would have a relatively free hand to go to the highest dose mentioned in Wiegand II if there was a good enough case from their perspective to do so. This means that I can consider the arguments on dose/concentration and on the pH/excipients largely separately.

Skilled team's interactions

605. One should not be too dogmatic about how the skilled team would interact in the light of the prior art; there is a range of possibilities that could take place in the real world, but one is dealing with a notional construct.

606. That said, the skilled team members whose initial reactions to Wiegand II are important are the clinician and the PK/PD expert. The formulator and the protein engineer would come later.

607. It is common ground that the reaction of the skilled team to the document as a whole but in particular Example 9 and Example 18 would be that VEGFR1R2 had had promising results and was well worth progressing into a phase 1 trial for wet AMD with patients (i.e. phase 1b), and although I have said that Example 17 is not for a phase 1 clinical trial and is not limited to VEGFR1R2, the proposal for use to treat wet AMD is clear.

608. It is possible that the skilled clinician could reach this conclusion on their own, especially if they in fact had some PK/PD knowledge, but it would make more sense for it to be made with the involvement of the PK/PD expert since it involves interpretation of animal data and PK observations are referenced in Example 18.

609. Next, a proposed dose range would have to be considered. In my view this would clearly involve the clinician and the PK/PD expert. Not only would the dose range for the phase 1 trial have to be chosen, but it is common ground (though important details are fiercely disputed) that the dose range for the phase 1 trial would be set with an eye to the eventual use of the drug in later phases and, crucially, if successful, in clinical practice. I agree with the Claimants that at this stage the two members would not be choosing a dosing interval since the phase 1 trial would be a single dose, but they would discuss the observation period and, as I have said, would also interact in relation to the desired dosing interval in clinical practice in due course. Similarly, I think the clinician and PK/PD expert would discuss the treatment objective in terms of measuring improvement in vision, in phase 1, and later.

610. To the extent that the Claimants said or maintained that the clinician alone would latch onto the 25-4000ug in Example 17 and dictate that to the PK/PD expert, I reject that. But I do not think that was the Claimants' case, at least by the end of the trial.

611. Assuming that the Claimants are right and the selected dose range for phase 1 went up to 4mg, what then? I do not accept the Claimants' extreme position that the clinician would just order the formulator to do it. That would be contrary to the law on whether the skilled team would have a leader to whom the other members were merely subservient and also makes no sense on the facts: what if the clinician was mandating something which from the formulation perspective was impossible or very risky?

612. In my view this interaction would be a dialogue of the skilled team (leaving aside the protein engineer for now). The clinician and PK/PD expert would explain the maximum dose and the maximum volume. That would indicate the concentration. They would articulate the case for going to a dose that high. On the evidence, the formulator would say that the concentration for a 4mg dose in 0.1ml was on the high side but potentially achievable.

613. In the event that the Claimants are right and the clinical and PK/PD case for 4mg was obvious and very strong then clearly the formulator would go ahead and try. In that way of thinking the two sets of decisions that make up the Claimants' case are independent (as I have already alluded to): was it obvious to go to 4mg, and then what formulation was obvious. In the event that the Claimants are completely wrong and 4mg was not obvious at all, then the formulation issues do not arise. I think there is theoretically a middle position, if there were a case for going up to 4mg to explore the therapeutic window but it was not clinically critical to do so. In that case a balance would have to be struck because the formulator would say that trying to formulate at 4mg was more difficult and risky than at, say, 2mg. There would have to be a (notional) discussion and negotiation about what to do and it would be part of the overall obviousness analysis. But while this may be possible in theory, it was not the Claimants' case and does not arise on my findings about exploration of the therapeutic window not being a goal of phase 1 trials and the non-obviousness of 4mg.

614. Assuming the formulator went ahead to try to make 4mg work, the protein engineer would enter the picture (my having rejected the argument that they never get a look in: the reverse *Schlumberger* point). On the facts, their CGK would enable them to provide information about any structural aspects of the protein which could make formulation difficult (they would also make the protein when required, but there is no material dispute about that). The information they would provide would include the solvent-exposed methionine, so that would be part of the formulator's thinking; it is disputed what they would make of it, however.

The 4 mg dose

615. Given my findings about their reaction to Example 17 the clinician and PK/PD team member would not simply go with the dose range suggested there. They would set about reasoning from the data in Wiegand II and their CGK about the scientifically logical and appropriate doses to use in the trial.

616. The Claimants indeed said that even if the skilled team did not simply take forward the Example 17 dose range, they would arrive at a range which included 4mg. As a general but I think very important point, this was the Claimants' secondary case on the evidence and indeed the written openings. The main case was based on taking the dose range in Example 17 much more seriously than I have held is warranted. I have already referred to Prof MacLaren's assumption about it, and Dr Wensel accepted in cross-examination that he had not presented in his reports (which were responsive to Dr Ward's) a method to reason to a dose range from the data in Wiegand II, in particular Example 9.

617. It was common ground that the skilled team's process of reasoning would have regard both to efficacy and to safety, but beyond that very high level of agreement there were numerous, deep disputes.

618. Key disputes/points included:

    i) What are the purposes of a phase 1 trial? I have covered this in relation to the CGK. The critical disagreement is whether or not they include finding the maximum tolerated dose. The Claimants said they do; Regeneron said not. I have essentially agreed with Regeneron.

    ii) What searches would the skilled team undertake (if any)? Dr Ward suggested they would do searches in relation to other similar drugs to determine a dose range. Dr Wensel said that no searches would be done but that if they were they would include searches in relation to VEGF Trap and that would throw up (in particular) Nguyen 2006 and the Regeneron Press Release. The latter expressly mentions 4mg.

    iii) How, if at all, should the monkey model doses in Example 9 be scaled up for a human phase 1 trial?

    iv) Would the skilled team include higher doses in a desire to get a more pronounced clinical effect than for Lucentis (as the Claimants said) or

would they aim for the lowest result that could confidently be said to be clinically significant?

v) Relatedly, would the skilled team include higher doses in a desire to get a longer duration of effect (again, the Claimants' position) or would they leave that kind of improvement for later trials?

619. I have dealt with points iv) and v) in connection with CGK and rejected the Claimants' case that it would be the CGK to aim for a better clinical effect and a longer duration of action than Lucentis and/or Macugen.

Would searches be done?

620. Regeneron said that the skilled PK/PD expert would do searches on similar drugs to help inform the choice of the right dose of VEGFR1R2.

621. I do not accept this part of Regeneron's case. The skilled team reading Wiegand II would know that VEGFR1R2 was much more potent than Avastin in the cell-based assay of Examples 14 and 15. That is a comparison of the two drugs in the same assay. Going off to look for other comparisons would be expected to be complex and speculative, not least because it was unlikely to allow a like-for-like comparison (as what Dr Ward in fact came up with confirms). I cannot see that it would be expected to give more reliable or useful information than Examples 14 and 15.

622. Regeneron submitted that Dr Wensel accepted that the skilled PK/PD expert would look for comparative information, but I do not think his evidence went that far at all. He said that the skilled person would want to know about mechanism-specific safety issues (i.e. did VEGF inhibition inherently cause side effects), and if they found dose/efficacy information in the course of doing that then they would read it. That is not to accept Regeneron's case, which is not founded on searches for mechanism-specific side effects but on efficacy searches. Dr Wensel said that comparative efficacy information would not be a focus even if it were come across.

623. Regeneron also submitted that Dr Ward strongly maintained the position that regulators wanted to see comparative information. I expect he was right about that, and of the two PK/PD experts he had more knowledge of the regulatory position, but my impression was that that information was needed as part of the (appropriately) stringent due diligence required for approval in due course, rather than as part of the initial dose selection.

624. Since I accept the Claimants' position that comparative searches would not be done, I do not need to consider their fallback position that if searches were done they would cover VEGF Trap as well, or what would be found. I only need observe that it is another mark against Dr Ward's approach that his initial searches did include other different drugs but did not include VEGF Trap. That was illogical and is not rescued by the fact that a VEGF Trap search would not turn up anything from PubMed, but only from abstracts and from the Regeneron website.

625. Since I am against Regeneron on the first decision point on this part of the case, I do not strictly need to decide what would be turned up by routine and obvious means if searches were done on comparative drugs, or on VEGF Trap. I will just briefly say that if searches were done on VEGF Trap I do not think they would necessarily have stopped with PubMed but would also have extended to ARVO abstracts, especially given the recency of VEGF Trap. I reject the notion that they would have extended to Regeneron's website, since the expectation that that would contain fully reliable scientific information would be low; that is not to say that the website would be dishonest, merely that its functions would include commercial promotion of Regeneron and not have science as its primary focus.

626. These conclusions make it doubly and triply unnecessary to resolve the application made by the Claimants to amend their Grounds of Invalidity to plead a mosaic of Wiegand II with Nguyen 2006 and/or the Regeneron Press Release. The application was indicated on the last day of trial but without its scope (as to which documents and in which combination(s)) being settled. It was then fleshed out in post-trial submissions to which Regeneron replied. Even had it been the case that I found that searches would have been done and that they would have turned up the Regeneron Press Release I would only have allowed the amendment if I was certain that it would not have affected the written and oral evidence. I could not possibly have been certain of that and on the contrary I think the evidence probably would have been different, at the very least because Regeneron would have made additional challenges based on other documents emerging from the same searches, and whether the way in which the data was presented in the Regeneron Press Release supported going to just 2mg rather than 4mg.

Obviousness – 4 mg analysis

627. For reasons given above I will consider obviousness of the 4mg dose on the basis that the skilled team regarded the 25-4000µg range in Example 17 as boilerplate, and did not do additional searches of the kind relied on by Regeneron as part of its case, or the searches relied on by the Claimants, contingently, in response. I also approach the issue on the basis that the PK/PD expert and the clinician were both involved.

628. My task is to decide whether the Claimants have shown that 4000µg was an obvious dose to use (as the top end of the range for a phase 1 trial). If I positively found some other dose to be the "right" answer for the top end of the range then of course I would reject the Claimants' position, but it is enough for Regeneron that I reject 4000µg as "wrong", in the sense of not an obvious possibility

629. The arguments facing me are complex, with a lot of factors invoked by both sides. Many of them are artificial or far more detailed and contingent than the skilled team would really have in mind. I think certain key points make it clear that the Claimants' case cannot succeed.

630. First, the Claimants' case was built on Prof MacLaren's view that 25-4000ug in Example 17 had a sound scientific/experimental basis, even if the data were

not provided. I have held that that was wrong. The Claimants repeatedly said that Prof MacLaren had reached his conclusions about the appropriate Phase 1 dose range before he had seen the Patents. I accept that, but all it means is that he had seen Example 17 and assumed the dose range was soundly based.

631. Second, the Claimants' case has as a key plank the 0.5mg dose given in Example 9. The Claimants take that and work it upwards by saying that the skilled team would scale up the Example 9 dose for the different volume of the animal's eye and because of the different kind of injury in the CNV model, and would want a longer duration of action than Macugen (or Lucentis), and a stronger effect. They bolster that by saying that the skilled team would want as a matter of CGK to explore the whole therapeutic window, something they say is shown by Ting to be CGK. This has a strong hindsight flavour; taking the 0.5mg from Example 9 and adding on other factors to work up towards 4mg. In addition, I have rejected nearly all the planks of the argument: scaling for the animal eye volume would be done, but the effect of the different injury was unclear as a matter of CGK; I have rejected the CGK arguments about better effect and longer duration both being sought; and exploring the therapeutic window was not the CGK purpose of a phase 1 trial, on my findings above.

632. Third, as well as the problem with Prof MacLaren giving too much weight to the numerical range in Example 17, the Claimants' case in written evidence and in its opening was that the range disclosed in Wiegand II was a range for a phase 1 trial, but I have rejected that. That undermines the cogency and weight of the Claimants' written evidence.

633. Fourth, the Claimants did not have a case in their written evidence about how to get to 4mg if it had to be arrived at independently from the bare statement of 4mg in Example 17: Dr Wensel confirmed in cross-examination that he had not done that, as I have already mentioned.

634. So as well as the numerous ingredients of the Claimants' case that I have rejected, I assess it overall in circumstances where the Claimants are seeking to assemble a new and different case from that which was in their written evidence, when there is a real sense of hindsight.

635. One other point which I should mention is that the skilled team would realise that it was very possible that the 0.5mg dose in Example 9 is more than was actually needed to achieve the effect seen, in the context of a very potent drug. This also pulls against obviousness because it would suggest a lower dose might be enough, but since I do not think the Claimants get close to 4mg it is not essential to my decision.

Secondary evidence of obviousness

636. The Claimants argued that their case on obviousness (of the 4mg dose) was supported because it could be seen from Nguyen 2009 (in particular) that Regeneron took exactly the course which the Claimants said was obvious from Wiegand II, in relation to the dose.

637. This point was not very well set up. It was not clear what Regeneron's reasoning was: the progression in the documents was a monkey safety trial at a dose of 0.5 mg published as an ARVO abstract in 2006 (first author Zimmer), followed by work published at the same time as an ARVO abstract (first author Nguyen) giving phase 1 human results at 1mg. This does not help the Claimants because it just shows taking the 0.5mg and scaling it for the difference in eye size but nothing else. The next step is the work shown in Nguyen 2009 when the 4mg dose is used – that is where the reasoning has not been gone into.

638. Nor was it clear to what extent Regeneron had information additional to that in Wiegand II (I can be confident that it had information essentially the same as Wiegand II and that it also had e.g. the imaging results from the monkey eyes from Example 9 – see above – but otherwise I am rather in the dark). It seems more than possible, indeed likely, that it had additional and material information that put it in a better position than the skilled team would have been from Wiegand II and which allowed it to persuade the regulators to permit the use of 4mg (or perhaps it made a reasoned case to them on some other basis). This kind of point needs more explanation to make it work: it would need looking into the details of how Regeneron proceeded. That can be done with disclosure and so on if the Court thinks it is appropriate, but it was not. I did not find the point at all convincing and it is very vulnerable to the answer that all that can be said is that the patentee itself did that which is said to be inventive, which is always the case.

639. So I reject this point. In any event, to be clear, it cannot have any bearing on the inventiveness of the formulation features, and was not argued to do so.

Assumptions put to Dr Ward

640. Dr Ward was cross-examined at one stage on the basis of four cumulative assumptions and his evidence on them then became the focus of some argument. Two of the assumptions were contrary to what I have found the CGK to have been (on whether there would be a desire to explore the therapeutic window and to extend the dosing interval) and two related to what would happen if searches were done (but different to his), and have no role to play given that I have found such searches would not be done.

641. So the evidence based on the assumptions is not relevant or useful given my other findings, and I found it contorted and hard to follow at the time, anyway. I mention it only because significant submissions were directed to it.

Obviousness – formulation aspects

642. I turn to the formulation side of the obviousness arguments. I begin by dealing with those issues where the parties deferred argument over the CGK to the context of obviousness. I repeat that I bear in mind that they are different concepts. Where I say below that something "is disputed CGK issue x" that is to give context and a cross-reference and does not indicate that I am addressing purely CGK. I am also dealing with aspects of the obviousness arguments.

Soft spot analyses

643. A potentially important issue which I think is partly one of CGK (it is disputed CGK issue 10) but which the parties dealt with as part of obviousness was whether the skilled PK/PD expert would analyse the protein to be formulated for "soft spots"; this means features of the protein sequence or predicted secondary or tertiary structure which might cause formulation problems later on.

644. It was disputed whether the formulator would want this information, whether they would ask for it, whether the protein engineering expert would know how to do it and would supply the information routinely, and what tools they would have to do it with.

645. The specific place where these disputes would bite in the obviousness arguments is that Regeneron said the analysis would show the presence of a solvent-exposed methionine in VEGFR1R2 which would militate against the use of polysorbate in a formulation because of an increased risk of oxidation.

646. Quite a lot of time in the oral evidence of Prof Leatherbarrow and of Dr Esposito was spent on this issue, looking at e.g. the modelling tools available. But the issue turned out to be a damp squib because in oral closing Counsel for the Claimants said it was accepted that whatever the position of the protein engineering expert, the formulator would appreciate from the sequence of VEGFR1R2 that there was a potentially risky methionine. An earlier focus on what the CGK disputes actually were and why this mattered would have avoided this waste of time.

647. That being so, I will state my conclusions very briefly:

    i) The question of whether the skilled protein engineer would know how to do the analysis was essentially the same as the issue over whether they were merely someone who could make the protein and not do anything else. I have agreed with Regeneron on that issue.

    ii) Even if the notional protein engineer was only the Claimants' "fermentation technician" they would know the idea of this kind of sequence analysis and would know they needed to ask someone else to do it if it was called for.

    iii) The analytical tools are not complicated and quite probably within the capacity of an undergraduate or early graduate student. They would flag the existence of the solvent exposed methionine easily and clearly.

648. None of this is to say that the Claimants accepted that the existence of the methionine would be seen as a major problem, or even necessarily a concrete problem with using polysorbate. They described it as just a "risk register" – a list of things to bear in mind – and I agree that that was the CGK (as were means to try to limit or head off the risk, such as using special bottles or testing for peroxide). So the skilled formulator would want to stop and think before using polysorbate, but might still use (or try) it. I agree that would be in

keeping with the CGK. The Claimants really took their stand on the argument that the formulator experts had agreed that polysorbate 20 would still be used/tried. I deal with that below.

The formulator's approach to the initial formulation

649. This is the subject matter of disputed CGK issue 19. There was a difference of opinion, or approach, between Prof Gukasyan and Dr Daugherty about how the skilled formulator would begin a protein formulation in terms of the initial combination of excipients they chose. Prof Gukasyan's view was that they would start with a minimal approach, using the fewest excipients that might be necessary, which would be a buffer and a tonicity agent. Dr Daugherty preferred the approach of also including a surfactant and a stabiliser, which she said was the approach she and colleagues had used at Genentech (a nuance which does not undermine the nature of the point is that the same excipient could function both as a stabiliser and a tonicity agent). I accept that that was what she had done. Regeneron did not dispute that she had done it, but said it was not CGK.

650. Dr Daugherty said the advantage of the approach she preferred was that the exploration of pH would be more robust and realistic. I accept the sense in this. She also said the approach was justified because it was likely, even if not certain, that the other excipients would indeed turn out to be necessary in due course. I accept this, too.

651. Regeneron however said that Dr Daugherty's approach was inconsistent with the overall desire of the formulator to use the fewest excipients possible, bolstered by the fact that in due course it would be necessary to justify each of them to the regulators by performing stability tests with and without. Superficially Regeneron's point sounds like a strong one, but on the evidence I think it is less powerful than at first appears. If one assumes that e.g. a surfactant was in fact going to be needed because aggregation was a risk for the protein in question at the concentration desired, then there would have to be a test with and without, whether one started with the surfactant in the first place, or started without and then added it later. There was no evidence that the regulators wanted a narrative of the order in which excipients were chosen, only that they wanted to see evidence that each was needed.

652. I find that on the evidence, both Prof Gukasyan's approach and Dr Daugherty's approach were in at least somewhat widespread use, and reasonable. They both were CGK.

653. There was also documentary support for Dr Daugherty's approach being CGK, in Gokarn, which said that liquid protein formulations usually contained a buffer, a stabiliser, a surfactant, and other excipients, and in Wang, which similarly referred to liquid protein formulations usually containing a surfactant, sucrose, and NaCl. These documents do not explicitly talk about the initial choice of excipients but are strongly consistent with Dr Daugherty's position on that, and they certainly support her evidence that it would be seen as likely that the eventual liquid formulation would contain what she said.

654. The Claimants did not really challenge that Prof Gukasyan's approach was a CGK one, but in any event it was supported as such by a 2006 article by Dr Daugherty herself, which she said took matters "much more sequentially". And it makes sense as one way to go.

655. Although I accept the Claimants' contention that Dr Daugherty's approach was a CGK one, it does not follow that the two approaches would always lead to the same result. It might be tempting to think that e.g. a surfactant is in fact needed at a particular concentration for a particular protein and that that is bound to be discovered in due course whether or not it is included in the first place. But as Counsel for Regeneron pointed out, starting with the minimal formulation might lead to a different conclusion about pH or buffer than starting with a fuller slate of excipients, and then a different surfactant, or the same surfactant at a different concentration, or even none at all might be needed (there were examples such as a 100mg formulation of the protein Synagis which had neither surfactant nor sugar, and others which had a stabiliser but no sugar). So I do not allow this point to oversimplify things, or detract from the very empirical nature of the task. The choice between a minimal and a full(er) menu of initial excipients is part of the decision sequence and of the obviousness analysis.

656. Also, a willingness to add more excipients than the minimal two does not mean that the skilled person would necessarily take one from every category, or the ones that Dr Daugherty proposed.

657. The Claimants argued that it was likely that in fact a surfactant would be found to be necessary, and they said that this could be inferred from the fact that both in the Patents and in Dix one had been included, following a formulation exercise. Naturally one has to be very careful about hindsight here, but in my view this is an exercise in trying to work out what, in the real world, would actually happen, and I agree with the Claimants that the right view on the balance of probabilities is that aflibercept at the sort of concentrations in question might well be found to require a surfactant. I also accepted Dr Daugherty's evidence that in a pre-filled syringe it would be expected to be needed or at least very desirable to avoid the risk of adherence to the closure.

658. The Claimants pointed out that there is nothing in the Patents to dispel any concern about particular excipients that were under debate at trial causing problems such as ocular irritation. I agree with the Claimants that this precludes Regeneron from relying on such a concern as a deterrent if the choice of the excipient would otherwise be obvious from a formulation perspective, but Regeneron did not try to do this.

Specific excipients as CGK

659. The parties traded blows about which specific excipients were CGK and in what contexts. They gave various examples of excipients in various formulations. The discussion ranged well outside what is necessary for me to decide so rather than make unneeded decisions about excipients which do not matter, I address the topic here and in the context of obviousness, to focus on what matters. Also, the real issue was not whether individual excipients were

CGK but whether the ones in the Patents' claims were especially attractive or appropriate.

660. The parties' examples can be looked at in a number of ways: were the formulations for proteins/antibodies or not? Were they lyophilised or not? Were they approved by the regulators? Were they for intraocular use? The trouble with these arguments is that there was not much precedent to go on for any of the subcategories in play. There were not that many antibody drugs; there were few intraocular drugs; a good proportion of the examples that did exist were lyophilised rather than liquid, and so on.

661. I do not think the picture about excipients used in actual formulations allows me to conclude either in the Claimants' favour that all the ones in the Patents' claims were individually stand-outs in terms of actual use in similar drugs, or in Regeneron's favour that they would have been regarded as outré or unprecedented. Much more generally, each was known in its own category in drug formulation generally as CGK for the function it was capable of serving (surfactant, preservative, etc.); each would be on the skilled formulator's radar as a possibility within their category, and for each there would be other options within the category in question, too. Prof Gukasyan essentially accepted that when one looks at the claimed formulations, each excipient was known at the priority and serves its CGK function (at Regeneron's first level).

662. Despite this lack of direct, close analogies, it was clear that the choice of sodium phosphate for the buffer and sodium chloride as a tonicity agent were, on the basis of wide knowledge of their use in many varied formulation contexts, especially well supported as part of the CGK, and if not the most preferred in general then certainly in the first couple to be considered. These two were sufficiently natural and simple choices that I will not say any more about them on obviousness. Regeneron did not rely on them individually.

pI assessment and use in the choice of pH

663. This is disputed CGK issue 9.

664. It was agreed CGK that the skilled team would know that a protein would be least soluble at its pI, and that the formulator would want to avoid that, by a margin of 1-2 pH units.

665. Implementing this requires some knowledge of the pI, and there was a dispute about that.

666. It was common ground between the protein engineers that software (the product referred to was called ExPasy) could be used to assess the theoretical pI of a protein. They also agreed that the value that would be provided by the software if it were just set on the primary sequence of the protein, which was its essential functionality, would be wrong. That would be because ExPasy did not adjust for protein folding, multimerization, or post-translational modifications such as glycosylation (especially the presence of sialic acids).

667. It was also common ground that the actual pI would be a range because the addition of sialic acids would differ from one protein molecule to another. The ExPasy result would not be a range, because it would not take account of this.

668. Dr Esposito's position was that the CGK approach would be for the protein engineer just to give the ExPasy result to the formulator, with the caveat that it was wrong (too high) because of the sialic acid addition etc. Prof Leatherbarrow said that the skilled protein engineer would do the best they could to estimate the pI, in terms of a range. In mechanical terms that would be done by changing some amino acids in the sequence given to ExPasy, and by adding some others. A variety of changes and additions would be input and hence a range arrived at for the overall pI. The details are very intricate; Prof Leatherbarrow's account of how to do this work was challenged in a number of ways, but while he accepted there was a degree of uncertainty about the exercise it was right within one of his core areas of expertise and I accept what he said. So far as there was a direct disagreement with Dr Esposito, which there was, for example, in relation to the number of sialic acids on glycans, I prefer Prof Leatherbarrow's evidence. Prof Leatherbarrow's expertise and comfort with the issues was palpably greater, and as I have mentioned in assessing the witnesses, Dr Esposito made one clear error which, while it did not reflect on his integrity, was a symptom of his relative lack of expertise compared with Prof Leatherbarrow.

669. Prof Leatherbarrow firmly rejected Dr Esposito's approach of just handing over the ExPasy result despite knowing it was wrong as "inaccurate" and "inappropriate". I accept the Professor's evidence. Given that the pI is an actual input for the formulator to decide what pHs to screen at, it makes no sense to give a number for it which both the provider and the recipient know to be wrong. I accept Prof Leatherbarrow's approach as the CGK one.

670. To be fair, Dr Esposito's approach was less problematic than might appear, because, it was common ground, the pI can be measured by isoelectric focusing on a gel, where the protein will show as a number of bands corresponding to the differently glycosylated species (and hence the pI will be expressed as a range).

671. A curiosity of this case is that the parties might be expected to have measured values for their proteins' pIs but that none of them submitted any evidence about it. The fact that Regeneron has a measured value for aflibercept came out adventitiously as a result of the cross-examination of Prof Gukasyan, though it would have been fairly obvious anyway. Regeneron offered to provide it if requested, but the Claimants felt able to decline the offer. Counsel for Regeneron made the submission, in the course of dealing with that interchange, that the Claimants would also have measured values, and that was not contradicted by Counsel for the Claimants. I think it is plain that they would have measured values. It is however no criticism of any party that they did not provide the values: they were never asked.

672. The oddity this leaves is that I have resolved what pI analyses would be done, and agreed with Prof Leatherbarrow, but also find that the pI would be measured, yet I do not know that, probably more reliable, figure. In agreement

with the submissions for Regeneron, I think the best that I can do, which is also fair and realistic, is to assume that the measured value would be somewhere close to the calculated value (6.5 – 7.3), accepting that an exact coincidence is unlikely. But in any event, the calculated value which Dr Esposito put forward would not be used.

pH choice

673. This was disputed CGK issue 18. I have already said that it was CGK to avoid the pI, by a margin of 1-2 pH units. Dr Daugherty also said that it would be CGK to prefer to be on the more acidic side, and that deamidation was known to be minimised at pH 5.0-6.0.

674. It was also CGK that the pH had to be chosen to accommodate the fact that the formulation was going to be injected into the eye. So there was a limit to the degree to which it could depart from physiological pH. That would generally be 6.0-7.0, but it would not be seen as impossible to go a bit lower (i.e. more acidic) – Lucentis was formulated at pH5.5.

675. The methods to screen different pHs to see their effect on stability were CGK and routine. This does not mean that it was routine to screen a large number of different pHs. The evidence was that a couple of buffers and a couple of different pHs would be chosen, at least initially. The pHs would be chosen rationally, not randomly.

Obviousness on the formulation matters – discussion

676. Having dealt with the background matters, I turn to analyse and decide whether the *Pozzoli* formulation/protein engineer differences were obvious. I do so bearing in mind that this was an empirical field where the work was inherently difficult; where there were numerous options as to which classes of excipients to use and within each class; and where the prospects of success were uncertain. Although I deal with certain key issues discretely below, they arise in this general context. I also remind myself, however, that the motivation to succeed would be considerable and that multiple different solutions might be obvious and I am not engaged in trying to decide what was the most obvious. I start by considering key evidence said by the Claimants to support obviousness.

Dr Daugherty's first report 11.22

677. In her first report, Dr Daugherty described the process of excipient selection, and then at 11.22, said this:

Formulations

11.22 The above process would likely result in a number of formulations including those with the following components and characteristics:

VEGFR1R2	40 mg/ml
Buffer	10 to 15 mM of sodium phosphate or histidine.
Surfactant	0.01 - 0.05% w/v of polysorbate 20 or polysorbate 80
Stabilizer	5-10% w/v sucrose
Tonicity agent	sodium chloride, as required
pH	6 - 7

678. The Claimants pointed out that it was never put to Dr Daugherty that this was the product of hindsight, of her having known the claims of the Patents when she wrote this. The process of sequential unmasking is described in her evidence and was not challenged, either. So I accept that I should treat this evidence as untainted by hindsight. It brings the Claimants close to the claims of the Patents, but the fact that it was not the product of hindsight does not mean that it cannot be challenged in other ways. I think the main points I should bear in mind are that:

i) It says that the formulations that would "result" would "include" the one set out in the chart. Dr Daugherty did not describe how many others she had in mind, although to be fair she was not directly asked that.

ii) It does not hit the nail on the head in terms of the pH. The range described covers but is not limited to the claimed range, and Regeneron challenged what would be reasoned, and the factors that went into, the pH 6-7 range. I return to this below.

679. The inclusion of polysorbate is challenged by Regeneron. Based on what I have said already, it was a CGK surfactant which would be considered as a possibility, but it appears that Dr Daugherty's initial proposal of it may have been made without considering the exposed methionine issue. In any event, Regeneron said that that issue makes the choice of polysorbate 20 non-obvious, and it is certainly entitled to make that point even given that Dr Daugherty's 11.22 was written without hindsight.

Obviousness of the pH choice

680. As just mentioned, Dr Daugherty said in her paragraph 11.22, that a pH of 6.0-7.0 would be used. The Claimants' position was that within that range an actual value would be found by routine screening. In coming to her suggestion of pH 6.0-7.0 she clearly had in mind the slightly acidic pH at which deamidation is minimised, which she also said was 6.0-7.0. She also referred to the theoretical pI given by Dr Esposito (8.2) and noted that the empirical

value may well be lower; she referred to the CGK approach of avoiding the pI by 1-2 pH units. Her approach to the pI seemed generally consistent with her pH 6.0-7.0 conclusion but cannot be said positively or specifically to have driven it, because the uncertainty and range are too big for that.

681. Dr Daugherty was challenged on the appropriate pH for avoiding deamidation, based on a chapter from Carpenter (which she had put in and identified as a CGK source). That said the pHs to use to avoid deamidation were 5.0-6.0, which is also what Prof Gukasyan had said. And Dr Daugherty also accepted that it was consistent with the use of pH 5.5 in the formulation of Lucentis.

682. Additionally, I have held that the notional skilled protein engineer would provide input that the calculated pI was in a range of 6.5-7.3 (accepting some uncertainty, and of course the different antibodies have differing glycosylations) and that that is the best approximation I have to what the measured value would be. Avoiding the pI on the acidic side of this (as Dr Daugherty accepted the skilled formulator would do) would not lead to trying a pH of 6.2-6.3. This was explicitly put to Dr Daugherty (describing the pI range as "6.8, 6.9 or a modest range centred around that", which I think was fair), and she accepted that the skilled person would not go above 6.0. She quickly qualified that by saying the skilled person "at the most … might creep in 6.1, 6.2, at the most, to at least, to test, but you would be thinking more around 6". I assess the real thrust of her evidence as being that the skilled person would not go above pH 6.0. I think the reference to creeping just a bit higher was informed by the claims of the Patents, which by the time of her oral evidence she of course knew (unlike when she wrote 11.22 of her first report).

683. The beneficial range to avoid deamidation, the margin by which to avoid the pI and the Lucentis pH of 5.5 all militate against choosing the pH of the claims of the Patents (the last of those supports my conclusion but is not essential to it).

684. The Claimants did not have much if any rational case for positively going to pH 6.2-6.3. They criticised the range of pHs which Prof Gukasyan said in his evidence would be used. They adhered to Dr Daugherty's initial proposal of 6.0-7.0, which I have rejected for reasons given above and without really addressing the problems with it identified in the oral evidence; they said that Prof Leatherbarrow's pI range was inaccurate and equally consistent with the pH range of 6.0-7.0 as with lower pHs, but I have held that his range is reasonably reliable and pushes towards a formulation range below 6.0, as Dr Daugherty (I have held) basically agreed.

685. The Claimants also relied on Prof Gukasyan's acceptance that it would be desirable to formulate in the physiological range, pH 6-7.5. That is true and consistent with the Claimants' overall case, but it is just part of the picture. He did not accept that any and every point in the range was obvious, if, for example, it meant formulating close to the pI.

686. The culmination of the Claimants' case can be captured in the following paragraph from its closing written submissions:

> "235. Ultimately, determining the optimum pH is part of the empirical exercise that the Skilled Formulator undertakes. It was CGK that for most proteins, the optimum pH range for stability was relatively narrow (see for example, Gokarn …). As a result, either the pH range of the claims (pH 6.2-6.3) represents the sweet spot that the Skilled Formulator will find as a matter of routine, or else, if a pH of 6 or 6.4 is just as good, it represents an arbitrary limitation on the claim."

687. As mentioned above, Gokarn is one of the CGK source textbooks. It does indeed say that the optimal range is narrow; it does not say whether finding it is easy or hard, but that it should be identified early.

688. I agree that the optimum pH range would tend to be narrow and that identifying it was part of the formulator's craft. I also agree that definite identification of it ultimately had to be empirical. But the evidence was clear that the possible ranges to explore were chosen rationally, and that only a relatively few different pHs (and buffers) would be tried. It was not a case of simply starting at pH 5.0 (say) and trying every pH in steps of 0.1 units all the way up to, say pH 8.0. No CGK text said anything like that. For one thing it would be too laborious and for another thing the changes in pH would interact in complex ways with the various excipients. It is a multi-dimensional question, not just a linear matter of choosing one point on a smooth spectrum. For the same reason it is not the case that pH 6.2 or 6.3 is just as good as pH 6.0 or 6.4 and thus arbitrary: Gokarn says the opposite. pH 6.2-6.3 is justified as giving good stability in conjunction with the other specified excipients and given their behaviour as a combined whole, and shown by the experiments in the Patents.

689. I reject the Claimants' argument that the choice of pH in the claims was obvious. This discrete finding, which I make in the overall context given above, is in my view on its own enough to reject the obviousness attack from Wiegand II as it was advanced by the Claimants.

Obviousness of polysorbate 20

690. The polysorbate 20 point is much more finely balanced, by contrast. It was quite widely used and in particular it was used in Avastin. Given a free hand the skilled formulator would be quite happy to use it and its choice as an obvious option would very probably be obvious. But Regeneron does not really contradict that. Its main point is that given the solvent exposed methionine in VEGFR1R2 the skilled formulator would not want to take the oxidation risk presented by it.

691. Both Prof Gukasyan and Dr Daugherty made statements about polysorbate 20 being a good, routine choice. The problem is that they were often not focusing, because of the context of the questions, on whether it was a good choice given the oxidation risk (although in one key passage Dr Daugherty did follow on from saying that there was a "big oxidation risk" to maintaining her position that polysorbate 20 would be tried "first", i.e. before the Triton and poloxamer options).

692. As I say, this is finely balanced but my overall assessment is that it would not be routine or obvious to start with polysorbate 20 in the light of the oxidation risk, and that the skilled formulator would know that if they did try it then there would be a substantially lower prospect of success than with CGK alternatives (which were available) that did not have the same baggage. There is a difference between trying something that might or might not work, which is the norm in this empirical field, and trying something with a concretely known risk. I do not doubt Dr Daugherty's sincerity in her views, but she appears to have said polysorbate 20 was an obvious choice at a time when she was not aware of the issue with the exposed methionine and then to have become a little anchored in that view.

693. So this provides another reason to reject the obviousness case. It reinforces my view based on the pH point, although as I have said above, that would have been enough on its own.

Pre-filled syringe feature/claims

694. Rather as a fall-back, Regeneron argued that even if all the other features of the claims were obvious, it was not obvious that the resulting formulation would be in a PFS.

695. The basis for this was that Dr Daugherty had said in her main written evidence that a formulation for a phase 1 trial would be developed in glass vials; it should be recalled that the obviousness attack was based on formulation for such a trial.

696. When this point emerged, very close to trial if not actually on the first day, the Claimants recalibrated their attack and put in a third report from Dr Daugherty saying that it was after all obvious to formulate for a PFS very early and (without invention) at the phase 1 stage.

697. I did not find the explanation for introducing the third report completely convincing and I think it might be said that in truth Dr Daugherty was changing rather than expanding her evidence. But it does not matter (and this sort of thing happens when a patentee emphasises a subsidiary point like this late in the day), because it remained her position, and Prof Gukasyan agreed quite readily that the closure of a PFS is part of the total formulation and has to be tested very early along with all the other excipients.

698. So if I had otherwise found in favour of the obviousness attack I would also have found that there was no additional invention in the PFS.

DOSE AND CONCENTRATION, ALLEGED LACK OF TECHNICAL EFFECT

699. The lions in the path point that I dealt with in connection with obviousness is related to another objection made by the Claimants: that the Patents lack a technical contribution in respect of the 40mg/ml concentration requirement of the claims. The relationship can be seen from the Claimants' pleading, in the

Grounds of Invalidity at 6A (the most directly relevant part is the second sentence of (d), my emphasis added):

> (a) It is inferred from the First Expert Report of Professor Kodjikian dated 7 April 2025 that the Defendants will contend at trial that, notwithstanding the disclosure in Weigand II of intravitreal injection of the VEGF trap protein of SEQ ID NO:6 … at a dose of 25 - 4000µg … the skilled team would not administer doses higher than the range 0.03 mg to 0.5 mg due to the risk of adverse effects at such higher doses.
>
> (d)…the Patents do not plausibly demonstrate that, contrary to the purported prejudice identified at (a) above, doses of 2 to 3.6mg or 2 to 4mg can be administered intravitreally without the relevant risk of adverse effects. ***Further and/or alternatively, the Patents do not plausibly disclose any technical contribution associated with the selection of a concentration the VEGF Trap Protein of 40mg/ml***. Accordingly, the purported prejudice is not to be taken into account in the assessment of obviousness…

700. In opening, Counsel for Regeneron argued that the contribution of the Patents "is the stable high concentration formulation" and that "it is nothing to do with any particular dose".

701. The Claimants said that could not be correct, essentially because of the inherent physical relationship between dose and concentration at a fixed volume: concentration is dose divided by volume. In the context of intravitreal administration volume is not fixed but it is capped, at 0.1ml, for reasons that were CGK (there is also a lower limit because of the difficulty of handling very small volumes, although that received less attention at trial and does not affect the points I am making here).

702. Regeneron also said that dose only entered the picture at all because of the Claimants' choice of prior art, their case being that the 4mg dose taught in Wiegand II would necessitate a concentration of 40mg/ml.

703. I do not think the situation is at all complicated and the parties were not really that far apart, which would have been more apparent had they been less concerned with picking each other up on exactly how they each expressed things. A more concentrated formulation allows more drug to be given in the same volume; for a given amount of drug the volume can be lower. For the 4mg dose mentioned in Wiegand II this means that the concentration of the claims allows (barely) it to be given intravitreally at the maximum clinically practical volume.

704. Although there is therefore little room for debate about the science, the Claimants contend that there is no technical contribution to the 40mg/ml concentration of the claims. The very example of Wiegand II shows that they are wrong: the relatively high concentration of the claims allows a dose which is desirable (so the Claimants allege, although of course this is vigorously disputed) to be given which otherwise could not be. But this is only an

example. A high concentration formulation would have benefits with a dose of e.g. 2mg because it would allow it to be given in a smaller volume than would be the case with a lower concentration formulation. While it might be possible to give 2mg with the lower concentration formulation, smaller volumes are still relatively desirable because they increase the intraocular pressure less (though this has its limits because the volume cannot go too low – see above).

705. So the 40mg/ml concentration is a real, physical parameter of the formulation which provides a tangible advantage. The Claimants made some very tortuous submissions about whether the skilled person would regard there as being a technical contribution or not depending on their motivation, as they came to the Patent, about the dose they wanted to administer (in particular whether it was 2-4mg or something else). I thought the submissions were a muddling up of factual obviousness over Wiegand with motivation and perception but anyway my conclusion is that there is a technical contribution in fact, for reasons I have just explained, and that is what matters. I do acknowledge that e.g. very small doses could easily be given in acceptable volumes at low concentrations which were, perhaps, easier to formulate, and in which case the Patent's technical contribution would not be needed, but that is not a reason to say there is none.

DIX

706. Dix is WO 2006/104852, entitled "VEGF antagonist formulations".

Disclosure of Dix

707. [0006] and [0007] are as follows:

> [0006] In a specific embodiment, the stable liquid formulation of a VEGF-specific fusion protein antagonist comprises 1-10 mM phosphate buffer, 1-10 mM citrate, 25-150 mM NaCl, 5-30% sucrose, 10-50 mg/ml of the fusion protein, at a pH of about 6-6.5. In a more specific embodiment, the stable liquid formulation comprises 5 mM phosphate buffer, 5 mM citrate buffer, 100 mM NaCl, 20% sucrose, 25 mg/ml of the fusion protein, at a pH of about 6.0. Additionally, polysorbate may be present, for example 0.05-0.15% polysorbate 20. The stable liquid formulation of the VEGF-specific fusion protein antagonist of the invention exhibits little or no precipitation after storage of a 25 mg/ml VEGF formulation for about 6 months at -80°C and little or no precipitation after storage for 6 months at 5°C.
>
> [0007] In a second aspect, the invention features a high concentration stable liquid formulation of a VEGF antagonist comprising 1-50 mM histidine, 25-150 mM NaCl, 5-30% sucrose, 50-100 mg/ml of the fusion protein, at a pH of about 6-6.5, and either 0.1-0.5% polysorbate or 1-5% PEG. In a more specific embodiment, the high concentration stable liquid formulation comprises 10 mM histidine, 50 mM NaCl, 5-20% sucrose, 50-100 mg/ml of the fusion protein, at a pH of about 6.0-6.5,

> with either 0.1% polysorbate (e.g., polysorbate 20) or 3% PEG (e.g., PEG 3350). The high concentration stable liquid formulation of the VEGF-specific fusion protein antagonist of the invention exhibits less than about 3% degradation after 15 months of storage at 5°C (75 or 100 mg/ml VEGF trap protein) or less than about 1.5% degradation after 24 months (50 mg/ml).

708. These are relevant both to the Claimants' argument that Dix impacts on assessing claim scope of the Patents (in relation to Actavis Q3) and on the point about potential anticipation by equivalence.

709. [0026] is as follows:

> **VEGF Antagonists**
>
> [0026] An VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO:2 or 4; more preferably, SEQ ID NO:4. In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308.

710. This is materially the same as [0030] in the priority document for the Patents so Regeneron is constrained to accept that it clearly and unambiguously discloses aflibercept.

711. Further information is given about formulations from [0032]:

> **Stable Liquid Formulations**
>
> [0032] In one aspect, the invention provides a stable pharmaceutically acceptable formulation comprising a VEGF-specific fusion protein antagonist, wherein the formulation is a liquid formulation. Preferably, the liquid formulation comprises a pharmaceutically effective amount of the fusion protein. The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, bulking agents, stabilizers, preservatives, and/or excipients. An example of a pharmaceutically acceptable liquid formulation comprises a VEGF-specific fusion protein antagonist in a pharmaceutically effective amount, a buffer, a co-solvent, and one or more stabilizers.
>
> [0033] A preferred liquid formulation comprises phosphate buffer, an organic co-solvent, and one or more thermal stabilizers to minimize formation of aggregates and low molecular weight products when stored, and about 10 mg/ml to about 50 mg/ml fusion protein, wherein the formulation is from about pH 6.0-6.5. A preferred liquid formulation comprises about 5 mM phosphate buffer, about 5 mM citrate, about 100

> mM NaCl, about 25% sucrose, and about 10-50 mg/ml fusion protein, wherein the formulation is at a pH of about 6.0; optionally polysorbate may be present (e.g., 0.1% polysorbate 20). Although either NaCl or sucrose can be used as a stabilizer, a combination of NaCl and sucrose has been established to stabilize the fusion protein more effectively than either individual stabilizer alone.

712. [0033] is again a disclosure said to impact on Actavis Q3 and on anticipation by equivalence.

713. Example 1 is relied on similarly:

> **Example 1. Stability of a 50 mg/ml Liquid Formulation of VEGF Trap**
>
> [0039] A liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25, was stored at 5 °C and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability was determined by SE-HPLC. The results, shown in Table 1, show that 98.6% and 98.3% of VEGF trap protein remained intact (non-degraded) at 12 and 24 months, respectively. Turbidity was measured at OD405 nm; and percent recovered protein by size exclusion HPLC.

Table 1, to which [0039] refers, is as follows:

Table 1. Stability of 50 mg/ml VEGF Trap Protein When Stored at 5 °C (VGFT-SS065)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	99.0
3	Pass	0.00	6.2	102	98.8
6	Pass	0.01	6.2	103	98.7
9	Pass	0.01	6.3	102	98.2
12	Pass	0.01	6.3	106	98.6
18	Pass	0.00	6.3	103	98.4
24	Pass	0.00	6.2	93	98.3

714. There was a dispute about what "VGFT-SS065" in the title denotes. I was not persuaded that it is clear or unambiguous.

715. Example 4 was also relied on:

> **Example 4. Further Embodiments of Stable VEGF Trap Formulations**
>
> [0045] In one embodiment, the invention provides a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% Polysorbate 20, 20% sucrose, 25 mg/ml VEGF trap protein, pH 6.0. This formulation can

> either be delivered subcutaneously or diluted and delivered by intravenous infusion. Due to the high osmolality of this formulation, it is diluted 3-fold to achieve an iso-osmolar solution for intravenous administration. Stability studies showed less than about 1 % degradation was detected after 3 years of storage at 2-8°C.
>
> [0046] In one embodiment, the invention features a lyophilized formulation which is preferably concentrated two-fold from the pre-lyophilized to the post-lyophilized formulation, e.g., 50 to 100 mg/ml; 75 to 150 mg/ml, or 100 to 200 mg/ml VEGF trap protein. In one specific embodiment, the pre-lyophilized formulation comprises 10 mM histidine, 1.5% PEG 3350, 0.75% glycine, 2.5% sucrose, 50 mg/ml VEGF trap protein, pH 6.3, and is reconstituted to a formulation comprising 20 mM histidine, 3% PEG 3350, 1.5% glycine, 5% sucrose, 100 mg/ml VEGF trap protein, pH 6.3. Stability studied showed no degradation of the VEGF trap was detected after 6 months of storage at 2-8 °C.
>
> [0047] In one embodiment of a liquid formulation, the formulation comprises 10 mM histidine, 50 mM NaCl, 5-20% sucrose, 50-100 mg/ml VEGF trap, and one of 0.1% polysorbate 20 or 3% PEG 3350. One advantage of this liquid formulation is that it provides a higher concentration of VEGF trap without requiring the manufacture of a lyophilized product. Thus, this formulation provides ease for subcutaneous delivery, for example, by allowing provision of a liquid pre-filled syringe at a concentration higher than that delivered by IV infusion. Also, this formulation could advantageously be used to provide lower infusion volumes and shorter infusion times. The amount of degradation determined by SE-HPLC following incubation at 5 °C for up to 15 or 24 months is summarized in Table 7.

716. Table 7, to which this refers, gives stability data for different time periods and different concentrations of VEGF Trap, with and without Polysorbate 20 or PEG:

Table 7. Stability of Liquid Formulation with 50-100 mg/ml VEGF Trap (VGFT-SS101)

Incubation (months)	VEGF Trap (mg/ml)	% Polysorbate 20	% PEG 3350	% Degradation
24	50	0.1	-	0.7
24	50	-	3	1.3
15	75	0.1	-	1.5
15	75	-	3	2.0
15	100	0.1	-	1.9
15	100	-	3	2.6

Would the skilled reader of the Patents go to Dix?

717. As the case law indicates (*Jushi v OCV* [2018] EWCA Civ 1416), whether it is legitimate to assess the claim scope of a patent by checking whether a piece of

prior art cited in it would present a validity problem is case-specific. The Patents merely mention Dix among a number of other citations in the "Statement of Related Art" section. There is nothing to draw attention to it and no reason to think that the claims are crafted around it. The Claimants drew attention to the fact that it is said to be concerned with VEGF antagonist formulations; I agree that that carries with it the possibility that it might be prior art that the patentee was particularly concerned with and which affected claim drafting, but equally without going to Dix (which would of course sell the pass and is not legitimate in the very act of assessing whether to go to it) it is perfectly possible that it is about very different formulations, or very different VEGF antagonists. It could be that almost any of the other citations in the related art section were the ones that impacted the claim drafting. The Claimants' argument would mean that any cited art which was not obviously irrelevant on its face would be consulted by the skilled reader of a patent. That would be a major task even for the dozen or so citations in Dix; there are often many more references in patent specifications. I note that Dix receives slightly more emphasis on the front page of the Patents at (56) under "References cited", but that is only a difference of degree, and anyway that is essentially a list of what the examiner found important; the patentee may had other views.

718. Dr Daugherty in her evidence said that the skilled person might turn up Dix because it could be of general interest. I am sure she was sincere in the statement but it is clearly not enough on the case law and is completely unrealistic, even worse that the proposition that any piece of prior art which might possibly impact validity in some unknown way would be turned up.

719. I do not consider that the skilled person would consult Dix at all.

<u>If the skilled person did go to Dix</u>

720. In case I am wrong about that, for the purposes of Actavis Q3 I need to consider what the skilled person would make of Dix if they did go to it. That would depend to some extent on what they thought about its prior art status. In fact it is a novelty-only citation if the Patents are entitled to priority. But the skilled person reading the Patents would not know about the priority position.

721. In *Alexion v Samsung Bioepis* [2025] EWHC (supra) the parties agreed that the skilled person should be assumed to know the position about priority date when considering the impact of references to the prior art. Regeneron said that that was correct; the Claimants did not necessarily agree but said that there was, again, no need to decide the point because the evidence was all directed to the possibility of Dix being seen as potentially anticipating, and not to obviousness. So I will proceed on the same basis as in *Alexion* but I am not deciding the point of approach, which will have to be argued out if it arises in a case where it matters.

722. Regardless of whether the skilled person would go to Dix from the Patents, I need to make factual findings about its disclosure in case the Claimants persuade a higher court that anticipation by equivalence is possible as a matter of law.

Findings requested by the Claimants

723. I asked the Claimants what findings they wanted me to make about the disclosure of Dix (on the assumption the skilled person did go to it for Actavis Q3, or for anticipation by equivalence). The Claimants identified the following:

    i) Whether the "VEGF trap" referred to in paragraph [0047] is the same protein as the protein of the claims;

    ii) Whether the pH of the formulation described in paragraph [0047] would be understood to be pH 6-6.5; and

    iii) Whether a formulation which comprises 5% sucrose, 50 mg/ml VEGF Trap and 0.1% polysorbate has an osmolality suitable for intravitreal administration.

724. As to i), [0026] says that the preferred embodiments use either SEQ ID NO: 2 or SEQ ID NO: 4. Example 4 generally and [0047] in particular do not say which. Dr Daugherty said in her written evidence that the skilled person would infer that it was SEQ ID NO: 4 from the fact that that was used in the other examples. She did not maintain that in cross-examination and accepted that one "just would not know". This is a matter of what the document means and not really for the witness, but I agree with her: it is not possible to know. I agree the position with the other examples might make it likely that SEQ ID NO: 4 was used in Example 4, but I am dealing with the anticipation standard here.

725. As to ii), [0047] is silent about the pH. However, the Claimants relied on the "more specific embodiment" of [0007]. Although it is not said explicitly, the detailed correspondence between the matters set out there and Example 4 is so great and on so many points that I am sure the skilled person would conclude with certainty that they were about the same thing and that the pH was 6-6.5. But one cannot tell what the pH was for any of the individual combinations of VEGF Trap concentrations and Polysorbate or PEG.

726. As to iii) the Claimants need this point because Dix is purely about formulations, not a specific disease or route of administration and does not explicitly refer to intravitreal administration. The evidence was that 5% sucrose would have an osmolality which was in fact suitable for intravitreal administration. 5% is however only one end of the range given and Prof Gukasyan said, without challenge, that the data in Table 7 was probably derived using 20%.

Overall finding on Example 4

727. Assuming the claim scope argued for by Regeneron for the purposes of infringement, Example 4 plainly does not disclose anything within that scope to the anticipation standard, for the following reasons:

i) It is not disclosed what the VEGF Trap protein is (SEQ ID NO: 2 or 4).

ii) The amount of sucrose used is specified only as a range and as a result the relevant osmolality and suitability for intravitreal administration might or might not be there.

iii) The VEGF concentrations used were 50, 75 and 100 mg/ml so there is no disclosure of 40 mg/ml.

728. There would be the additional question of whether a pH of 6.2-6.3 (as in the claims of the Patents) is adequately disclosed by the wider range of pH 6-6.5; a similar point might arise on the sucrose percentage and there would be the yet further matter of whether it would be legitimate to combine them for the purposes of anticipation. But I do not need to go into those because on any view points i) and iii) mean that it is impossible for Example 4 clearly and unambiguously to disclose something falling within the scope of the claims of the Patents as relied on by Regeneron for anticipation. If the skilled reader of the Patents went to Dix from the Patents they would realise there was no anticipation.

729. The VEGF concentration received no real attention from the Claimants until oral closing when I asked about it. It was obvious that the point had not been thought through. Counsel for the Claimants said that a consequence of Regeneron's infringement arguments was that all the elements of the claims were subject to expansion. That is of course wrong. Regeneron has always said that the 40mg/ml is a key part of the invention; it has never argued for a scope other than the normal interpretation of it. It has said that some features do not require strict compliance, but not the protein concentration.

730. These points all lead to the conclusion that even if anticipation by equivalence were available in law it would fail on the facts as they relate to Dix.

Impact on Actavis Q3

731. Dix was said by the Claimants to impact on Actavis Q3 for two reasons. I have touched on this already but now draw together my conclusions.

732. The first reason was that the skilled person would turn Dix up and then realise that on the claim scope argued for by Regeneron on equivalence, it was an anticipation. This fails on my findings that the skilled person would not turn Dix up at all, and if they did, (and focused on Example 4) they would not think it was even arguably an anticipation.

733. The second reason was that Dix mentions histidine. The Claimants said that this shows that the patentee was aware of histidine but did not claim it. This is an extreme extension of the disclosed-but-not-claimed principle. What Dix did or did not claim or disclose, in a different patent family, is much too remote from the Patents.

Conclusion on Dix

734. Dix does not help the Claimants on any front. It was a potpourri of points, many rather obviously bad. The Claimants' position was not well thought out on some of them and I had the distinct sense of the Claimants improvising on the hoof to meet some really basic problems (such as the 40mg/ml point). The additional points Dix raised were an unwelcome distraction in a trial with already too many in play and Dix should have been dropped a good deal earlier, probably when it became clear that that Patents were accepted to be invalid if priority was lost, leaving Dix as a novelty-only citation.

APPLICATIONS TO AMEND THE PATENTS

735. The only objection to the amendments proposed was that they did not cure the invalidity alleged. I have found '691 valid and so allow it to be amended in the form of the unconditional amendments advanced. '306 is invalid for added matter and the amendments proposed do not cure that and so are not allowable.

CONCLUSIONS

736. My conclusions are:

i) Neither the Formycon nor the Samsung product infringes either of the Patents. All the allegations of infringement by equivalence fail.

ii) The '306 Patent is not entitled to priority and by the same reasoning is invalid for added matter. Those attacks fail against the '691 Patent.

iii) The Claimants are not permitted to amend the Grounds of Invalidity to add the Nguyen 2006 or Regeneron Press Release prior art.

iv) The obviousness attack over Wiegand II fails.

v) The allegations of insufficiency and lack of technical contribution fail.

vi) Regeneron's claims for infringement therefore fail. The '306 Patent must be revoked but the '691 Patent is valid.

vii) The unconditional amendments to the '691 Patent are allowable but the amendments to the '306 Patent are not.

737. I will hear Counsel as to the form of Order if it cannot be agreed. I direct that time for seeking permission to appeal shall not run until after the hearing on the form of Order (or the making of such Order if it is agreed). I draw attention to paragraph 19.1 of the Patents Court Guide, which says that a hearing on the form of Order should take place within 28 days of hand down. In the present case, 28 days from hand down will be 7 November 2025.