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Case No: HP-2023-000024

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

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

Date: 30 January 2025

Before :

HIS HONOUR JUDGE HACON

- -

Between :

CELLTRION INC.	**Claimant**
- and -	
(1) GENENTECH, INC **(2) NOVARTIS AG**	**Defendants/ Part 20 Claimants**
(3) NOVARTIS PHARMACEUTICALS UK LIMITED	**Part 20 Claimant**
- and -	
(1) CELLTRION INC. **(2) CELLTRION HEALTHCARE UNITED KINGDOM LIMITED**	**Part 20 Defendants**

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Iain Purvis KC and **Adam Gamsa** (instructed by **Bird & Bird LLP**) for the **Claimant/Part 20 Defendants**
Thomas Mitcheson KC and **Stuart Baran** (instructed by **Bristows LLP**) for the **Defendants/Part 20 Claimants**

Hearing dates: 24-25 and 28-29 October and 1 November 2024

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Approved Judgment

This judgment was handed down remotely at 10.30am on 30 January 2025 by circulation to the parties or their representatives by e-mail and by release to the National Archives.

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HIS HONOUR JUDGE HACON

Judge Hacon :

Introduction

1. Asthma is an inflammatory disease of the airways of the lungs, leading to wheezing, coughing, chest tightness and shortage of breath. The UK has among the highest prevalence of asthma in the world. Estimates vary, although the National Institute for Health and Care Excellence reports that 6.5% of adults in England have the condition. There is no known cure for asthma but there are many alternative treatments to alleviate symptoms.

2. A frequent cause is an allergy which triggers the inflammation. Common allergens are dust mites, pollen and allergens produced by animals, often pets. The immune system of the individuals affected overreacts to allergens to which they are susceptible, producing a type of antibody called Immunoglobulin E ('IgE').

3. One of the pharmaceuticals used to treat asthma is a monoclonal antibody designated rhuMAB E25, having the generic name omalizumab. It is an anti-IgE antibody which binds to IgE, reducing or eliminating the allergic reaction.

4. The First and Second Defendants are the joint registered owners of European Patent (UK) No. 3 805 248 B1 ('the Patent') which claims a pharmaceutical liquid formulation of omalizumab with stated constituents.

5. The Claimant ('Celltrion') seeks revocation of the Patent on various grounds. There is a counterclaim for infringement, which is admitted if the Patent is found valid.

6. After the trial an application was made for permission to allow a UK company in the Novartis group to join the counterclaim as a further Part 20 Claimant and for a UK company related to the Claimant to be added as a Part 20 Defendant. By an order dated 13 January 2025, I gave permission with directions for amended pleadings. I will refer to the Claimant/Part 20 Defendants collectively as 'Celltrion' and the Defendants/Part 20 Claimants as 'the Defendants'.

7. Iain Purvis KC and Adam Gamsa appeared for Celltrion, Thomas Mitcheson KC and Stuart Baran for the Defendants.

The skilled team and the witnesses

8. It was agreed that there would be a skilled team in this case, consisting of a clinician and a formulator of medications. Each side called a clinician and a formulator as expert witnesses.

9. Celltrion's clinician was Professor Neil Barnes. He is a Professor of Respiratory Medicine at St Bartholemew's Hospital and at the London School of Medicine and Dentistry. He also practices as a locum respiratory consultant at the Barts Health NHS Trust.

10. Professor Paul Dalby was Celltrion's expert formulator. He is Professor of Biochemical Engineering and Biotechnology, and Deputy Head of the Department of Biochemical Engineering at University College London. He is also Co-Director of the Engineering

and Physical Sciences Research Council Future Targeted Healthcare Manufacturing Hub and a Fellow of the Royal Society of Chemistry.

11. The Defendants' expert clinician was Professor Ian Pavord. He is Professor of Respiratory Medicine at the University of Oxford and Honorary Consultant Physician at the Oxford University Hospitals Foundation Trust. Professor Pavord specialises in asthma and chronic obstructive pulmonary disease.

12. Finally, Professor Bernhardt Trout was the Defendants' expert formulator. He is a Professor of Chemical Engineering at the Massachusetts Institute of Technology. He has over 20 years of experience working in the field of therapeutic protein formulation.

13. Professors Barnes, Pavord and Trout received little or no criticism from the parties in closing. I thought all three were excellent witnesses.

14. The Defendants suggested that Professor Dalby's evidence was tainted with hindsight and that he lacked independence, partly as a consequence of the way in which he was instructed. It was said that he was shown documents in the wrong order, he was not put in a position to comment properly on the perspective of a skilled formulator before starting a project on omalizumab and that he misunderstood the correct approach in law of the skilled person to the prior art.

15. In my view there was no real force in any of these criticisms. Professor Dalby was generally a good witness.

The Patent

16. The title of the Patent is 'Process for concentration of antibodies and therapeutic products thereof', which is misleading because all of its six claims are for a product, each a solution containing omalizumab with a stated formulation. The Patent has a filing date of 8 September 2005 and a priority date of 9 September 2004.

17. The specification explains means for making the formulations claimed. Examples are given of experiments carried out to make formulations within the claims, notably examples 5 and 6, with data supplied. More detailed discussion of the content of the Patent will be given in the context of the issues in the case.

18. These are claims 1 and 2:

> '*1 A pharmaceutical formulation of anti-IgE antibody rhuMAB E25, characterised in that the formulation is about 150g/L of the anti-IgE antibody in 0.02M histidine, 0.2M arginine-HCl, 0.04% polysorbate 20, pH 6.*
>
> *2. The formulation of claim 1, wherein the formulation is substantially free from aggregates.*'

Construction

Liquid

19. It was common ground between the experts that since claim 1 specifies pH 6, the formulation must be in liquid form. Celltrion argued that this does not, however,

exclude a lyophilised formulation which has been reconstituted into a liquid. The Defendants submitted that claim 1 (and hence all the claims) is restricted to a formulation that was made up as a liquid and remains as such.

20. The Defendants relied on the evidence of their expert formulator, Professor Trout. He said that typically the terms 'reconstituted' and/or 'lyophilised' would be used wherever the user meant a liquid solution that has been reconstituted from a lyophilised formulation; a formulation made up from the start as a liquid formulation or at least supplied to the user and thereafter stored for use as a liquid, would be described simply as a 'liquid' formulation.

21. Professor Dalby's reports read as if he assumed that the formulation of claim 1 would be made up and supplied in liquid form and he discusses problems of stability that would follow from this.

22. These views are consistent with the parties' joint statement of the common general knowledge ('CGK'):

> '2.25 A liquid formulation is a formulation which is manufactured, stored, transported and administered as a liquid. The Skilled Formulator would be aware that from a clinical perspective (both for healthcare professionals and, where possible, patients using the product at home), liquid formulations are generally preferred to lyophilized formulations. This is due to their relative ease of use – they do not require any further preparation before administration. In a particularly convenient scenario and subject to the indication, liquid formulations can be provided in, for example, a pre-filled syringe that makes administering the required dose even more straight forward.
>
> …
>
> 2.27 At the priority date, the Skilled Formulator would have understood liquid formulations for SC administration to be the most preferred type of formulation/route of administration for monoclonal antibodies. However, the Skilled Formulator would have understood that there were challenges posed by the high concentration liquid formulations typically required for SC administration of monoclonal antibodies.'

23. I take from this that those skilled in the art would have expected that a formulation in liquid form which had been reconstituted from lyophilised material would be described as such. Further, none of the processes set out in the Patent involve lyophilisation. Accordingly the formulations disclosed and claimed would have been understood to be liquid formulations in the sense defined in the joint statement.

Temporal stability of the formulation

24. Celltrion rightly pointed out that there is nothing in the claims or the description of the Patent which states anything about the temporal stability of the formulation. However, the parties' agreed statement of CGK means that a liquid formulation, as that term would have been understood, must be manufactured as a liquid and thereafter be stored, transported and administered as such. It follows it must be sufficiently stable in the period between manufacture and administration to remain suitable for administration.

The Defendants submitted that this meant about a year. Professor Dalby stated the figure of three months in his written evidence but in cross-examination agreed that the shelf life aimed for was between six months and two years.

25. It is not surprising that there is no firm figure, but I find that the skilled team would expect the omalizumab formulation of claim 1 to be stable for at least six months and possibly much longer.

About 150 g/L anti-IgE antibody

26. There was disagreement about how far 'about' 150 g/L of the antibody stretches the stated figure.

27. Celltrion pointed to the conventional rounding convention which, to one decimal point, would take 150 standing alone to be anything from 145.0 to 154.9. Celltrion added that the word 'about' adds further flexibility, so that the range encompasses 125 g/L. It also relied on evidence from Professor Pavord who said that it is the dose of antibody administered that matters, not its concentration. This could be achieved just as well by using 1.2ml of formulation with 125 g/L antibody as that which is taught in the Patent, i.e. 1ml of formulation with 150 g/L antibody.

28. The Defendants said that the evidence of both Celltrion's experts was that the skilled team would have been trying to achieve the highest concentration of antibody as possible so as to minimise the volume to be injected and that the Patent discloses a particularly high concentration.

29. I agree with the Defendants' characterisation of this part of the evidence. It is true that Professor Pavord for the Defendants accepted in cross-examination that there was no clinical significance in reducing the injection from 1.2ml to 1ml if the amount of antibody was the same. But he was not challenged on this part of his first report:

> 'In general, the lower the injection volume, the less discomfort a patient would suffer from being administered a subcutaneous injection so the Skilled Clinician would expect that a 0.2ml reduction in injection volume would provide some clinical benefit to patients.'

30. I think that Professor Pavord meant that a higher volume injected in lower concentration provided the same dose and made no clinical difference in that sense. But the level of discomfort to the patient would increase. I am reinforced in this view by the evidence of Professor Dalby who said that the skilled team would have been looking for an injection of the smallest volume possible. Celltrion's other expert, Professor Barnes, said much the same.

31. The flexibility, if any, to be given to a number in a patent claim will always be fact dependent. Where the number is preceded by 'about' or something similar, some variation on the stated figure must be assumed. On balance, I think that in this case the skilled team would take 'about' to mean that 150 g/L is not intended to be completely inflexible. The rounding convention proposed by Celltrion probably gives as good a guide as any to the degree of flexibility that the skilled team would have taken the Patent to mean, so between 145 and 155 g/L.

0.04% polysorbate 20

32. Celltrion made a similar point about the quantity of polysorbate in the claim, submitting that the figure of 0.04% is arbitrary. Professor Dalby's evidence was that the skilled formulator would understand that some polysorbate must be present, in an amount constituting at least 0.01%, but that a further 0.02% would make no difference. Professor Trout thought that the skilled formulator would have expected the figure of 0.04% to be an optimum figure.

33. Professor Trout gave no reason why the amount of polysorbate would sufficiently affect the nature or performance of the formulation such as to require an optimum concentration. I accept Professor Dalby's evidence that the skilled formulator would have known that at least around 0.01% was necessary and thereafter increasing the amount, certainly up to 0.03% and probably higher, was unlikely to make a difference. But this cuts both ways. The skilled team would know this and would note that the claim does not, as one might expect, require at least 0.01% polysorbate, but instead specifies 0.04%. I think the skilled team would therefore have understood the patentee must have intended a limitation by stating that figure of 0.04%.

34. The discussion here concerns the 'normal' construction of the claim (see *Actavis UK Ltd v Eli Lilly & Co* [2017] UKSC 48, at [66]-[67]). In *Société Technique de Pulverisation STEP v Emson Europe Ltd* [1993] RPC 513, Hoffmann LJ said at 522,

> 'The well known principle that patent claims are given a purposive construction does not mean that an integer can be treated as struck out if it does not appear to make any difference to the inventive concept. It may have some other purpose buried in the prior art and even if this is not discernible, the patentee may have had some reason of his own for introducing it.'

35. In *Regen Lab SA v Estar Medical Ltd* [2019] EWHC 63 (Pat) I doubted that Hoffmann LJ's dictum remains good law if the scope of a patent claim, thereby including equivalents, is under consideration. I see no reason why it should not retain full force in the context of the normal construction of a claim.

36. In the present instance the skilled team would have assumed that the patentee may have had good reason to specify that particular figure and would treat it accordingly. Neither of the expert formulators suggested that in making up a formulation there would have been any difficulty in using precisely 0.04% polysorbate if so instructed. To the extent that any flexibility would have been considered, it would not have gone beyond the usual rounding convention.

Histidine

37. The dispute about histidine was not about its concentration but about what the word would be taken to mean.

38. Histidine is an amino acid. It would be added to the other contents specified in claim 1 in the form of a salt. The most commonly used is histidine-HCl. In solution the salt would dissociate in part, so that it and its components, namely histidine as a free base and the counteracid, exist in equilibrium. At pH 6 they act as a buffer, resisting small changes in pH.

39. The Defendants submitted that the salt has to be histidine-HCl because also added is arginine-HCl. Both will partially dissociate in solution. If some other salt were used, for instance histidine phosphate, some of the phosphate ions would associate with arginine free base, in which case the molarity of arginine-HCl would no longer be 02M, instead some lesser molarity. The only way to maintain the required molarity of the arginine-HCl is by using histidine-HCl.

40. Celltrion submitted that this is to misinterpret claim 1. It is a claim to a recipe. 0.2M histidine and 0.2M arginine-HCl are two ingredients to be added to the make the whole. What happens to the respective free base amino acids and their counterions in solution is irrelevant. The recipe does not specify a particular salt of histidine. If, taking the Defendants' example, 0.2M histidine phosphate were to be used, the molarity of the arginine-HCl in solution would indeed differ from 0.2M, as confirmed by Professor Dalby in cross-examination. But that is of no relevance to a recipe claim.

41. I agree with the Defendants. Claim 1 is a claim to a formulation of a liquid solution. If it is to be treated as a recipe, then it is a recipe for the contents of the solution, not a list of the ingredients before they are tipped in. It follows that the arginine-HCl must have a molarity of 0.2M and therefore the histidine ingredient added is histidine-HCl.

Novelty

The prior art

42. The single item of prior art cited in respect of Celltrion's argument on lack of novelty is a PCT Application with publication no. WO 2004/091658 A1 ('Liu').

43. Liu was published after the priority date of the Patent and so is available only as a prior art citation in respect of novelty. Genentech is the proprietor. The contents of Liu mark an earlier or parallel stage of Genentech's research into antibody formulations. The title is 'High Concentration Antibody and Protein Formulations' and the focus of the invention claimed is the discovery that arginine, specifically arginine-HCl, is particularly suited for highly concentrated liquid protein or antibody formulations.

44. The section on the summary of the invention contains this:

> '… the present invention concerns highly concentrated antibody formulations arginine-HCl (50 – 200 mM) and polysorbate (0.01% – 0.1%), having a pH of 5.5 – 7.0, a viscosity of 50 cs or less and osmolarity from 200 mOsm/kg – 450mOsm/kg.'

45. The description identifies two IgE antigens which provide a specific aspect of the claimed invention, one of which is rhuMAbE-25 (shortened to E25 later in the description), i.e. omalizumab. The other is rhuMAbE-26 or E26.

46. Polysorbates are among the surfactants stated to be suitable for the formulation disclosed in Liu:

> 'Suitable non-ionic surfactants include polysorbates (20, 40, 60, 65, 80. *etc*.), …'

47. Example 2 of Liu identifies two specific formulations, of which one is shown in the left hand box below:

Formulations	Protein Ranges	Buffer/Ranges	Excipients/Ranges
150 mg/ml E25 20 mM Histidine-HCl 200 mM ArgHCl 0.02% Polsorbate 20 pH 6.0	40-260 mg/ml	His-HCl or His-Acetate Ranges: 10 mM – 100 mM	ArgHCl Ranges: 50 mM –200 mM Polysorbate: 0.01%-0.1%

48. The box on the left is the formulation of claim 1 of the Patent save that the polysorbate (misspelt in the box) has a concentration of 0.02% rather than 0.04%. The other boxes provide for alternative ranges for the constituents and an alternative in the case of histidine-HCl. The range disclosed for polysorbate is 0.01% – 0.1% and no particular polysorbate is specified.

49. Celltrion pointed out that example 4 in the description, which used E26, says this:

> 'The addition of at least 0.01% of polysorbate is essential for reducing the particulate formulation under the stressed condition. Similar results were also observed for concentrated E25 liquid formulation.'

50. This could be taken to imply that provided at least 0.01% is added, particulate formation is reduced as required. Figure 4 confirms this implication. It is in the form of a graph which shows the results of the experiment in example 4, an agitation study for a concentrated E26 liquid formulation. The graph measures turbidity, i.e. the degree of particulate formation, against the time for agitation of the formulation. The plotted figures show that the addition of 0.01, 0.02 and 0.05% polysorbate 20 all keep turbidity at about the same low level, whereas in the absence of any polysorbate 20, turbidity rises markedly to a maximum after 20 hours.

The issue

51. Attention was focused on example 2 of Liu. The difference between the specific formulation in the left-hand box shown above and claim 1 is that in the former the concentration of polysorbate 20 is 0.02% and in the latter it is 0.04%. I have found that the figure of 0.04% in the claim would not be interpreted by the skilled team to encompass 0.02%.

52. As shown above, example 2 of Liu also allows a range of other polysorbate concentrations and alternative types of polysorbate, of which there appear to be at least five alternatives, probably more.

53. Celltrion argued that because the left-hand box in example 2 specifies polysorbate 20, the box on the far right would have been taken to mean polysorbate 20 as well. I disagree. The left-hand box is headed 'Formulations' which would have been understood to indicate specific formulations. (I have not shown another formulation, not relevant to the discussion, which appears under the headings). The other three boxes, as their headings indicate, show variations on the formulation. In the case of

polysorbate 20, the variations include other suitable polysorbates which may be used, alternatives identified in the description.

54. As to the range of concentrations, Liu indicates that least 0.01% polysorbate should be present. Otherwise its concentration, whether 0.01%, 0.02% or 0.05%, makes no significant difference to turbidity.

55. The issue is whether Liu's disclosure of a formulation with alternative polysorbates, each having a range of concentrations, taken with the other disclosed elements of example 2, i.e. 150 mg/ml E25 and so on, anticipates claim 1 of the Patent.

Overlapping ranges or lists, or a selection from a range or list – the law

56. *Jushi Group Co Ltd v OCV Intellectual Capital, LLC* [2018] EWCA Civ 1416 concerned a formulation for a type of glass strand used in the reinforcement of plastic and other materials. The formulation of the prior art disclosed a range of values for each of several constituents. The same was true of the formulation claimed in the patent. The two ranges clearly overlapped if each was taken to consist of all possible combinations of all the alternative values of every constituent. The Court of Appeal ruled that there was no anticipation on the facts as found at first instance.

57. Floyd LJ, with whom Kitchin and Henderson LJJ agreed, considered the law on ranges more broadly, including a selection from a range or list, referring to decisions of the Technical Board of Appeal of the European Patent Office (EPO). In the simplest case the prior art discloses the invention in suit save that in respect of one element a range between X and Y is disclosed in the prior art, not the specific figure for that element claimed in the patent. The specific figure in the patent claim falls between X and Y. Is the invention claimed anticipated?

58. Some years ago the EPO developed a guideline to tackle this. The criterion to be applied under that guideline is whether the prior art would lead to the skilled person to 'seriously contemplate' use of the specific value for the element as claimed in the patent. I was told by the Defendants that the test has been discarded by the EPO since the judgment in *Jushi*. I am not sure about that – it seems to be alive and kicking in the current (March 2024) edition of the Guidelines for Examination in the European Patent Office, see Part G, Chapter VI, section 7.

59. In any event, in *Jushi* Floyd LJ stated that he had no difficulty with the serious contemplation test on the basis that it was consistent with the English law on novelty as explained in *Synthon* and *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2009] EWCA 1362, but he thought it better to stick with the guidance of those English authorities.

60. I will follow Floyd LJ's preference for leaving the serious contemplation test to one side. I also note from the current EPO Guidelines a warning against confusion with the test for inventive step and I can see that there is room for confusion.

61. The passage from *Dr Reddy's* which Floyd LJ had in mind was the one he quoted in his paragraph 46, taken from the judgment of Jacob LJ:

'[30] Thus logic dictates rejection of the argument that a disclosure of a large class is a disclosure of each and every member of it. So also does EPO case-law. Mr Carr accepted that was so, so I can take the matter quite shortly, going to just one case, *Hoescht/Enantiomers* T 0296/87, 30 August 1988 , which effectively sums up earlier cases. It said:

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

So what one must look for by way of an anticipation is an "individualised description" of the later claimed compound or class of compounds. …

[31] It is not necessary here to go into what is sufficient to amount to an "individualised description." Obviously the question may partly be one of degree, but other considerations may come in too, for instance the specificity of any indicated purpose for making the compounds. A mere woolly indication of the possible use of the prior class may require less specificity than a precise one.

[32] This view of the law accords with the decision of the House of Lords in *SmithKline Beecham plc's (Paroxetine Methanesulfonate) Patent* [2006] R.P.C. 10 . Lord Hoffmann said:

> "22. If I may summarise the effect of these two well-known statements, the matter relied upon as prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent. That may be because the prior art discloses the same invention. In that case there will be no question that performance of the earlier invention would infringe and usually it will be apparent to someone who is aware of both the prior art and the patent that it will do so."

Where you have a patent for a particular chemical compound and a prior art general disclosure, performance of the general disclosure (which means no more than using anything within it) does not necessarily result in infringement of the patent. In this case, for instance, you can "perform" 235 in any of 1019 ways – only one of them would result in infringement of the later patent.'

62. Celltrion relied on another observation by Floyd LJ in *Jushi*:

'[55] I would accept that there may be circumstances where a prior disclosure of a numerical range, such as a range of temperatures to be used in a process, may carry with it an implicit disclosure that the skilled person may choose any value within the range. Whether that is so will depend on the disclosure of the document understood with the benefit of the common general knowledge. It is

> wrong, however, to elevate that possible conclusion into a rule of law, so that every numerical range must be so understood, whatever the context.'

63. I do not understand Floyd LJ to have been saying there that if the cited prior art would be understood by the skilled person to mean that any individual value within a disclosed range is suitable for performing the invention, and the range includes the value or range of the invention in suit, the invention is anticipated. Cited prior art disclosing a range may be understood that way but this does not mean that there is an individualised description of every value within the range. To adapt slightly an example favoured by Jacob LJ (see *Dr Reddy's* at [28]), a disclosure of any book at all in the Bodleian is not an individualised description of each and every book in the library.

64. This leads on to what constitutes an individualised description. The EPO Guidelines summarise the current approach of the EPO in the following way (at G/VI/page 12):

> 'A sub-range selected from a broader numerical range of the prior art is considered novel if both of the following two criteria are satisfied (see T 261/15):
>
> – the selected sub-range is narrow compared to the known range;
>
> – the selected sub-range is sufficiently far removed from any specific examples disclosed in the prior art. The meaning of "narrow" and "sufficiently far removed" has to be decided on a case by case basis.'

65. In Case T 738-09 *Antidiabetic combinations/Novartis* (25 January 2011) the EPO Technical Board of Appeal said (at 5.6):

> 'Thus, the "disclosure status" of subject-matter individualised from lists has to be determined according to the circumstances of each specific case by ultimately answering the question whether or not the skilled person would clearly and unambiguously derive the subject-matter at issue from the document as a whole …'

66. An important factor is the size of the range (or list) from which the selection has been made. Where there is selection from two or more ranges or lists, regard must be had to the effective size of the total number of alternatives from which the overall selection is made. In doing so, it is important to note whether the values in the ranges or the items in the lists are independent of each other since the effective scope for selection may be limited by an interdependence. Also, as was the case in *Jushi*, the nature and degree of interdependence may not be clear to the skilled person; doubt on this score may tend to point away from the prior art anticipating the claimed invention.

67. There are other potentially relevant factors. Where the patent in suit claims a range, the extent of overlap with a prior art range matters. Statements of preference in the prior art which point towards the claimed invention can be important. Selection from a list or multiple lists was recently considered by Meade J in *ModernaTX, Inc v Pfizer Ltd* [2024] EWHC 1695 (Pat), at [127]-[146], where he referred to possible pointers.

68. The Defendants drew my attention to example decisions of the EPO Technical Board of Appeal, said to give an indication of where the line is to be drawn. In Case T 686/99

Lubricant for refrigeration compressors (22 January 2003) the Board considered whether an amendment to claim 1 was permissible pursuant to art.123(2) EPC or whether it added matter relative to the application as filed. The criterion in law is the same as that which applies to the question whether a claim is novel over prior art. The application as filed disclosed a base oil selected from ester oils, alkylbenzene oils and mineral oils, plus the use of either hydrofluorocarbon or hydrochlorofluorocarbon as refrigerant. None of the oils or refrigerants was preferred, so there were six alternative combinations. The amended claim claimed just one of them, an embodiment with ester oil and hydrofluorocarbon refrigerant. The Board held that this contravened art.123(2).

69. In Case T 7/86 *Xanthine derivatives* (16 September 1987) the xanthine claimed in the patent in suit could be derived from the prior art only by selecting from two possible substituents for position 8 of the molecule and from five for position 3, i.e. a total of 10 alternatives. The prior art was held not to deprive the claim of novelty.

This case

70. In the present case, the selection is both from a range, 0.01% – 0.1% and from a list of polysorbates, at least five alternatives. I agree with Celltrion that the skilled team would probably interpret the range of concentrations as a series of alternatives in integers of 0.01%, i.e. 10 in all.

71. I also agree that given the teaching of Liu, the skilled team would think that any one of those concentrations is as good as any other, at least up to 0.05% and probably up to 0.1%. I do not agree that the consequence is that there is really no selection at all. The prior art must, on a correct analysis, provide an individualised description of the invention as claimed, including the relevant value of the element in issue, in order to deprive the invention of novelty.

72. As is clear from the law discussed above, the correct analysis is not just a numbers game. That said, it does not mean that one should shy away from the numbers. The selection in this case is broadly one out of at least 50 alternatives, much higher than the 1 out of 10 in the *Xanthine derivatives* case. The skilled team would not have thought that there is an interrelationship between the range of concentrations of polysorbate and the type of polysorbate. There are no indicated preferences in Liu.

73. Taking all this into account I find that claim 1 of the Patent is novel over Liu.

Anticipation by an equivalent

The Argument

74. Celltrion had an alternative argument on lack of novelty. The scope of a patent claim in relation to infringement includes equivalents of the invention as construed on a normal construction, see *Actavis UK Ltd v Eli Lilly & Co* [2017] UKSC 48. A fundamental pillar of patent law, Celltrion continued, is that the scope of a claim must be the same when assessing its validity. If it were not, all patentees would have a legislative warrant to be an Angora cat (see below on the Angora cat).

75. There can be no varying scope of a single patent claim, Celltrion submitted, because ss.2 and 3 of the Patents Act 1977 require validity to be assessed by reference to the

invention. The invention is defined in s.125(1). It states that the extent of protection conferred by a patent shall be determined by reference to the claim. Section 125(3) provides that the Protocol on the Interpretation of art.69 of the EPC shall apply for the purposes of s.125(1). The extent or scope of protection has been explained by the Supreme Court in *Actavis*, with the Protocol in mind. The scope of protection afforded by a claimed invention must therefore be the same as the scope of the invention when considered under ss.2 and 3. It follows that when applying ss.2 and 3, the assessments of validity and obviousness must be done not just by reference to the invention claimed and interpreted according to a normal construction, but also by reference to equivalents to the invention. If an equivalent lacks novelty or is obvious over the prior art, the patent is invalid.

The Angora cat

76. The Angora cat is an image relayed by Jacob LJ in *European Central Bank v Document Security Systems Inc.* [2008] EWCA Civ 192, at [5]:

> 'Professor Mario Franzosi likens a patentee to an Angora cat. When validity is challenged, the patentee says his patent is very small: the cat with its fur smoothed down, cuddly and sleepy. But when the patentee goes on the attack, the fur bristles, the cat is twice the size with teeth bared and eyes ablaze.'

77. The point of Professor Franzosi's simile, of course, is to emphasise that a patentee cannot have it both ways: the scope of patent when asserting infringement cannot be changed at will to something narrower when defending an attack of lack of novelty or of obviousness. Allowing a patentee to vary the scope of his claim in that way would create an injustice in favour of the patentee.

English authority

78. In *Generics (UK) Ltd v Yeda Research and Development Co Ltd* [2017] EWHC 2629 (Pat), at [163]-[167] Arnold J concluded that a claim would only lack novelty if the prior publication disclosed subject-matter which fell within the claim on a normal construction. It was not sufficient that the subject-matter would infringe the claim applying the doctrine of equivalents.

79. More recently Meade J addressed the point in *Optis Cellular Technology LLC v Apply Retail UK Ltd* [2021] 1939 (Pat), at [252]:

> 'In addition to raising how equivalence should be pleaded, the present case raises the issue of whether, as a matter of law, equivalence is available to broaden a claim as the target for an anticipation attack, or only applied to infringement. This is an extremely important point for UK patent law. It seems certain to need the consideration of the Court of Appeal and very probably the Supreme Court. When it is first ruled on in a case where it is decisive to the result, it will need to be fully argued, including with reference to the law of other EPC jurisdictions and with regard to how and whether people can be prevented from practising the prior art, or if not, how and why not.'

Equivalents and inventive step

80. The correct view on the relevance of equivalents in relation to novelty is connected closely with that in relation to inventive step, but I am here concerned only with an attack of lack of novelty. For simplicity of discussion I will consider only novelty and will do so by reference to product claims.

The alleged injustice

81. The apparent injustice inherent in the Defendants' proposal is that in a claim for infringement the patent monopoly would cover a product which is an equivalent to the claimed invention, yet if that product was made available to the public before the patent's priority date, this will not invalidate the patent for lack of novelty because it is not within the claim according to a normal construction. That would seem to be a violation of what I called the '*Merrell Dow* principle' in *Technetix BV v Teleste Ltd* [2019] 126 (IPEC), at [87]-[88], namely that a patentee should not be able to prevent a person from doing what they had lawfully been entitled to do before the patent was granted.

82. In reality the *Merrell Dow* principle would not be compromised. In respect of infringement the defendant would be entitled to a Formstein defence on the ground that the claim would be deemed not to extend in scope to cover an equivalent that would be anticipated by the prior art. The origin and effect of the Formstein defence is explained in *Technetix* at [93]-[98].

83. Thus, although in principle the scope of a claim is wider when assessing infringement, for all practical purposes the scope of the claim that may be imposed against the world goes no wider than its scope when assessing novelty under s.2. The Angora cat is tamed, no teeth or blazing eyes as described by Professor Franzosi.

84. In *Technetix* I suggested that it would take a judgment of the Court of Appeal or the Supreme Court before the Formstein defence becomes part of English law. As it has turned out, there has so far been no definitive ruling though Birss LJ gave obiter approval to the existence of the defence in *Facebook Ireland Ltd v Voxer IP LLC* [2021] EWHC 1377 (Pat) and it has been assumed more than once at first instance that the defence exists, see *Sycurio Ltd v Pci-Pal plc* [2023] EWHC 2361 (Pat), at [187]-[188] and *Safestand Ltd v Weston Homes plc* [2024] EWHC 2807 (Pat). I think that now it would be more accurate to say that the Formstein defence has become part of English law subject to a ruling to the contrary by the Court of Appeal or the Supreme Court.

The correct analysis of the Formstein defence

85. Before turning to case law of the EPO and EPC Contracting States, a potential point of confusion needs to be clarified. Under the doctrine of equivalents the scope of a claim is expanded to include equivalents of the claimed invention. If, as Celltrion proposes, novelty were to be assessed against the claim with equivalents taken into account, the contents of the prior art *as disclosed* would be compared with the claim including equivalents. Where the disclosure falls within the broader claim, including any equivalents, the claim would lack novelty.

86. I emphasise this because taking equivalents into account would *not* involve considering the prior art as disclosed plus equivalents of the prior art and comparing that broader disclosure with the invention as claimed.

87. I will call the second of these the 'prior art equivalents' approach. It was common ground between the parties that on any view this is not a legitimate means of analysing novelty. The distinction is relevant because of reasoning of authorities from the EPO and EPC Contracting States on which the Defendants relied.

EPO cases

88. If equivalents form part of the scope of a claim when assessing novelty, it would require patent examiners to come to a view about, and take into account, equivalents of the invention during prosecution. Do they?

89. The current edition of the Case Law of the EPO Boards of Appeal (10th ed., 2022) states (at I.C.4.5, p.127-8):

> '**4.5. Taking equivalents into account**
>
> The case law of the boards of appeal is based on a narrow concept of novelty, i.e. the disclosure of a prior document does not include equivalents of the features which are explicitly or implicitly disclosed; equivalents can only be taken into account when it comes to considering inventive step (T 517/90). This narrow concept of novelty, which excludes equivalents, is of particular importance for the application of Art. 54(3) EPC. In T 167/84 (OJ 1987, 369) the board commented that conflicting applications within the meaning of Art. 54(3) EPC 1973 were included in the state of the art solely from the point of view of novelty, but were considered in the light of their "whole contents". In order to mitigate the harsh effects of the "whole contents approach", its application was confined to novelty. Further, in order to reduce the risk of "self-collision", it had always been considered justified to adopt a strict approach to novelty. For this reason, the Guidelines expressly stated that "when considering novelty, it is not correct to interpret the teaching of a document as embracing well-known equivalents which are not disclosed in the document; this is a matter of obviousness" (see Guidelines G-VI, 2 – March 2022 version). According to the case law of the boards of appeal the "whole contents" of an earlier document did not also comprise features which were equivalents of features in the later document (see also T 928/93, T 1387/06). T 167/84 and T 517/90 were applied in T 1657/14.'

90. Although at first sight this seems to be a clear rejection of the notion that equivalents should be included in an assessment of novelty, I think on a fair reading the case book is discussing and rejecting the prior art equivalents approach to novelty. It does not unequivocally follow that the EPO does not take equivalents of claimed inventions into account when assessing novelty, although reference to the importance of the 'narrow concept of novelty, which excludes equivalents' quite strongly implies that it does not.

91. I also note that this passage from the casebook suggests that the Boards of Appeal can and do take 'equivalents' into account when considering inventive step. That on its face is puzzling, but I am not sure what is meant here by 'equivalents'. I think it may mean no more than that subject-matter which is obvious over a prior art document is, of course, taken into account for inventive step.

92. I was not told what the practice of the UKIPO is with regard to novelty and equivalents.

EPC Contracting States

93. The following are authorities from courts of EPC Contracting States to which I was referred.

94. The first was the judgment of the German Federal Supreme Court in Case X ZR 89/07 *Olanzipin*, 16 December 2008:

> '[25] The assessment as to whether the subject matter of a patent is affected by a prior publication that is detrimental to novelty requires the determination of the overall content of the prior publication. It is decisive what technical information is disclosed to a person skilled in the art. … It is therefore not necessary to determine in what form a person skilled in the art can implement a given general teaching, for example with the help of his technical knowledge, or how he can possibly modify this teaching, but only what a person skilled in the art derives from the prior publication as the content of the given (general) teaching. …
>
> [26] … The understanding of what is not explicitly mentioned in the features of the claim and in the wording of the description [of the prior publication], but which is, from the point of view of a person skilled in the art, self-evident or essential according to his general technical knowledge for the implementation of the teaching under protection, does not require any special disclosure (BGHZ 128, 270, 276). This does not aim to supplement the disclosure with technical knowledge, but rather, is no different than when looking at the literal wording of a claim, to determine its meaning, i.e. the technical information, which the skilled reader takes from the respective source in the context of his expert knowledge (Benkard/Melullis ibid, margin number 75). The same applies to the modifications included in the scope of disclosure in the "electric plug connection" decision, which, according to the overall context of the document, are so obvious to a person skilled in the art that they are readily accessible to him when reading attentively, paying less attention to the words than their recognisable meaning, so that he reads them in his thoughts to a certain extent, even if he is not aware of this (BGHZ 128, 270, 276 et seq.). In this context, the word "obvious" may superficially indicate the range of equivalence. However, the term reads makes it clear that it is not about the inclusion of variants, but rather about the technical information that a person skilled in the art receives through a written document in its entirety (cf. Rogge, GRUR 1996, 931, 935). Modifications and further developments of this information are no more a part of the disclosure than those conclusions that a person skilled in the art may draw from the technical information obtained by virtue of his expert knowledge …'

95. This is a discussion about the technical information which the skilled person is deemed to derive from an item of prior art when considering whether that prior art deprives the patent in suit of novelty. Celltrion submitted that the Federal Supreme Court was rejecting an argument that such information includes equivalents to that which is disclosed. I agree. It addresses prior art equivalents, not the issue in hand.

96. On 29 September 2023 the District Court of The Hague gave judgment in Case C/09/634073 *VerifyIP BV v Crystal Clear Codec, LLC*. A cited item of prior art in the case was a published standard, MPEG-4, which referred to a tool for spectral band

replication, the SBR tool. This is a translation of paragraph 5.18 (Verify IP is the claimant, CCC is the defendant):

> 'VerifyIP further argues that, in CCC's view, users of the patented technology could surely not get out of infringement by briefly transforming the decoded signal to a time-domain signal and back to the frequency domain, and then carrying out the rest of the operating steps. That argument misses the point. In MPEG-4, there are more processing steps than just transforming from one domain to another and back after decoding and before the signal is entered into the SBR tool. Moreover, it is not sufficient for lack of novelty that the SBR tool is equivalent to the method according to the patent.'

97. This is a dismissal of an argument on lack of novelty based on the prior art being equivalent to the invention, thus is a rejection of the relevance of the doctrine of equivalents, in the correct sense, to the assessment of novelty.

98. Next is a passage from the Guidelines for Patent and Utility Certificate Applications, published (also in English) by the French Patent and Trade Mark Office (INPI), March 2020:

> '**4.2. Novelty assessment**
>
> Novelty is established if there is no prior art document providing evidence to the contrary.
>
> Conversely, an invention shall be considered to be lacking novelty if the subject matter of the invention, the features of which are defined in the claims, can be found in its entirety in a single document or disclosure.
>
> Thus, for the invention to lack novelty, its subject matter must be found in a single prior art document with definite character, which presents the constituent elements of the invention in the same form, arrangement and functioning, and in order to achieve the same technical result(s).
>
> Thus, the examiner shall not take into account any prior art document that would disclose, for example:
>
> – equivalent means, since switching from a given form to an equivalent form is a matter for inventive step assessment;'

99. This too is a rejection of the prior art equivalents approach.

100. I was shown a short judgment of the *Cour de Cassation*, Commercial Division, of 6 June 2001, Appeal No. 98-17.194, *Galvepor v Société Technel*, specifically this paragraph (in translation):

> 'Whereas in so determining, while in order to be included in the prior art and to be deprived of novelty, the invention must be found in its entirety in a single prior disclosure of certain character, with the same elements constituting it in the same form, the same arrangement and the same operation with a view to achieving the same technical result, the Court of Appeal did not provide a legal

> basis for its decision when it did not find that the closure, which was the subject of the disputed claim, had flaps cut at an angle as in the alleged prior disclosure;'

101. It is not clear to me that this paragraph is discussing any sort of equivalent but if by implication it is, the point being made concerns prior art equivalents.

102. Finally, this is from a translation of the Spanish Examination Guidelines for Patent Applications, March 2023:

> 'For there to be an implicit disclosure, the explicit evidence relied upon by the examiner must clearly state that the missing descriptive elements are forcibly present in the reference document, and would be recognised as such by the person skilled in the subject matter. However, it cannot be established that there is implicit disclosure on the basis of probabilities or possibilities. Therefore, the possibility that a certain aspect might be the result of a certain set of circumstances does not suffice. Well-known equivalents not disclosed in a state-of-the-art document are not taken into consideration for the assessment of novelty, as these pertain to the matter of obviousness or inventive activity.'

103. This joins the majority, being only a statement that equivalents of the contents of a prior art document are not relevant to an assessment of novelty

Discussion

104. Celltrion is right to say that with the exception of the Dutch *Verify IP* case, the authorities from EPC Contracting States do not directly support the Defendants' argument. Yet if the courts and IPOs of the majority were intending to reject the prior art equivalents approach while maintaining that equivalents of the claimed invention were relevant to novelty, I think they would have said so. It is a good deal more likely that in those States the view taken is that no equivalents of any kind are relevant to novelty. It seems clear, at least, that this is the view taken in the Netherlands.

105. As I have said, the description in the EPO case book of the EPO's 'narrow concept of novelty' also implies that no equivalents are taken into account by the EPO when assessing novelty.

106. Looking at the matter from a practical standpoint, I can see why IPOs may not want to consider equivalents of the invention claimed in a patent application. There is no common European approach in law to identifying what is and what is not an equivalent. Introducing equivalents into the consideration of novelty during examination would introduce a layer of complexity into the process that might well be unwelcome – better to leave this to national courts which can each apply their own doctrine of equivalents.

107. In my judgment the equivalents of a claimed invention are not relevant to the assessment of the novelty of the claim. I agree with the courts of the Netherlands. There may be some pedantic satisfaction to be had in making the scope of a claim identical from the perspective of both novelty and infringement, but this is outweighed by practical difficulties that would follow in the train of that view of the law. And there is no practical injustice inherent in the view that equivalents of the invention are irrelevant to an assessment of novelty.

108. I therefore do not accept Celltrion's alternative argument that claim 1 of the Patent lacks novelty because of equivalents of the invention. In my judgment, the argument has no basis in English law.

Inventive Step

109. No issue arose on the law in respect of inventive step.

The Prior Art

110. The prior art relied on by Celltrion was a paper published in the *Journal of Biochemistry*, 132, 591-595 (2002), Biophysical Effect of Amino Acids on the Prevention of Protein Aggregation, Kentaro Shiraki et al. ('Shiraki').

111. Proteins fold into their native structure spontaneously. Under certain conditions they may unfold and refold. During either, undesirable protein aggregation may occur. Professor Shiraki and his colleagues tested the effect of 15 alternative amino acids for their effect on preventing aggregation, primarily using the protein lysozyme as a model system. Arginine exhibited the best results with lysozyme and other proteins:

> 'These results indicated that Arg has the most significant effect on the prevention of aggregation of various kinds of proteins despite differences of pI and molecular weight.'
>
> (pI is the pH value at which the molecule carries no electrical charge).

112. The discussion at the end of the paper includes these observations:

> '(i) The addition of Arg at 200 mM improves heat-induced protein aggregation. … (ii) The addition of Arg at 200 mM also improves dilution-induced aggregation from the denatured form. However, dilution-induced aggregation is related to the balance of folding competition … (iv) Keeping protein concentration low is one of the easiest ways to minimize protein aggregation. Previous reports have suggested that optimum refolding yields can be expected in the range of 10-50 μg/ml.'

113. Three tests are described. The experts agreed that the most relevant of these involved heat-induced aggregation at 98^{o}C.

The Xolair Label

114. The starting point for Celltrion's argument on lack of inventive step was the lyophilised form of omalizumab sold under the name 'Xolair', specifically the information contained in the label which accompanies the product, referred to in the evidence as the 'Xolair Label'. It was agreed that the information formed part of the CGK and that by extension liquid omalizumab made by reconstituting the lyophilised product, which I will call 'Liquid Xolair', and its constituents, were CGK.

115. The Defendants argued that the Xolair Label was not a permissible starting point because it had not been pleaded as such. I think there is nothing in this. Cited prior art is usually the starting point because it has been chosen as the closest prior art to the invention in suit. An item of CGK can be relied on by itself for an attack of

obviousness. I see nothing wrong in taking as the relevant hypothesis that the skilled team has the Xolair Label primarily in mind and then reads Shiraki at the priority date of the Patent. The question is whether, having done so, the skilled team would contemplate an antibody formulation falling within claim 1.

116. Even looked at the other way, i.e. starting with Shiraki, it seems to me legitimate to argue that the skilled team would perceive its most promising use to be in the modification of the Xolair Label formulation, providing a possible solution to a known potential problem of the stability of a liquid formulation.

117. Starting with the formulation of Liquid Xolair, three changes would be required to arrive at the formulation of claim 1: (i) the addition of Arginine-HCl, (ii) the adjustment of anti-IgE antibody from a concentration of 125 g/l to 'about 150 g/l' as in claim 1 and (iii) whereas Liquid Xolair has 0.03% polysorbate 20, claim 1 has 0.04%.

The relevance of technical contribution to obviousness over prior art

118. Celltrion argued that in resolving the issue of obviousness over Shiraki it is important to appreciate that the differences between claim 1 of the Patent and Shiraki were in each case nothing more than arbitrary changes of no technical value. Lack of technical contribution is a separately pleaded ground of invalidity and I think that it should be kept distinct from the first pleaded ground of obviousness – that making a claim 1 formulation was obvious once the skilled team had read Shiraki. The two are conceptually different.

119. In principle an invention may offer no advantage over the prior art but be hidden among many other alternatives such that it would not have been contemplated by the skilled person and was therefore not obvious over the prior art.

120. Lack of technical contribution is more a policy reason for not allowing a patent monopoly, a breach of the bargain at the core of patent law – the grant of a monopoly in return for contributing (and sufficiently disclosing) a technical advance in the art.

Knowledge of arginine in relation to formulating a protein

121. A point arose regarding the CGK. Professor Trout was asked about work he was carrying out with colleagues at the time of filing date of the Patent, September 2005. He was referred to a paper published in 2005. Its abstract begins:

> 'The amino acid arginine is frequently used as a solution additive to stabilize proteins against aggregation, especially in the process of protein refolding. Despite arginine's prevalence, the mechanism by which it stabilizes proteins is not presently understood. We propose that arginine deters aggregation by slowing protein-protein association reactions, with only a small concomitant effect on protein folding.'

122. Professor Trout said that part of the innovation of the paper was to introduce into the field of protein formulation an understanding from the separate field of bioprocessing, in which one of his co-authors, Professor Daniel Wang, had expertise, namely that arginine is frequently used to stabilise proteins. Bioprocessing is the use of a living

source to achieve a desired process, such as the use of microorganisms in the production of pharmaceuticals or in sewage treatment plants.

123. I have no reason to doubt Professor Trout's evidence on this, but it was not made clear whether the introduced idea was the use of arginine as an additive to stabilise proteins, or the prevalence of arginine as an additive for that purpose. When giving evidence about Shiraki, Professor Trout said:

> 'I think, and I think this came out yesterday, arginine had been well known to be used in refolding, and I think Shiraki, with the studies done, which I think are, you know, they seem to be good experiments, they were done properly, although there are some issues with the data presentation, would have reinforced the use of arginine for protein refolding.'

124. The overall burden of Professor Trout's evidence was that the skilled formulator would have been aware of the possible use of arginine to facilitate refolding as part of the CGK, but the prevalence of its use for that purpose was confined to the world of bioprocessing.

125. It was part of the acknowledged CGK that proteins are unstable in aqueous solution and degrade by a variety of routes, including aggregation. Professor Dalby said, and it was not contested, that aggregation was the first thing to go wrong as he concentrated a protein. It is the major and most common mechanism of instability. Therefore there was an incentive to add one or more excipients which would have the effect of decreasing the propensity of the protein in question to aggregate.

Inventive step over Shiraki

126. Shiraki states that the addition of Arg at 200 mM reduces heat-induced protein aggregation and that this applies to various kinds of proteins despite differences of pI and molecular weight.

127. The work done in Shiraki differed from any work that would lead to a formulation of omalizumab in the following respects:

(1) Aggregation in Shiraki is induced by heating the protein to 98^{o}C, whereas the formulation process of the Patent would be conducted at room temperature or under cooler conditions (Professor Trout said that 2-8^{o}C could be used).

(2) None of the proteins tested in Shiraki was an antibody of any sort and, as Professor Dalby accepted, it was part of the CGK that an excipient which reduced the aggregation of one protein would not necessarily have the same effect on another protein.

The overall arguments

128. Celltrion submitted that the skilled team considering a liquid formulation of omalizumab would not have started with a blank page. The formulation of the Xolair Label would have been the appropriate starting point. The skilled team would have been very aware of a potential problem of aggregation. Shiraki would have offered a potential solution to that problem, recommending the use of 200 mM arginine.

129. Professor Dalby's evidence for Celltrion was that with this potential solution in mind, so starting with the Xolair formulation, the skilled team would have created about 6 different formulations with three different molarities of arginine: 150, 200 and 250 mM, plus histidine buffer, some with and some without sucrose and all with 0.03% polysorbate (as in the Xolair Label). There would also have been a control with no arginine. This was referred to in the evidence as the 'Dalby Screen'.

130. Celltrion said that the Dalby Screen required only quick and easy bench chemistry and I did not understand that to be disputed. This is the content of the screen (without the no-arginine control):

Sample No	Target [mAb]	pH	Buffer (mM)	Arginine (mM)	Sucrose (%w/v)	Polysorbate 20 (%w/v)
1	125 mg/ml	6.0	15.4 mM (L-histidine hydrochloride monohydrate / L-histidine)	150 mM	8.98%	0.03%
2	125 mg/ml	6.0	15.4 mM	150 mM	0%	0.03%
3	125 mg/ml	6.0	15.4 mM	200 mM	8.98%	0.03%
4	125 mg/ml	6.0	15.4 mM	200 mM	0%	0.03%
5	125 mg/ml	6.0	15.4 mM	250 mM	8.98%	0.03%
6	125 mg/ml	6.0	15.4 mM	250 mM	0%	0.03%

131. Professor Dalby said that Shiraki would lead the skilled team to believe that samples 3-6, with at least 200 mM arginine, would sufficiently limit aggregation.

132. The differences between claim 1 and samples 3 and 4 are (i) a concentration of omalizumab at 150 rather than 125 mg/ml and (ii) 0.04% instead of 0.03% polysorbate 20.

133. Sample 3, unlike sample 4, has sucrose. Sucrose is also present in the Xolair Label as a stabilizing factor. Professor Dalby's idea so far as sucrose was concerned was to test whether its presence was a necessary, or at least an important factor in maintaining stability of a liquid formulation – i.e. restricting aggregation. If not, it could be omitted. Both experts said that if stability was achieved without the need for sucrose, in principle the fewer excipients used the better. Further, sucrose led to greater viscosity which could be undesirable.

134. Celltrion argued that the changes needed to go from sample 4 of the Dalby Screen to claim 1 of the Patent were of no technical significance. Accordingly, a formulation within the scope of claim 1, incorporating those two arbitrary changes, would have been obvious to try with a reasonable expectation of success.

135. The Defendants' overall argument was that Shiraki would not have prompted the skilled team to try making a liquid formulation at all. Even if it had, the team would not have

carried out the Dalby Screen or anything similar and so would not have arrived at anything within claim 1. A number of points arise.

Whether making a liquid formulation was an unrealistic goal

136. In his first report Professor Trout said that the skilled team would never have embarked on a project to make a liquid formulation of omalizumab irrespective of anything learned from Shiraki. He gave three reasons.

137. First, the skilled team would have inferred from presence of the lyophilised formulation, Xolair, on the market that those working in the field had been unable to make a liquid formulation.

138. Secondly, the target concentration of 125 mg/ml, as found in Liquid Xolair, was much higher than the figure of 50 mg/ml, the highest concentration for an antibody liquid formulation available at the priority date (the concentration of liquid Humira).

139. Thirdly, a liquid formulation would have been perceived to pose a risk of anaphylaxis (a severe, possibly life-threatening allergic reaction).

140. I find none of these reasons persuasive. Professor Trout maintained the first in cross-examination but also agreed that the fact that a lyophilised formulation has come to market before a liquid formulation would not be taken to mean that a liquid formulation was not feasible or would not follow the lyophilised version on to the market – there would be no expectation either way. It seems to me that this latter point must be correct. It would be fair to infer nothing more than that for technical or commercial reasons or both, it had been simpler to make a lyophilised formulation and market that first. This was Professor Dalby's view. There could be no inference that everyone working in the field had abandoned the goal of a liquid formulation especially since, as was common ground, a liquid formulation was the more commercially desirable.

141. Professor Trout accepted that the fact that Humira was marketed in a concentration of 50 mg/ml could have meant nothing more than that it was convenient to the manufacturer to use that concentration rather than a higher one. Nor could the skilled team have extrapolated from the characteristics of one antibody the characteristics of others. It was common ground that a concentration of 125 mg/ml or higher for omalizumab was likely to present challenges, see the section of the common statement of CGK quoted above. The evidence overall did not indicate that 150 mg/ml was so ambitious as to be rejected as a target not worth pursuing.

142. With regard to anaphylaxis, Professor Trout laid particular emphasis of the risks inherent in a liquid formulation. But he agreed that while the risk of degradation leading to a risk of anaphylaxis upon administration was a matter which would have to be monitored in the case of a liquid formulation of omalizumab, this was just as true in the case of a reconstituted lyophilised formulation. This equivalence of monitoring suggests that the undoubted concern about the possibility of anaphylaxis was not a reason to abandon the idea of a liquid formulation.

Temperature and the amount of unfolding

143. There was an issue about degrees of unfolding and refolding. The studies conducted in Shiraki on heat-induced unfolding involved heating the protein to a temperature of 98^{o}C, causing them not just to unfold but to denature and aggregate. The process was likened to what happens to egg white when an egg is poached.

144. Professor Trout said that Shiraki was discussing aggregation during protein refolding after there has been a complete unfolding of the protein due to the high temperature used. He contrasted this with the lower temperatures at which the formulation of omalizumab would take place, where there would be only partial unfolding of the protein.

145. Professor Dalby said this in his first report:

> 'Shiraki refers to aggregation studies, with which the Skilled Formulator would be very familiar. It also refers to studies regarding the re-folding of protein, which is unlikely to be something that the Skilled Formulator would be considering when formulating a biopharmaceutical, …'

146. Professor Dalby's observation that the skilled formulator would not be concerned with refolding when formulating a biopharmaceutical – it is to be inferred that he included omalizumab – seems to confirm Professor Trout's evidence that the partial unfolding which can occur at modest formulation temperatures and any subsequent refolding is not the sort of unfolding and refolding that Shiraki was discussing.

147. It would have been apparent to the skilled team that the high temperature process used in Shiraki to generate aggregation had no direct application to the task of reformulating a protein. Professor Dalby thought that the skilled formulator would nonetheless believe that if arginine limits aggregation under the conditions used in Shiraki, it would be promising as a means of reducing aggregation at lower temperatures with more limited unfolding, refolding and therefore limited aggregation.

148. Professor Trout looked at this differently: the skilled formulator would have been concerned with aggregation at levels of a few percentage points. The relevant graph in Shiraki showed the aggregation of lysozyme over time due to a temperature close to boiling. After a few minutes without arginine, aggregation occurred at 5-10% and then continued to climb rapidly. With arginine, even after those few minutes there was a marked reduction in aggregation. Professor Trout's point was that the resolution of the graph was insufficient to show what was going on at the early stages of low-level aggregation and whether arginine had a significant effect at those low levels. The graph told the skilled team nothing about the effect of arginine on aggregation at the sort of low temperatures in play during formulation of a protein like omalizumab.

149. I accept the evidence given here by both Professor Trout and Professor Dalby, which was not inconsistent. I find that the skilled team would not have regarded the experiments in Shiraki as providing direct evidence that arginine would have an effect by way of the prevention of aggregation during the reformulation of a protein. On the other hand, Shiraki provided encouragement that it would.

Protein size

150. The Shiraki team used model proteins, principally lysozyme, not antibodies. A monoclonal antibody such as omalizumab is about 2-3 times larger than the largest protein tested by the Shiraki team. On the other hand, Shiraki states that arginine has the most significant effect on the prevention of aggregation of various kinds of proteins despite differences of pI and molecular weight.

151. Professor Trout said that this indication on Shiraki notwithstanding, the skilled team would not think that using 200mM arginine would be a good starting point in the search for an excipient to reduce aggregation. The use of extreme temperatures and the fact that there was still a significant degree of aggregation indicated in Shiraki, even with arginine, would not encourage the skilled person to believe that 200 mM arginine would be satisfactory in the formulation of omalizumab.

152. Professor Dalby acknowledged that the results with the eight proteins with which arginine was tested in Shiraki provided no certainty as to the effect of arginine with omalizumab. But in his view, the very positive effect of arginine in reducing aggregation in five out of eight cases shown in Shiraki, there would be a strong possibility that arginine would have a positive effect with any other protein. He added that there would be some expectation for arginine to succeed with another protein, including larger proteins such as an antibody. He also said that Shiraki 'just screams out with a new possibility' for stabilising a liquid formulation of omalizumab.

153. The experts were looking at this issue from opposite directions. Professor Trout identified reasons why the skilled team would not be encouraged to believe that arginine would sufficiently reduce aggregation. I accept that there were such reasons. But in my view Professor Dalby's approach was the more realistic one: Shiraki offered no guarantees and certainly would not have led the skilled team to believe that arginine was bound to be the ideal agent for reducing aggregation, but the paper indicated that arginine was worth trying when contemplating a formulation of liquid omalizumab. Whether this would have screamed out does not much matter. I interpret Professor Dalby's evidence to mean that he believed that there would have been a reasonable expectation that arginine would satisfactorily limit aggregation and I accept that evidence.

Shelf life

154. A satisfactory limit to aggregation implies a temporal factor. I have found that a liquid formulation within the meaning of claim 1 must be stable from the point of manufacture to the point of administration. That would have been very much in the mind of the skilled team as would the associated potential problem of maintaining a sufficient limit on aggregation for the whole of the required period.

155. For the reasons I have discussed above, Shiraki's recommendation of arginine as the excipient that could solve the problem offered nothing close to a guarantee but made arginine worth trying with a reasonable expectation of success.

The Dalby Screen

156. As explained above, Professor Dalby's evidence was that once a decision had been taken to try arginine as an excipient to limit aggregation, the skilled team would have prepared alternative samples along the line of those in the Dalby Screen. He said that

the team would have used a concentration of 125 mg/ml because that was used in the Xolair Label and resulted in a satisfactory liquid formulation when the product was reconstituted. He accepted that it may have been necessary to carry out pre-formulation work but maintained that this would have been a route worth trying with a reasonable expectation of success.

157. In cross-examination Professor Trout's criticism of the Dalby Screen was not that it was a bad idea to try alternative formulations, but that he could think of other formulations that could have been tried.

158. It seems to me reasonable to suppose that the skilled team would have tried alternative formulations and I accept that something like the Dalby Screen would have been tried since it is based on Liquid Xolair and takes into account that although arginine was being assessed as a stabilizer, it was appropriate to see whether sucrose was also required, a reasonable precautionary step.

The concentration of omalizumab

159. This is from Professor Dalby's first report:

> '9.4 In order to be comfortable moving forward with a concentration of 125 mg/ml the Skilled Formulator would ideally want to achieve close to 150 mg/ml before precipitation. This solubility 'headroom' would provide an initial indication that the target 125 mg/ml would have the desired stability. The Skilled Formulator would have carried forward the candidates in which acceptable solubility and viscosity were maintained with 'headroom' above 125 mg/ml and then moved on to evaluate stabilities.'

160. In cross-examination Professor Dalby said that he had not tried making the samples of the Dalby Screen himself. He conceded that the figure of 150 mg/ml to provide 'headroom' was arbitrary – it could have been less.

161. Professor Trout rejected the notion of 'solubility headroom' and going for 150 mg/ml:

> '… the Skilled Formulator would have understood that there were real challenges associated with achieving such high protein concentrations in a liquid formulation – to the extent that the Skilled Formulator was minded to target 125 mg/ml … I do not consider that the Skilled Formulator would have tried to concentrate as high as 150 mg/ml with any expectation that this could ultimately be used in a stable liquid formulation. Increasing the protein concentration would only serve to amplify the challenges (which would already have been seen to be considerable). Even if the Skilled Formulator did make the formulation up to about 150 mg/ml, the purpose of this would be to test the target concentration of 125 mg/ml rather than because 150 mg/ml would be taken forwards. In other words, 150 mg/ml would be a transient concentration and the Skilled Formulator would not have expected it to be the basis of a stable liquid formulation.'

162. I find the evidence of Professor Trout more persuasive on this point. Professor Dalby's evidence was a speculation that he was entitled to make but his reasons for the 'solubility headroom' were not supported by reference to CGK material which adopted

such an approach. Professor Trout provided convincing and unchallenged reasons why the skilled formulator would not have embarked on the creation of the headroom. Even if he or she had done, Professor Dalby conceded that the headroom could have been lower than 150 mg/ml and lower than the range around 150 mg/ml which, as I have found, the skilled team would interpret to correspond to 'about 150 mg/ml'.

163. I find that the samples that would have been tried by the skilled formulator, along the lines of the Dalby Screen, would – just as the Dalby Screen does – have stuck to 125 mg/ml for the concentration of omalizumab.

Polysorbate 20

164. Celltrion's argument with regard to the amount of polysorbate was that the skilled formulator would have believed that there is no technical difference between using 0.03% and 0.04% and therefore it would have been obvious to use 0.04%.

165. However, in cross-examination he accepted that there would be a preference to reduce the amount to the lowest satisfactory amount and that Liu indicates that this would turn out to be 0.01%. It was put to Professor Dalby that in his evidence given in the United States he had emphasised the unpredictability of varying the amount of polysorbate with regard to its likelihood of causing aggregation or auto-oxidising. He said that his evidence in the US was related to very particular facts. I do not have enough information to reach a clear view on that.

166. Professor Trout thought that the skilled formulator would have believed that the figure of 0.04% in claim 1 had been selected for a reason compatible with suitability for therapeutic application and bio equivalency trials.

167. I find that, given the hypothesis of starting with the Xolair Label formulation, the skilled formulator would either have used 0.03% polysorbate 20, as appears in the Dalby Screen, or had any change been contemplated it would have been downwards, towards 0.01%, not upwards.

What was obvious to try

168. Celltrion's case was that the skilled team would have been inspired by Shiraki to adapt the formulation of the Xolair Label to make a liquid formulation of omalizumab, i.e. it would have been obvious to try, and there would have been a reasonable expectation of success.

169. It is important to be precise about what, if anything, would have been obvious to try. I take the view that the skilled team would have been inspired by Shiraki to try arginine as an excipient to prevent or reduce aggregation in a liquid formulation of omalizumab. I accept that the starting point would be the formulation of Liquid Xolair, so that it would have been obvious to try adding arginine. I also find that alternative formulations would have been tried resulting in something like the Dalby Screen.

170. This would have been done by the skilled team with a reasonable expectation of success in finding a liquid formulation of omalizumab which is both sufficiently stable and is suitable for administration to patients as a treatment for asthma.

171. There was some argument about whether such an expectation would have been below or above 50%. In my view no such precise cut-off applies. Resolving the statutory question of obviousness potentially invites consideration of many factors, notably those identified by Lord Hodge in *Actavis Group PTC EHF v ICOS Group* [2019] UKSC 15, at [65]-[73], and possibly others. All that are relevant must be borne in mind in the required multi-factorial assessment. It was common ground in the present case that 'obvious to try with a reasonable expectation of success' is an important criterion, but not the only one. The motivation to find a marketable liquid formulation was high. It was part of the agreed CGK that liquid formulations were preferred and more marketable than lyophilised formulations, see the section of the statement of agreed CGK quoted above. The agreed CGK also sets out several disadvantages associated with lyophilised formulations. The higher the motivation, the lower is the expectation of success required for that expectation to be reasonable.

172. In my judgment it would have been reasonable for the skilled team to expect that a modification of the Xolair Label formulation, with arginine, would give rise to arrive at a liquid formulation of omalizumab which is both sufficiently stable and is suitable for administration to patients as a treatment for asthma. Whether the expectation was above or below 50% does not matter.

173. However, it would not have been obvious to try a formulation with about 150 g/L omalizumab, or with 0.04% polysorbate 20. The evidence indicated that the skilled team would have had no reason to depart from the figures in the Xolair Label for those components, or at least not such as to arrive at the figures of claim 1. No expectation in relation to the claim 1 formulation would have arisen one way or the other.

Conclusion on inventive step over Shiraki

174. It follows from what I have said that claim 1 of the Patent does not lack inventive step over Shiraki. Leading counsel for the Defendants said more than once that the invention claimed is 'an incredibly narrow invention'. I agree. The scope of claim 1 (and thus each of the claims) is tied closely to the stated concentrations of omalizumab and polysorbate. But at least in relation to Shiraki there is an invention.

Lack of technical contribution

175. The Defendants suggested that the short point in relation to technical contribution is the strong inference that Celltrion would not be wasting time and money on seeking to revoke the Patent unless the particular formulation of the Patent was technically advantageous. Counsel did not go so far as to say I should take that short cut and stop there. Rightly, because it could just be, for instance, that there are purely commercial pressures for an alleged infringer to use the invention, pressures which have nothing to do with any technical contribution made by the invention, although I would add that no such commercial pressures were identified in the present case.

176. Professor Trout said this in his second report:

> '70. In paragraph 11.2 of Dalby 1, Professor Dalby refers to the choice of buffer/excipients, their concentration, and the pH. In my opinion, the Skilled Formulator would not consider a formulation just as a list of separate excipients and concentrations. Instead, they would be interested in the formulation as a

> whole. In the context of EP 248, the Skilled Formulator would understand the claimed formulation to be a pharmaceutical formulation containing a very high concentration of E25 which is suitable for administration to patients.'

177. In closing, Celltrion quoted and focused just on the words as the end: 'a pharmaceutical formulation containing a very high concentration of E25 which is suitable for administration to patients', stating that this was the technical contribution identified by the Defendants. Celltrion argued that identifying the mere idea of a concentration of 150 g/L omalizumab in a formulation was not a technical contribution that justified an invention.

178. The alleged technical contribution advanced by the Defendants is not that. It is the identification of a formulation of omalizumab which is suitable for administration to patients, this being a formulation having all the integers of claim 1.

179. I have found that there was nothing inventive in identifying the use of arginine as an excipient in an omalizumab formulation and to vary the formulation of the Xolair Label accordingly. I have also found that it would not be obvious to vary the Xolair formulation to include omalizumab in a concentration of 150 g/L and 0.04% polysorbate 20. The question is whether the technical contribution, being the formulation of claim 1 including those concentrations, justifies a claim to the formulation identified.

180. The principle was summarised by Birss J in *Takeda UK Ltd v F. Hoffman-La Roche AG* [2019] EWHC 1911 (Pat):

> '[204] One way in which this principle has been applied in the context of inventive step is to deny validity to a selection from the prior art "which is purely arbitrary and cannot be justified by some useful technical property". Such a selection "is likely to be held to be obvious because it does not make a real technical advance". These passages are taken from Floyd L.J. in *Generics UK Ltd (t/a Mylan) v Yeda Research & Development Co. Ltd* [2013] EWHC Civ 925; [2014] R.P.C. 4, citing Jacob L.J. in *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2009] EWCA Civ 1362; [2010] R.P.C. 9.'

181. The formulation of claim 1 of the Patent is not on its face arbitrary since the Defendants say that this particular formulation is suitable for administration to patients in the treatment of asthma, a clearly desirable characteristic.

182. Celltrion submitted that the disclosure said to justify the invention claimed must be assessed by reference to the five questions identified by Birss J in *Takeda*, at [207]:

> 'In relation to each disclosure there are five questions to answer: Is it disclosed in the patent? Is it plausible? Is it true? Is it a technical advance? Does it support claims of the breadth they are?'

183. There is no dispute that the disclosure in question is disclosed in the patent. Regarding plausibility, Celltrion argued that the facts of this case were analogous to those of *Sandoz Ltd v Bristol-Myers Squibb Holdings Ireland Unlimited Co* [2022] EWHC 822 (Pat), upheld on appeal [2023] EWCA Civ 472, without taking me to either judgment. The Defendants equally briefly said that it was not analogous. I think the Defendants

are right. In *Bristol-Myers* Meade J found that there was not even a bare assertion in the description of the patent in suit that the product in issue had the advantage said to justify the invention claimed in relation it. There was data, but none of it related to that product. By contrast, in the present case, as was common ground, the relevant assertion in respect of the claim 1 formulation is made. Moreover, the evidence clearly supports the plausibility of the assertion as would have been in the mind of the skilled person. It was put to Professor Dalby that this was an empirical field, the reader of the Patent was told that the formulation works, he or she would not necessarily know why but would have no reason to believe that it does not. Professor Dalby said that this was true. Professor Trout stated that the skilled formulator would have understood – I take him to have meant that it would have been seen as plausible – that the claimed formulation is suitable for administration. On that evidence, the disclosure in question would have been plausible.

184. It was common ground that the disclosure was true. Regarding the fourth question, there was a technical advance in that unlike the Xolair product the disclosure is of a liquid formulation.

185. As to the final question, Celltrion relied on evidence from Professor Dalby that the skilled person would not have seen the rationale of choosing the figure of about 150 g/l omalizumab in claim 1 as opposed some other concentration. This is not to the point. The need for any rationale must relate to the formulation as a whole, not just the concentration of omalizumab and as I have found, the assertion of the advantage of that formulation over the prior art would have been seen to be plausible.

186. I have also found that the breadth of the claim is very narrow. In my judgment that narrow breadth is supported.

187. Claim 1 is not obvious on the ground that the invention claimed makes no technical contribution to the art.

Insufficiency

188. Celltrion's argument on insufficiency depended on claim 1 covering formulations with histidine salts other than histidine-HCl. I have found that it does not. The attack of insufficiency fails.

Added matter

189. This short point made by Celltrion under this head was that the claims of the application for the Patent (PCT publication no. WO 2006/031560 A2 'the Application') contained only process claims. Therefore so far as products were concerned, the disclosure was limited to formulations made by the processes disclosed. Taking claim 1 of the Patent as an example, Celltrion argued, the new matter disclosed in the Patent is that product made by any means, i.e. divorced from the process for making it disclosed in the Application.

190. This would be a good point if the relevant disclosure of the Patent were confined to the claims. It is not. The summary of the invention disclosed in the Application begins:

> 'In general terms, the present disclosure generally relates to processes for concentrating proteins, such as processes for concentrating antibody preparation, pharmaceutical formulations containing such a preparation, and there [sic] use human therapy or animal therapy.'

191. The reader is thus told that what follows will include the disclosure of formulations as such. The formulation of claim 1 is explicitly disclosed three times: at page 21 of the Application lines 34-35, at p.37 lines 9-10 and at p.39 lines 18-19. On each occasion it is identified as the final formulation of a process set out in preceding passages. In my view on each occasion the notional reader of the Application would understand that a particular formulation was clearly being disclosed as such, in other words a formulation howsoever created.

192. The Patent is not invalid on the ground of added matter.

Conclusion

193. The Patent is valid and infringed.