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Case No: HP-2018-000008

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

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

Date: 17/07/2019

**Before** :

**MR JUSTICE BIRSS**

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**Between :**

| | |
|---|---|
| **Takeda UK Limited** | **Claimant** |
| **- and -** | |
| **F. Hoffmann-La Roche AG** | **Defendant** |

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**Andrew Waugh QC**, Joe Delaney and Georgina Messenger (instructed by **Bird & Bird**) for the **Claimant**
**Richard Meade QC**,William Duncan and Thomas Jones (instructed by **Marks & Clerk**) for the **Defendant**

Hearing dates: 12th -14th, 17th - 21st, 23rd - 27th June 2019

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# Approved Judgment

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

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MR JUSTICE BIRSS

**Mr Justice Birss :**



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*Introduction*

1. This is a patent action concerning European Patent (UK) EP 2 007 809 entitled "Glycosylated Antibodies". The patentee is the defendant Roche. The claimant Takeda has a product called Entyvio which is approved for ulcerative colitis and Crohn's disease. The product is a formulation of a monoclonal antibody called vedolizumab. Roche claims that vedolizumab infringes the patent. Takeda denies infringement and claims the patent is invalid. The action started with Takeda bringing a claim for revocation.

2. The patent was filed on 10th April 2007 claiming its earliest priority from a European filing EP 06007565 on 11th April 2006. The patent was granted on 12th September 2012. It was opposed by GSK and Novartis. In decision T1784/15 of 22nd June 2017 the Technical Board of Appeal of the EPO upheld the validity of the patent with slightly amended claims. The B2 specification was published on 12th September 2018. The claims in this case are the claims upheld by the EPO. By the time the matter came before the Technical Board of Appeal Novartis had settled with Roche. GSK attended the hearing as an observer but did not present oral submissions.

3. Claim 1 is in this form:

> Monoclonal antibody of human IgG1 or IgG3 type being glycosylated with a sugar chain at Asn297,
>
> said antibody being characterized in that the amount of fucose within said sugar chain, related to the sum of G0, G1, G2 without mannose 4 and mannose 5 as 100% and as analyzed by Liquid Chromatography/Mass Spectrometry (LCMS) peptide map analysis is at least 99%
>
> and in addition the amount of NGNA within said sugar chain, related to the sum of G0, G1, G2 without mannose 4 and mannose 5 as 100% and as analyzed by Liquid

> Chromatography/Mass Spectrometry (LCMS) peptide map analysis, is 1% or less,
>
> and the amount of N-terminal alpha 1,3 galactose within said sugar chain related to the sum of G0, G1, G2 without mannose 4 and mannose 5 as 100% and as analyzed by Liquid Chromatography/Mass Spectrometry (LCMS) peptide map analysis is 1% or less.

4. The clauses in claim 1 have been separated out for clarity. Claim construction will be addressed below but right away one can see that the claimed antibody is characterised by three relative quantities of things within the sugar chain.

5. Claims 2 to 9 are:

> 2. Antibody according to claim 1, characterized in that the amount of NGNA is 0.5% or less.
>
> 3. Antibody according to claims 1 or 2, characterized in that the amount of N-terminal alpha 1,3 galactose is 0.5% or less.
>
> 4. Antibody according to claims 1 to 3, characterized in that the antibody is a chimeric, humanized or human antibody.
>
> 5. CHO cell line DSM ACC 2795.
>
> 6. Use of an antibody according to claims 1 to 4 for the manufacture of a medicament.
>
> 7. Pharmaceutical composition comprising an antibody according to claims 1 to 4.
>
> 8. Use of a CHO cell according to claim 5 for the recombinant production of a monoclonal antibody according to claims 1 to 4.
>
> 9. Method for the recombinant production of a monoclonal antibody according to claims 1 to 4 in a CHO cell according to claim 5.

6. An amendment to claim 1 was proposed but that was dropped shortly before trial.

7. The issue of infringement turns on claim construction and questions of fact about the properties of vedolizumab. If vedolizumab is within claim 1, no other infringement issue arises. If it infringes claim 1, vedolizumab would also infringe claims 2, 3, 4, 6 and 7. These are the only relevant claims. The other claims (5, 8 and 9) are all limited to a particular deposited cell line DSM ACC 2795 which Takeda does not use.

8. In terms of validity, Takeda advances a large number of attacks. Many of them interrelate to some extent in that they arise from what Takeda contends is the lack of any technical contribution to the art made by the disclosure in the patent. The grounds on which validity is challenged are:

i) Lack of novelty over:

a) International Patent Application WO 2005/040221 A1 published 6th May 2005 ("Bihoreau");

b) The article by Shinkawa et al entitled "*The Absence of Fucose but Not the Presence of Galactose or Bisecting N-Acetylglucosamine of Human lgGl Complex-type Oligosaccharides Shows the Critical Role of Enhancing Antibody-dependent Cellular Cytotoxicity*" (2003) in the Journal of Biological Chemistry, Vol.278, No.5, Issue of January 31, pp 3466-3473, 2003;

c) The article by Ferrara et al entitled "*The Carbohydrate at FcγRIIIa Asn-162 An Element Required for High Affinity Binding to Non-Fucosylated IgG Glycoforms*" published in The Journal of Biological Chemistry Vol.281, No.8 pp.5032-5036

d) A prior use by the company Novartis of chimeric monoclonal antibody known as basiliximab (trade name Simulect). This was advanced in the EPO opposition and supported by declarations given the numbers D57, D58 and D59.

ii) Lack of inventive step:

a) On the basis of lack of technical contribution;

b) Bihoreau;

c) Simulect;

iii) Insufficiency:

a) Ambiguity in that the skilled person cannot identify what calculation is required by the claims;

b) Ambiguity in that the skilled person cannot know whether they are carrying out the right test to find out if they are within the claims;

c) A breadth of claim argument linked to lack of technical contribution;

d) A classic insufficiency argument linked to deposited cell line DSM ACC 2795.

9. When the case was opened Takeda also relied on a paper by Jun et al. published in Applied Microbiology & Biotechnology (2005), vol. 69, pp.162-169 but that was dropped during the trial.

10. Further insufficiency grounds were pleaded however the points made are addressed within the ones set out above. The point on the deposited cell line DSM ACC 2795 was, Takeda argued, that when reconstituted the deposited cells do not produce antibodies within the claims. That point is not a free standing basis for a finding of invalidity of any of the relevant claims but it is relevant as a squeeze.

11. In terms of the relevant claims, claim 4 is not said to be independently valid. Also claims 6 and 7 stand or fall together.

*Terminology*

12. The critical feature of claim 1 is the requirement for at least 99% fucose. In evidence there were at least five different ways of calculating that quantity. It is sometimes important to appreciate which method is being used when referring to a given number. One may not know of course. Although it will make things a bit cumbersome at times, when necessary the figures will be used with a label. The detailed explanations for the labels will come in context. The labels are:

    i) "99%-Roche" – means 99% calculated using the method advanced by Roche as its primary case on construction of claim 1.

    ii) "99%-Takeda" –means 99% calculated using the method advanced by Takeda as its primary case on construction of claim 1.

    iii) "99%-TRM" – means 99% calculated using the method advanced by Roche as a modified version of the Takeda method. It is Roche's fall back alternative case for the construction of claim 1.

    iv) "99%-Shields" – means 99% calculated by the method used in a seminal common general knowledge paper called Shields.

13. A further method ("99%-Morris") was advanced by the Professor in his oral evidence.

*The witnesses*

14. Takeda called four fact witnesses: Caterina Farnleitner, Prof. Friedrich Altmann, Pamela Brauer and Anne Kowal.

15. Ms Farnleitner is the Business Development Manager at InVivo BioTech Services GmbH. InVivo was engaged by Takeda to source a publicly available sample of deposited "clone 5" for the purposes of making a recombinant antibody in accordance with the patent. Ms Farnleitner explains where the clones were sourced, how the cells were stored upon receipt, how they were revitalised and that they were cultured and the expressed recombinant antibody was purified, as described in Part A of Takeda's Notice of Experiments. Ms Farnleitner's evidence was not cross-examined.

16. Prof. Altmann is a Professor of Natural Resources and Life Sciences at BOKU University in Vienna. He was engaged by Takeda to perform an LCMS peptide map analysis on the "clone 5" samples sent to him by InVivo in May 2018. His evidence is to confirm that peptide map analysis was performed under his supervision as described in Part B of Takeda's Notice of Experiments. Prof. Altmann was not cross-examined.

17. Ms Brauer is a Scientist at Millennium Pharmaceuticals. Millennium developed Entyvio and were acquired by Takeda. From around 2004 Ms Brauer was part of the team responsible for supporting the development of vedolizumab into a commercial product. Ms Brauer is the scientist who conducted the experiments to develop and screen for the CHO cell line that became the cell line that was ultimately used in the commercial production of vedolizumab. Ms Brauer explains that she did not screen for

the level of fucosylation of the antibodies, and (in her second statement) explains how MTX was used in the process. Ms Brauer was not cross-examined.

18. Dr Kowal is a Senior Director of Analytical Development at Millennium. Dr Kowal was involved with the vedolizumab development project since she joined Millennium in 2004. She attests to the accuracy of Takeda's Product and Process Description. Her evidence concerns the glycosylation and ADCC activity of vedolizumab through various stages of its development and goes to reply to the experiments performed by Roche. She explains that the clone chosen for the Master Cell Bank was not screened for the level of fucosylation of the antibody.

19. Roche called a single fact witness Dr Bastian Zimmermann. His statement was produced under a CEA notice. Dr Zimmermann performed the Surface Plasmo999n Resonance (SPR) experiments reported in Roche's Amended Notice of Experiments and attests to the methods used and the results obtained.

20. Takeda called three expert witnesses: Professor Carolyn Bertozzi, Professor Falk Nimmerjahn and Professor Max Crispin. Takeda also served evidence from Professor Michael Butler of the University of Manitoba but decided not to call him as a witness. This decision was communicated to Roche and the court in the evening of the second day of trial, while Prof Bertozzi was being cross-examined. The timetable of the trial had to be reorganised accordingly.

21. Prof. Bertozzi has been Professor of Chemistry at Stanford University since 2015 and is also Professor of Radiology and Chemical & Systems Biology at the same institution. She has been an investigator at the Howard Hughes Medical Institute since 2000. Her PhD was in 1993 at Berkeley. Today Prof. Bertozzi is a Fellow of the US National Academy of Sciences and a Foreign Member of the Royal Society. She is on the Board of Directors of Eli Lilly.

22. During her PhD Prof. Bertozzi developed a research interest in the role of glycoconjugates in the targeting and binding of cell-surface receptor-specific ligands. Today Prof. Bertozzi is an expert in protein glycosylation and has experience relating to recombinant antibody production and immunology. Prof. Bertozzi gave evidence across the breadth of the case.

23. Prof. Nimmerjahn is the Professor and Chair of Genetics in the Department of Biology at the University of Erlangen-Nuremberg. Prof. Nimmerjahn reviewed Roche's surface plasmon resonance experiments but also gave evidence on wider issues about antibody function.

24. Professor Crispin is the Professor of Glycobiology at Southampton University. He reviewed the data produced as part of Takeda's Notice of Experiments on clone 5 and data from the work underlying the patent which was produced by Roche in disclosure.

25. Roche called evidence from two experts, Prof. Paul Parren and Prof. Howard Morris.

26. Prof. Parren is a Professor of Molecular Immunology at the Leiden Medical Center in the Netherlands. He has over 25 years of experience in the field of immunotherapy and biotechnology. Prof. Parren has worked in both academia and also in industry,

particularly at Genmab. His particular expertise and experience is in antibodies, in particular in antibody glycosylation and the development of antibody therapeutics.

27. Prof. Morris is the Emeritus Professor of Biological Chemistry and a Senior Research Investigator at Imperial College, London, a Fellow of the Royal Society and a recipient of the Royal Medal. Prof. Morris is a distinguished expert in the field of biomolecular mass-spectrometry, in which field he has worked for over 40 years. Prof. Morris has pioneered the field of Glycoproteomics, a sub-discipline in mass spectrometry.

28. Each side made various submissions about the other party's experts designed to justify discounting their evidence to a greater or lesser extent. The main points were a focus on the way they had been instructed, the way the reports were written and the references included (or not), the details of their expertise and the manner in which they answered questions. I did not find any of these lengthy submissions helpful in resolving the matters I have to decide. That does not mean all the evidence was prepared in a perfect manner (some certainly was not) but none of those points assist me. Having read the reports and listened to the cross-examination, in my judgment all the witnesses in this case were highly experienced scientists who were expressing their honestly held views seeking to help the court to understand the issues in order to decide this case. I am grateful to each of them for their evidence. Some of the topics some witnesses covered were further from their core area of interest than some others, however each witness was amply qualified to comment upon all the areas that witness addressed. The fact the recent experience of some experts (such as Prof. Bertozzi) was in managing a team which carried out detailed work did not disqualify them from giving evidence.

*The skilled person and the common general knowledge*

29. In this case the skilled person is a team. The areas of expertise they would cover are antibody glycosylation, including glycoprotein analysis and detection; recombinant antibody production, in particular the use of cellular expression systems for the production of monoclonal antibodies; and immunology, in particular knowledge and expertise relating to antibody structure and antibody effector functions (including ADCC (see below)).

30. There was a debate about the level of analytical expertise. The debate was, I think, actually a proxy for an argument about the experts. In my judgment the team would either have sufficient expertise themselves to carry out whatever glycoprotein analysis was required or they would have access to that expertise either directly or by approaching a third party.

31. The relevant common general knowledge in this case is very extensive. It includes the following topics:

    i) The use of monoclonal antibodies as therapeutic agents;

    ii) How to make antibodies for therapy and for research relating to therapy;

    iii) The biochemistry of antibodies - particularly glycosylation, its nature and importance, the various monosaccharides and oligosaccharide structures encountered;

iv) Immunology and in particular antibody effector functions; and

v) Techniques for analysing glycosylation.

32. Fucose is one of the monosaccharides found in glycosylation patterns on proteins, including antibodies. Others are GlcNAc, galactose, mannose and sialic acid. The fucose is usually found attached to the GlcNAc which is bound to the asparagine (Asn) in the protein chain (N-linked glycosylation). In antibodies the relevant glycosylation is bound to Asn-297, that is the Asn at position 297 in the chain. The oligosaccharide structure may branch to form a biantennary structure. These structures contain a number of different monosaccharides including GlcNAc, mannose, galactose and (perhaps) fucose. One kind of structure is called a complex biantennary structure. It is one of the main types in this case. A different structure consists essentially of mannose alone. These are called higher mannoses. Higher mannoses themselves are thought to contribute to ADCC. There are also structures called hybrids which contain one arm like a complex biantennary and the other arm like a higher mannose type.

33. A particular aspect of common general knowledge which bears a focus is antibody dependent cellular cytotoxicity (ADCC) and what was known about its relationship with fucosylation. ADCC is an effector function which is triggered when an antibody binds to its target cell. The target binding is by the variable region of the antibody which makes it specific to that target. At the other end of the antibody is the constant region, which is the same for all antibodies. When the antibody binds the target, the constant region can then interact with other cells in the immune system such as NK (natural killer) cells. Those NK cells go on to attack the target cell to which the antibody is bound. So if an antibody recognises a pathogen cell, the NK cells will be triggered to attack it. The target cell is lysed (split open). This simplistic description is sufficient for present purposes. NK cells are not the only cells which can do this. ADCC will not be triggered by one antibody binding to the target, it may need many antibodies to bind and the triggering process will be statistical in nature. The trigger involves an interaction between the constant region and a receptor on the relevant cell (such as the NK cell). One relevant receptor is the FcγRIIIa receptor. There are others.

34. A paper by Shields et al was common general knowledge. It was published in 2002 in the Journal of Biological Chemistry with the title "*Lack of Fucose on Human IgG1 N-Linked Oligosaccharide Improves Binding to Human FcγRIIIa and Antibody-dependent Cellular Toxicity.*" The authors were from Genentech (now part of Roche). The paper explored the relationship between the level of fucosylation of the antibody and ADCC. The properties of a number of antibodies with different levels of fucosylation are reported. They include antibodies with 98% fucosylation (that is 98%-Shields) as well as levels as low as 4% (see Table 1). The Shields % is simply the proportion of all the glycans which are fucosylated glycans. The paper showed that there was an inverse correlation between ADCC and fucosylation, such that a low level of fucosylation enhances ADCC. This would be useful if, for example, the therapeutic antibody is used to treat cancer. That is because it might mean that the antibody with a low level of fucosylation will have a greater propensity to kill cancer cells at a given concentration than the same antibody with a higher amount of fucosylation.

35. Figure 6 of Shields is:

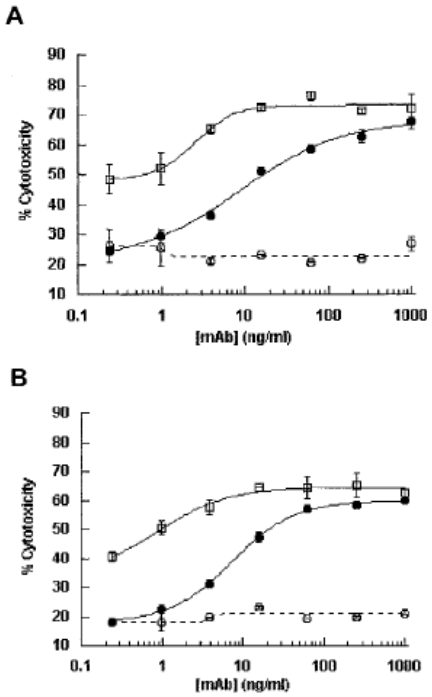



FIG. 6. **ADCC assays using anti-HER2 Hu4D5 mAbs, SK-BR-3 cells as target, and PBMCs as effector cells.** The effector/target ratio was held constant at 30:1, and [mAb] varied. *A*, representative plot for one of three FcγRIIIA(Val$^{158}$/Phe$^{158}$) donors. *B*, representative plot for one of three FcγRIIIA(Phe$^{158}$/Phe$^{158}$) donors. *Open squares*, Hu4D5 Lec13-A; *filled circles*, Hu4D5 CHO-S; *open circles*, spontaneous lysis. Each assay was performed in duplicate with *error bars* shown.

36. Taking either plot A or B, the open circles represent spontaneous lysis, in effect a background level of cell death. The filled circles are the antibodies expressed in CHO-S cells with a high fucosylation (98%-Shields) whereas the open squares are the same antibody but expressed in Lec13 cells, which give a much lower level of fucosylation. The experiment looks at the effect across a range of concentrations and one sees an S-shaped curve with a plateau (more or less) at each end (perhaps cut off for Lec-13). So at the lowest concentration the antibody with low fucosylation still exhibits ADCC (40% or 50%) whereas the ADCC produced by the same antibody with a high level of fucosylation is down to background. Or, putting it another way the concentration of antibody to give a 50% ADCC effect is about 0.2 ng/ml for low fucosylation but about 20ng/ml for the high fucosylation. 100 times as much antibody is needed to get the same effect.

37. Roche submitted that the utility of a low level of fucosylation was really the limit of what was common general knowledge from Shields. This was put to Prof Bertozzi. She did not agree. I accept this part of her evidence. While it is true that the text of the paper does not focus on this, nevertheless the skilled person understood as a matter of common general knowledge that Shields also demonstrated implicitly that the converse was the case, namely that a high level of fucosylation was associated with a reduction of ADCC.

38. Moreover for the skilled person this latter point was something with potential therapeutic relevance too. Prof Bertozzi's evidence was that this was obvious to the skilled person. They knew there were kinds of therapeutic antibodies for which ADCC would be useful, such as anti-cancer therapies, but there were also kinds of antibodies for which ADCC was not only not useful but was actually undesirable because they did

not rely on effector functions for their therapeutic efficacy. The skilled person would not want to kill the cells to which these latter kind of antibodies are bound if they could avoid it. An example was antibodies targeted at autoimmune diseases. I have considered whether Prof Bertozzi's evidence (by reference to something being "obvious") justifies a finding that this is part of the common general knowledge. In my judgment it does because what she was explaining was the thinking process of the skilled person.

39. Roche relied on an answer given by Prof Bertozzi that it was impossible to say based on Shields what would happen if one went from 98% fucosylation to 100% fucosylation. The reason for her answer was that this is an empirical art and she wanted to see a dose response curve across a range of concentrations.

40. Another common general knowledge approach to abolishing effector functions such as ADCC was to make mutations to the amino acid sequence in the constant region. There were known mutations called LALA and LAGA. The former means that two amino acids, both L (leucine), at positions 234 and 235 in the constant region are changed to A (alanine), hence L→A, L→A. LAGA is similar ($L_{235}$→A and $G_{237}$→A). G refers to glycine.

*Making antibodies*

41. In this section I address what would happen when a skilled person (really a team) sets about making an antibody. Essentially the same point comes up in different places in this case.

42. At the priority date in 2006 a skilled person (team) using only their common general knowledge and without knowledge of the patent would have no undue difficulty at all making an antibody to a given target antigen. Starting from an amino acid sequence of an antibody they would be able to make a suitable vector to transfect a suitable cell line, such as CHO cells. The cell line would be grown and clones made and selected. Amplification using methotrexate selection would be used if need be.

43. Starting from a given target, i.e. an antigen, they would be able to raise antibodies to that target, select a suitable antibody to that target and carry out the necessary genetic engineering to produce an amino acid sequence for it. If they wanted to target a particular epitope, again they could do that. If they wished to do so they could make antibodies of this kind which were chimeric, humanized or human antibodies. They could make a pharmaceutical composition comprising such antibodies and they could use them for the manufacture of a medicament comprising the antibody. In this brief paragraph is encapsulated an enormous amount of work of a fairly large team of well funded people. However all of it is common general knowledge and none of it involves an undue burden either in the context of sufficiency or novelty. In that sense the simple phrase "a pharmaceutical composition of a human antibody to target X" is an enabling disclosure. None of this is especially controversial.

44. Roche contended that as a matter of common general knowledge the skilled person would expect to see fucosylation of 90-95% coming out of CHO cells as a matter of course and would have no expectation of being able to use CHO cells to produce antibodies fucosylated to a higher degree, particularly >99%. They relied in Prof Parren's evidence to that effect. That was his evidence in his report and he supported

it by reference to a review article *van Berkel et al* published in 2009 of which he was also an author. He did not say the paper was common general knowledge but he said it was reflective of the common general knowledge. Roche contended that the cross-examination of Prof Parren on this issue did not directly challenge his view and did not establish that anything put to him was common general knowledge.

45. Roche accepted that it was not impossible to produce CHO clones which fully fucosylated. Roche also made clear that it was not saying that such a thing was perceived at the priority date to be impossible. Roche also explained that there was nothing special about methotrexate selection steps. A special way of carrying out methotrexate selection does not give rise to an ability to produce >99% antibodies. The relevance of that concession was that it had seemed, I think in the EPO, that Roche was contending that the fact the example in the patent used a one step methotrexate selection method rather than a stepwise method could be significant. However the evidence is very clear that it was not significant at all. One step methotrexate selection is not a special technique. It is not a reason why the approach disclosed in the patent, which is conventional, might produce >99% fucosylation. Nor do I accept that to achieve this requires other special techniques such as the over-expression of fucosyl-transferase.

46. In his report Prof Parren said that the team would have no expectation that they could get antibodies higher than 95%. I do not accept that evidence, whichever way of calculating the 95% it refers to. Shields reports fucosylation levels of 98% and was part of the common general knowledge. Moreover the numerical ranges in fact overlap since an antibody can be both above 99.0% fucosylation by the patent method(s) and below 98.0% by the Shields method. There was no evidence at all that the skilled person's common general knowledge included a perception that the values in Shields were the upper limit of what was possible in CHO cells. There was nothing special about the concept of a product with any level of fucosylation, all the way up to 99%-Shields, 99.5%-Shields or 100%-Shields. The skilled person did not, as a matter of common general knowledge, know of a product with those levels of fucosylation but they had no prior expectation that such a thing was impossible or particularly difficult to make. Whether they would have a reason to make it is another matter.

47. As I have said a skilled person who wished to make an antibody with a particular level of fucosylation has no expectation that they would have difficulty doing so. They know what they have to do. The knowledge and the expectation are common general knowledge. Assuming the level of fucosylation was high, the way they will do it is to transfect a CHO cell line such as CHO DG44 and produce a population of clones. The skilled person could readily screen this population. They would produce a large number of clones, the exact number being up to the skilled person. Among the clones will be a Gaussian distribution of different fucosylation levels. That is common general knowledge. The distribution means that the extremes are less common than the mean, but it also means that the more clones you make, the more likely it is that you will include clones at the extremes. Takeda put evidence to Prof Parren that when Roche scientists did this they found 8 subclones producing at >99% out of a population of subclones of about 1,200. He did not quarrel with a description of this as a relatively small number of subclones. In my judgment that is reflective of the common general knowledge. It is all just a matter of numbers. If you want a higher level of fucose (or for that matter a lower level) from a given CHO cell line, you know you simply have

to make enough clones to cover the ends of the Gaussian distribution. Moreover the number required is not unusually large from the skilled person's point of view.

48. In particular I find that a skilled person, given an instruction or motivation to make an antibody with a fucosylation level as high as 99%-Shields (which will necessarily be at least 99%-TRM) and without any knowledge of the patent, can do so without an undue burden in the manner described above. It is a lot of work but the burden is not undue.

49. I do not doubt that Prof Parren was right that the skilled person would "usually expect to see" levels of 90-95%. That does not mean the skilled person thought those figures represented some sort of limit to CHO cell fucosylation. I have seen no evidence from contemporary papers which would back that up and in my judgment they did not think any such thing. Rather Prof Parren's evidence simply reflects that that was what workers did. If they had no reason to select more highly fucosylated clones then they would not do so.

50. In terms of analytical techniques, a wide range was referred to in evidence but in the end only a few mattered. I will deal with them in context.

*The patent and claim construction*

51. The patent is entitled "Glycosylated Antibodies". Paragraph [0001] states that the patent concerns a particular glycosylation pattern on a recombinant antibody where the antibody is fully fucosylated.

52. Paragraphs [0002] to [0006] set out the background. They explain that monoclonal antibodies exhibit various different effector functions: ADCC, phagocytosis, and CDC. There is also reference here to half life/clearance rate but it is common ground that is not an effector function. The patent explains that ADCC and phagocytosis are mediated via cell bound antibodies via the interaction with FcγR and that a known method of dealing with this is to modify the constant domains of the antibodies to improve effector functions. Mutations mentioned in paragraph [0004] include the LALA mutation and a mutation at position 297. Paragraph [0006] sets out a list of publications. One of them is Shields. In referring to some of the papers, the patent identifies the amount of fucosylation or afucosylation reported. The highest fucosylation mentioned is 94% (a paper by Mori). The method by which these values are calculated is not stated.

53. Everything in [0002] to [0006] is common general knowledge.

54. The summary of the invention section starts at paragraph [0007] which sets out claim 1. Reading this paragraph with paragraph [0001], the reader would see that a fully fucosylated antibody is one which has 99% fucosylation as determined by the claimed method. The skilled reader would understand that the low levels of NGNA and N-terminal alpha 1,3 galactose (α-Gal) referred to make sense because those species are immunogenic in humans and thus low levels were desirable for a therapeutic antibody.

55. Paragraph [0008] states:

> "According to the invention 'amount' means the amount of said sugar within the sugar chain at Asn297, related to the sum of G0,

> G1, G2 (without mannose(4 and 5) as 100% and as calculated in example 3."

56. There is a stray bracket in this paragraph. The simplest way of dealing with that is to ignore the open bracket between "G2" and "without". This passage is telling the reader how to calculate the amounts referred to in the claim. Those are of fucose, NGNA and α-Gal and plainly the calculation for each of these species should correspond to one another. What the paragraph really adds to the claim is the clause at the end which refers to example 3.

57. Paragraph [0009] states that "according to the invention it is possible" to provide antibodies with a fucosylation of "even" 99.4% or more up to 99.9% or more. These numbers are clearly calculated in the same way as the 99% limit in claim 1.

58. Most of paragraphs [0010] to [0023] are consistory clauses for the dependent claims. Paragraph [0014] refers to the deposited clone and states that this cell line is capable of producing an antibody according to the invention. Paragraph [0020] refers in general terms to the selection technique of growing DHFR deletion mutants of CHO cells under selective pressure and selecting a clone which produces the desired antibody. This is common general knowledge.

59. The detailed description starts at paragraph [0025]. It explains about the carbohydrate structures attached to antibodies as N-linked structures, and that IgG1 and IgG3 antibodies have a conserved site at Asn297 where complex-biantennary glycans are attached, whose presence is essential to ADCC. This topic is returned to at [0035] where the glycosylation leading to the core-fucosylated biantennary complex oligosaccharides terminated with up to two galactose residues is described. These are described as being designated as G0, G1 or G2. This terminology deviates from standard usage but it is clear enough.

60. Paragraph [0028] is relevant:

> "[0028] The term "antibody" encompasses the various forms of antibodies including but not being limited to whole antibodies, antibody fragments, human antibodies, humanized antibodies and genetically engineered antibodies as long as the characteristic properties according to the invention are retained. Therefore an antibody according to the invention contains at least a functionally active (FcR binding) Fc part of lgG1 or lgG3 type comprising glycosylated Asn297."

61. This defines the term "antibody" to include "various forms of antibodies" provided that the "characteristic properties according to the invention are retained" and that "an antibody according to the invention contains at least a functionally active (FcR binding) Fc part of IgG1 or IgG3". This latter expression is at the heart of one of the two infringement issues and I will address it below.

62. From [0029] until [0060] the description covers antibody technology, glycosylation, production and selection in CHO cells and other matters. Nothing turns on the details in that section, all of which would be familiar and unremarkable to a skilled reader.

63. The examples start at paragraph [0062]. First the cell line used is described. They are CHO-DG44 cells. This is a conventional cell line. Then at paragraph [0064] the details of the plasmid used to transfect the cells are set out. The particular antibody to be made is identified (at [0064]) as an antibody against IGF-1R (Insulin-like Growth Factor 1R). An earlier published patent application is cited as a reference for it (PCT application published as WO 2005 005635). Example 1 is transfection and selection while example 2 is cultivation and purification. These are standard techniques. There was a possible point about the fact that there is no stepwise amplification in Example 1 but the evidence was clear that this was unremarkable.

64. Paragraph [0067] refers to selecting clones providing defucosylation of 2.0% or lower referring to total molar oligosaccharide amount. Although nothing turns on it, I understand that method of counting to be different from the one in the claim and to be the same as the one in the common general knowledge paper, Shields. Eight clones were chosen and eight antibodies made and analysed.

*Patent – Example 3*

65. Example 3, from [0069] onwards describes the analysis of the glycostructure of the antibodies. Paragraph [0069] itself describes how the antibodies were analysed. It was "by Liquid Chromatography/Mass Spectrometry (LCMS) Peptide map analysis". Samples were reduced, carboxymethylated and cleaved with trypsin. The mixture of peptides and glycopeptides was separated using RP-HPLC and "analysed online with electrospray mass spectrometry". The results are in Table 2:

| Relative amount of glycosylation variants | | | | | |
|---|---|---|---|---|---|
| Clone No. | G0 [%] | G1 [%] | G2 [%] | NonFuc[%] | Man1 [%] |
| 1 | 38,4 | 51,4 | 10,2 | 0,1 | 0,5 |
| 2 | 44,3 | 47,6 | 8,1 | 0,1 | 0,6 |
| 3 | 42,8 | 48,7 | 8,5 | 0,2 | 0,8 |
| 4 | 49,2 | 43,6 | 7,2 | 0,3 | 1,2 |
| 5 | 62,7 | 33,0 | 4,3 | 0,6 | 1,0 |
| 6 | 60,4 | 35,5 | 4,2 | 0,5 | 1,2 |
| 7 | 40,4 | 49,8 | 9,8 | 0,3 | 0,6 |
| 8 | 46,9 | 45,9 | 7,3 | 0,3 | 1,1 |

66. It will be seen that the numbers in the three columns G0, G1 and G2 on their own add up to 100% (save for a bit of rounding for clones 6 and 8). Paragraph [0070] of the patent is obviously meant to explain some of the text in the table. It explains that "Man" refers to "High mannose structures bearing four and five mannose residues respectively". It also explains that "G0, G1 and G2" refer to reduced heavy chains with fucosylated biantennary complex type carbohydrate "with 1, 2, or 3 terminal galactose residues". That is an obvious typographic error and the skilled reader would understand the inventors meant to say "with 0, 1 and 2 terminal galactose residues". The term non-Fuc means reduced heavy chains with biantennary complex type carbohydrate without fucose.

67. Paragraph [0071] explains that the deposited CHO cell line DSM ACC 2795 is clone 5.

68. Paragraph [0073] explains that LCMS peptide map analysis was done by integration of the specific ion chromatograms of all charge states for all glycopeptides. In other words the analysis aimed to take into account all the glycopeptides found.

69. The patent then sets out two tables, Tables 3a and 3b, which are said to be exemplary calculations related to clones 3 and 5 respectively. Table 3a is:

| | Area z=2 | Area z=3 | Area z=4 | Sum | rel. amount% |
|---|---|---|---|---|---|
| H27_G0 | 616 | 198 | 0 | 814 | 28,7 |
| H27_G1 | 734 | 425 | 0 | 1158 | 40,9 |
| H27_G2 | 103 | 135 | 0 | 238 | 8,4 |
| H27_G3 | 0 | 0 | 0 | 0 | 0,0 |
| H27_G4 | 0 | 0 | 0 | 0 | 0,0 |
| H27_G1_1NGNA | 0 | 0 | 0 | 0 | 0,0 |
| H27_G2_1NGNA | 0 | 0 | 0 | 0 | 0,0 |
| H27_G2_2NGNA | 0 | 0 | 0 | 0 | 0,0 |
| H27_G3_1NGNA | 0 | 0 | 0 | 0 | 0,0 |
| H27_G3_2NGNA | 0 | 0 | 0 | 0 | 0,0 |
| G0 minus GIcNAc and minus | 0 | 57 | 0 | 57 | 2,0 |
| G0 minus GIcNAc | 330 | 0 | 0 | 330 | 11,7 |
| G1 minus GIcNAc | 208 | 0 | 0 | 208 | 7,4 |
| Man5 | 22 | 0 | 0 | 22 | 0,8 |
| G0 minus Fuc | 5 | 0 | 0 | 5 | 0,2 |
| G1 minus Fuc | 0 | 0 | 0 | 0 | 0,0 |
| Man4 | 0 | 0 | 0 | 0 | 0,0 |
| Total | | | | 2833,15 | 100,00 |
| rel. amount of glycostructures with NGNA | | | | | 0,0 |
| rel. amount of glycostructures with Galactoses (G3 and G4) | | | | | 0,0 |
| rel. amount of high mannose | | | | | 0,8 |
| rel. amount of G0 minus Fuc and G1 minus Fuc | | | | | 0,2 |
| | | | | | |
| Sum G0 | | | | | 42,4 |
| Sum G1 | | | | | 48,2 |
| Sum G2 | | | | | 8,4 |
| Total Sum | | | | | 99,0 |
| Related to 100% G0-1-2 | | | | | |
| G0 | | | | | 42,8 |
| G1 | | | | | 48,7 |
| G2 | | | | | 8,5 |
| | | | | | |
| Sum without Man | | | | | 99,2 |

| | |
|---|---|
| Sum G0/1 minus Fuc | 0,2 |
| Relative amount without Fuc | 0,2 |

70. Then Table 3b deals with clone 5 in a similar way, with the same list of seventeen glycan species. There is no need to set out Table 3b. However given the centrality of the calculation method in this case, it is worth analysing the tables with a little care. Strikingly, nowhere in the tables nor anywhere in the text of the patent, is there a statement of the value for the amount of fucose for any of the 8 clones calculated in the manner required by claim 1.

71. In both tables 3a and 3b the areas referred to are peak areas and z refers to the charge state. The skilled reader would interpret this table as showing all the glycan species which were found in the analysis. A figure of 0.0 for some of them would be understood to mean that that glycan was detected but the quantity found was either too low to measure reliably or the amount rounded to 0.0.

72. The first thirteen glycan species in the table are fucosylated. Consistent with the skilled person's understanding of what is produced by CHO cells, species with NGNA saccharides were low to undetectable. The last three of the thirteen fucosylated species (G0 minus GlcNAc and minus Man, G0 minus GlcNAc, and G1 minus GlcNAc) are fragments. Some or all of them may be artefacts of the LCMS process.

73. The four glycans in the list before the total are not fucosylated. That includes two mannose species (Man 4 and Man 5) and two complex biantennary glycans (G0 minus Fuc and G1 minus Fuc). The total amounts of all the species in this part of the table sum to 100%.

74. Turning to Table 3a in particular, the table then states the relative amounts of four groups including "high mannose" (at 0.8) and of the afucosylated species G0 minus Fuc and G1 minus Fuc (at 0.2). Those two numbers correspond to the values in Table 2. The table then shows that the totals for the fucosylated species G0, G1 and G2 are added up (including the fragments) to produce three numbers stated as "Sum G0" etc. Next the "total sum" is given as 99.0 – which is the total of the fucosylated glycan species in the original list.

75. The three fucosylated glycan sums are then adjusted to add up to 100% and three figures are given (G0 as 42.8 etc.). These three numbers correspond to the numbers for G0, G1 and G2 in table 2 (clone 3). The table ends with three quantities, each of which relate back to the full list of relative quantities of the various species. "Sum without Man" seems to be simply 100% minus the % amount of Man species. The second quantity, "Sum G0/1 minus Fuc", is the sum of G0 minus Fuc and G1 minus Fuc and comes to 0.2 (because 0.2 + 0.0 = 0.2). Prof Morris then explains in his first report (paragraph 170) that the final value, "Relative amount without Fuc", (which is mentioned in paragraph [0077]) is actually the ratio of the previous two figures but since 99.2 is so high, when expressed to one decimal place the figure is still just 0.2.

76. Roche's approach to calculating the amount of fucose in accordance with the claims, as well as the Takeda approach and Roche's modification of the Takeda approach all produce the same answer when applied to Table 3a. The result using the numbers in

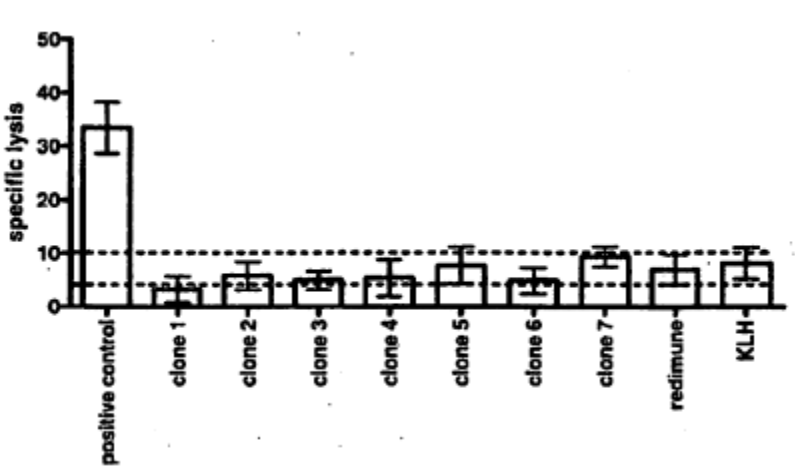
the patent is a figure of 99.8% for clone 3 (it is the "total sum" divided by the "sum without Man" expressed as a % (99.0/99.2 rounded to 1 decimal place)). The Shields approach would give 99.0%. For clone 5 based on Table 3b the Roche/Takeda/TRM value for amount of fucose is 99.4% (=98.4/99.0) whereas the Shields figure for clone 5 would be 98.4%. Rounded to no decimal places 98.4% is 98%-Shields.

*Patent – Example 4*

77. Example 4 is entitled "Determination of antibody mediated effector functions by anti-IGF-1R HuMAbs". Paragraph [0078] explains that studies were done to determine the capacity of the antibodies to elicit ADCC. Paragraph [0080] explains that suitable cells were cultured and plated and then antibodies added "at a final concentration ranging from 25-0.1 ng/ml". This would be understood to indicate a titration of the dose of antibody by serial dilution down from 25ng/ml to 0.1 ng/ml. It indicates that a number of doses in that range were tested. The effector cells were added and the magnitude of cell lysis expressed as a % of the maximum release of TDA caused by lysis with detergent. Paragraph [0081] then states:

> "As reference standard of an antibody showing "no ADCC" is used an (monoclonal) antibody against KLH (keyhole limpet hemocyanin) or an lgG mixture isolated from about 35.000 donors ("Redimune"). A 75% fucose free antibody against IGF-IR was used as positive control. An antibody according to the invention showed a TDA release which is within 3xSD of the TDA release of the standard antibody (Fig.1)."

78. The skilled reader would understand that the reason no ADCC is in inverted commas is likely to be because, as a matter of common general knowledge there will always be some TDA release / cell lysis in this sort of experiment. That is shown in figure 1 since the error bars for the results for the negative control antibodies KLH and redimune are above zero. Figure 1 is set out below along with the legend for it which appears at paragraph [0024]:




[0024] Figure 1 is a bar chart showing the ADCC activity or lack thereof in antibodies of the invention and in control and comparative antibodies.

79. The horizontal dashed lines are not explained. They may correspond to the error bars for Redimune and/or they may be intended to represent the 3 standard deviations referred to in the passage quoted above from paragraph [0081]. In any case one can see that the seven clones referred to give values with error bars all of which overlap with the negative controls. The reader would assume the y-axis is the % referred to in the text. The positive control antibody, which has 25% fucosylation (75% fucose free) elicits ADCC at a level in this assay of 28-38%. There is no statement of the antibody concentration at which these results were obtained.

*Claim construction*

80. Claim 1 calls for a monoclonal antibody of IgG1 or IgG3 type. Although the word antibody is something the skilled reader is very familiar with, the reader would understand that it is used in a special sense defined by paragraph [0028]. That takes one to one of the two arguments about construction (below). The claim also contains a requirement to calculate the relative amounts of fucose, NGNA and α-Gal, by relating the sum of the fucosylated/NGNA/α-Gal species to the sum of G0, G1 and G2 (i.e. the complex biantennary glycans) without mannose 4 and mannose 5 as 100%. This latter point takes one to the other disputes on construction (below).

81. In each case the amounts are measured by LCMS peptide map analysis and there is a debate about the scope of that term, although some aspects are clear. The common general knowledge includes various ways of determining the oligosaccharide content of a glycoprotein. One method involves digesting the protein chain into short peptides, extracting the peptide to which the glycan chain is attached and then using that to further analyse the sugars themselves. That is peptide map analysis. One could instead cleave the sugars off the protein altogether before analysing them. That is another approach but it is not peptide map analysis.

82. LCMS means Liquid Chromatography Mass Spectrometry. This involves using a liquid chromatographic technique to try and separate individual species for analysis and a mass spectrometer to characterise the species found. In the description at paragraph [0069] the patent explains that the work which was done used an "online" LCMS technique. This means the LC column is connected directly to the mass spectrometer and in effect the machine works as a single unit. However the word online is not in the claim. While reserving the right to contend in other courts that the claim covered techniques which are not online, Takeda did not argue that point here. They were content to argue their case on the footing that the focus was on online methods. Three online techniques are in issue: LCMS with Orbitrap, micro LCMS with Q-TOF, and nano LCMS with Q-TOF. Orbitrap and Q-TOF are different ways of measuring the charge/mass ratio of the samples in the mass spectrometer. Orbitrap is an ion trap method in which the ions orbit in a confined space. Q-TOF uses a time of flight technique to make the measurement. Nano and micro refer to the bore of the chromatography instrument. The reason for these three being in issue is simply that they are each mentioned in a paper by Reusch et al which reported on a comparison of methods of analysing antibody glycosylation profiles. The paper was published well after the priority date, in 2015. The authors were either at Roche or at Leiden University. I will come back to that under insufficiency.

83. Claim 2 changes the relative amount of NGNA required to be 0.5% or less and claim 3 changes the relative amount of α-Gal to be 0.5% or less.

*What is an antibody within claim 1?*

84. The key paragraph [0028] is quoted above. The reader would understand that the patentee intended to exclude from the claim some things which one might otherwise have called an antibody. They are only antibodies within the claim as long as they retain the characteristic properties of the invention. These "characteristic properties" are not explained and on its own that risks being circular, particularly since the point of what is disclosed is the idea of not having a property (the causing of ADCC) which antibodies have. Roche contends it just means very high fucosylation. I will accept that.

85. The last sentence explains that the antibody must at least have a functionally active (FcR binding) Fc part of an antibody, with glycosylation at Asn 297. So the last sentence at least excludes unglycosylated antibodies and excludes certain antibody fragments such as Fabs (which have no constant region at all).

86. Takeda contended that the last sentence excludes an antibody with an Fc region in which the sequence contains a mutation, such as LALA or LAGA, which abolishes ADCC. That antibody is said not to have a functionally active Fc region since the receptor binding by the Fc region is the activity which causes the effector functions such as ADCC. Roche did not agree, arguing that there is nothing in the patent to exclude a case in which two means of reducing or eliminating ADCC are used (say both LALA and high fucosylation). That may or may not be so, but it remained unclear to me what Roche's case actually was as to what the claim did mean. In my judgment the reader would understand that these words describe a positive feature which an antibody must have in order to be within the claim. It must have a functionally active (FcR binding) Fc part. If it does not have that, it is outside the claim. But how can an antibody which (say) abolishes the effector function of ADCC still have a functionally active Fc part? In my judgment the explanation is that this is talking about the amino acid sequence and it is linked to paragraph [0004], which expressly refers to mutations to the amino acid sequence which can have an effect on binding to the Fc receptor. In other words Takeda is correct that the passage would be understood to exclude antibodies with a mutation such as LALA or LAGA if they make the Fc part cease to be functionally active.

87. Roche is correct that mutations to reduce ADCC are specifically mentioned in paragraph [0004] but not correct that this means the patent would be understood as not excluding antibodies with two means of reducing or eliminating ADCC. By including language which could exclude antibodies with mutations like LALA the patentee is avoiding the very problem which arose in this case of trying to decide what is causing the abolition of ADCC – how much is due to LALA and how much due to fucosylation.

88. However the language also makes clear that functionally active means FcR binding. It is not necessary to do a functional assay such as an ADCC assay. Rather one needs to examine receptor binding. I will revisit this on infringement.

*99% amount of fucose*

89. The question is whether the claim means 99%-Roche, 99%-Takeda or 99%-TRM. All three operate as a fraction (expressed as a percentage) based on a numerator consisting

in effect of fucosylated glycans and a denominator which is in effect 100-X, where X is related to the amount of higher mannose glycans.

90. Taking 99%-Roche first, the Roche method is that for the numerator one only examines glycans found in table 3a or 3b of the patent (the list is the same). For the denominator X is the sum of Man 4 and Man 5 – i.e. the sum of the amounts of these two higher mannose structures. Man 4 has four mannoses and Man 5 has five.

91. There are a number of problems with this construction. First the patent simply does not say that one should only take into account the species found in tables 3a and 3b. The high point is the cross-reference to tables 3a and 3b via the reference to example 3 at paragraph [0008], but it does not say that there. In fact, as the skilled person would think, there could be other fucosylated species not listed in the tables and other non-fucosylated species too. The presence of either would make the calculation meaningless. For example a G2 without fucose ("G2 minus fuc") even if it was found in the sample, is not to be taken into account in the calculation. Also other glycans such as what are called hybrid forms, which are not in the tables either, would not be taken into account in the equation. The value calculated as %-Roche would vary independently of the true amount of fucosylation in the sample as a result of this. No skilled person would think that made sense. Prof. Bertozzi called it crazy math.

92. Moreover the calculation must be the same for fucose as for NGNA and for α-Gal. These latter two are immunogenic. The skilled person knows as a matter of common general knowledge that NGNA is found on hybrid glycans. Therefore the skilled person would expect to take those into account.

93. I reject the Roche construction.

94. I also reject it for another reason. The word "parameteritis" was coined by patent lawyers long ago to describe the technique of inventing a new spurious parameter to use in a patent. The great thing about a *new* parameter is that by definition no item of prior art uses it. So it is impossible at a glance to tell whether the prior art falls within the claim. It may require costly experiments to find out and no patent office is going to embark on that. There was a famous light hearted article written I think in the 1970s by a British patent attorney called "How to patent the prior art". One of the techniques described in the article was to invent a new parameter and claim the prior art that way.

95. The %-Roche works in a similar way because it is limited to the specific list of glycans in Table 3. Nowhere in the prior art have I been shown an example of the same calculation. Unless one has a complete list of all the glycans found in an analysis, one cannot apply the %-Roche and cannot tell if a prior product is within the claim. That is not fair protection for the patentee nor does it give reasonable certainty for third parties (see the Protocol on Art 69 EPC).

96. The Takeda construction makes more sense of the numerator than the Roche construction. All fucosylated glycans found are taken into account. This eliminates many of the problems described above about not taking glycans into account. It is what the skilled person would think the patentee used the words to mean at least in relation to the numerator. Table 3 simply shows how to do the calculation with the species which the inventors happened to find. The skilled person would draw up their own

table of the species they found and calculate the numerator in the same way, based on what they found.

97. However for the denominator the Takeda construction requires one to take account only of Man 4 and Man 5, even if there are other higher mannose species present such as Man 6 or Man 7. Now Takeda's argument has the significant virtue that the claim refers expressly to Man 4 and Man 5 and does not mention any other mannose species. That is a strong point, particularly given that patent claims are written in words of the patentee's own choosing.

98. That takes me to the %-TRM. This is Roche's alternative case. This uses Takeda's method for the numerator but for the denominator, all higher mannose species should be taken into account in the same way. In my judgment this is the right construction. The reader would see the express reference to Man 4 and Man 5 but would also see that they were all the inventors found. The inventors didn't find any Man 6. What would they have done if they had found Man6? There is only one answer, the skilled person would think they would have treated it in the same way as Man 4 and 5. So that is what should be done. In effect the words Man 4 and Man 5 would be understood as a reference to higher mannoses as a class, by reference to paradigm examples of the class.

99. Prof. Bertozzi regarded all these calculations as "crazy math" but in my judgment %-TRM is much less crazy than the other two. %-Roche has no virtue at all for the skilled person. %-Takeda is better but the denominator is still arbitrary. The presence of Man 6 would skew the results in a way which makes no sense. %-TRM is consistent and it has the significant virtue of indicating how much, of the glycans which could be fucosylated, have been fucosylated. That is because higher mannose glycans cannot be fucosylated. This chimes with the expression "fully fucosylated" in paragraph [0001] of the patent.

100. I reach this conclusion without getting involved in the debate about what the state of the common general knowledge was concerning whether higher mannoses have different clearance rates either from other glycans or as between themselves the same kinetics. In my judgment the answer to those issues does not have a significant effect on construction. If need be I would hold, based on Prof Parren, that the skilled person did think as a matter of common general knowledge that higher mannoses all had clearance rates which were likely to be somewhat higher than for other glycans. But they would not know whether this was likely to make any real physiological difference.

101. Prof Morris had his own construction, different from all these others. Neither side submitted it was the right approach. I agree. While it made sense, one problem with it was that the Prof wished to exclude hybrids. I sympathise because he was not focussing on NGNA or α-Gal, but when one does, it seems to me to be clear that hybrids ought not to be excluded.

*Infringement*

102. The active ingredient in Entyvio is the antibody vedolizumab, which binds to a4β7 integrin and prevents T-cells expressing this integrin from migrating into the gut. The T-cells targeted by vedolizumab are therapeutic targets where it is desirable just to prevent their entry into the gut and not to cause cell death (via ADCC) as this would deplete the white blood cells of the patient.

103. There are only two issues (1) whether vedolizumab has the >99% fucosylation as defined in the claim and (2) whether vedolizumab is an "antibody" within the meaning of the claim.

*Vedolizumab – fucose level*

104. The analysis of vedolizumab was done by Dr Azadi. She conducted three digests. She found glycans not in tables 3a or 3b of the patent such as non-fucosylated G2 and she found higher mannoses other than Man 4 and Man 5. Therefore the amount of fucosylation for vedolizumab varies depending on which method one uses to describe it. By the various calculations, stated to one decimal place, the amount of fucose in vedolizumab is:

i) 97.8%-Shields

ii) 99.8%-Roche

iii) 97.75%-Takeda

iv) 99.8%-TRM

105. Therefore on the construction of claim 1 I have adopted, vedolizumab satisfies the requirement for the amount of fucose.

106. I also note that vedolizumab is an example of an antibody with a level of fucose at or below the highest level reported by Shields (98%-Shields).

107. Takeda gave evidence about how vedolizumab was developed. The particular point, which I accept, was that there was no attempt to select for high fucose level nor was vedolizumab developed with any knowledge of the patent.

*Vedolizumab – functionally active (FcR binding) Fc region*

108. This point became very involved but it boils down to some short points. The first concerns whether vedolizumab exhibits ADCC. Tests were done and shown to the regulator. Although they can be criticised (and were criticised by Prof Parren), in my judgment the criticisms were unwarranted. Vedolizumab exhibits no ADCC.

109. The second is that vedolizumab has the LAGA mutation in its Fc region. That clearly makes a significant contribution to the absence of ADCC exhibited by vedolizumab. However Prof. Parren's view was that the LAGA mutation would not be expected to completely eliminate all ADCC. He said that was the case in fact and was common general knowledge. The reason was because it results only in a reduction in binding, not elimination of binding altogether.

110. Roche conducted SPR experiments to show binding. They are sometimes called Biacore experiments. They were done by Dr Zimmerman. Roche tested three antibodies designated A-01, B-01 and C-01 to determine binding to FcγRI and FcγRIIIa. Rituxan was also used as a control antibody and was also tested for binding against each receptor. A-01 has an amino acid sequence identical to vedolizumab but is produced in HEK293 cells which will give fucosylation levels of around 95%. B-01 is a positive control formed of vedolizumab without the LAGA mutation, and C-01 is

a negative control formed of vedolizumab with a different PGLALA mutation, which would be expected to further reduce ADCC in comparison to the LAGA mutation.

111. Roche's case was that A-01 still showed some binding to receptor FcγRIIIa which was small but concentration dependent. B-01 showed a strong response as you would expect and C-01 had no residual binding. There were also results for receptor FcγRI. They do not add anything in relation to the issues I have to decide.

112. Roche, supported by Prof Parren, contended that the experiment shows some, albeit small binding by A-01. Therefore vedolizumab has an Fc region which is functionally active and falls within the claim. Since vedolizumab exhibits no ADCC, it must have the benefit of a further tool for getting rid of ADCC beyond the LAGA mutation. That tool is a high level of fucosylation, within the claim.

113. Takeda, supported by Prof Nimmerjahn, did not agree. Vedolizumab has been engineered so as to disrupt the Fc receptor binding by using the LAGA mutation. While in some in vitro assays one can see that LAGA does not completely silence ADCC, that did not mean that Roche was correct that the only explanation for the complete absence of ADCC was the level of fucosylation. The binding was small. Although there are examples with other antibodies of some functional activity in a case of very small binding, that does not mean the presence of such a small degree of binding proves that a functional effect takes place. At no point has Roche done an ADCC assay to prove its point.

114. Another dimension is this. In development vedolizumab was expressed in cells (NS0). This antibody will have had a lower fucosylation level than the commercial product (made in CHO). The earlier antibody is called the Process A antibody. It was tested in an ADCC assay. I do not accept anything can be drawn from this test, the details were too uncertain, that is details of the test and of the glycosylation of the antibody.

115. Standing back, I find that the LAGA mutation is not regarded as something which necessarily will eliminate effector functions like ADCC altogether. It will strongly reduce them but it might not eliminate them. I find also that there is some binding to the receptor shown in the SPR assay by the A-01 antibody and that is indicative of receptor binding by vedolizumab. It is a close call but in the end in my judgment it is more likely than not that the mutation alone does not account for the absence of ADCC in vedolizumab. A contribution is made by the level of fucosylation. However, in case it matters, I am not satisfied the evidence shows that the fucosylation of vedolizumab alone would be responsible for eliminating ADCC. There is no evidence of that because the LAGA mutation will already have reduced the level of ADCC to a low level.

116. These findings mean that vedolizumab falls within all the relevant claims of the patent.

*Novelty*

117. Art 54 EPC defines novelty as follows:

> (1) An invention shall be considered to be new if it does not form part of the state of the art.

> (2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.

118. In ***Synthon BV v SmithKline Beecham plc*** [2006] RPC 10 the House of Lords considered the law of novelty. For a patent claim to lack novelty over the prior art there are two requirements: disclosure and enablement (paragraphs 19-33). That is not in dispute. The issue of law between Roche and Takeda concerned what exactly it was which had to be disclosed and enabled. The issue is really about enablement. Roche contended that for anticipation what had to be enabled was the very thing disclosed in the prior art. It argued that this was supported by decisions of the Boards of Appeal of the EPO and the summary in the EPO's Case Law textbook (2016 edition). Although the cases in which the point had been decided were about prior use, Roche submitted the same principle applied to documentary prior art. Roche also argued that if all the skilled person could produce was something different from the prior art then that was a matter to be addressed under the lack of inventive step, it was not concerned with novelty. Takeda did not agree with the basic submission and argued that as long as the prior art enabled the skilled person to produce something within the claim, the claim would be anticipated. Takeda argued that ***Synthon*** was authority for its case and to the extent they were inconsistent, the EPO decisions were wrong.

119. There is a clear line of authority in the EPO, starting from the Enlarged Board of Appeal's decision ***G1/92 Availability to the Public***, that for a product which was on public sale to form part of the state of the art it must be possible for the skilled person to reproduce it without undue burden. The principle arising from ***G1/92*** is summarised in the following passage from ***T1833/14*** of 7th December 2017 the Technical Board of Appeal, as follows:

> "1.9 *[…]* the appellant submitted that it would not be reasonable to consider that a product falling under granted claim 1 which was in the public's hands before the filing date of the patent in suit could be held not to anticipate the subject-matter of said patent. However, this is the conclusion reached in view of the condition which is derivable from decision G 1/92 (as explained in sections 1.3 and 1.4 above), namely that in order to be part of the prior art pursuant to Article 54(2) EPC, a public prior use must also amount to an enabling disclosure. A similar conclusion was already reached e.g. in T 977/93 (OJ EPO 2001, 84: sections 3, 4, 11 and 13 of the reasons), T 370/02 (sections 8.6 to 8.8 of the reasons), T 2045/09 (sections 29, 31 and 32-38 of the reasons) and T 23/11 (sections 2.1 to 2.5 of the reasons). The same line of argumentation was also adopted in T 301/94 (sections 3.3 to 3.5 of the reasons), albeit the conclusion in that case was that the alleged public prior use was part of the prior art because it could be reproduced without undue burden. Therefore, the appellant's argument is not persuasive."

120. To take an extreme example, assume a product is freely on sale and anyone who wants it can buy as much of it as they like and assume also that for some reason it was not possible for the person skilled in the art (without undue burden) to analyse it sufficiently

in order to be able to reproduce it for themselves. In that case this line of authority means that the product is not part of the state of the art. It could be patented by a future patent. Of course the future patent would have to contain an enabling disclosure which allowed the public to make the product.

121. Although I have often wondered if the law could have taken a different line – since if the product really is freely available in as large a quantity as anyone would want and no-one actually needs to make it themselves, one might say it had been "made available to the public" (Art 54(2)) – it is clear that that is not the law. G1/92 represents the correct approach and has been followed repeatedly (see e.g. ***Synthon*** paragraph 29).

122. However the question then arises about what it means to say that the skilled person must be able to reproduce the product. The EPO cases have explored the extent of the requirement for "reproduction". How exact must the reproduction be? The situation being addressed in the relevant passages of ***T 1833/14*** and also ***T 2045/09*** of 14th May 2014 was on the footing that the prior used product could be analysed, the skilled person could make their own version of it, and it would fall within the patent claim. However the prior product had other features. They were features which made no difference to whether it fell within the claim or not, but the skilled person could not reproduce those other features. So in ***T 2045/09*** there was a patent claim to an antibody for a target. The glycosylation pattern of the antibody was not a feature of the claim. There was a prior used antibody, also to the claimed target. The Board was not convinced the skilled person could determine its amino acid sequence (in 1994). That was enough to find the claim novel. But the Board went further and also held that even if the skilled person could determine the amino acid sequence of the prior antibody, they could not know in which host cell line it had been made. That meant they could not reproduce the glycosylation pattern of the prior antibody and so the prior antibody could not be "reproduced" in accordance with ***G1/92*** (see paragraphs 37 and 38). Therefore the prior antibody was not part of the state of the art at all.

123. Similarly in ***T1833/14*** cited already, the Board said:

> "1.7 *[...]* the appellant argued that it would not have been difficult for the skilled person to prepare a composition having the features of the public prior use product which were specified in claim 1. However, this is not the issue at stake. Rather, in order for the product to be state of the art, the question is whether or not the skilled person would have been in a position to prepare the product as such, i.e. a sample identical to Rigidex®P450xHP60 in all its properties (not only those specified in claim 1, but exhibiting e.g. also the same properties as indicated in [*a prior art datasheet]*). It was however not shown by the appellant that this was the case. *[...]*"

124. I do not believe there is anything in ***G1/92*** itself which takes the principle that far. The core of the decision in this respect was simply that:

> "1.4 *[...]* Where it is possible for the skilled person to discover the composition or the internal structure of the product and to reproduce it without undue burden, then both the product and its composition or internal structure become state of the art."

125. That makes sense but to reach that conclusion it was not necessary to grapple with the point which is now before me. The term "reproduce" could be read as referring to each and every characteristic of a product whether claimed or not but the words are also apt to cover a case in which the skilled person can discover enough about the composition of a product to be able to reproduce that without undue burden. If they can do this then one might have thought that information about the composition would be part of the state of the art and a patent claim covering a product with that composition would lack novelty. After all, as has been recognised since the EPC began, the purpose of the law of novelty is to prevent the state of the art from being patented again (***T12/81 Bayer/Diastereomers***). The fact that other characteristics of a product could not be determined or reproduced does not suddenly mean that no information about the composition at all had been put into the state of the art by the prior use.

126. Of course if the inability to determine a feature of the product or the inability to reproduce it, prevented the skilled person from making their product at all then the product has not been enabled at all. That is a different issue. However if the feature which cannot be reproduced has nothing to do with the invention and does not prevent a skilled person from making something which, from their point of view, is the product of the prior art for all practical purposes, then I do not see why its absence is relevant.

127. Roche also argue that this principle applies to documents too. So it is argued that the three cited prior art documents are not enabling disclosures, not because a skilled person could not make their own version of what is described in the document, but because that version would not be identical to the thing which was being referred to in that document. Roche contends that this follows from the cases on prior use.

128. I do not accept Roche's submission either about prior use or prior disclosure. I will start with prior use.

129. I will refer to the product which was actually used in the past as the "old product" and I will refer to the product the skilled person makes, assuming they can make anything, as their own version of the product, or the "TOV-product".

130. In my judgment the correct approach to prior use is as follows. The requirement of enablement is that whatever has been disclosed must be something the skilled person can use to produce a practical result (see ***Synthon*** paragraph 31 referring to Lord Reid in ***Van der Lely v Bamfords*** [1963] RPC 61 and also ***Synthon*** paragraphs 20 and 31 referring to Lord Westbury in ***Hill v Evans*** (1862) 31 L.J. Ch (NS) 457). In other words, in the case of a prior use, as long as the information the skilled person can obtain by analysing the old product is enough to enable the skilled person to put it to practical use by making their own version of that product, that second version is part of the state of the art and a patent claim which covers it would lack novelty. The fact the TOV-product was not identical with the old product in every particular would not matter as long as those differences did not take it outside the claim. Also, if the skilled person cannot make their own version of the old product at all then the claim would be novel.

131. After all, what if the skilled person can analyse the old product to their satisfaction and can make the TOV-product based on that information and, as far as the skilled person is concerned the two are identical. One might think a later patent should not be able to claim the product. But the logic of the argument would be that that answer would change if it later emerged that there was a characteristic of the old product, entirely

irrelevant to the claim, but which was not known about and which meant that the old-product and the TOV product were actually different from one another. That does not make sense. Now it might be said that the outcome is different then because the feature was one the skilled person did not know to look for, but I do not see why that is a justification.

132. The problem is made worse by the fact that the claims in this case, although they are product claims, are not claims to a simple chemical compound. Strictly speaking the claims are to populations of antibodies. Some of the antibodies in the population can be afucosylated, and yet the population as a whole falls within the claim. But it is unrealistic to think that one can "reproduce" a prior art population of antibodies down to counting individual molecules. It cannot be that a prior antibody product – which is a population – is incapable of being part of the state of the art because there will always be a level of detail at which one can distinguish between the old-product and the TOV-product. The answer, as it seems to me, is that the relevant place to draw the line is and can only be the claimed features. This is not a criticism of the claims, far from it. But it illustrates why the principle ought not to be as Roche contends it to be.

133. Another way of looking at this is to consider what is disclosed by a prior use. Take facts similar to ***T 2045/09***. If at the priority date the skilled person can fully analyse the amino acid sequence of an antibody and could reproduce that amino acid sequence without undue burden by making an antibody with it, then that amino acid sequence has been disclosed and enabled and is therefore part of the state of the art. A claim which covered a product with that amino acid sequence would be patenting the prior art. It ought to lack novelty. If the skilled person could not determine the glycosylation pattern of the antibody then an antibody with that glycosylation pattern has not been disclosed. Even if they could characterise the glycosylation pattern, if the skilled person could not make an antibody with the same amino acid sequence and the same glycosylation pattern, then an antibody with the relevant glycosylation pattern has not been enabled. Either way it is not part of the state of the art and a claim to the antibody, limited to the glycosylation pattern, would be novel.

134. The same approach applies to documents. If a document published an amino acid sequence of an antibody and if the skilled person could make an antibody with that amino acid sequence, then a claim to that amino acid sequence lacks novelty. The fact that the document states that the amino acid sequence is of an antibody called "Antibody A" makes no difference. Nor does it matter that "Antibody A" will have had a particular glycosylation pattern which is unstated in the document and which a skilled person might never be able to reproduce because they can never know what it was. This makes no difference to the disclosure of the amino acid sequence as long as that disclosure is enabling.

135. None of this is concerned with inventive step. A different case would be if what was enabled by the prior disclosure did not inevitably fall within the later claim, then the question of obviousness would arise. It is true to say, as Takeda does, that a claim will lack novelty as long as the prior art enables the skilled person to produce something within the claim, provided one is careful about what enablement refers to. It refers to enablement of whatever is disclosed in the prior art. It does not mean that a claim would lack novelty just because a person could or would make something within the claim armed with the knowledge of the prior art. That would be a question of obviousness.

*Bihoreau*

136. Bihoreau is in French. There is an English translation and no translation issues arose. As the abstract makes clear, the focus of Bihoreau is on the effect of the ratio of fucose and galactose glycans in the glycosylation pattern in the Fc region of an antibody. The idea is that high ADCC activity is associated with a low fucose:galactose ratio whereas low ADCC activity is associated with a high fucose:galactose ratio. The document proposes that this phenomenon could be used to make therapeutic antibodies. For example antibodies with a low ratio will have high effector activity and could be used against cancer tumors or as anti-virals. Conversely antibodies with a high fucose:galactose ratio will have low effector activity and could be used to treat auto-immune diseases (see e.g. claim 56).

137. Roche point out that the document gives more prominence to harnessing the low fucose:galactose ratio to obtain therapeutics which have a high level of ADCC than to the converse. That is true but it cannot be taken too far. Both ideas are put forward.

138. Table 1 of Bihoreau (in English) is as follows:

TABLE I

| Antibody name | Fucose content (%) | Galactose content (%) | Fucose/ galactose ratio | ADCC (%) |
|---|---|---|---|---|
| EMAB1 | 42.3 | 75.3 | 0.56 | 85 |
| EMAB2 | 25.6 | 72.9 | 0.35 | 100 |
| EMAB3 | 82.1 | 56.1 | 1.46 | 25 |
| EMAB4 | 40 | 60.6 | 0.66 | 73 |
| HH01 | 38.1 | 79.3 | 0.48 | 89 |
| Anti-D WinRho* | 76.1 | 120 | 0.63 | 70 |
| Anti-DI | 100 | 88.8 | 1.13 | 0 |
| Anti (D2 | 95.7 | 71.8 | 1.33 | 0 |
| Anti-D3 | 24.3 | 58.4 | 0.42 | 70 |

*Immunopurified polyclonal anti-Ds

139. The relevance of Bihoreau to these proceedings arises from the entries in that table for the antibodies to the Rhesus D antigen (Anti-D). Three of them are referred to as Anti-D1, Anti-D2 and Anti-D3. One of them, Anti-D1, is stated to have a fucose content of 100%. It is also said to exhibit zero ADCC. The ADCC figure is derived from a functional assay described in the text. The assay is described at a range of concentrations but only one figure is given. 100% represents total lysis of the relevant cells and 0% is background. The oligosaccharides in the glycosylation of the Fc region of the antibodies were cleaved from the protein using PNGase F and analysed by high performance capillary electrophoresis with laser induced native fluorescence (HPCE-LIF). Therefore the method does not involve peptide mapping nor is it an LCMS technique.

140. The method used to determine the galactose involves determining the quantities of individual glycan species which contain galactose and weighting the amount to reflect the number of galactose monosaccharides in the chain. The way the fucose content is determined is different. The glycans are treated with glycosidase enzymes to reduce

them to a core structure of five saccharides, two Glc-NAcs and three mannoses. Two peaks are derived from this sample corresponding to the fucosylated and afucosylated versions and the fucose content determined accordingly:

$$\text{Fucose content} = \frac{\text{Fucosylated [}\textit{GlcNac2-Man3}\text{] x 100}}{\text{[}\textit{GlcNac2-Man3}\text{] + fucosylated [}\textit{GlcNac2-Man3}\text{]}}$$

141. There was a dispute about the reliability and accuracy of the HPCE-LIF technique (and, to a lesser extent, the enzymatic digestion). Prof Morris thought it was unreliable and lacked sensitivity so that it was fine if you wanted to measure to the nearest 5% but not if you were trying to show 100%. Prof Bertozzi regarded the method used as an accurate method for quantitating oligosaccharides and that the skilled person would have no reason to doubt the accuracy of the figures in the table from that perspective.

142. I was not persuaded that Prof Morris's views reflect the approach of the skilled person. They were unduly negative about HPCE-LIF. Concerning the results in Table 1, I find the skilled person would not regard the methods used to generate them as a reason to doubt their accuracy. The skilled person would regard the methods used as capable of producing accurate answers.

143. A different question is whether HPCE-LIF produces systematically different results, for the amount of fucose in a sample, from the results produced by LCMS peptide map analysis of the same sample. I did not understand either party to advance such a case and no evidence to support it has been drawn to my attention. As a consequence, given I have rejected Roche's case about the reliability and accuracy of HPCE-LIF, there is no other point arising from the method by which the data was generated. The fact the numbers for fucose were not generated by LCMS peptide mapping analysis does not mean they are irrelevant as a piece of evidence. Absent evidence to the contrary, they represent the best evidence of what the values measured using the claimed techniques would be.

144. Figure 1 of Bihoreau show the glycans present in three of the antibodies referred to in Table 1. The figure is:

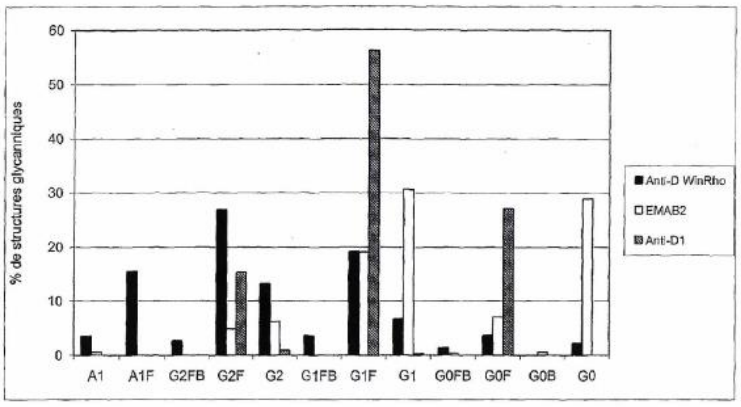



**Figure 1**

145. This data separates out individual glycans in the same kind of way that the method for measuring the amount of galactose is conducted. It includes both fucosylated and afucosylated species. G2 and G1 are both afucosylated species.

146. Prof Morris drew attention to the fact that there are small but visible bars for G2 and G1 relating to antibody Anti-D1. Anti-D1 is the 100% fucosylated antibody of Table 1, but based on Figure 1, Prof Morris's view was that there was between 1% and 2% afucosylated species and that the reader would think the two graphs related to the same antibody sample. Therefore Roche contended the skilled reader of Bihoreau would not think the 100% figure in Table 1 represented a disclosure of an antibody with truly 100% fucose. Prof Bertozzi did not agree that such a conclusion could be drawn simply by "eyeballing" the graph, nor was it possible to tell that the small bars were statistically significantly different from zero. She also said that the skilled reader would not believe that Figure 1 necessarily represented the same sample of the relevant antibody. There was known to be appreciable batch to batch variation. Takeda also pointed out that if one applies the Roche method for expressing the % amount of fucose required by the patent, the species G2 is not taken into account. Hence even if one might be persuaded by the eye of faith that the G2 bar for Anti-D1 is about 1% given its relative size compared to 10%, it is irrelevant. Whereas the bar for G1 is tiny and on any view less than 1%.

147. The fucose content figures in Table 1 are generally expressed to one decimal place (42.3% etc.). The skilled person would regard the 100% content figure in Table 1 similarly. There was a suggestion that since the focus of Bihoreau is on the fucose/galactose ratio rather than on the absolute amount of fucose or galactose, the skilled person would not place as much weight on a value for fucose alone. I do not accept that. The skilled person would see the paper's emphasis on the ratio but would regard the 100% figure as a real data point intended to be taken seriously.

148. The G2 bar in Figure 1 is obviously large enough to at least suggest there is a small but appreciable amount of afucosylated material present. In my judgment the skilled person would notice that apparent discrepancy between Figure 1 and Table 1 in relation to the amount of fucose in antibody Anti-D1.

149. There are a number of ways a skilled person might reconcile the discrepancy. One would be to conclude that despite it being put forward, the 100% figure is simply inaccurate and the true value should be a bit lower. Another would be that the Figure and the Table are presented in the document as illustrative examples out of a much wider body of experimental work and therefore do not relate to the same sample of material. No doubt there are other options.

150. The skilled person would see that the G1 bar in Figure 1 was very small, much less than 1%, whereas the G2 bar is bigger, very roughly 1%. Beyond that the skilled person would not embark on trying to read amounts of glycans by scaling off Figure 1. The skilled person would conclude that the likeliest explanation for the data presented in Bihoreau as a whole is that the Figure and the Table are not inconsistent results based on measurements of the same sample but rather that these data are illustrative examples of true data actually derived by the scientists. At the most the differences between the numbers would be seen as unlikely to be statistically significant, since no such information about that is given.

151. There were other detailed arguments about the disclosure of Bihoreau but I have addressed the main ones. I conclude that Bihoreau discloses an antibody (Anti-D1) which, within the limits of statistics and sample variation, the amount of fucose can be said to be 100% fucose (by the method used in the paper) or, if one ignores G2 glycans, an amount much closer to 100% than 99%. If G2 glycans are taken into account then the amount of fucose would be regarded as somewhere between 99% and 100%. They would not see Bihoreau as a disclosure of an amount of fucose statistically significantly less than 99%.

152. The skilled person would regard the antibody Anti-D1 as having effectively no relevant NGNA or α-Gal at all, and therefore less than the narrowest relevant claim limits of 0.5%. That is because Bihoreau explains that the antibody was expressed in CHO-DG44 cells. They are a conventional CHO cell line and do not add NGNA or α-Gal in appreciable quantities.

153. Therefore I conclude that Bihoreau discloses an antibody within claims 1, 2 and 3. That is true whichever method of calculating the amount of fucose in the patent claims is applied.

154. Turning to enablement, the facts are simple enough. The skilled person (team) could not, and would know they could not, make the very same antibody as is labelled Anti-D1 in Bihoreau. No amino acid sequence data is given for antibody Anti-D1, nor any details of the expression vector and particular clone of CHO-DG44. A skilled person who wanted to make the very antibody Anti-D1 would not be able to do so. It is simply impossible.

155. Roche contended that means claim 1 is novel. I do not agree. In my judgment that is too narrow an approach to novelty as a matter of law, for the reasons already expressed above.

156. Another way of looking at the facts is also simple enough. Bihoreau discloses the idea of an antibody with somewhere between 99% and 100% fucose. It is an enabling disclosure because, for the reasons given the common general knowledge section above, a skilled person given that disclosure is able to make such a thing without an undue burden. They would express the sequence in CHO-DG44 cells (referred to expressly in Bihoreau). A skilled team seeking to make their own version of Anti-D1 would make a number of subclones and screen them for the same fucose and galactose content as reported in Table 1 for Anti-D1. It would be a great deal of work and it would not be identical to the antibody which the authors of Bihoreau but from all the evidence in this case it is clear that a skilled team seeking to make their own version of Anti-D1 would succeed. The TOV-product would fall within claims 1, 2 and 3.

157. The question is whether this means the claims lack novelty or whether this analysis means the claim is novel albeit there might (or might not) be a strong obviousness case. In my judgment these facts do show that claims 1, 2 and 3 lack novelty. The reason why is that Bihoreau expressly discloses the idea of an antibody with that amount of fucose. It is not inevitable that a single clone would produce 99-100% fucose but that does not matter. The skilled person knows what is disclosed and knows how to make it by carrying out nothing other than routine work. The contrast is with the amounts of NGNA or α-Gal. Bihoreau says nothing about those and so the test of inevitability must apply to them. To deprive the claim of novelty in relation to the levels of NGNA or α-

Gal, the skilled person is not following a teaching in Bihoreau. It might be obvious to make sure those levels are low but that would not satisfy the test for novelty. The reason the test for novelty is satisfied for those two levels is because it is to all intents and purposes inevitable that expressed in CHO DG44 cells the levels of NGNA or α-Gal will be within the claims.

158. I conclude claims 1, 2 and 3 lack novelty over Bihoreau.

*Shinkawa*

159. The Shinkawa paper is concerned with showing that an absence of fucose enhances ADCC. Part of the context of this work relates to the therapeutic antibody known as Rituxan (aka Rituximab) which targets CD20 and is used in cancer treatment. The results relate to anti-CD20 antibodies which the group had made and tested. Comparative results for Rituxan are also provided. The authors note (final paragraph pp3472-3473) that while some recombinant antibodies are used in a way which does not rely on effector functions, other such agents, used to target tumors, do rely on ADCC. Having identified that the high ADCC activity of the antibodies studied appears to correlate with their low degree of fucosylation, the authors predict that non-fucosylated IgG1 antibodies would result in an improvement in clinical response and may allow for use in lower doses without a reduction in efficacy.

160. Table 1 of the paper reports the monosaccharide composition of various antibodies. In Table 1 Rituxan is said to have a molar ratio of fucose calculated versus 3 mannoses of 94%.

161. Another of the antibodies made by the authors is described in a passage bridging pp3469-3470, as follows:

> "To verify the combined effect of bisecting GlcNAc with Fuc, LEC10 cells, a variant CHO cell line overexpressing GnTIII (12), were used to produce chimeric anti-CD20 monoclonal IgG1. In oligosaccharide analysis, bisecting GlcNAc-binding fucosylated oligosaccharides were the majority on LEC10-produced anti-CD20 IgG1 (74% of bisecting GlcNAc and 100% Fuc; data not shown). In the ADCC assay, LEC10-produced IgG1 showed only severalfold enhancement of ADCC compared with Rituxan™ (Fig 5B)."

162. The antibody was made in a variant cell line called LEC10 and it is convenient to refer to it as the LEC10 antibody. The enzyme GnTIII which the variant cell line overexpresses is an enzyme which adds a bisecting GlcNAc monosaccharide to the glycosylation. Reading this passage in the context of the paper as a whole the skilled person would interpret it as describing an antibody consisting of the variable region (Fv) of Rituxan coupled with an unspecified constant region (Fc) of an IgG1. The authors have measured its activity in an ADCC assay and have analysed the glycosylation pattern. On the face of it this is a disclosure of the LEC10 antibody had 100% fucosylation.

163. Notably the Shinkawa paper has the words "data not shown" beside some of the values, including the 100% fucose. In his report Prof Morris said this was "always a red flag

for reliability". I do not accept that reflects the view of the skilled person. The reader would not assume the fact the underlying data was not shown had anything to do with a question mark over the reliability of the data.

164. In closing part of Roche's submissions were on a premise that if the skilled person interpreted the value of 100% as a figure stated with +/- 5% precision then certain conclusions followed. It was not established that that is how a skilled person would interpret the value stated. In my judgment the skilled person would take it that the data had been collected and reported with care and precision. The fact that the scientific phenomena addressed in the paper did not depend on the accuracy of the particular measurement of 100% fucose would not alter that. To a skilled person the text makes an assertion of a value for the fucosylation which, considered in the context of this case, would be within the patent claim. Of course the skilled reader does not know that, but that is not the issue.

165. The measurements were done by an HPLC separation method and fluorescence detection with identification of the species by retention time. There was an issue about the use of MALDI to confirm the species. I find that the skilled person would take it MALDI had been used to confirm all species and not only those with cleanly separated peaks, since that would be normal practice. The reader would take it that the authors did not permethylate their samples but, while that is a way of improving sensitivity in general, I was not persuaded its absence makes a material difference in this case.

166. Figure 2 of Shinkawa deals with the oligosaccharide profiles of some of the antibodies studied. They are not the LEC10 antibody but that does not mean they are irrelevant. The figure includes schematics of various oligosaccharide species, labelled (a) to (l). Some are fucosylated and others not.

167. Figure 2 also includes chromatograms for two antibodies. Prof Morris examined them. His opinion was that they showed plain problems and gave grounds for concern about the reliability of the data. He did not think the data should be used to measure down to below 1%. This is relevant because if the Professor's concerns reflect the views of the skilled person, then they would be relevant to the skilled person's view of the value of 100% fucosylation for the LEC10 antibody.

168. In summary the concerns about the chromatograms raised by Prof Morris were concerned with artefacts, missing species and irreproducible retention times. Prof Bertozzi did not agree. Her view was that Prof Morris's approach based on a visual assessment of the (small) printed chromatograms in the paper was inappropriate. Her view was that the two traces were from samples which differed in various ways and were not comparable, therefore the retention time difference was not significant. Artefacts would be addressed by the MALDI and for missing species, there was no reason to doubt that if species were at 1%, they would be detected. Overall I preferred Prof Bertozzi's evidence on this to that of Prof Morris.

169. Nevertheless, as Roche pointed out, Prof Bertozzi accepted that if two of the non-fucosylated oligosaccharide species (i) and (j) were present in amounts greater than 0% but less than 1% then on her approach they would not be detected. She agreed that they could be present in that way. Roche made the point that if, say, these two species were present at 0.6% each then in fact, all other things being equal, the true level of fucose in the LEC10 antibody would be 98.8%. The logic is impeccable but I do not accept it

reflects the thinking of the skilled person reading Shinkawa. Roche did not establish that the skilled person would actually think there was a sufficient amount of undetected non-fucosylated oligosaccharide in the samples to undermine the 100% figure reported to a relevant degree.

170. There were other detailed points but I have addressed the main ones. In my judgment Shinkawa amounts to a disclosure of an antibody within claims 1, 2 and 3 of the patent. The LEC10 antibody was made in CHO cells and the skilled person would take it that there was no appreciable NGNA or α-Gal.

171. Before turning to enablement, I will address the fact that the measurement technique used in Shinkawa is not LCMS peptide map analysis, as required by the claim. The argument at trial was about the reliability and accuracy of the technique used in Shinkawa. I have rejected that. It was not suggested by Roche that if the amount of fucose in the LEC10 antibody were to be determined using LCMS peptide map analysis the answer would be materially different.

172. Turning to enablement, one issue was the availability of the LEC10 cell line. Shinkawa explains that the cell line was kindly provided by Dr Pamela Stanley of the Albert Einstein College of Medicine. Prof Bertozzi was cross-examined on her evidence that she thought Dr Stanley would give out the cell line if asked for it. The main points were: that the court could not be sure the cell lines would be distributed freely, Dr Stanley might at least impose a material transfer agreement (MTA) with restricted terms; there were in fact two LEC10 cell lines and the paper did not say which one was used; and Takeda's evidence was lacking because they could have contacted Dr Stanley to clear up the issues. Prof Bertozzi maintained her view that Dr Stanley would give out the cell line freely if asked and would have records which meant she would, if asked, give out the same LEC10 cell line as had been given to the authors of Shinkawa. In my judgment it is much more probable than not that Prof Stanley would give the skilled person the cell line if she was asked for it and she would give the skilled person the right LEC10 cell line. As for the terms of any MTA – the evidence was speculative. I am not satisfied it was more likely than not that a relevant MTA would be imposed. It would either not be imposed at all (most likely) or it would not contain any contract term which made a difference in terms of patent law.

173. The skilled person would take it (see above) that the LEC10 antibody had the Fv of Rituxan. That was publicly available or could be determined analytically. For the IgG1 Fc region they would not know what Shinkawa had actually used but there would be no reason to think it mattered and it was well within the skill of a skilled person to use a suitable Fc region. The skilled person would be able to produce their own version of the LEC10 antibody in the right LEC10 cell line. I refer to that as the TOV-LEC10 antibody.

174. What of the glycosylation of the TOV-LEC10 antibody? I accept Prof Parren's evidence that moving a cell line from one lab to another is likely to cause changes in the glycosylation pattern. However the fact that the glycosylation patterns will differ to some degree is different from saying that it is more likely than not that the amount of fucose will differ by more than a certain amount. That is because the amount of fucose is an aggregated measurement of the population in a sample as a whole. The detailed glycosylation patterns of two samples can differ even if the amount of fucose for each of them is the same to a certain level of precision.

175. Absent evidence to the contrary, it seems to me that the Shinkawa paper itself is the best evidence of what happens when an antibody of that kind is expressed in the LEC10 cells. Given the disclosure of Shinkawa, I find that without an undue burden the skilled person will make the TOV-LEC10 antibody with an amount of fucose sufficiently close to 100% as to be within the claim. The TOV-LEC10 antibody will also satisfy claims 2 and 3 in terms of NGNA and/or α-Gal.

176. Therefore in two respects the TOV-LEC10 antibody would not be absolutely identical to the LEC10 antibody actually made and used by the authors of Shinkawa in their work, that is in the antibody sequence of the Fc region and in the fine detail of the glycosylation pattern. Nevertheless in my judgment the TOV-LEC10 antibody is disclosed and enabled by the Shinkawa paper. Claims 1, 2 and 3 lack novelty over Shinkawa.

177. Takeda submitted that Shinkawa discloses the use of the particular LEC10 antibody in human therapeutics. I do not agree. Shinkawa does not disclose the LEC10 antibody as a pharmaceutical agent and so claims 6 and 7 are novel.

*Ferrara*

178. The Ferrara paper was produced by authors working at Roche. The paper looks into the contribution of carbohydrates to the interaction between the FcγRIIIa receptor and non-fucosylated antibodies. The context of the work is again the anti-cancer CD20 antibody Rituximab and the exploitation of effector functions. The paper tests "GE" (genetically engineered) anti-CD20 antibodies with high proportions of non-fucosylated oligosaccharides. These test antibodies have been modified relative to a "native" antibody. They were produced in HEK-293 EBNA cells. These are human embryonic kidney cells.

179. Figure 1 of Ferrara summarises the oligosaccharide characterisation of the nature and test antibodies. The characterisation was done by MALDI-MS of neutral oligosaccharides released from the antibodies (therefore not peptide map analysis and without permethylation). The figure includes a diagram of the carbohydrate moiety attached at the Asn-297 position, which is a complex biantennary glycan. It includes the fucose attached to the first GlcNAc linked to the Asn-297. The five monosaccharides which make up the core structure familiar to the skilled person are in bold in the diagram. The other aspects –the fucose, terminal galactoses and sialic acids, and a bisecting GlcNAc are not in bold type to indicate they are variable. The figure also includes some MALDI-MS spectra; and then in section (c) of the figure, there is a table of the oligosaccharide distributions, as follows:

c)

| | relative % of | | |
|---|---|---|---|
| | native | Glyco-1 | Glyco-2 |
| high mannose | 1 | | |
| non-fuc, hybrid, bisected | | 92 | 12 |
| fuc, hybrid, bisected | | 8 | |
| non-fuc, complex, bisected | | | 50 |
| fuc, complex, bisected | | | 12 |
| non-fuc, complex | | | 22 |
| total bisected | 0 | 100 | 74 |
| total non-fuc | 0 | 92 | 84 |
| total non-fuc, complex | 0 | 0 | 72 |
| total complex | 99 | 0 | 88 |

180. On the face of it therefore the table shows that the oligosaccharide composition of the native antibody consists of 1% high mannose and 99% fucosylated complex non-bisected biantennary glycans. That conclusion follows because no values are given for any non-fucosylated species, or any bisected or hybrid species, in relation to the native antibody. The figures are plainly rounded to the nearest 1%.

181. The case over Ferrara adds nothing to the case over Shinkawa. In terms of disclosure the same issues between Prof Morris and Prof Bertozzi arose. Prof Morris looked closely at the chromatograms in Figure 1 and expressed the opinion that there were in fact afucosylated species present, which gave him reasons to doubt the 99% figure. Prof Bertozzi did not agree that was a legitimate exercise and did not agree one could identify what the species in the peaks actually was without more analysis. They might not even contain glycans. There were also points on the permethylation and the fact that the exact amount of non-fucosylated oligosaccharide in the native antibody was not central to the authors' thesis reported in the paper. As before I prefer Prof Bertozzi's view about what is disclosed in the paper. The skilled person would take it as a disclosure that the native antibody had glycosylation consisting of 99% fucosylated complex glycans and 1% high mannose species.

182. There was no suggestion that a point arose over Ferrara about NGNA or α-Gal; nor was there a point on the method of expressing the amount of fucose (%-Roche, etc.). Given the 99% does not include high mannose, the 99% of Ferrara would be 100%-TRM.

183. In terms of enablement, again similar kinds of issues arose. Prof Parren's evidence was that the skilled person would not be able to make the native antibody because its amino acid sequence is not set out in Ferrara. The premise is of course correct (no sequence) but I do not accept the conclusion. This is a paper published in the highly respected Journal of Biological Chemistry. It is more likely than not that the authors would respond favourably to a request for cell lines, hybridomas and DNA clones referred to in the paper, supplying them without any relevant fetter. That is particularly so given that the antibody in question is the native one. Prof Parren also said it was not clear to him that the cell line used was available from the laboratory. Bearing in mind Ferrara emanated from a Roche laboratory, if Roche wanted to establish that they could have done so. I am not satisfied it was not available.

184. I find claims 1, 2, and 3 are anticipated by Ferrara. Claims 6 and 7 are not.

*Simulect*

185. Simulect is the trade name for a therapeutic antibody product, marketed by Novartis as an immunosuppressant. It has been commercially available since before April 2006. The drug substance is basiliximab, a chimeric IgG1 monoclonal antibody produced from a murine myeloma cell line (SP2/0). The target antigen is CD25. The primary evidence relating to Simulect comes from declarations of Novartis employees which were submitted to the EPO in the opposition proceedings. Novartis had opposed the Roche patent and argued it lacked novelty over Simulect.

186. One of the declarations was of Matthias Berg, the Head of Analytical Development and Characterisation-Mass Spectrometry in the Biological Product and Process Development unit of the BTDM group at Novartis Technical Operations in Basel. This explained the LCMS analysis he had undertaken of the glycosylation profiles of

samples from five manufacturing batches of Simulect. Also submitted were two supporting declarations of Sercan Terhani and Manuela Weidner describing the sales of Simulect products made from the manufacturing batches analysed by Matthias Berg.

187. For each sample measured by Dr Berg the amount of fucose was more than 99.0%, the amount of NGNA was 1.0% or less and the amount of alpha 1,3 galactose was 0.0%. However there is an issue about the NGNA level. One of the batches tested by Dr Berg (C0001) gave an NGNA level of 0.5% whereas in a declaration of Kurt Forrer, test results for the same batch are given, with an NGNA level of 0.64%. Both values are within claim 1 but only Dr Berg's is within claim 2.

188. The evidence also showed that the composition actually sold was made by blending batches. Roche pointed out that this meant one could not say the commercial product fell within claim 2. Takeda pointed out that mathematically and taking into account rounding, it was possible that a blend could be within the claim. That is true but I am far from satisfied that it is more likely than not that commercial batches of Simulect fell within claim 2.

189. Aside from the NGNA point, the evidence is that commercial Simulect was in fact a product accordingly to claims 1, 3, 4, 6 and 7.

190. I turn to the question of what a skilled person would find out from analysing a vial of Simulect. The skilled person would be able to analyse the material and find out it had all the features of claims 1, 3, 4, 6 and 7. They would be able to analyse the glycosylation pattern and find out that the amount of fucose was more than 99.0%, the amount of NGNA was 1.0% or less and the amount of α-Gal was 0.0%.

191. However determining the full amino-acid sequence of Simulect in 2006 would be a lot of work. Prof Morris's view was that a full analysis would take a team of 2-3 scientists around 3 months. The full analysis would include the amino acid sequence, glycosylation and the formulation; and ¾ of the work would be on the amino acid sequence. I accept that. That is a lot of work but it is not an undue burden. It means that the amino acid sequence of the antibody, as well as the other aspects – glycosylation and formulation – were made available to the public.

192. Given that information, I am sure a skilled team would be able to make their own version of the Simulect antibody with all the features of those claims. Again it is a lot of work but no undue burden is involved. As before I will refer to this antibody as TOV-Simulect to distinguish it from Simulect. TOV-Simulect would not have been made in the same cell line as Simulect, since the skilled person cannot identify the cell line used from the sample, but that does not impose an undue burden in the skilled person making their own version of the product. They would choose a suitable cell line. A skilled team seeking to make an antibody with an amount of fucose more than 99.0% is able to do so. There is no trick to it disclosed in the patent. That is a consequence of Prof Parren's evidence. Like Simulect, TOV-Simulect falls within the various claims (not claim 2).

193. TOV-Simulect would not be identical to Simulect and the skilled person would know that. However in my judgment, as a matter of law, that does not preclude a finding of lack of novelty of 1, 3, 4, 6, and 7 as a result of the public availability of Simulect. The prior use of the Simulect product made certain information about that product available

to the public. That information describes a product which is within the claim. The skilled person was able, without undue burden, to make their own version of that product, based on the available information.

194. Simulect does not anticipate claim 2.

195. On the approach above it is not necessary to examine the matter of novelty any further, but since there was an argument about following up published information about Simulect, I will address that. Takeda showed that by the priority date a PCT application (WO 00/06604) and a patent (EP 0 449 769) concerning basiliximab/Simulect had been published. These documents together disclose the amino acid sequence of the antibody. They also identify a cell line to use SP2/0. I am not convinced this would help Takeda if the previous conclusion was wrong. Knowing the amino acid sequence would save some work but the work did not represent an undue burden. Having a cell line described does not help either. The antibody which a skilled person would make would still not be identical in all respects to Simulect, for the same reasons already discussed above in relation to other prior art. It also raises a further problem: Prof Parren gave evidence of a difficulty with producing a level of NGNA below 1% from an SP2/0 cell line, or from another possible mouse myeloma cell line (NSO). I am not aware of any specific evidence from Prof Bertozzi addressing this. Whereas in relation to the amount of fucose, Prof Parren had given evidence that a skilled person could produce high levels of fucose, there was no such evidence about NGNA.

*Obviousness*

196. I will address Simulect and Bihoreau first before turning to Takeda's case based on lack of technical contribution.

*Simulect – obviousness*

197. Takeda maintained that even if Simulect did not deprive claim 2 of novelty, it would be entirely obvious for the skilled person to have as low a level of NGNA as possible and so claim 2 was obvious. The same point was made about claim 3 and α-Gal but it does not arise on the facts.

198. Roche contended this point was not pleaded because the only plea of obviousness over Simulect was put in a paragraph of the Grounds of Invalidity which were expressly directed to the claims as proposed to be amended but since Roche had now dropped the proposed amendments, the point was no longer open. I will not prevent Takeda from taking this point. The paragraph of the Grounds of Invalidity is directed to the amended claims but the assertion pleaded was, or to be more accurate included, an assertion that claim 2 as proposed to be amended, was obvious over Simulect. That claim would be identical in scope to claim 2 as granted, with the same lower level of NGNA, save that unlike the granted claim it would be limited to a humanized or human antibody as a result of the proposed amendment to claim 1. If such a claim was indeed obvious then claim 2 as granted would necessarily also be obvious. The fact Roche dropped the amendment does not give them the right to prevent Takeda from advancing a case which is expressly pleaded. Mind you, the Grounds of Invalidity could have been better drafted to avoid this logical difficulty.

199. However I am not satisfied that claim 2 would be obvious over Simulect, for the following reasons. In general terms a skilled person making an antibody for human therapy would, as Takeda asserts, aim to have as low a level of NGNA (and α-Gal) as possible. That is due to the well known immunogenicity problem caused by those species. It was obvious. Moreover a skilled person who wished to produce such a thing would be able to do so purely by the application of common general knowledge, for example by expressing the antibody in a suitable CHO cell line. However that is not the only question to be answered. To arrive at claim 2 the skilled person also has to make an antibody with an amount of fucose within claim 1. A skilled person given Simulect would analyse it and would find out what the amount of fucose was. They would be able to make their own version with the characteristics they had identified without any undue burden. Therefore such a thing cannot be patented. It would lack novelty. However for obviousness the question is a different one. There is no evidence I am aware of which addresses whether a skilled person given that information as a result of analysing Simulect would think there was any reason to maintain the same very high level of fucose, let alone to do so at the same time as reducing the NGNA to a different lower level from the one in Simulect. Maintaining the fucose level is not difficult to do if you want to do it, but without a reason to do it, the skilled person would not bother to do so. This point highlights a fundamental difference between the law of novelty and obviousness and the policy underlying them. Novelty prevents the state of the art being patented again. If something is disclosed then the question is simply whether it is enabling, irrespective of whether someone would be motivated to follow up the disclosure. On the other hand when asking what is obvious over a piece of prior art, factors like motivation are usually very important. So I reject the case of obviousness of claim 2 over Simulect.

*Bihoreau – obviousness*

200. Given the way it was pleaded, one might have thought Takeda was advancing a conventional obviousness attack based on Bihoreau. However that is not the case. In its closing Takeda made the following submission:

> "611. In giving her evidence the question asked of Professor Bertozzi was, correctly, "*what, if anything, does the Patent make by way of a technical contribution over Bihoreau*". Professor Parren on the other hand was asked to comment on what the skilled team "*would do, if anything, if presented with the teaching of Bihoreau*". The evidence he gives is therefore based on an incorrect premise."

201. Prof Parren did indeed give evidence about what, in his opinion, a skilled person would or would not do if presented with Bihoreau. That evidence would counter a conventional obvious case. The essential point made by Roche and supported by Prof Parren is that Bihoreau is concerned with the ratio of fucose to galactose. A skilled person given Bihoreau would either follow that up – in which case they would have no reason to set about making antibodies with very high fucosylation irrespective of their galactose level or would reject it as a way forward at all. If they followed it up the antibodies they would contemplate would be characterised by the fuc:gal ratio rather than the absolute amount of fucose. They would not arrive within the claim (without hindsight). Alternatively, a skilled person might well be so sceptical about Bihoreau's ratio idea so as not to place weight on it, but in that case then to take the teaching

forward at all would only be obvious with hindsight. There is no evidence or submissions to the contrary of these points from Takeda. I would reject a conventional obviousness attack over Bihoreau.

202. Takeda's real case, supported by Prof Bertozzi, is based on an allegation of lack of technical contribution over Bihoreau and I will consider it in that context.

*Obviousness – lack of technical contribution*

203. The law is clear enough that a ground of invalidity exists which can be called different things including: lack of technical contribution, ***Agrevo*** obviousness, and failure to solve the technical problem. Depending on the facts one of these descriptions may be more apt in a given case than another but they are all getting at the same thing. I can do no better than refer to the decisions of the Technical Board of Appeal of the EPO in ***EXXON/Fuel Oils*** T 409/91 and ***Agrevo/Triazoles*** T 939/92. The general principle there identified is that the extent of the patent monopoly, as defined by the claims should correspond to the technical contribution to the art. This theme – that the patent monopoly should be justified by the actual technical contribution to the art – has often been referred to with approval in the UK, most recently in the two recent Supreme Court decisions: ***Warner-Lambert v. Generics (UK) Ltd t/a Mylan*** [2018] UKSC 65 and ***Actavis v ICOS Corp*** [2019] UKSC 15.

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 LJ in ***Generics UK Ltd t/a Mylan v Yeda*** [2013] EWHC Civ 925, citing Jacob LJ in ***Dr Reddy's Laboratories (UK) Ltd v Eli Lilly and Co Ltd*** [2010] RPC 9.

205. Sometimes the argument in this case is put on the basis that the claim makes no technical contribution over an item of prior art. The two candidates are Shields, which was common general knowledge and Bihoreau. Not every case looks at this issue in that way but it is a legitimate way of putting the argument.

206. Roche was dismissive of this issue in closing, identifying three contributions to the art which, it argued, the patent obviously made. The contributions were made by:

i) Disclosing that CHO cells can be obtained having fucosylation of >99%;

ii) Disclosing the idea of increasing fucose for a therapeutically useful purpose;

iii) Disclosing the idea that increasing fucose to 99%+ would reduce ADCC to background.

207. I will take these in turn below. 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?

*Disclosing that CHO cells can be obtained having fucosylation of >99%*

208. This idea is disclosed in the patent although one needs to take a bit of care about construction of what 99% means. The idea is plausible and it is true. However it is not

a technical advance contributed by the patent. As I have held under novelty, the prior art included disclosures of antibodies with fucosylation of >99%. It is not a new idea.

209. Moreover, and entirely distinct from the issue of novelty, I am satisfied that it is not at all a surprising idea that CHO cells can be obtained which produce antibodies with fucosylation of >99%-TRM. This is addressed in the common general knowledge section. Leaving aside the other contributions relied on, this is simply an arbitrary level of fucosylation.

210. A separate point is the following. As vedolizumab itself illustrates, antibodies which to a skilled person would have the same level of fucosylation as Shields (98%-Shields) can also be >99%-TRM.

211. A different question (addressed below on the second and third ideas) is whether a skilled person would have a reason to make such a thing.

212. Even if this was a technical advance, as it is put the contribution is limited to CHO cells. That does not support claims of the width of the relevant claims in this case, because they are product claims not limited to products made in CHO cells and because fucosylation is well known to depend on cell type.

213. I reject the case based on this contribution either alone or in combination with the second one relied on.

*Disclosing the idea of increasing fucose for a therapeutically useful purpose*

214. This idea is also disclosed in the patent. The idea is plausible and it is true. Increasing fucose reduces ADCC and reducing ADCC is a therapeutically useful thing to do for certain antibodies.

215. The critical issue here is whether this is a technical advance. Roche submitted that from the point of view of therapeutic utility all the prior art, including the common general knowledge Shields, was focussed on decreasing fucose for a therapeutically useful purpose. Although the inverse relationship between fucose level and ADCC was known, no-one thought of putting the other end of the scale to use. The skilled person had in mind making therapeutic use of low fucose but did not see therapeutic utility in high fucose.

216. I have already addressed this to some extent in relation to Shields but at the risk of repetition, I do not agree. The idea that reducing ADCC was a therapeutically useful thing to do for certain antibodies was part of the common general knowledge and so too was the idea that increasing fucose would reduce ADCC. This is not an advance over what was known. I reject this case too.

*Disclosing the idea that increasing fucose to 99%+ would reduce ADCC to background*

217. A core aspect of Roche's case is that one of the technical contributions made by the patent is that the claimed level of fucosylation reduces ADCC to background. The patent never says this in words. The patent description is obviously concerned with glycosylation in general and fucosylation in particular, it is also obviously concerned with mediating effector functions in general and ADCC in particular; but nowhere in

the text is there any express statement of what the antibodies of the invention actually do. Roche's case is that it is shown in Figure 1. The argument is that the natural assumption of the skilled reader would be to expect that what is reported in the data would be for the highest concentration tested since that would be the concentration most likely to be able to induce ADCC and the experiment was designed to study the capacity of the antibodies generated to elicit ADCC. Prof Parren gave clear evidence that that was the expectation for that reason and, after being pressed, Prof Bertozzi agreed.

218. In my judgment the skilled reader would indeed expect that figure 1 showed results for the highest concentration tested (i.e. 25ng/ml). Nevertheless the skilled reader would also be aware that the patentee could easily have said so but didn't. There is a risk of hindsight here. The trial was opened on the basis that the case is all about antibodies which are highly fucosylated and thereby abolish ADCC. Knowing that is the case it is tempting to see it in the patent. But this patent is from one of the most sophisticated biotech companies in the world with access to the best firms of patent attorneys. The skilled reader would not think it was an accident that the patent does not make these statements expressly.

219. Another aspect to note is that whatever one makes of Example 4 and Figure 1, these experiments do not purport to show a difference in ADCC between an antibody of the invention and a known antibody with (for example) 95% fucosylation. The positive control was a much lower level of fucosylation than that.

220. As I have said, I think the reader would interpret Figure 1 as a disclosure that ADCC was eliminated in that test, probably at the 25ng/ml concentration. Would the skilled person go on to infer that this was a disclosure or assertion that the claimed antibodies would eliminate ADCC at higher concentrations? In my judgment it is not. The assertion is not made in words and the Figure, since it is only one concentration, does not say anything about the effect at a higher concentration. For all the skilled person knows, Figure 1 of the patent is the equivalent of the left hand side of a graph like Figure 6 of Shields.

221. I do not accept that the skilled person would set about trying to determine what the $K_D$ of the antibody tested was by conducting a paper chase to find other publications for the antibody in the patent. That was Prof Parren's evidence but it does not reflect what a skilled person would do without hindsight knowledge of the case Roche now seeks to advance. The skilled person would be entitled to take it that the patentee had told the reader whatever it was the reader needed to be told. Even if they did find the $K_D$, I am not satisfied that would satisfy the skilled person that the teaching of the patent was that ADCC was reduced to background across the board. That was the essence of Prof. Bertozzi's view of the disclosure, which was that this is an empirical field and the skilled person would wish to see experimental data. I find that would reflect the view of the skilled person.

222. In any event I am not convinced it is plausible. The point is really the same. Figure 1 makes plausible the idea that the antibody tested reduces ADCC. It also makes plausible the idea that the antibody exhibits no ADCC at the concentration (presumably) tested. However it does not make plausible a wider proposition about the effect at higher concentrations since it simply does not address it. Rather than eliminating ADCC at any relevant concentration, for all the skilled person knows what

has happened is simply that for the antibody tested, the concentration at which ADCC occurs has been increased above the level in the Figure.

223. Nor am I convinced the proposition is true. Vedolizumab does not prove it since that antibody has a LAGA mutation. There is no other proof to which my attention has been drawn.

224. It would be a technical advance but for the reasons already given, I reject the case based on this third disclosure. That is before one considers whether the data in the patent could support a claim of the breadth of claim 1.

*Lack of technical contribution - conclusion*

225. Overall I find the case of invalidity based on lack of technical advance is made out.

*Insufficiency*

226. Takeda's pleaded insufficiency case ran to eleven distinct paragraphs. By closing I think the case can be boiled down to four points:

i) A free standing issue, added during trial, relating to the rival approaches to calculating the amount of fucose;

ii) A kind of classic "it can't be done" kind of argument which is really a squeeze;

iii) A claim breadth argument which is a counterpart of the technical contribution case;

iv) An ambiguity type insufficiency concerned with how the skilled person works out whether a product is within the claim or not.

227. Neither party argued the points in this order but I do so in order to clear out some of the undergrowth before getting to the major debate about ambiguity.

*The rival approaches to calculating the amount of fucose*

228. Takeda argued that if the claims are not construed its way then the claims were "truly ambiguous" because the skilled person cannot identify the calculation required by the claims. The premise is satisfied, since I have rejected %-Takeda as the right method, but the conclusion does not follow as a matter of fact. The skilled person does not have any undue difficulty arriving at what I believe is the right construction. In any case I am very doubtful this plea is correct in law but since it fails on the facts I will go no further.

*The classic "it can't be done" argument*

229. This shades into the next point but is worth addressing distinctly. The point is not that the skilled person cannot make something within the claim, rather the point is to highlight what a skilled person must be able to do in order to achieve that, without any undue burden. One critical point is that the deposited clone (DSM ACC 2795) does not get the skilled person anywhere relevant. Takeda's experiment in obtaining and growing up the deposited clone was a fair test of what a skilled person would do. The

clone was obtained, grown up, and an antibody made and characterised appropriately. It was not within the claimed limit of 99% by any of the calculation methods. It was about 95% fucosylated. Although Prof Parren suggested that this would be a good place to start to produce a product within the claim, that will not do. The deposited clone takes the skilled person no further forward than the common general knowledge. As Prof Parren also explained cell lines in different laboratories produce different glycosylation patterns. This does not help either. It just serves to illustrate the difficulty.

230. Of course on my findings of fact about what the skilled person can do given a high level of fucosylation as a target, there is no difficulty. They can make an antibody with such a level. That is true for 98%, 99% or 99.5% (measured by TRM). However to do this the process described in the common general knowledge section above is what would be done. It is a lot of work but there is no undue difficulty. All that is required is a target fucosylation level. The patent is not insufficient on this ground but the reason why not has consequences elsewhere in the argument.

231. A different argument raised during trial was whether a paper by Li et al showed that an antibody which is fully fucosylated is still capable of eliciting ADCC. Prof Bertozzi gave evidence about this. It is what the Li paper appears to show but I am not satisfied that the experiment in Li does demonstrate that the antibody tested was within the claim. The way in which glycosylation was measured in Li means that some non-fucosylated material could have been counted as fucosylated material.

*Claim breadth as a counterpart of the technical contribution case*

232. This adds nothing to the lack of technical contribution case.

*Ambiguity type insufficiency*

233. There was no dispute as to the law. The recent cases are ***Glaxo v Vectura*** [2018] EWHC 3414 (Pat), ***Unwired Planet v Huawei*** [2016] EWHC 576 (Pat) and ***Sanvik v Kennametal*** [2011] EWHC 3311 (Pat). The principles set out there are not too hard to state but they can be tricky to apply.

234. Before turning to the facts, a point of common general knowledge is worth highlighting. That is the difference between accuracy and precision. It is usually explained with an image of a dartboard. Imagine the true result is the bull's eye and a dart is a measurement. If the darts are all over the board then the individual measurements may not be precise, but if their average is the bull's eye then the overall result is accurate. If all the darts are clustered around the bull's eye then the measurements are both accurate and precise. However say all the darts are tightly clustered but they are clustered around the double 20. That result is precise but not accurate. Now take a different case, more like the real world, in which one does not know what the true result is. A cluster around double 20 may be just as precise as a cluster around the bull's eye, but which is accurate? The skilled person cannot know.

235. The argument in this case is about the inferences to be drawn from the Reusch paper. Various techniques were used to evaluate the various individual glycans in an antibody sample. Results of runs on two different days are reported. The results are set out in Table 2. By the closing of the trial the relevant columns were the first column of data – for the technique HILIC, and then three other columns: LCMS with Orbitrap, micro

LCMS with Q-TOF, and nano LCMS with Q-TOF. The three LCMS techniques are all within the scope of the words of claim 1.

236. As an illustration of the differences, one row of the table gives results for the glycan G2F. I chose G2F at random. It is a complex biantennary glycan with a fucose, four GlcNAcs, three mannoses, two terminal galactoses but no sialic acid. The results are:

| | HILIC | LCMS/Orbitrap | Micro LCMS/ Q TOF | Nano LCMS / Q TOF |
|---|---|---|---|---|
| G2F | 9.5 (<0.1)<br>9.6 (0.1) | 10.1 (0.1)<br>9.3 (0.1) | 9.0 (0.1)<br>9.0 (0.1) | 9.7 (0.1)<br>9.0 (0.3) |

237. The numbers are percentages of the total. The value in brackets is the standard deviation. The pair of values above and below were taken on different days. The test equipment was at one of two different institutions – presumably Roche or Leiden University.

238. The differences for other glycans are similar. Some are much larger but it is apparent that even differences of the level shown for G2F could well take a product inside or outside the claim depending on which instrument was used. Now one needs to take care because the total fucosylation is an aggregate result and in the Reusch data there are fragments, which means that it is not necessarily representative of the aggregate to focus on one glycan. However a sense of the impact on a figure for fucosylation overall can be seen from these aggregate totals produce by Takeda:

| | HILIC | LCMS/Orbitrap | Micro LCMS/ QTOF | Nano LCMS / QTOF |
|---|---|---|---|---|
| Total non-fuc<br>without Man | 8.6<br>8.9 | 12.7<br>12.9 | 9.1<br>8.9 | 9.8<br>11.0 |

239. These data show that while each instrument produces a relatively close pair of values in aggregate, in this test the four instruments gave different answers.

240. Prof Morris's firm opinion was that the only one the skilled person would regard as the right one to use was micro LCMS with QTOF. If that represents the skilled person's approach then these data reveal no insufficiency.

241. Prof Bertozzi did not agree. Her view was that all three techniques were ones the skilled person could use, and they would have no reason to choose one over the other.

242. Taking the individual issues, nothing turns on the fact that HILIC gives a different answer from the other three in this test. Prof Morris and Prof Bertozzi did not agree whether HILIC would be regarded as reliable and sufficient for accurate results. I find that it would be seen as reliable and accurate but it would not be regarded as within the claim. The fact it gives a different answer in this test is a reflection of a wider point made by Prof Bertozzi, which was that, as she put it, there is no ground truth. In other words there is no single "right" answer.

243. In terms of precision, each of the three techniques is capable of being run to give a precise answer. However that does not mean they given the same, precise, answers.

244. Prof Morris and Prof Bertozzi did not agree about the status of the Orbitrap device at the priority date. Prof Morris was clearly a fan of the QTOF system not least because he invented it. But he explained that at the priority date the Orbitrap was a new system with less of a track record than QTOF. It is an ion capture device and was perceived as having the drawbacks associated with ion capture systems which QTOF does not. He agreed that today the Orbitrap is an excellent system but maintained his view about the position at the priority date. Prof Bertozzi did not agree with Prof Morris about the position at the priority date. Her firm view was that the Orbitrap was, and was seen as, an excellent instrument at that time. There was some apparently inconsistent evidence in Prof Bertozzi's report which appeared to suggest that at around the priority date she did not regard the Orbitrap with the favour she now does, but Prof Bertozzi explained that was not what she meant.

245. Standing back, I found Prof Morris' view on this more convincing as a representation of the approach of the skilled person than that of Prof Bertozzi. Today both instruments are excellent but judged at the priority date I find that the skilled person would wish to carry out the measurement using a QTOF device. Therefore the difference between the Orbitrap results and those for the QTOF systems in Reusch is not relevant to insufficiency.

246. I recognise that the data on which infringement has been established was taken using an Orbitrap device. Since there is no other evidence I am aware of which provides a different answer, there is no reason not to take those data as representative. I have taken the same approach with the prior art. The fact that a different but good technique has been used to measure fucose does not of itself mean the result is of no evidential value. There is no evidence of the existence of a simple systematic difference between the techniques. They can produce different answers but on a given day for a given sample, there may or may not be differences. The right legal analysis is that a result produced by one reliable technique shifts the evidential onus onto the other party to rebut it.

247. However setting aside Orbitrap does not get Roche home, since there is still a relevant difference between micro LCMS QTOF and nano LCMS QTOF. One point was that, based on looking at the Reusch data, the skilled person would choose micro because the results are more consistent. I do not accept that. The skilled person does not have the Reusch data before them.

248. Although the Reusch article was not the only evidence relied on by Takeda to make good this point, it was by far the best evidence and other matters, such as a hypothetical example given by Prof Bertozzi in her oral evidence and a different point on software, are not sufficient to make Takeda's case without Reusch.

249. Prof Morris said that a skilled person who had sufficient material to use would prefer a micro-bore HPLC column to a nano-bore column to avoid the risk of overloading. I do not doubt that all things being equal the skilled person with a choice might well take that approach but in my judgment it only represents part of the thinking of the skilled person. These are expensive and substantial instruments. A skilled person with ready access to a nano-bore machine would think that was a suitable machine to use in accordance with the claim. They know how to set it up appropriately and avoid

overloading. They would not think there was any reason to go to the trouble of using a micro-bore machine instead. Prof Morris's opinion would not lead to a micro-bore machine in that, realistic, case.

250. Accordingly if the results in Reusch at face value are representative of what happens in practice then there is a problem. Roche argued that the results were not representative. The major issue was machine set up. Prof Morris described a system suitability test as something routinely done, particularly with online techniques. Prof Bertozzi had not heard of it and Takeda took issue with it. I prefer Prof Morris's view that the skilled team carrying out the tests required in the patent would do a system suitability test. As an aside, as I understand it such a test would be one way of avoiding a problem of overloading a nano-bore column.

251. Roche also argued that the Reusch data was created by running the tests without a system suitability test. The paper itself does not say that although Roche contended that a statement in the discussion section which recommends running a system suitability sample for tuning the mass spectrometer could be interpreted as a hint that no such thing had been done. I am prepared to assume that is true, but I am not prepared to draw anything from it. This work was done by workers at Roche (and Leiden). Dr Reusch has given declarations in the EPO and in Germany. However he has not given evidence in this trial. Takeda say it is a tactical decision by Roche to prevent Takeda from cross-examining him. Tactical or not, I infer that Roche has the means to call direct evidence about the work underpinning the Reusch paper. It would allow the matter to be tested in this court and resolved. Roche has chosen not to do this and for that reason I do not draw the inference that the data in Reusch was unreliable in some way, whether or not system suitability tests were done.

252. Roche rightly point out that Takeda could also have brought more evidence, they could have tested vedolizumab on further machines aside from the Orbitrap of Dr Azadi. That is true and I have taken it into account.

253. Finally there was a debate about how the Reusch paper itself characterised the results. This turned on a reference to not having optimised the LC-MS separation for resolution of glycosylated peptides. Taken out of context this sounds significant but it is not. The point is that the authors are addresseing a point of detail about resolving monogalatosylated species. It is not an indication of a lack of reliability overall.

254. In conclusion, I find that the skilled person given the patent would think they could use a nano-bore or a micro-bore LCMS system with QTOF. They could set up either system to produce highly precise results. The machine, set up properly would be able to distinguish between either side of the claim boundary. However depending on which machine they used, the result could either fall inside the claim or outside it. Whichever result the skilled person got, they would not know that if they used the other machine they would get a different answer. A product that fell within the claim measured on one machine could fall outside the claim measured on the other machine. The ambiguity is not of a kind which reveals a fuzzy boundary at the edge of the claim. The claim is truly ambiguous and invalid.

255. The other issue was about the data processing techniques for measuring glycans. This was dealt with by Prof Crispin and Prof Morris. One of the parts of the evidence was based on his analysis of the underlying data generated by the inventors which led to the

patent. That data showed that species other than those in Tables 3a/b were in fact present in the samples. This is a mystery. In the end however I preferred Prof Morris's approach to the data than the one Prof Crispin was instructed to take. The approach Prof Crispin took was based on what he understood the Roche scientists had actually done. As I understand he was asked to do that by the legal team and he did so. Prof Morris's view was that that was not how a skilled person would approach the data. I accept Prof Morris's evidence that his approach is what a skilled person would do. Looked at that way the results are within the claim by the %-TRM method. Therefore they do not give rise to any separate insufficiency.

*Conclusion*

256. This case raised a host of issues. I have addressed what seem to me to be the major points.

257. Vedolizumab is an antibody within the claims but all the relevant claims are invalid. They lack novelty, lack a technical contribution and are insufficient. The patent ought to be revoked.

*Postscript*

258. After judgment was handed down Takeda submitted that there was no finding whether Bihoreau anticipates claims 6 and 7 and invited me to make a finding that these claims were anticipated, drawing attention to Bihoreau claim 56 (referred to in paragraph 136 above). The absence of a finding about claims 6 and 7 is a mistake on my part and I will go ahead and consider the point. In my judgment Bihoreau does not anticipate claims 6 or 7. Claim 56 does disclose the idea of using an antibody with a high fucose:galactose ratio in therapy and Roche's argument to the contrary is wrong. However there is no explicit or implicit link between that idea and antibody Anti-D1 in particular. Without it there is no disclosure of using antibody Anti-D1 in therapy. Without that there is no anticipation of claims 6 or 7.