Neutral Citation Number: [2018] EWHC 2264 (Pat)

Case No: HP-2016-000063

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: 24/08/2018

Before :

THE HON. MR JUSTICE BIRSS

- -

Between :

CHUGAI PHARMACEUTICAL CO. LTD	**Claimant**
- and -	
(1) UCB PHARMA S.A.	
(2) CELLTECH R&D LIMITED	
(3) UCB BIOPHARMA SPRL	**Defendants**

- -
- -

Richard Meade QC and **Mark Chacksfield** (instructed by **Marks & Clerk Solicitors**) for the **Claimant**
Michael Tappin QC and **James Whyte** (instructed by **Powell Gilbert**) for the **Defendants**

Hearing dates: 27th, 28th February, 1st, 6th, 7th, 8th March 2018

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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 case is about United States patent 7,566,771. The patent is entitled Humanised Antibodies and names Robert Adair, Diljeet Singh Athwal, and John Emtage as inventors. The patent is licensed to the claimant Chugai under a patent licence agreement between Chugai and the first defendant UCB. The licence was entered into on 10th December 2007. It is a worldwide licence. For any given territory, royalties are due on sales in that territory pursuant to clause 3.1 as follows:

> "Royalties shall be payable only upon Net Sales in countries where, but for the licence granted by UCB to CHUGAI pursuant to Article 2, CHUGAI or a Permitted Sublicensee would infringe a Valid Claim of the relevant patent …"

2. The meaning of this clause is not in dispute. Royalties are due on sales of a relevant product in a territory if that product falls within the scope of one of the claims of a patent which is in force in that territory, unless and until that patent expires or is finally held invalid.

3. The effect of this clause is the same as a similar clause addressed in ***Celltech v Medimmune*** [2004] EWCA Civ 1331 in which Jacob LJ held that the word "infringe" in such a clause means: to fall within the scope of the claims assuming the patent is valid such that royalties will be payable if the product does fall within the scope of the claims regardless of its validity unless and until the patent is finally declared invalid. As Jacob LJ went on to explain, a bargain of that kind makes commercial sense even though it means that royalties would be due under a patent which might in fact be invalid, provided the patent had not actually been declared invalid (see paragraph 13 of ***Celltech***).

4. Just as in ***Celltech***, so here the licence agreement is governed by English law and has an exclusive jurisdiction clause in favour of the English court (clause 18). Thus, again as in ***Celltech***, the English court has jurisdiction concerning the scope of a licensed patent but the issue of validity can only be tried by the courts of the country of that

patent. Nevertheless considerations about validity, to the extent they are relevant under the applicable law, may be taken into account in this court in resolving the question of claim scope and the fact those considerations arise does not undermine the jurisdiction of this court to decide the issue in this case (see ***Chugai v UCB*** [2017] EWHC 1216 (Pat) Henry Carr J).

5. Since 13th January 2016 the 771 patent has been the last patent left in the licensed portfolio. All the others had expired by that date. That the other patents have expired is not surprising because the portfolio is essentially based on patent applications for which the earliest claimed priority was derived from a British application GB 8928874 filed on 21st December 1989. A UK patent which claimed priority from that filing would normally have to have been filed within one year of it and would expire 20 years later (December 2010). Today, most jurisdictions in the world have patent systems which will generally produce a similar result, with expiry dates counted from the date of filing the appropriate application rather than the date the patent office decides to grant the patent. US law today is similar as well but that similarity is the result of a change in US law. Prior to that and in appropriate circumstances the term of a US patent ran from the date of issue (i.e. grant) for the term of 17 years. The application for the 771 patent was filed with the USPTO on 7th June 1995. That was before US law changed. The prosecution of the application which became the 771 patent through the USPTO took about 13 years and it was issued on 28th July 2009. Accordingly the 771 patent expires on 28th July 2026. Chugai place some emphasis on this, as if to submit that UCB has done something worthy of criticism. Such a criticism would be unwarranted. The fact the term of the 771 patent works in the way it does is no basis for criticising UCB. The patentee simply took a course it was entitled to take under US practice and law at the relevant time.

6. Chugai has a pharmaceutical product called tocilizumab. Tocilizumab is an immunosuppressive drug mainly used in the treatment of rheumatoid arthritis. It is a humanised antibody to the interleukin-6 (IL-6) receptor. The brand name for Chugai's tocilizumab in the USA is Actemra.

7. Chugai has been paying royalties under the licence in relation to sales of tocilizumab. Chugai has not disputed that royalties were due when the licensed patent portfolio contained more patents than the 771 patent. However Chugai contends that tocilizumab does not "infringe a Valid Claim" (within clause 3.1) of the 771 patent and therefore does not attract royalties to the extent the product is manufactured after 13th January 2016. Accordingly Chugai contends that once the 771 patent is the only remaining patent in force, no royalties are due under the licence for such products. Chugai seeks an appropriate declaration to that effect from the English court.

8. UCB accepts that once the 771 patent is the last remaining patent, Chugai's liability to pay royalties for tocilizumab made after 13th January 2016 depends on the question of whether tocilizumab "infringes a Valid Claim" of the 771 patent. UCB's case is that tocilizumab does indeed fall within the scope of the claims of the 771 patent and so a royalty is still due. UCB denies that the declaration should be granted in Chugai's favour.

9. The issue is of some commercial significance. Given that the 771 patent lasts until 2026 and given the high value of sales of tocilizumab, the sums potentially due are substantial. The details are confidential and irrelevant.

10. By the trial the issues had narrowed down to the single question of whether tocilizumab falls within the scope of claim 2 of the 771 patent. That issue is a matter of claim construction and falls to be decided under US law. The nature of tocilizumab is not in dispute. No issues arise relating to parties and so there is no need to distinguish between the three defendants, whom I will refer to simply as UCB.

11. Chugai contends that on UCB's construction of the claim, the claim would be invalid because it would cover a prior art antibody called anti-Tac described in a reference called Queen. UCB admits that on its case on claim construction the antibody in Queen would indeed fall within the relevant claim and also admits, for the purposes of these proceedings only, that that would make the claim invalid. However UCB's submission is that subject to one point, this consequence is irrelevant to the issues the English court has to decide. UCB maintains its case on construction and argues that Chugai's true remedy is and has always been to bring proceedings in the US court to invalidate the relevant claims. If those proceedings were to be commenced, one of the things UCB has made clear is that it would defend such an invalidity attack on the basis that it can "swear behind" Queen. Swearing behind is a feature of US law whereby if a patentee can establish the necessary facts, then a putative item of prior art is not prior art. The facts to be established would essentially be that although the putative prior art dates from before the earliest effective filing date of the patentee's patent, the patentee's invention was actually made before the prior art. Establishing a right to swear behind involves a factual inquiry into the conception of the invention and its reduction to practice. The details of swearing behind do not matter for the purposes of this judgment.

12. The one point on which UCB accepts validity does play a role under US law relating to claim construction is as what has been called a "tie-breaker". In other words if, having applied all the available tools of claim construction, the claim is still ambiguous, then the claim should be construed to preserve validity. However UCB contends that in this case the claim is clear and that principle does not apply.

13. At one stage in these proceedings the factual question of swearing behind was one of the issues to be decided. Chugai does not accept that UCB can establish the facts necessary to swear behind Queen. However UCB's admission for the purpose of these proceedings that the claim would be invalid over Queen on UCB's construction meant that those issues could be dropped. This was discussed at the pre-trial review (PTR) on 8th February 2018. Chugai were initially reluctant to agree that the swearing behind issues should therefore be dropped because of a concern that even if Chugai won this UK case, despite the binding nature of the declaratory relief, there might be scope for UCB to try to bring infringement proceedings in the USA against Chugai. Whether that was a realistic concern or not does not matter. The issue was resolved at the PTR by UCB giving an undertaking that if Chugai obtain the declaration sought from this court, UCB and its future assignees will not commence proceedings alleging infringement of any claim of the 771 patent relating to tocilizumab. Accordingly swearing behind is no longer in issue.

14. The sole question before the court therefore is whether tocilizumab falls within claim 2 of the 771 patent.

The witnesses

15. Chugai's technical expert was Professor Tony Rees. He is Emeritus Professor of Biochemistry at the University of Bath. He was well qualified to address the issues in this case and was a good witness.

16. UCB's technical expert was Dr Geoffrey Hale. Following his PhD Dr Hale remained at Cambridge University as a post-doc and later as manager of the Therapeutic Antibody Centre. In 1981 Dr Hale discovered a family of rat monoclonal antibodies called "Campath" which became well known in the field. Campath-1G was the first therapeutic antibody to be humanised. Chugai suggested Dr Hale's work and experience was not directly related to the issues in this case. I do not agree. Dr Hale's unrivalled experience in antibody technology meant he was also well qualified to assist the court, just as Prof Rees was.

17. Chugai also contended that Dr Hale took a restricted approach to the documents. That is not a criticism of Dr Hale as a witness but is said to undermine the utility of his evidence. UCB contended he took the correct approach mandated by US law. It is not fruitful to spend time analysing in depth what approach Dr Hale actually took. The expert's function is to educate the court as to the technology and express opinions on technical matters. Dr Hale did exactly that.

18. Chugai also submitted that Dr Hale was careless, e.g. in his treatment of mapping examples to the claims and in relation to the L929 assay. There were some slips but they were no indication of carelessness and are no reason to place less weight on Dr Hale's evidence.

19. There was also a suggestion (by UCB) that Dr Hale was tired at the end of the cross-examination. That was advanced to account for what Chugai said were in effect concessions made by Dr Hale. Cross-examination on the scientific issues in a case like this is demanding on all concerned – the cross-examiner, the judge and the witness. Dr Hale was tiring slightly at the end of the day but not enough to warrant a break. He was still fully focussed on the questions and issues. There is no reason to discount his answers at that time.

20. Chugai also submitted that Dr Hale sometimes did not answer the question. So he did, but so too did Prof Rees. Neither witness was taking an argumentative or advocacy based approach to answering the questions. Both experts gave their oral evidence fairly and were seeking to help the court. I am grateful to both Dr Hale and Prof Rees for their evidence in this case.

21. Chugai's US law expert was Judge Paul Redmond Michel (a retired judge of the United States Court of Appeals for the Federal Circuit). UCB's US Law expert was Professor Donald Chisum (author of *Chisum on Patents*). Each gentleman is a well known expert in the field of US patent law. Neither was cross-examined. I am grateful to them both for the work they have done to explain US law to the court and for the clarity with which they both expressed themselves.

Technical background

Antibody structure

22. In nature, an antibody molecule is a protein created by the immune system of animals. Its function is to locate and bind foreign antigens in the body, which then leads to a downstream immune response to that foreign antigen. For example, an antibody bound to a foreign antigen may interfere with the function of the antigen or the bound complex may be recognised by another part of the immune system that can destroy the foreign antigen.

23. As protein molecules, antibodies are chains of amino acids linked by peptide bonds (polypeptides). An individual amino acid in the chain is sometimes referred to as a residue. When comparing two sequences features can be said to be "conserved" when they are the same. That can apply to particular residues and to other features such as the three dimensional shape of the protein. The fact that two sequences have the same residue at the same place may or may not be scientifically interesting. A conserved residue may indicate that there is a technical reason why that particular residue has to be in that place to make the antibody work or it may be random happenstance.

24. There are several different classes of antibody. The most common type of antibody, and most relevant to this case, are IgG antibodies. In nature IgG antibodies consist of four polypeptide chains; two identical chains called heavy chains and two identical chains called light chains. The heavy chain is made up of about 440 amino acids, split into four "domains" of about 110 amino acids each; one domain contributes the variable portion (Variable Heavy or V_H) and three domains of about 330 amino acids make up the heavy chain constant region (Constant Heavy or C_H1, C_H2 and C_H3). The light chain correspondingly has one variable portion (V_L) and one constant region (C_L).

25. Within each of the variable domains, there are three hypervariable sequences known as complementarity determining regions (CDRs) interspersed between less variable sequences known as framework regions. The antigen is bound at the antigen binding site. Each antigen binding site is made up of six CDRs, three from the V_H and three from the V_L. These differ from one antibody to the next in their amino acid sequence, and provide the specificity and variation in antibody binding.

26. The four chains are bound together by disulphide bridges and non-covalent bonds to form a Y shape:

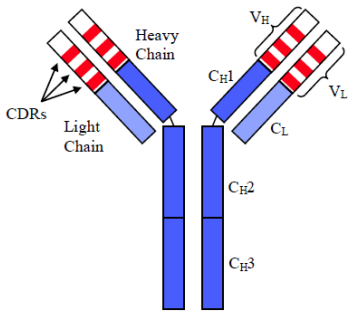


Figure 1: Antibody structure[3]
Traditional antibody schematic representation of the "Y" shape of the heavy and light chains. The oblongs represent the antibody chain primary sequence with constant domains in blue and variable domains in red and white. Positions of the CDRs in the primary structure are shown as red bars.

27. The CDRs have been defined in two ways. Kabat and Wu analysed and aligned the sequences of numerous antibodies and produced a well-known reference work

containing their database of sequences (Kabat et al (1987)). Based on the extent of residue variability, they defined the CDRs of the heavy chain as being at positions 31-35 (CDR1), 50-65 (CDR2) and 95-102 (CDR3), using a numbering system that they developed which is now called the Kabat system. Chothia and colleagues arrived at similar, though not identical, results by structural analysis of numerous antibodies, identifying loops between strands of beta-sheets that formed hypervariable regions. In the heavy chain the first hypervariable region defined by Chothia starts at residue 26 (using the Kabat numbering system). Chothia also had a numbering scheme and it is an alternative to the Kabat numbering system. The framework regions between the CDRs were known, through the work of Novotný and others, not only to be less variable in terms of sequence than the CDRs, but also to be highly conserved in terms of their three-dimensional structure.

28. Certain amino acid side chains in the framework residues and in the CDRs approach each other at particular points so that parts of the framework residues can influence the structure or shape of the CDRs. Different combinations and numbers of amino acids in the six CDRs and small variations in the framework residues can produce antigen binding sites with very different three-dimensional topographies and hence different binding specificities.

Antibody technology

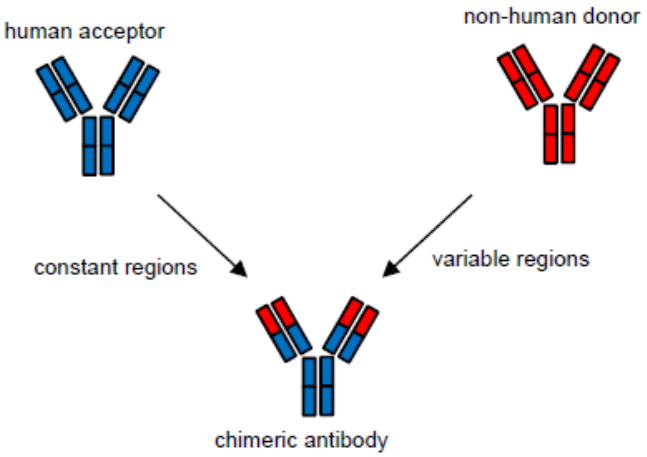
29. Antibodies are made by a kind of white blood cell called a B-cell. One B-cell produces one kind of antibody, so "monoclonal" antibodies comes from cultured clones of a single B-cell. However B-cells cannot be grown in culture for any length of time and could not be used as a source of sufficient quantities of antibodies for therapeutic use. A major breakthrough in the 1970s was the work of Kohler & Milstein which allowed monoclonal antibodies to be produced in large quantities using a murine hybridoma technique. In this context "murine" means mouse or rat. The hybridoma technique works by fusing a murine B-cell which produces the antibody of interest with a myeloma cell. The myeloma cells are an immortal cancer cell line which grows in culture. The hybrid cell is also immortal.

30. However this technique has drawbacks due to the murine nature of the antibodies. The way the antibodies were generated to aim at a therapeutic target is that the target molecule (say human TNF protein) is injected into a mouse (or rat). The mouse may have its own kind of TNF (mTNF) but human TNF (hTNF) is different and the mouse's immune system recognises the injected protein as foreign, treats it as an antigen, and raises antibodies to that protein. The mouse is then killed and its B-cells are analysed to find one which produces a useful anti-hTNF antibody. A hybridoma made from that B-cell is used to make therapeutically useful quantities of the antibody. But the antibody is still a mouse antibody. When it is injected into a human to treat a disease, the human will have his or her own antibodies but a mouse antibody is a different kind of protein and the human's immune system may begin to recognise the injected protein as foreign, treat it as an antigen, and raise antibodies to that protein. This is called the human anti-mouse antibody (HAMA) response.

31. Now one might think the simple answer is to make human antibodies instead of murine antibodies but that does not work for two reasons. First a human immune system is not supposed to raise antibodies to human proteins like hTNF because that would mean the immune system was attacking the host's own body. Second, the hybridoma technique

requires the skilled person to isolate a particular B-cell from the host which produces the antibody of interest. This involves killing the murine host and is obviously impossible for a human host.

32. So the first response to the problem was the production of chimeric antibodies. These antibodies contain human constant domains and mouse variable domains. Dr Hale produced a useful diagram showing this:



(The diagram only makes sense in colour. The human is blue, the non-human is red and the chimeric antibody has blue constant parts and red variable parts.)

33. The idea is that because most of the antibody which will be used is human, with any luck the human immune system will accept it as human and not raise antibodies to it. In fact administration of those antibodies also led to a HAMA response, attributed to the mouse variable domains. I will come back to that below.

34. To make the chimeric antibody the skilled team starts with two antibodies. The human antibody is used for the constant regions so as to try and reduce the HAMA response. The non-human antibody has antigen binding sites specific for the therapeutic target (say hTNF). It is necessarily non-human (usually murine) because it is not possible directly to make human antibodies specific for useful therapeutic targets, for the reasons explained above. On the other hand the human antibody also has antigen binding sites but they are irrelevant and are going to be discarded in the final chimeric structure.

35. Another feature of chimeric antibodies worth highlighting at this stage is the involvement of genetic engineering technology. Although the diagram above is drawn as if chunks of antibody are cut out and stuck together, that is not what is going on. Once the skilled team has a suitable human antibody and murine antibody, the protein and DNA sequences for the antibodies are determined (the team will probably have a library of known acceptor sequences). The editing happens at the level of DNA sequences. A new DNA sequence is produced using sequences which code for the relevant polypeptide chains of the human and murine antibodies. The new DNA sequence therefore codes for the chimeric antibody sequence.

36. At the heart of the matter is the idea that these sort of antibodies are designed things. The antibody is constructed to a plan. That plan is an amino acid sequence encoded in DNA. The plan is itself something which has been specified by the scientists concerned. To say that part of the antibody is human is really to say something about the plan from which the antibody is constructed. The amino acid sequence has two conceptual sources – a human source and a non-human source.

37. There were at least two well-known techniques by which the new DNA sequence could be created. First, a DNA sequence coding for the desired amino acid sequence could be constructed from synthetic oligonucleotides. This can be called gene-assembly. Secondly, a cDNA sequence coding for an antibody could be obtained, and the required DNA sequence obtained by a series of site-specific mutagenesis steps. In either case, the DNA sequence would then be inserted into an expression vector which is then introduced into a suitable host cell for the expression of the antibody in order to make antibody proteins on a large scale.

38. However, as mentioned already, a problem with chimeric antibodies is that they did still produce HAMAs.

39. In order to address this, in 1986 and 1988 the Winter group in Cambridge published work in which they had created heavy chains containing murine CDRs and human constant domains and framework regions. Antibodies made this way (when the heavy chains were co-expressed with murine light chains) were referred to as 'CDR-grafted'. These antibodies are called "humanised" antibodies.

40. Note that compared to chimeric antibodies, CDR-grafted humanised antibodies are now in effect entirely human but with only the CDRs (which you need for target specificity) being murine in nature. That might be thought to be as good as you could get in order to deal with the HAMA response, and so it proved. The HAMA response was not a problem. However there was a new drawback. The CDR-grafted antibodies did show some affinity for the antigen in question but it was reduced. Simplifying crudely, one could imagine that the antibody making system inside the mouse, which made the murine donor antibody in the first place, had constructed its CDRs to work on a murine framework. In the CDR-grafted humanised antibody the murine CDRs are now held in a human framework, which is not their natural framework. This difference might mean that the resulting three-dimensional shape of the whole antigen binding site structure in a CDR-grafted antibody is slightly different from the three-dimensional shape in the original murine antibody. So the binding site, formed by the interaction of the CDRs and parts of the framework, is still functional to some extent but less well.

41. A development of this work was published by the Winter group in 1988 (Riechmann et al (1988) "Reshaping human antibodies for therapy"). The CDR-grafting approach was extended to include the CDRs of the light chain. Further, a residue in the human heavy chain framework region was changed to be a mouse residue. Using the crude explanation given above for the possible cause of the affinity problem with CDR-grafting, one can see that changing the human framework region to make it more like a mouse framework region might make sense. Riechmann reported that the technique did increase binding affinity.

42. A point of detail in Riechmann is that the residue which was changed was in the framework region by the Kabat definition, although by the Chothia definition it was in the hypervariable loop regions.

The issue

43. The relevant claims in the patent are in this form:

> 1. A humanised antibody molecule having affinity for an antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), wherein, according to the Kabat numbering system, in said composite heavy chain at least residues 26 to 35, 50 to 58 and 95 to 102 in the CDRs and at least residues 48, 49, 71, 73, 76, 78, 88, and 91 in the framework regions are non-human donor, provided that said heavy chain is not a chimeric antibody heavy chain having a donor variable domain and a human constant domain.
>
> 2. A humanised antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs) and framework regions, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs are non-human donor at residues 31 to 35, 50 to 58, and 95 to 102; and said framework regions are non-human donor at:
>
> a) residue 6;
> b) one or more of residues 23 and 24;
> c) one or more of residues 48 and 49;
> d) one or more of residues 71 and 73;
> e) one or more of residues 75, 76, and 78; and
> f) one or more of residues 88 and 91;
>
> provided that said heavy chain is not a chimeric antibody heavy chain having a donor variable domain and a human constant region
>
> 3. The antibody molecule of claim 2 wherein residue 2 of said composite heavy chain is donor.
>
> 4. The antibody molecule of claim 2 wherein residue 72 of said composite heavy chain is donor.
>
> *[…]*
>
> 6. The antibody molecule of claim 2 wherein residue 110 of said composite heavy chain is donor.

44. Claim 1 is not alleged to cover tocilizumab but has a part to play in the construction issues. The critical claim is claim 2. UCB also pleaded reliance on claims 3, 4 and 6. However, as the issues have narrowed, nothing turns on them because if tocilizumab falls within claim 2 then UCB win, whereas if tocilizumab does not fall within claim 2 then it cannot fall within claims 3, 4 or 6. Nevertheless it is worth setting out the terms of those claims as well.

45. Claim 2 will be construed below but at this stage it can be seen that for an antibody to fall within the claim requires that certain specified residues in the framework region "are non-human donor". The simple problem is what to do when the amino acid is conserved, in other words is the same in the mouse (i.e. non-human) donor antibody and the human acceptor.

46. To see the significance of the conserved residues in this case, it is convenient to consider tocilizumab itself. Tocilizumab is a humanised antibody based on a mouse donor antibody called PM-1 and a human acceptor antibody called NEW.

47. The amino acid residues in tocilizumab relevant to claim 2 (and then claims 3, 4 and 6) are summarised in the following table. Of those residues, the ones which are conserved are noted in the right hand column:

Position	**Mouse**	**Human**	**Tocilizumab**	
6	Glutamic Acid (E)	Glutamic Acid (E)	Glutamic Acid (E)	*conserved*
23	Threonine (T)	Threonine (T)	Threonine (T)	*conserved*
24	Valine (V)	Valine (V)	Valine (V)	*conserved*
48	Methionine (M)	Isoleucine (I)	Isoleucine (I)	
49	Glycine (G)	Glycine (G)	Glycine (G)	*conserved*
71	Arginine (R)	Valine (V)	Arginine (R)	
73	Threonine (T)	Threonine (T)	Threonine (T)	*conserved*
75	Lysine (K)	Lysine (K)	Lysine (K)	*conserved*
76	Asparagine (N)	Asparagine (N)	Asparagine (N)	*conserved*
78	Phenylalanine (F)	Phenylalanine (F)	Phenylalanine (F)	*conserved*
88	Serine (S)	Alanine (A)	Alanine (A)	
91	Tyrosine (Y)	Tyrosine (Y)	Tyrosine (Y)	*conserved*
The residues below are relevant to claims 3, 4 and 6 but not claim 2				
2	Valine (V)	Valine (V)	Valine (V)	*conserved*
72	Aspartic Acid (D)	Aspartic Acid (D)	Aspartic Acid (D)	*conserved*
110	Threonine (T)	Threonine (T)	Threonine (T)	*conserved*

48. The importance of conserved residues is obvious from the table. Of the residues relevant to claim 2, there is only one where the amino acid used in tocilizumab is both the same as the mouse donor residue and different from the human acceptor residue. That is at position 71. Chugai point out, correctly, that tocilizumab would infringe on UCB's construction irrespective of that change at position 71 because the claim requires non-human donor at "one or more of residues 71 and 73" and so the conserved threonine residue at position 73 would satisfy the claim anyway.

49. UCB's case is that "donor" includes conserved residues. Chugai's case is that the term "donor" is used to describe source and so, since the source of the acceptor framework region is human, only framework residues which have been changed into a different mouse residue count as donor. An unchanged framework residue is an acceptor residue.

Thus for the numbered framework residues set out in the claims, any framework residues which are conserved as between the murine and human sequences are not "donor".

50. It can be seen therefore that tocilizumab only infringes if conserved residues are counted as donor within claim 2. As it happens some changes were made to the human framework acceptor sequence in tocilizumab, but none of them are necessary to render tocilizumab infringing on UCB's construction. Accordingly Chugai point out that on UCB's construction the claim would cover an antibody for which no changes to the human acceptor sequence had been made at all. UCB contend there is nothing surprising about this result, it would only apply because the human acceptor sequence which had been used had the right residues (i.e. the same ones as appear in the non-human donor antibody) at the defined positions in the set defined by claim 2.

51. The other aspect of the issue is the fact that on UCB's construction the prior art humanised anti-tac antibody in Queen would fall within the claims. It is common ground that this is so. The relevant residues in the humanised anti-Tac antibody are set out below in the same format as above.

Position	**Mouse**	**Human**	**Queen Anti-Tac**	
6	Glutamine (Q)	Glutamine (Q)	Glutamine (Q)	*conserved*
23	Lysine (K)	Lysine (K)	Lysine (K)	*conserved*
24	Alanine (A)	Alanine (A)	Alanine (A)	*conserved*
48	Isoleucine (I)	Methionine (M)	Isoleucine (I)	
49	Glycine (G)	Glycine (G)	Glycine (G)	*conserved*
71	Alanine (A)	Alanine (A)	Alanine (A)	*conserved*
73	Lysine (K)	Glutamic Acid (E)	Glutamic Acid (E)	
75	Serine (S)	Threonine (T)	Threonine (T)	
76	Serine (S)	Asparagine (N)	Asparagine (N)	
78	Alanine (A)	Alanine (A)	Alanine (A)	*conserved*
88	Alanine (A)	Alanine (A)	Alanine (A)	*conserved*
91	Tyrosine (Y)	Phenylalanine (F)	Tyrosine (Y)	
The residues below are relevant to claims 3, 4 and 6 but not claim 2				
2	Valine (V)	Valine (V)	Valine (V)	*conserved*
72	Aspartic Acid (D)	Aspartic Acid (D)	Aspartic Acid (D)	*conserved*
110	Threonine (T)	Threonine (T)	Threonine (T)	*conserved*

52. Chugai also advance an alternative construction of the claims, that they are product by process claims, limited to products made by a design method which involved considering and changing residues at the defined positions. As a matter of fact, in the course of development of tocilizumab residues at positions 1, 27, 28, 29, 30, 48 and 71 were considered as positions to change the human acceptor residue into the (different) mouse donor residue, although in the final product changes were only made at 27-30 and 71. That is a different set of residues from the set in the claims of the 771 patent and they were identified by a different approach from the one described in the patent. UCB deny the claims are product by process claims and submit therefore that the way tocilizumab was actually developed is irrelevant. There is no challenge to Chugai's factual evidence about how tocilizumab was developed and therefore it is common

ground that if the claims are to be construed as product by process claims then tocilizumab does not infringe.

US law

Claim construction

53. It is common ground that the question of infringement in this case is to be determined under U.S. law. I have been assisted by detailed submissions from the parties on the applicable U.S. law principles and authorities in support of their respective positions and further, by the foreign law expert reports on U.S. patent law.

54. Over the course of these proceedings, the U.S. law issues in dispute between the parties have narrowed considerably.

Claim construction: General principles

55. The leading authority on claim construction is the *en banc* decision of the CAFC in ***Phillips v. AWH Corp.***, 415 F.3d 1303 (Feb. Cir. 2005).

56. The words of a claim are generally given their ordinary and customary meaning, which is the meaning that the term would have to a person of ordinary skill in the art as of the effective filing date of the patent application (***Phillips*** at pp1312-1313).

57. Claim construction is an objective exercise. The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation. Such a person is deemed to read the words used in the patent documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field (***Phillips*** at p1313).

58. As to the sources available to assist the Court in the claim construction analysis, the person of ordinary skill in the art is deemed to read the claim term in the context of the entire patent, including the meaning and scope with which the relevant terms are used in the claims themselves, the specification and the prosecution file, including the prior art cited therein (***Phillips*** at p1313) (together the "intrinsic evidence"). The Court is also free to examine extrinsic evidence concerning scientific principles, the meaning of technical terms and the state of the art. That extrinsic evidence includes expert and inventor testimony, dictionaries and learned treatises (***Phillips*** at pp1313-1314 and p1317).

59. There is a presumption that the same terms appearing in different portions of the claims should be given the same meaning, or read consistently, unless it is clear from the specification and prosecution file that the terms have different meanings in different portions of the patent. This presumption is sometimes characterised as a "strong one".

60. In ***Modine Manufacturing Co. v. US ITC*** 75 F.3d 1545, 1551 (Fed. Cir. 1996), the CAFC held that "all rules of construction must be understood in terms of the factual situations that produced them, and applied in fidelity to their origins". This statement is relevant generally (i.e. the rules have exceptions depending on the facts) although the particular context of ***Modine*** was about reading limitations from preferred embodiments.

61. I turn to consider in turn the various sources which form part of the intrinsic evidence.

Intrinsic evidence - the claims

62. There is a long established principle that the "claims of a patent define the invention to which the patentee is entitled", and as such, the patent claims themselves have been found to provide "substantial guidance as to the meaning of particular claim terms" (***Phillips*** at p1312; p1314). It is also the norm to use claim terms consistently throughout a patent and the usage of a term in one claim can illuminate the meaning of the same term in other claims (***Phillips*** at p1312). The patentee's lexicography has been repeatedly held to govern the meaning of terms in the patent.

63. In construing claims, the court is aware of the risk of imposing improper limitations on the claims. This concern is at the forefront of any construction analysis. As was said in ***Phillips*** (at pp1330-1331), disapproving the approach taken in ***Texas Digital Systems, Inc. v. Telegenix, Inc.***, 308 F.3d 1193 (Fed. Cir. 2002), when construing a disputed claim term, a court should not start with dictionaries, encyclopaedias and/or treatises to determine the ordinary and customary meaning of a disputed term, if it then limits itself to reading the intrinsic evidence only to displace the pre-identified or presumptive 'textbook' meaning. The CAFC in ***Phillips*** said at p1331:

> "The main problem with elevating the dictionary to such prominence is that it focuses the inquiry on the abstract meaning of words rather than on the meaning of claim terms within the context of the patent. Properly viewed, the "ordinary meaning" of a claim term is its meaning to the ordinary artisan after reading the entire patent."

Intrinsic evidence - the specification

64. The specification is always highly relevant to the claim construction analysis and has been described as the "single best guide to the meaning of a disputed term" (***Phillips*** at p1315). In addition to describing what the inventors did invent, the specification may also assist to identify what the inventors did not invent, such as where prior art is distinguished. As the claims are part of a fully integrated written instrument, it is necessary to consider the specification as a whole, and to read all the portions of the specification, if possible, in a manner that renders the patent internally consistent (see ***Phillips*** at p1315).

65. Claims cannot be of broader scope than the invention that is set forth in the specification and hence, the Court should adopt the construction which will secure to the patentee his actual invention (***Phillips*** at pp1321-1322).

Preferred embodiments

66. Care should also be taken to ensure that extraneous limitations from the specification such as features and processes disclosed as embodiments or examples are not read into the claims. On the other hand, the specification is not to be used to expand the scope of protection beyond that delineated by the terms of the claims (as properly construed). It has been acknowledged that the line between construing claims with the aid of the specification and the prohibition on importing extraneous limitations is fine and

sometimes difficult to delineate. The guidance provided in ***Phillips*** (at p1323) is as follows:

> The line between construing terms and importing limitations can be discerned with reasonable certainty and predictability if the court's focus remains on understanding how a person of ordinary skill in the art would understand the claim terms. For instance, although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments. In particular, we have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment. That is not just because 35 U.S.C.S. § 112 requires that the claims themselves set forth the limits of the patent grant, but also because persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments.

67. It is common ground between the parties that U.S. law recognises, for a number of reasons, that all claims need not cover all preferred embodiments. Both parties agree that there may be reasonable reasons to explain why some embodiments in a patent specification are excluded from some claims, such as where the disclosed embodiments are within the scope of other allowed but un-asserted claims or where a family of patent applications have been filed based on the same initial application (and unclaimed embodiments have been pursued in other applications in the family).

68. In ***Sinorgchem Co. US Int'l Trade Comm'n*** 511 F. 3d 1132, 1138 (Fed. Cir. 2007), the CAFC said, "where multiple embodiments are disclosed, we have previously interpreted claims to exclude embodiments where those embodiments are inconsistent with unambiguous language in the patent's specification or prosecution history". Where the prosecution history requires a claim construction that excludes some but not all of the preferred embodiments, such a construction is permissible (***Sinorgchem*** citing ***Rheox, Inc. v. Entact***, *Inc*., 276 F.3d 1319, 1327 (Fed. Cir. 2002)).

69. However, a claim construction that excludes all preferred embodiments is rarely, if ever, correct (***Vitronics Corp. v. Conceptronic, Inc.***, 90 F.3d 1576 (Fed.Cir. 1996 at p1583)). Professor Chisum explained that adopting a construction which excludes all preferred embodiments from the claims is disfavoured, and would require "highly persuasive" evidentiary support. All the more so if the proposed construction would not encompass any disclosed embodiments at all (not just preferred ones).

Re-definition and disclaimers

70. Where a claim term is considered to have a clear and well-established meaning, then the specification would have to redefine or disclaim that meaning in order to displace it. While a redefinition and disavowal must be clear in order to limit the claim scope, there are no special words required to signal deviations from the ordinary meaning. The U.S. courts have not excluded the possibility of a clear implicit redefinition or disavowal.

Intrinsic evidence – the prosecution file

71. In addition to consulting the specification, the court should also consider the patent's prosecution file, which includes the complete record of the proceedings before the United States Patent and Trademark Office and includes the prior art cited during the examination of the patent (***Phillips*** at p1317). The prosecution file helps inform the meaning of the claim language by demonstrating how the inventor and the USPTO understood the invention.

72. Furthermore, the prosecution file serves an important public notice function in relation to any prior art that the patentee identified and distinguished, even in circumstances where the examiner did not rely on the particular statements.

73. The parties agree that as the prosecution file represents an ongoing negotiation between the USPTO and the applicant, it often lacks the clarity of the specification, which may make it less useful for claim construction purposes (***Phillips*** at p1317). However, there may also be cases where the specification provides little or no guidance on a particular issue and the prosecution file is a more valuable source of such guidance, or where the prosecution file is useful to demonstrate how the inventor understood the invention and claim scope (***Phillips*** at 1317). The relative importance of each source will turn on the particular facts of the case.

74. On both parties' cases, if the claim construction was not clear on the basis of the claim language and specification, the court should turn to the prosecution file (as a whole) to inform its construction of the claim.

75. As with the specification, the customary and ordinary meaning of a term can also be changed by the contents of the prosecution file. However, the standard for a prosecution disclaimer is high and it is necessary for there to be a clear and unmistakable disclaimer or disavowal of scope which is neither ambiguous nor amenable to multiple reasonable interpretations. One example of this could be a statement distinguishing an invention or the claims from prior art.

76. Professor Chisum says that an 'apparently-disclaiming' statement during prosecution which is inaccurate factually or inconsistent with the specification and claim language may not give rise to a disclaimer. The test he sets out is whether a reasonable reader (who is a person of ordinary skill in the art) would recognise that the statement was a mistake in light of the other intrinsic evidence. Chugai did not submit any evidence to challenge this view of US law. In ***Biotech Biologische Natuverpackungen GmbH v. Biocorp, Inc.***, 249 F.3d 1341, 1348 (Fed. Cir. 2001), the CAFC said:

> "An error in the prosecution record must be viewed as are errors in documents in general; that is, would it have been apparent to the interested reader that an error was made, such that it would be unfair to enforce the error."

77. In ***Biotech***, the erroneous statement in the file was contrary not only to the plain language of the claims and the specification, but also to other statements in the same prosecution document.

Extrinsic evidence

78. Aside from the intrinsic evidence, what US law calls "extrinsic evidence" can also be relevant. Since a patent is both a technical and legal document, this extrinsic evidence can be used to educate the court on the field of the invention and how it works, to determine what a person of ordinary skill in the art would understand the claim terms to mean or to establish that a particular term in the patent or the prior art has a particular meaning in the relevant field.

79. Extrinsic evidence is a secondary source however and may be less significant than the intrinsic record in determining the legally operative meaning of the claim language (***Phillips*** at p1317). Care must therefore be taken to ensure that it is consistent with the description of the invention as set out in the patent and prosecution file, and it may not be used to contradict a claim meaning that is unambiguous in light of the intrinsic evidence (***Phillips*** at pp1318-1319).

80. In ***Vitronics***, the CAFC set out how extrinsic evidence should be used in claim construction. At page 14:

> However, as we have recently re-emphasized, extrinsic evidence in general, and expert testimony in particular, may be used only to help the court come to the proper understanding of the claims; it may not be used to vary or contradict the claim language. Id. at 981, 34 USPQ2d at 1331. Nor may it contradict the import of other parts of the specification. Indeed, where the patent documents are unambiguous, expert testimony regarding the meaning of a claim is entitled to no weight. *Southwall*, 54 F.3d at 1578, 34 USPQ2d at 1678.

81. In ***Phillips*** the CAFC also addressed the role of extrinsic evidence. The judgment included the following at p1317-1318:

> … Finally, undue reliance on extrinsic evidence in construing patent claims poses the risk that it will be used to change the meaning of claims in derogation of the indisputable public records consisting of the claims, the specification and the prosecution history, thereby undermining the public notice function of patents. *Southwall Techs.*, 54 F.3d at 1578.
>
> [18.19.] In sum, extrinsic evidence may be useful to the court, but it is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence. Nonetheless, because extrinsic evidence can help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean, it is permissible for the district court in its sound discretion to admit and use such evidence. In exercising that discretion, and in weighing all the evidence bearing on claim construction, the court should keep in mind the flaws inherent in each type of evidence and assess that evidence accordingly.

Claim Construction: Validity

82. If after consideration of all the intrinsic and extrinsic evidence, the claim is still ambiguous, the parties agree that the court should adopt the construction, if possible, which preserves the validity of the patent (***Phillips*** at pp1327-1328). The CAFC stressed that the validity analysis should not be a "regular component of claim construction" and is limited to cases in which a claim was ambiguous after all available claim construction tools from the intrinsic and extrinsic evidence had been applied. As the CAFC put it, the applicability of the doctrine in a particular case therefore depends on the strength of the inference that the [Patent Office] would have recognised that one claim interpretation would render the claim invalid, and that the [Patent Office] would not have issued the patent assuming that to be the proper construction of the term.

83. However, where the claims are only susceptible to one reasonable construction, this tie-breaker step does not allow the court to construe them differently from their plain meaning in order to preserve the patent's validity (***Phillips*** p1327 citing ***E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.,*** 849 F.2d 1430, 1434 (Fed.Cir.1988)).

84. While this principle is based on it being reasonable to infer that the USPTO would not knowingly issue an invalid patent, the applicability of the tie-breaker in any particular case depends on the strength of the inference that the USPTO would have recognised that one claim interpretation would have rendered the claim invalid and the USPTO would not have issued the patent assuming that to be the proper construction of the claim (***Phillips*** at 1328).

Product-by-process claims

85. Chugai's alternative construction case is that to the extent it is wrong on its proposed construction of the claim(s), the claim should be construed as a product-by-process claim. It is common ground that US law recognises product by process claims. Unsurprisingly the fact that a patent specification describes how to make a product does not mean a claim to the product is to be limited to the method by which it was made (***Research Corp. Tech. v Microsoft Corp.*** 627 F.3d 859, 873 (Fed. Cir. 2010)).

Issues of U.S. law which are in dispute

86. I will now address the points of US law which are in dispute.

A limit to the use of prosecution history?

87. The parties agreed that there is no rigid hierarchical approach to claim construction, although both parties recognise that as a practical matter, the CAFC's decisions often address the claims, specification and prosecution file in that order.

88. UCB argues, supported by Prof Chisum, that if the ordinary and customary meaning of a disputed term can be firmly established from consideration of claims and the specification, the prosecution file is then only considered by the court either to: (a) identify 'clear and unmistakable' disclaimer or disavowal or (b) to confirm, not displace, the meaning that was clear on the basis of the specification. As part of this submission UCB argues that there is no authority in support of the proposition which it says Chugai advances, that the prosecution file (even in the absence of a disclaimer or disavowal) can be used to change, rather than confirm, the construction of a claim term that was clear on the basis of the claims and specification. One decision relied on by

UCB is a case cited as ***In re Gabapentin Patent Litigation*** 503 F.3d 1254 (Fed. Cir. 2007) (***Warner-Lambert Co., et al v Purepac Pharmaceuticals Inc. et al***). Here the CAFC were not persuaded by the appellant's reliance on the prosecution history to support their construction "particularly in this case where the claim language provides a clear definition of the disputed claim term, supported by the specification."

89. Chugai argues, supported by Judge Michel, that UCB's approach is artificial and that ***Phillips*** stands for the proposition that courts should consider all of the intrinsic evidence without any hierarchy or restriction (which prevents the court from looking at all the sources in their entirety), before coming to a view on construction. In its submission, one does not, therefore, seek to make interim conclusions about construction and clarity based on only part of the intrinsic record.

90. As a general proposition, I prefer Judge Michel's opinion to that of Professor Chisum because it seems to me to follow what the CAFC said in ***Phillips***, for example at p1324:

> "In *Vitronics*, this court grappled with the same problem and set forth guidelines for reaching the correct claim construction and not imposing improper limitations on claims. 90 F.3d at 1582. The underlying goal of our decision in *Vitronics* was to increase the likelihood that a court will comprehend how a person of ordinary skill in the art would understand the claim terms. See id. at 1584. In that process, we recognized that there is no magic formula or catechism for conducting claim construction. Nor is the court barred from considering any particular sources or required to analyze sources in any specific sequence, as long as those sources are not used to contradict claim meaning that is unambiguous in light of the intrinsic evidence. See id. at 1583-84; *Intel Corp. v. VIA Techs., Inc.*, 319 F.3d 1357, 1367 (Fed. Cir. 2003). For example, a judge who encounters a claim term while reading a patent might consult a general purpose or specialized dictionary to begin to understand the meaning of the term, before reviewing the remainder of the patent to determine how the patentee has used the term. The sequence of steps used by the judge in consulting various sources is not important; what matters is for the court to attach the appropriate weight to be assigned to those sources in light of the statutes and policies that inform patent law. *Vitronics*, 90 F.3d at 1582. In *Vitronics*, we did not attempt to provide a rigid algorithm for claim construction, but simply attempted to explain why, in general, certain types of evidence are more valuable than others. Today, we adhere to that approach and reaffirm the approach to claim construction outlined in that case, in *Markman*, and in *Innova*."

91. However I suspect that in truth there is less to this point of disagreement than meets the eye. I believe Prof Chisum is correct as a matter of observation that no example can be produced in which a court has used the prosecution file to change the construction of a claim term which was already clear from the specification and claims and, for similar reasons, the only examples in which the prosecution file has been found to have a value in such a case are when there is a clear disclaimer or as confirmation of a view already

formed. These observations are true because in practice the application of the legal principles works out that way.

92. In other words what one is likely to get from the prosecution file is likely to differ depending on whether one has been able to form a clear view of construction from the claims and specification themselves. If such a clear view has been formed then the prosecution file is likely only to have utility as a source of disclaimers or confirmation, but if no clear view has been formed the prosecution file may well help resolve the issue.

The approach to prior art cited in the patent or prosecution file

93. The parties do not agree how the court should approach prior art cited in the specification and/or prosecution file. The debate is whether the court is limited to what the specification and/or prosecution file states or refers to about the prior art and in particular the distinction between the invention and the prior art; or whether the court is permitted to review the actual disclosures in the prior art, not limited to the references or statements in the specification and/or prosecution file. UCB, supported by Prof Chisum, argues for the more limited approach, Chugai, supported by Judge Michel, argues for the wider approach.

94. UCB contends it is proper for the court to consider if and how the patentee sought to distinguish any prior art cited in the specification and/or the prosecution history and also that it is legitimate to take into account how prior art cited in the specification and/or the prosecution history uses terms that also appear in the claims to be construed (which would go beyond express references or extracts in the patent).

95. However UCB submits that this exercise does not give the court free rein to independently analyse what the prior art in fact discloses, and to then use disclosures not discussed in the patent to limit the claims. The particular concrete point that UCB has in mind is the question of validity. UCB argues that the question of validity should not arise until the 'validity tie-break'; when the court is assessing rival claim constructions as the intrinsic and extrinsic evidence have not resolved the construction issue. To allow such an approach in the course of the court's review of prior art, would make considerations of validity, by the back door, a routine part of the claim construction process.

96. Chugai's position can be summarised by the following extract from Judge Michel's evidence (paragraph 158 of Michel I):

> "First and foremost, the Queen Patent and Paper are both referenced in the 771 Patent and were cited in examination, and they therefore form part of the intrinsic record of the 771 Patent. A US court would therefore necessarily consider the disclosures of the Queen Patent and Paper as part of the usual claim construction process discussed in Phillips. That process would include, for example, the court assessing whether the Queen references provide any "clues" as to what the claims of the 771 Patent do not cover (see paragraph 52 above). The court would also consider any statements made in the specification or during prosecution to distinguish the invention of the 771 Patent from

> Queen's work, in order to assess whether those statements limit the scope of the claims by indicating, for example, that a claim term should be viewed as having a narrow meaning which does not read on the Queen art."

97. Thus Chugai argues that the court should consider the prior art itself, as a whole, including the disclosures relating to it in the patent. The purpose of the review extends to understanding the scope of the patentee's claims based on for example, any statements of limitation that arise implicitly or expressly to distinguish the prior art.

98. One case relied on by Chugai was ***Autogiro Co of America v United States*** 384 F.2d 391, 399 (Court of Claims, 1967). This includes the following:

> "One use of the file wrapper is file wrapper estoppel, which is the application of familiar estoppel principles to Patent Office prosecution and patent infringement litigation. […] The file wrapper also has a broader and more general use. This is its utilization, like the specification and drawings, to determine the scope of the claims. For example, the prior art cited in the file wrapper is used in this manner. In file wrapper estoppel, it is not the prior art that provides the guide-lines, but the applicant's acquiescence with regards to the prior art. In its broader use as source material, the prior art cited in the file wrapper gives clues as to what the claims do not cover."
>
> [Emphasis added]

99. This statement does support Chugai's submission. However while ***Autogiro*** has been cited subsequently (in ***Vitronics*** and then in ***Markman***) I was not shown any consideration of this passage in later cases from the point of view of the question I now have to resolve.

100. Chugai also rely on ***Avid Technology, Inc. v. Harmonic, Inc,*** 812 F.3d 1040 (Fed. Cir. 2016) but I believe that case, when read carefully, is an example of the approach which UCB contends is legitimate, examining the prosecution file for a disclaimer. It does not support Chugai's wider submission.

101. In my judgment the answer to this debate is the following. As intrinsic evidence, as is accepted by both parties, the court will take into account any references or statements in the specification or prosecution file made in relation to the prior art including statements to distinguish it or limit claim scope. The rationale for this is the public notice function of the intrinsic record. When used this way, while the prior art document itself will need to be read and understood, the context will always be concerned with what has been said about it in the prosecution file or patent specification. Separately, prior art is also capable of being used as a form of extrinsic evidence of how terms are used (see ***Vitronics*** p14-15). Used that way and given appropriate weight, it does not matter what has been said about the prior art at all.

102. However I find that where the intrinsic file does not include a relevant reference to the point at issue, US law does not countenance an approach to claim construction which involves generally reviewing cited prior art and then, based on that review, preferring

one proposed claim construction over another as a result of considerations of validity over that prior art. This is the case even if the prior art is cited in the specification or prosecution file. In my judgment following ***Phillips***, as a matter of US law, questions of validity in general only become relevant at the 'tie-breaker' stage, after all the intrinsic and extrinsic evidence has been considered.

The examiner's reasons for allowance

103. There is no dispute that statements by the patentee in the prosecution file are relevant to claim construction. It is also not in dispute that this is so whether or not the examiner appears to or did rely on them.

104. UCB argues, supported by Prof Chisum, that statements by the examiner about the claimed invention, such as in the "reasons for allowance" do not limit claim scope or bind the patent owner. Chugai argues, supported by Judge Michel, that the authorities merely point out that the examiner's statements may be of less weight than the applicant's statements when they clearly conflict with those statements, but they are capable of limiting claim scope.

105. Quite a number of cases were cited in the reports. The main ones were ***Springs Window Fashions L.P. v. Novo Industries***, L.P. 323 F.3d 989, 993-994 (Fed. Cir. 2003), ***Fenner Investments, Ltd. V. Cellco Partnership,*** 778 F.3d 1320, 1325 (Fed. Cir. 2015), ***Ancora Technologies, Inc. v. Apple, Inc,***. 744 F.3d 732 (Fed. Cir. 2014), ***Salazar v. Proctor & Gamble Co.,*** 414 F.3d 1342, 1345 (Fed. Cir. 2005), ***Biogen Idec, Inc. v. GlaxoSmithKline LLC,*** 713 F.3d 1090, 1097 n.6 (Fed. Cir. 2013), ***Alfred E. Mann Foundation for Scientific Research v. Cochlear Corp.***, 841 F.3d 1344 (Fed. Cir. 2016), ***3M Innovations Properties Co. v. Tredegar Corp.,*** 725 F.3d 11315 (Fed. Cir. 2013), ***Grober v. Mako Prods., Inc.,*** 686 F.3d 1335, 1342 (Fed. Cir. 2012) and ***C.R. Bard, Inc. v. U.S. Surgical Corp.,*** 388 F.3d 858, 869 (Fed. Cir. 2004).

106. I find that the examiner's reasons for allowance are not inadmissible. For one thing the applicant's reaction to or responses to examiner's statements (whether ultimately relevant for the grant of the patent) clearly inform claim construction. However, the weight to be attributed to an examiner's statement is very limited for the simple reason that they are not statements by the applicant or patent owner. No case has been cited in which an examiner's statements alone was sufficient to limit claim scope.

Another tie-breaker – preference for a narrow construction?

107. Chugai argues that in addition to construing to preserving validity, there is another canon of claim construction which can be used as a 'tie-break' to examine rival claim constructions, that is to prefer the narrower construction. It is based on ***Athletic Alternatives, Inc. v. Prince Manufacturing, Inc.*** 73 F.3d 1573 (Fed. Cir. 1996).

108. UCB does not agree. Its case is that ***Athletic Alternatives*** has been effectively overruled because its application would undermine the standard of indefiniteness prescribed by the U.S. Supreme Court decision in ***Nautilus, Inc v. Biosig Instruments, Inc.*** 134 S. Ct. 2120 (2014). That is because ***Nautilus*** decides that a claim with two equally plausible constructions would be held invalid for indefiniteness. Professor Chisum explained that in his view ***Athletic Alternatives*** now has no role to play in claim

construction because to apply it would have the effect of evading the indefiniteness prohibition under 35 U.S.C. section 112(b)·

109. Judge Michel was not aware of a decision which has considered the interplay between the principle of construing narrowly espoused by ***Athletic Alternatives*** and the indefiniteness standard in ***Nautilus***. However, having not been overruled by the CAFC sitting *en banc* or the U.S. Supreme Court, Judge Michel explained his view was that it remains binding authority, and District Courts have continued to cite and apply it since 2014, when ***Nautilus*** was decided. The example given to me is ***Boston Scientific Corp. v. Cook, Inc.,*** 187 F.Supp.3d 249 (D.Mass.2016) in which both ***Nautilus*** and ***Athletic Alternatives*** are cited (see p271 and p290) without any suggestion the former overruled the latter.

110. Judge Michel also expressed the view that ***Athletic Alternatives*** and ***Nautilus*** are not necessarily inconsistent on the basis that if the court chooses a narrower and unambiguous construction following ***Athletic Alternatives***, the issue of potential indefiniteness has been resolved by the court.

111. I do see the force in Prof Chisum's point that on one view of ***Nautilus*** the Supreme Court has left no room for the application of the ***Athletic Alternatives*** doctrine. However that reasoning seems to me to apply to the validity tie breaker as well. Either ***Nautilus*** is the last word on the consequences of reaching the end of the process of claim construction and still having at least two alternative constructions, in which case neither tie breaker should apply, or it is not, in which case there seems to be room for both tie breaker to apply. Since both sides agree (including Prof Chisum in particular) that the validity tie breaker remains good law irrespective of ***Nautilus***, it seems to me that ***Athletic Alternatives*** must survive as well.

112. That leaves the question of what to do if both tie breakers are applicable. To that question I was given no clear answer. Logically it seems to me that if one is having to apply these sorts of tie breakers at all and if the information is available to apply the validity tie breaker, it ought to come first so as not to leave a potentially invalid claim.

The 771 patent - construction

113. A patent is to be read through the eyes of a person of ordinary skill in the art as of the effective filing date, 21st December 1989. Dr Hale and Prof Rees give similar evidence about the characteristics of the person of ordinary skill in the art. I find that the person would have had a doctorate in molecular biology, structural biology or a closely related field, as well as practical academic or industrial experience in the production of recombinant proteins and protein engineering. They would have an interest in manipulating antibodies to decrease immunogenicity while maintaining antigen binding.

114. The person of ordinary skill in the art would be aware of the matters set out in the technical background section above.

The claims

115. Claims 1 and 2 are both to a "humanised antibody molecule" with certain characteristics. On the face of it, the person of ordinary skill in the art would recognise

that these appear to be claims to a product – a molecule – rather than to a process or method. The term "humanised" is defined in the specification but focussing just on the claims at this stage in the analysis, although a layman would not recognise the term in this context, a person of ordinary skill in the art would. They would understand it to be a reference to an antibody composed of human and non-human sequences as described in the technical background section.

116. To be within claim 2 the antibody molecule has to have "affinity for a predetermined antigen". There is similar language in claim 1. The person of ordinary skill in the art would understand that affinity refers to the ability to bind to a target.

117. The antibody also has to have "a composite heavy chain and a complementary light chain". The term "composite" indicates that the heavy chain is composed of parts with different origins, such as human and murine, while the light chain is complementary because it has to match up with the heavy chain. Nothing turns on the meanings of these terms.

118. The remainder of the language in either claim 1 or claim 2 then relates to the heavy chain. I will now focus on claim 2 in particular. The heavy chain has "a variable domain including complementarity determining regions (CDRs) and framework regions". All of this would be familiar to the person of ordinary skill in the art and no issue of construction arises.

119. The claim then defines three characteristics. The first two characteristics relate to amino acid residues at particular locations defined using the Kabat numbering system. This numbering system would be familiar to a person of ordinary skill in the art.

120. The first characteristic is that in the composite heavy chain the "CDRs are non-human donor at residues 31 to 35, 50 to 58, and 95 to 102". The person of ordinary skill in the art would recognise the three groups of numbers as corresponding to CDRs (1), (2) and (3) in the Kabat numbering system. The reference to non-human donor here links to the idea that the molecule is a humanised antibody so that the sequence of residues in the CDRs is from the non-human source.

121. The second characteristic consists of a defined set of positions in the framework region which must be non-human donor. These are defined at sub-paragraphs (a) to (f) of claim 2.

122. Finally the claim ends with the third characteristic, which is a disclaimer. The disclaimer excludes from the claim a case in which the heavy chain is "a chimeric heavy chain with a donor variable domain and human constant domain". The usage of the term "donor" there will be in the same sense as "non-human donor" elsewhere in the claim.

123. Notably the claim language has focussed almost entirely on the variable region of the heavy chain. The claim has not spelled out anything about the constant region of the heavy chain. Nevertheless the person of ordinary skill in the art would assume the constant region was meant to be a human sequence since that is part of what they understand a humanised antibody to be.

124. Turning to the term "non-human donor", while a layman might not understand the word "donor" used in this context, a person of ordinary skill in the art would. At least at first sight they would relate it to the context of chimeric and humanised antibodies. UCB emphasises that using human and mouse sources in this familiar context was concerned with antibodies or parts of antibodies rather than at the level of individual residues. I agree (despite Reichman (1988) altering a single framework residue). Nevertheless, the term "non-human donor" would make sense to the person of ordinary skill in the art in this context. Again at first sight they might assume it was being used in the same sense.

125. Furthermore, whatever the ambit of the term "non-human donor", the person of ordinary skill in the art would think it ought to mean the same thing in both places in the claim. If there was any doubt about that, the fact that the term "non-human donor" only appears once in claim 1, and refers both to the CDRs and to the framework residues, assists.

126. Overall, at least at first sight, the skilled person would understand the claim language as a whole to be contemplating that the antibody molecule is made up of sequences with different conceptual origins – a human origin (which can be called "acceptor" although that word is not in the claim) and a non-human origin (which can be called "donor"). They would also see that to apply the definitions in the claim, one does need to know what the sequences of two source antibodies were.

127. Focussing on the term "non-human donor" in isolation, it could bear either meaning contended for by the parties. There is nothing in the claim language which expressly clarifies whether a residue which is the same in both the human and the non-human sequences should be regarded as non-human or as human. Nevertheless some light can be shed by thinking about how the claim works in other respects. Considering the constant regions of the molecule, the person of ordinary skill in the art would expect them to be human. They would not think these regions ceased to be human just because there happened to be residues in the constant region which were conserved as between donor and acceptor.

128. Considering the CDRs, if one asked a person of ordinary skill in the art what they made of the presence of a conserved residue in a CDR, they would be puzzled by the question. These are the hypervariable regions specific to the particular target antigen in question. The target of the human acceptor antibody is of no relevance at all. The human CDRs in the human acceptor antibody are going to be replaced by the non-human donor CDRs which are aimed at the (different) antigen of interest. The fact that there might be conserved residues in both CDRs would be seen entirely coincidental and not as an indication that the origin of the non-human CDR was anything other than non-human.

129. This analysis shows that the fact a residue is conserved does not prevent it from being regarded as "non-human donor". That assists UCB. However it is not the same as saying that "non-human donor" by definition always means or includes conserved residues. The analysis also shows that the construction of the claim language is highly context dependent.

130. These examples also indicate that if the person of ordinary skill in the art felt able to ascribe an origin to a residue, then the fact that residue is conserved would not change that origin. In other words if Chugai is right and the correct construction of "non-human

donor" relates to the origin of the residue, then the fact it is conserved will not change its designation.

131. Considering a conserved residue in one of the defined framework positions and simply considering the claims themselves, either party's construction is tenable. Such a conserved residue clearly could be understood to be human acceptor, rather than non-human donor, for the simple reason that its origin was in the acceptor sequence. On the other hand it could be understood to be non-human donor for the equally simple reason that it is the same as the residue in that position in the non-human donor antibody.

132. Overall, based on the claims themselves, there is no clear answer.

133. Before leaving the claims however I will address the alternative product by process argument. There is little support for that in the claim language. The claim is to a product with defined features. No doubt the person of ordinary skill in the art would expect the antibodies to be made by expression in suitable cells but there is nothing in the language to impose limitations about that manufacturing process. Indeed unlike some product by process claim arguments, this argument is at a distance from the process of actually making the product anyway. Chugai's case is about the process of designing the DNA sequence used to express the protein. The claim does refer to a "humanised" antibody but while that expression does reflect the design of the molecule the person of ordinary skill in the art understands it as defining the antibody product itself by reference to its sequence.

The specification

134. The 771 patent was issued on 28th July 2009. It was filed on 7th June 1995 and claims priority from a GB filing on 21st December 1989.

135. The text of the specification starts at col 1 ln13 stating that the present invention relates to humanised antibody molecules, to processes for their production using recombinant DNA technology and to their therapeutic uses. That sets a clear context for the reader. Bearing in mind the product by process argument, the distinct references here to products (molecules), process and therapeutic uses supports the view that the claims, which are to molecules, are not claims to processes (or therapeutic uses).

136. The specification defines the term "humanised antibody molecule" at col 1 ln16-20 as follows:

> "The term "humanised antibody molecule" is used to describe a molecule having an antigen binding site derived from an immunoglobulin from a non-human species, and remaining immunoglobulin-derived parts of the molecule being derived from a human immunoglobulin."

137. Antibodies are immunoglobulin molecules. This passage would confirm the person of ordinary skill in the art's essential understanding of the term humanised in claims 1 and 2. A point of detail is that by referring to the case in which only the antigen binding site is derived from a non-human species while the remainder is human, this part of the specification indicates that the idea of a "humanised" antibody corresponds to the CDR grafting technique of Winter (see also col 2 ln37) and not simply to a chimeric antibody

(cf col 2 ln 14-31 which applies the term to chimeric antibodies too). I do not believe anything turns on this point.

138. The next section of the patent deals with the background to the invention. From col 1 ln33 to col 2 ln 8 the idea of using murine monoclonal antibodies (MAbs) as therapeutic agents is described along with the hybridoma technique and the HAMA response. This would be familiar to the skilled person. A particular mouse monoclonal antibody (OKT3) is mentioned. This recognises an antigen in the T-cell receptor-CD3 complex, has recognised therapeutic uses to treat transplant tissue rejection, but also has a HAMA response which limits its utility. At col 2 ln4 the patent states:

> "Clearly, it would be highly desirable to diminish or abolish this undesirable HAMA response and thus enlarge the areas of use of these very useful antibodies."

139. The specification then goes on to summarise proposals to render non-human monoclonal antibodies less antigenic in humans (i.e. less prone to eliciting HAMAs). The techniques are described as "humanisation" and involve recombinant DNA technology. The production of chimeric antibodies is described as an early method (col 2 ln14-31) ending with a recognition that the fact they contain a complete non-human variable domain means they may still elicit a HAMA response when used over a long period.

140. Next the CDR grafting work of the Winter group is described from col 2 ln 32. The passage reads:

> "In an alternative approach, described in EP-A-0239400 (Winter), the complementarity determining regions (CDRs) of a mouse MAb have been grafted onto the framework regions of the variable domains of a human immunoglobulin by site directed mutagenesis using long oligonucleotides. The present invention relates to humanised antibody molecules prepared according to this alternative approach, i.e. CDR-grafted humanised antibody molecules. Such CDR-grafted humanised antibodies are much less likely to give rise to a HAMA response than humanised chimeric antibodies in view of the much lower proportion of non-human amino acid sequence which they contain."

141. In addition to describing the Winter group's CDR grafted technique and its rationale in terms of lowering the HAMA response, this passage (in the middle) also confirms that the "present invention" is concerned with such antibodies.

142. The next paragraph (col 2 ln44-52) refers to the further work on CDR grafted antibodies including work by Verhoeyen as well as the Riechmann work. Then the following paragraph starting at col 2 ln 53 focusses specifically on the Riechmann work and on the changes made to individual residues. It includes these two statements:

> "Riechmann et al found that it was necessary to convert a serine residue at position 27 of the human sequence to the

> corresponding rat phenylalanine residue to obtain a CDR-grafted product having improved antigen binding activity."
>
> and
>
> "These results indicate that changes to residues of the human sequence out-side the CDR regions, in particular in the structural loop adjacent to CDR1, may be necessary to obtain effective antigen binding activity for CDR-grafted antibodies which recognise more complex antigens. Even so the binding affinity of the best CDR-grafted antibodies obtained was still significantly less than the original MAb."

143. Following this discussion of Riechmann the specification turns to Queen. The discussion starts at col 3 ln7 as follows:

> "Very recently Queen et al (9) have described the preparation of a humanised antibody that binds to the interleukin 2 receptor, by combining the CDRs of a murine MAb (anti-Tac) with human immunoglobulin framework and constant regions. The human framework regions were chosen to maximise homology with the anti-Tac MAb sequence. In addition computer modelling was used to identify framework amino acid residues which were likely to interact with the CDRs of antigen, and mouse amino acids were used at these positions in the humanised antibody."

144. Here the specification is drawing attention to work by Queen. Following up the bracketed reference (9) (to col 30 ln 54) shows that in fact it defines two documents – a PNAS paper published in 1989 and an international patent application published under the PCT as WO 90/07861. The latter ("the Queen PCT") is also listed on the front page of the 771 patent as one of the References Cited. Also in that list is a Queen US patent 5,530,101. Before me Chugai has dropped reliance on the paper as prior art.

145. As the paragraph set out above provides, Queen is said to describe the preparation of a humanised antibody which combines CDRs from a murine antibody called anti-Tac and human framework and constant regions. A choice was made to select human framework regions so as to maximise homology with the murine antibody. Also certain human acceptor framework residues were selected by computer modelling and mouse residues were used at those positions in the humanised antibody. This passage does not distinguish between the Queen paper and the Queen PCT.

146. The next two paragraphs of the specification relate expressly to the Queen PCT. The first paragraph explains that Queen proposes four criteria for designing antibodies. These criteria are based on considering the sequence or sequences of the human acceptor and the non-human donor. They can be used singly or in any combination. They are:

i) First - to use "as the human acceptor" the framework from a particular human antibody that is unusually homologous to the non-human donor antibody. Alternatively a consensus framework from many human antibodies could be used.

ii) Second - to use the donor amino acid rather than the acceptor if the human acceptor residue is unusual and the donor residue is typical for human sequences at a specific residue of the framework.

iii) Third - to use the donor framework amino acid residue rather than the acceptor at positions immediately adjacent to the CDRs.

iv) Fourth - to use the donor amino acid residue at particular framework positions based on predictions about the proximity of side chains (within 3 Angstroms) and other criteria.

147. With an eye on the point at issue, the fact that first criterion is explained as being to use a sequence which is homologous to the non-human donor "as the human acceptor" (my emphasis) slightly favours Chugai's construction over UCB's. UCBs case is that a homologous (conserved) sequence is regarded as non-human donor where here the language refers to it as human.

148. The second paragraph (at col 3 ln 39) explains that the Queen PCT describes in detail the preparation of a single CDR-grafted humanised antibody which has specificity for the p55 Tac protein of the IL-2 receptor. That humanised anti-Tac antibody has about one-third of the affinity of the corresponding murine antibody. The specification describes that all four criteria were employed in its design and the variable region of a human antibody called Eu was used as acceptor. The donor CDRs were as defined by Kabat and the specification goes on to explain that in addition:

> "… the mouse donor residues were used in place of the human acceptor residues, at positions 27, 30, 48, 66, 67, 89, 91, 94, 103, 104, 105 and 107 in the heavy chain and at positions 48, 60 and 63 in the light chain, of the variable region frameworks."

149. In this paragraph the expression "in place of" (which is at col 3 ln48) would be understood to refer to changes. Moreover the reader would understand this list of residues as being a specific list applicable to the humanised anti-Tac antibody of Queen by the application of Queen's criteria in that case.

150. After this passage the specification then turns at col 3 ln 55 to describe what the present inventors have done and draws a distinction over the work of Queen. The paragraph (with the sentences separated out for clarity) is as follows:

> "We have further investigated the preparation of CDR-grafted humanised antibody molecules and have identified a hierarchy of positions within the framework of the variable regions (i.e. outside both the Kabat CDRs and structural loops of the variable regions) at which the amino acid identities of the residues are important for obtaining CDR-grafted products with satisfactory binding affinity.
>
> This has enabled us to establish a protocol for obtaining satisfactory CDR-grafted products which may be applied very widely irrespective of the level of homology between the donor immunoglobulin and acceptor framework.

> The set of residues which we have identified as being of critical importance does not coincide with the residues identified by Queen et al (9)."

151. The first sentence of this final paragraph in the background relates to the work of the inventors, explaining that they have carried out further investigations (further than the other work referred to including that of Winter, Riechmann and Queen) and identified a hierarchy of positions in the framework regions outside the CDRs which are important for obtaining binding affinity. Although here the specification refers to a hierarchy, there is no clear hierarchy within the relevant claims. In any event however the objective described here is not concerned with the HAMA response (cf. col 2 ln4), it is concerned with binding affinity. In other words it is concerned with, in effect, recovering in a humanised antibody the affinity which was available in the mouse donor antibody but which has been compromised by humanisation.

152. The second sentence explains that the inventors have established a protocol. That in itself might support the idea that the invention is really about products defined by reference to the process (protocol) by which they were designed but it does not say that in terms. The fact the inventors have derived a protocol does not mean the claims are defined in that way.

153. The protocol is said to give good results irrespective of the level of homology between the donor and the acceptor framework. UCB relies on this passage. It argues that the only way the invention can give good results irrespective of the level of homology is if conserved residues in the claim set count as donor. Otherwise the invention cannot really be used in cases of high homology at all. That is because high homology means a high number of conserved residues and so few changes will be needed. In other words if the donor and acceptor have high homology the humanised antibody is likely to fall outside the claim on Chugai's construction whereas the degree of homology does not matter on UCB's construction, as long as the right residues are non-human donor either by being changed or by being conserved. UCB is correct. This passage does support its construction.

154. The third sentence relates to Queen in particular. There was some dispute about this but in my judgment the person of ordinary skill in the art would see from the background section as a whole and from the discussion about Queen, that the inventors are treating Queen as prior art (at least the PCT) and telling the reader that what they have invented is different from Queen both in general terms and in that the humanised anti-Tac antibody, as a molecule, is different from the claimed invention.

155. UCB submit that the specification is not saying in effect "I distinguish anti-Tac on this or that basis". UCB is right that there is no express statement in those words but in my judgment the person of ordinary skill in the art would grasp from these passages as a whole that that is what they are being told. No person of ordinary skill in the art would read these paragraphs as an indication that the CDR grafted humanised antibody of Queen was or could be within the claims.

156. Focussing on the last sentence, it draws a distinction between the residues identified by Queen as having been changed from human acceptor to mouse donor in the humanised anti-Tac antibody, and the set of residues which the inventors have identified as being of critical importance. Importantly, with an eye on the point at issue, this distinction

relates to residues which had been changed. The skilled person would understand that in the humanised anti-Tac antibody the framework residues at the positions other than the ones identified in the specification as having been changed in Queen, must presumably be unchanged human residues. There is no hint of the idea that those other residues could be regarded as non-human donor if they were conserved as between the human acceptor and the murine donor nor any hint that one might need to investigate that in order to work out whether the humanised anti-Tac antibody is in truth within what is being claimed. On the contrary the passage teaches the reader that because the set of residues changed from human to mouse in Queen is a different set from the set of residues the inventors have identified, it follows that the Queen antibody is different from the invention. That can only be correct on Chugai's construction. It is wrong on UCB's construction.

157. Thus, taking stock of the Background section, it contains passages which favour both arguments.

158. The next section of the specification is entitled "Summary of the Invention". It is a long section, running from col 4 ln3 to col 11 ln 39. The first paragraph reads:

> "Accordingly, in a first aspect the invention provides a CDR-grafted antibody heavy chain having a variable region domain comprising acceptor framework and donor antigen binding regions wherein the framework comprises donor residues at at least one of positions 6, 23, and/or 24, 48 and/or 49, 71 and/or 73, 75 and/or 76 and/or 78 and 88 and/or 91."

159. This "first aspect" of the invention generally corresponds to claims 1 and 2 in terms of describing a humanised CDR grafted antibody based on an acceptor and donor. The definition uses the same numbered set of 12 residues as claim 2 however it does not correspond to claim 2 because it is wider. The paragraph provides that the framework must comprise donor at at least one of the defined positions. So an antibody with donor only at position 6 and with residues which are not donor at the other positions would fall within this definition but would not fall within claim 2. To be within claim 2 at least 6 donor residues are needed in the framework (in the locations specified in sub-paragraphs (a) to (f)).

160. In the next paragraph (from col 4 ln 9) various preferred embodiments are defined by reference to numbered residues which are within the same set of 12 as the previous paragraph. None of those correspond to claim 2 or any other claim.

161. The second sentence refers to residues at positions 71, 73 and 78 as either all donor or all acceptor. There was a disagreement between the experts about this. What it amounted to was the application of the rival constructions. So on Dr Rees' approach in a case in which two residues were conserved it would not be possible for all three to be donor. It was put to him that this made no technical sense because, as long as all three residues are the same as in the donor, whether that is because three were changed or because two were conserved and one was changed, from the point of view of binding affinity the result would be the same. He accepted this was a technical anomaly and the point assists UCB as a concrete way of putting the argument about homology and binding affinity, but it cannot be taken too far. The sentence in the specification does not just state that they must all be donor, it also contemplates as just as preferable the

case when they are instead all acceptor. That is not within claim 2 nor, I believe, is it within any other claim. UCB suggested that the "all donor" case was Example 3 but (see below) that example is not within the claims either and, although the word "preferably" is not applied to them there are also cases in which all three of these residues are changed to be donor in Example 1 (e.g. JA 185).

162. The next paragraphs (from col 4 ln14) define various particularly preferred embodiments, now using some of the same residues as before and also further residues not mentioned before. The second sentence in that paragraph refers to a set of positions which are commonly conserved and provides that if they are not conserved between donor and acceptor, they should be donor. The last sentence states that "most preferably" a heavy chain framework will comprise donor at a longer list of residues, which includes the positions previously described as commonly conserved. This statement is said by UCB to link to example 2 and I will deal with it in one go in that context. The list of residues does not correspond to claim 2.

163. A further list of residues, again not the same as claim 2, is specified at col 4 ln 24-37.

164. Next is a set of three general paragraphs which refer to the first and other aspects of the invention. Up to now the specification has been concerned with the "first aspect" of the invention and embodiments of it. There is a paragraph (col 4 ln 38) which refers to acceptor framework and donor antigen binding regions generally and contemplates that the donor and acceptor antibodies could be from the same species (which is different from all the claims). The paragraph ends by stating that typically the donor is a rodent Mab and the acceptor is human. The other two paragraphs refer to CDRs and the Kabat numbering system. Nothing turns on them.

165. Second, third and fourth aspects of the invention are described in similar terms to the first aspect from col 5 ln13 to col 6 ln 3. Nothing turns on this nor on the next paragraph (col 3 ln4-14).

166. A paragraph at col 6 ln15-40 describes acceptor variable region framework sequences, stating that any appropriate one may be used. This includes a teaching to maximise the homology between the acceptor and the donor, particularly at positions close to the CDRs. There is a statement that "the present invention" identifies a hierarchy of framework residue positions at which donor residues may be important or desirable for obtaining CDR grafted antibodies having satisfactory binding properties. Also in this paragraph is another statement that the present invention is applicable to any combination of donor and acceptor antibodies irrespective of the level of homology. There is another reference to a protocol for applying the invention and finally a list of possible human frameworks to use. UCB relies on these passages for the same point as the reference in the Background section to a protocol giving good results irrespective of homology, namely that the only way the invention can give good results irrespective of the level of homology is if conserved residues in the claim set count as donor.

167. Chugai contends that this passage is part of various wider teachings in the patent which are not focussed on the invention claimed either at all or at least in claim 2. I will come back to that point below.

168. From col 6 ln41 to col 8 ln 40 there are references to the constant regions, to general molecular biological techniques for expression etc. and to possible targets. A process

for producing the claimed antibody using a DNA expression vector, transforming a host cell and culturing the transfected cell line is mentioned in very general terms at col 7 line 44-58. There are statements that the invention includes therapeutic compositions and uses in therapy and also methods of therapy although none of this is clearly reflected in the claims.

169. At col 8 ln 41 the specification states that "a preferred protocol" for obtaining CDR-grafted antibody chains in accordance with the invention is set out below but that this protocol and rationale is given without prejudice to the generality of the invention. For what it is worth that seems to me to be another fairly clear indication that the claims are not product by process claims.

170. The protocol is then set out from col 8 ln 47. The first part of it is set out below. Letters have been included in this judgment to identify individual paragraphs for clarity:

> "Protocol
>
> (a) It is first of all necessary to sequence the DNA coding for the heavy and light chain variable regions of the donor antibody, to determine their amino acid sequences.
>
> (b) It is also necessary to choose appropriate acceptor heavy and light chain variable regions, of known amino acid sequence.
>
> (c) The CDR-grafted chain is then designed starting from the basis of the acceptor sequence.
>
> (d) It will be appreciated that in some cases the donor and acceptor amino acid residues may be identical at a particular position and thus no change of acceptor framework residue is required.
>
> (e) 1. As a first step donor residues are substituted for acceptor residues in the CDRs. For this purpose the CDRs are preferably defined as follows:
>
> [table – detail not relevant]
>
> (f) The positions at which donor residues are to be substituted for acceptor in the framework are then chosen as follows, first of all with respect to the heavy chain and subsequently with respect to the light chain.
>
> (g) 2. Heavy Chain
>
> (h) 2.1 Choose donor residues at all of positions 23, 24, 49, 71, 73 and 78 of the heavy chain or all of positions 23, 24 and 49 (71, 73 and 78 are always either all donor or all acceptor).
>
> (i) 2.2 Check that the following have the same amino acid in donor and acceptor sequences, and if not preferably choose the

> donor: 2, 4, 6, 25, 36, 37, 39, 47, 48, 93, 94, 103, 104, 106 and 107.
>
> (j) 2.3 To further optimise affinity consider choosing donor residues at one, some or any of: [list]
>
> (k) 3. Light Chain […]"

171. This protocol assists UCB in that it clearly contemplates aiming for high homology which reduces the number of changes required (paragraphs (d) and (i)). It does clearly refer to changing from donor to acceptor at paragraph (f) but that is clearly only needed if they are different.

172. On the other hand although the residues in claim 2 are mentioned, the protocol relates to a very different and more extensive set of residues. Furthermore the protocol does not state in terms that an unchanged acceptor residue is to be treated as "donor", rather the protocol just refers to them as identical residues without saying any more about what to call them.

173. After the protocol is a rationale section from col 9 ln 52 to col 11 ln 39. Neither party submitted anything significant can be derived from that section which has a bearing on the issue I have to decide.

174. Reflecting on the "summary of the invention" section, it is confusing because nowhere is there a summary which corresponds to claim 2 (or so far as I am aware any of the other claims). That diminishes its value as an aid to interpretation of the claims. On the other hand it does contain passages which support UCB's approach to the comprehension of the teaching of this specification as a whole.

175. Finally in the specification from col 11 ln 40 onwards there are figure legends followed by five examples. This is an important part of the patent because here the inventors have set out detailed experimental work in concrete terms. The heading about the example section is "Detailed Description of Embodiments of the Invention". A relevant question in testing rival constructions of any patent claim is the extent to which examples fall inside out outside the claim on the different constructions. It is clear as a matter of US law that if a particular claim construction had the result that none of the worked examples fell within any claims, whereas a rival construction did not have that result, then that would be a strong indication in favour of the rival. All the same, like all rules of construction, it is not immutable.

176. Example 1 is a fully worked through set of experiments involving CDR grafting based on a mouse donor antibody called OKT3. The procedure starts from a hybridoma producing OKT3 antibodies, sequencing of the gene coding for that antibody, construction of chimeric and CDR grafted genes for antibodies based on OKT3, and gene expression in COS and CHO cells. Various gene constructs are summarised in Table 1. The example describes the examination of the framework residues and the choices made for residues in various positions in the framework regions of the light chain and heavy chain. The design of the framework residues for various antibody chains produced is explained. Thirteen different heavy chains are produced. The antibodies are tested in binding and blocking assays and results are in Figures 7 to 13. The binding ability of the chimeric antibody is used as a comparator. The inferences

about the significances of various framework positions, drawn from the assay results are discussed from col 24 ln63 onwards. There is no need to address it all in detail. A sense of the conclusions drawn can be understood from the following paragraph (col 24 ln 65-col 25 ln 4):

> "The JA198 and JA207 constructs appear to have the best binding characteristics and similar binding abilities, both substantially the same as the chimeric and fully grafted gH341A products. This indicates that positions 88 and 91 and position 76 are not highly critical for maintaining the OKT3 binding ability; whereas at least some of positions 6, 23, 24, 48, 49, 71, 73 and 78 are more important."

177. The design of the framework regions of the thirteen heavy chains is summarised in Table 2:

TABLE 2

OKT3 HEAVY CHAIN CDR GRAFTS
1. gH341 and derivatives

RES NUM	6	23	24	48	49	63	71	73	76	78	88	91	
OKT3vh	Q	K	A	I	G	F	T	K	S	A	A	Y	
gH341	E	S	S	V	A	F	R	N	N	L	G	F	JA178
gH341A	Q	K	A	I	G	V	T	K	S	A	A	Y	JA185
gH341E	Q	K	A	I	G	V	T	K	S	A	G	G	JA198
gH341*	Q	K	A	I	G	V	T	K	N	A	G	F	JA207
gH341*	Q	K	A	I	G	V	R	N	N	A	G	F	JA209
gH341D	Q	K	A	I	G	V	T	K	N	L	G	F	JA197
gH341*	Q	K	A	I	G	V	R	N	N	L	G	F	JA199
gH341C	Q	K	A	V	A	F	R	N	N	L	G	F	JA184
gH341*	Q	S	A	I	G	V	T	K	S	A	A	Y	JA203
gH341*	E	S	A	I	G	V	T	K	S	A	A	Y	JA205
gH341B	E	S	S	I	G	V	T	K	S	A	A	Y	JA183
gH341*	Q	S	A	I	G	V	T	K	S	A	G	F	JA204
gH341*	E	S	A	I	G	V	T	K	S	A	G	F	JA206
gH341*	Q	S	A	I	G	V	T	K	N	A	G	F	JA208
KOL	E	S	S	V	A		R	N	N	L	G	F	

(the table also deals with light chains but there is no need to deal with that)

178. The residue numbers run along the top. The letters in the body of the table are the single letter identifiers for amino acids. The identifiers on the left are gene constructs. The identifiers on the right are plasmids carrying the relevant DNA sequences. The underlining shows the changes from the human acceptor to mouse donor sequence. It is convenient to refer to these as antibodies although they are in fact heavy chains.

179. In the table the top row is construct OKT3vh. That is the murine donor. Next is construct gH341. That has the human acceptor sequence. It is in effect a Winter style CDR grafted antibody. It has the same framework residues as the actual human acceptor antibody KOL (bottom row). Next are thirteen rows which, using plasmid numbers because they are unique, run from JA185 to JA208. These are all CDR grafted antibodies in which various changes have been made to the human acceptor framework sequence to make the residue a mouse donor residue.

180. Three points arise from Example 1. The first point is that what is described and focussed upon here involves changing human acceptor residues into donor residues at the various positions described. That is clear support for Chugai's case.

181. The second point is about the extent to which these antibodies fall within the claims on the rival constructions. That is addressed below. The third point is an issue about the gene construction and CDR3. That will be done after the second point.

182. It is common ground that not all of these antibodies would fall within the claims on either party's construction. It is also common ground that on each side's construction eight of the thirteen antibodies fall within at least one claim.

183. UCB points out that on its construction there are two antibodies which fall within all the claims of the patent. As far as I know that fact was not disputed, but it is not a significant virtue of UCB's construction. If there was only one embodiment described in the specification then that might be more significant.

184. UCB also points out that on what UCB says is the truly consistent way of applying Chugai's claim construction, none of the antibodies fall within any claims. The point here is about CDRs rather than framework residues. UCB contends that non-human donor must mean that same thing through the claim and UCB says that Chugai says that non-human donor means it excludes conserved residues. However if non-human donor excludes conserved residues then the CDRs in these antibodies in Example 1 are all excluded because they are not non-human donor at all the residues called out in claim 2, because some of those residues are conserved between the human acceptor and mouse donor.

185. There is no dispute about the underlying fact. Chugai argues that the submission is based on a mischaracterisation of its case on construction. I agree. Chugai's construction is not that the term "non-human donor" actually excludes conserved sequences as a matter of the meaning of words. Chugai's construction is that the rule to be applied is based on source. The CDRs are brought in as a unit from the donor. So they are donor because they came from the donor. That has the consequence that residues which are in fact matching are donor when they were brought there from the donor, and they are acceptor when they were not changed in the acceptor. But that is not an inconsistency. It is just a consequence of how a consistent approach works in different circumstances.

186. That takes one to the third point, which UCB deploys as an answer to Chugai's argument about taking the CDRs as a unit. UCB argues that Table 1 of Example 1 shows that CDR3 was not taken as a unit. To explain this one starts from the fact that CDR3 (using Kabat numbering) consists of residues 95 to 102 and the claims are drafted on that basis. However as Table 1 shows the "mouse sequence content" used in the CDR grafted gene constructs only went from position 95 to 100B, leaving out 101 and 102. That was done because the residues match as between mouse and the human acceptor sequence being used at 101 and 102. So while CDR3 runs up to 102, the mouse sequence inserted stopped at residue 100B.

187. There is no dispute about the facts but I agree with Chugai that this does not undermine its case. This example is about the underlying mechanics of how the sequences used to construct the genes which will express the antibodies are constructed in DNA. It is not

concerned with the design of the amino acid sequence of the antibody itself. The fact that it was convenient from the point of view of DNA manipulations and gene construction to take advantage of common residues is not related to the question of how a person of ordinary skill in the art would think about the design of the antibody itself. The person of ordinary skill in the art reading Example 1 would understand that from the point of view of the design of the antibody of interest, the CDRs have been taken as a unit from the mouse donor antibody. How the mechanics of DNA sequence manipulation and gene construction is done is not relevant to that way of looking at the antibody design. Accordingly this third point does not assist UCB.

188. Example 2 relates to CDR-grafting of an anti-CD4 T cell receptor antibody. The donor is a murine antibody OKT4, the human acceptor framework is KOL and the resulting antibody heavy chain is called HCDR10. The specification explains that (in addition to the CDRs) the heavy chain HCDR10 has human to mouse changes at positions 24, 35, 57, 58, 60, 88 and 91. In addition the specification draws specific attention to conserved framework residues, explaining (at col 26 ln12-19) that:

> "Moreover, a comparison of the murine OKT4A and human KOL heavy chain variable amino acid sequences reveals that the murine and human residues are identical at all of positions 23, 49, 71, 73 and 78 and at all of positions 2, 4, 6, 25, 36, 37, 39, 47, 48, 93, 94, 103, 104, 106 and 107.
>
> Thus the OKT4A CDR-grafted heavy chain HCDR10 corresponds to a particularly preferred embodiment according to the present invention."

189. It is common ground that this antibody falls outside any claims on Chugai's construction but within claims 2 and 3 on UCB's construction. This supports UCB. Most of the residues relevant to claim 2 are conserved in this antibody but to be within the claim one also needs to rely on residues 88 and/or 91 – which were changed from human to mouse.

190. The reference to this antibody corresponding to a particularly preferred embodiment ties in to col 4 ln 23. The list of residues there is the list starting "2, 4, 6…" in the quotation above.

191. Example 3 describes CDR-grafting of a murine antibody B72.3 using a human acceptor called EU. The reason EU was used was because the murine donor had poor homology for KOL (the human acceptor used in the Examples 1 and 2) and another human acceptor (NEWM) but the murine heavy chain was very homologous to EU. A human to donor change was made in the framework at position 73 and the example also explains that the mouse and human residues are identical at positions 23, 24, 71 and 78, ending "Thus the mutated CDR-grafted B72.3 heavy chain corresponds to a preferred embodiment of the present invention."

192. Based on the information set out in the specification, it is common ground that the antibody of Example 3 is not within any claims on either party's construction. To be precise, it is not in the claim on Chugai's case on any view whereas, from the point of view of UCB's case, the information given does not state that enough of the residues are either changed or conserved to be within the claims.

193. However as Dr Hale explained in his second report, having first expressed the view that it did not appear to fall within the claims (since he assumed that silence about a framework residue implied it was acceptor not donor), Example 3 at col 26 ln28 gives a reference for the mouse antibody B72.3. In fact there are two references but one is WO/01783. Following that up one can find the residue at position 49 for the mouse antibody (Glycine). Then going to the paper Kabat (1987) gives the full sequence of the EU acceptor and one can see that it also has a Glycine at position 49. Armed with that information one can say that the antibody actually does fall inside claims 2-4 on UCB's construction. I am not persuaded that this paper chase represents how the person of ordinary skill in the art would approach reading the specification. The specification itself has not chosen to give the reader the information necessary to make that determination and there is nothing in it which invites the skilled person to follow up those references for that purpose. In another case – if for example this was the only example in the patent – then that sort of follow up exercise might carry more weight - but in this case it does not.

194. Accordingly Example 3 is a concrete example which is said to be "a preferred embodiment of the present invention" but which the person of ordinary skill in the art would understand was not within the claims.

195. Example 4 is similar to Example 3 but this time using a murine anti-ICAM-1 donor and the EU human acceptor. The specification explains that changes from human to donor at positions 24, 48, 69, 71, 73, 80, 88 and 91 while the murine and human sequences are identical at positions 23, 49 and 78. Like Example 3, the antibody is outside the claim on Chugai's case and, since not every residue which one would need to know about for the claims is identified in this Example as either donor or conserved, as described it is not in the claim on UCB's case either.

196. Again like Example 3, Example 4 has a cross-reference for the murine antibody. This is a British patent application (Col 28 ln26) however Dr Hale found that the sequence information necessary to characterise the other residues is only available in a post-published PCT application which claims priority from that British application. Armed with that information the antibody is within claims 2-4 on UCB's case but this exercise is even further from what a person of ordinary skill in the art would do than the one for Example 3 and I find it is not relevant to the issue of construction.

197. The final example 5 describes four antibodies based on CDR grafting from a murine anti-TNFα antibody and using various human acceptor framework sequences. The antibodies described are called 61E71, hTNF1, hTNF3 and 101.4. They all include changes from human to donor residues but none are within any claims on Chugai's construction because not enough of the framework residues are changed. Again as with Examples 3 and 4, since not every necessary residue is characterised as donor or conserved, as described in this specification none of these antibodies are in any claim on UCB's construction either.

198. It is convenient at this point to mention a declaration which was filed during prosecution. It was by a Dr Yarranton and gives more sequence information about a number of antibodies. Since the prosecution file forms part of the intrinsic evidence it seems to me to be legitimate to take it into account. Doing so one can see that 61E71 and hTNF3 are not within the claim on UCB's construction on any view, whereas hTNF1 and 101.4 are within claims 2 to 6.

199. That concludes my review of the specification. Having been through it in detail, I will stand back and look at the document as a whole. There is clear support in the document for each side's case. For Chugai the most significant points are the way Queen is dealt with, the fact that the document and all the examples describe changing human to non-human donor framework residues at the positions of interest, and the fact that no antibody is described as an embodiment of the invention for which no changes were made at all. For UCB the most significant points are that the invention is said to work regardless of homology and the fact that the document and many of the examples place clear emphasis on conserved residues at the positions of interest.

200. However what stands out from looking at the document as a whole is that it is not easy to construe. Many patents use the word "invention" in a loose sense including a reference to how the inventors arrived at the end point they have now claimed as their invention. For that and other reasons one cannot always be too pedantic about whether what is said in a patent to be "the invention" marries up with the claims. However it is not pedantry to observe that in this specification what is described as the invention or as an embodiment of the invention, does not match the claims at all. The "Summary of Invention" section is very confusing. While parts of it come close to marrying up with some claims, other parts do not. Many of what are stated to be "preferred embodiments" either do not fall within the claims on any view or are much wider. The examples, which unsurprisingly are portrayed as a detailed description of embodiments of the invention, include a number of antibodies which the person of ordinary skill in the art reading the document would understand did not fall within the claims at all. That is not very significant in Example 1 because that example shows a testing process working out the significance of various positions. However the position of examples 3 to 5 relative to the claims is another indication that the document is hard to interpret.

201. I conclude that the person of ordinary skill in the art reading the specification would see that what the inventors have thought about and described in this document and what they have gone on to claim in the claims, are not necessarily the same. As a result the reader would be wary of placing too much weight on inferences drawn by trying to work out the implications of general statements about what the invention is or what an embodiment of the invention is when trying to interpret the claims.

202. Supportive of UCB's case would be a statement in the specification which unambiguously named a conserved residue as "donor". The document generally does not do that because instead it refers to conserved residues as being "conserved", "identical" or "the same". So in the protocol at col 9 ln15 para 2.2 (quoted above) and in col 4 ln 19-20 the specification tells the reader to identify if certain residues have "the same amino acid in donor and acceptor sequences" (or "are conserved across species") and if not make them donor.

203. UCB contends that the last sentence in the paragraph at col 4 ln14-23 does indeed call conserved residues donor. UCB argues that read in context that is what it says and that that is reinforced because it should be linked to Example 2, which only works on UCB's construction. That link is because the last sentence has the same set of residues as Example 2 and the paragraph starts by explaining that it is a particularly preferred embodiment while Example 2 itself also states it corresponds to a particularly preferred embodiment at col 26 ln 18.

204. One way of reading that paragraph does suggest that the last sentence is meant to include conserved and changed residues, especially since they are commonly conserved but it is not the only reading and it is not clear. The previous two paragraphs use donor and acceptor as alternatives to one another. The preceding sentence in the relevant paragraph introduces the idea of commonly conserved residues and distinguishes between a residue which is conserved between donor and acceptor and a residue which, if not, should be donor. So the key final sentence could equally be using donor in the same way as a preceding sentence i.e. as donor rather than conserved. Thus this passage does not unambiguously support UCB.

205. On the link to Example 2, it is correct that the example can be linked to this passage at Col 4 on UCB's construction but not on Chugai's construction. That supports UCB's case.

206. Finally, product by process claims. The specification clearly describes methods of designing the antibodies (and producing them) but none of that supports the idea of construing the claims as product by process claims.

The prosecution history

207. The prosecution file starts in 1996 and runs for 12 years until a notice of allowance in May 2008 and notification of issue in July 2009. The interactions between the examiner and the applicant seems to have taken place fairly steadily over the years. During the prosecution process the claims were amended. Some amendments were substantial and others minor. One needs to take care to orient oneself when reading the file as to which claims are under consideration at the relevant time.

208. This is not a case in which there is a clear answer to the issue of construction which has emerged from the claims and the specification. That matters because, as I explained above, if a clear construction had emerged from the claims and specification then it is only likely to be displaced by a disclaimer. However in the circumstances I find to exist, one is not simply reviewing the prosecution file to look for disclaimers, rather it is being reviewed for whatever light it can shed on the issue of construction.

209. I have been through the file, focussing on the documents and points the parties have emphasised. Although in principle one should review the prosecution history as a whole, I do not propose to work through all that in this judgment, which is lengthy enough already. I will focus on the particular points relied on. A final preliminary point to deal with is product by process claims. Given the lack of support for reading the claims as product by process claims in the other parts of the intrinsic evidence, the discussion about design and method in the prosecution history (which does exist) is nowhere near enough to justify reading the claims as product by process claims.

If donor and acceptor are identical they are counted as acceptor

210. The first point is about a letter written by the applicant on 29th August 2000. The context was that by an Office Action dated 29th February 2000 the examiner had rejected all the pending claims. The rejected claims were numbered 56-73. That does not mean there were 73 claims in issue. The numbering follows the consecutive numbering practice before the US PTO whereby if claims 1 to 23 are to be replaced,

they are replaced by claims numbered 24 onwards etc. At page 7 of the letter is the following statement:

> "Claims 56-73 have been rejected as allegedly indefinite in the recitation of "said variable domain comprising predominantly human acceptor..." Applicants respectfully disagree and note that this term is present in the claims of issued U.S. Patent No. 5,859,205, the parent of the present application. The term is used to distinguish the claims from chimeric antibodies in which the entire variable domain is from the donor antibody. Clearly, since the claims recite that the variable domain comprises predominantly human acceptor framework residues, the Examiner's query whether only framework residues are counted is correct. Further, the Applicants respectfully submit that it is clear to one skilled in the art that, if the donor and acceptor residues are identical for a particular position, they are counted as acceptor. Applicants respectfully submit this term is definite and request that this rejection should be withdrawn."
>
> [emphasis added]

211. Chugai contends this lends substantial support to its case. It is a clear and straightforward statement on the applicant's behalf that conserved residues count as acceptor and not donor. Chugai argues the applicant never sought (at least in any clear way) to qualify or reverse it in the file and that Dr Hale accepted the statement was consistent with Prof Rees' approach based on source. The point being that since the source of the framework regions was the acceptor, the fact they might be identical to the donor sequence did not change their source – which was acceptor.

212. UCB contends it is not that simple. The context is important. This statement was made concerning what was then claim 56. That claim was filed on 20th August 1997 is was as follows:

> "56. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain,
>
> said composite heavy chain having a variable domain including complementarily [sic] determining regions (CDRS),
>
> said variable domain comprising predominantly human acceptor antibody heavy chain framework residues,
>
> the remaining heavy chain residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen,
>
> wherein, according to the Kabat numbering system, in said composite heavy chain

> at least residues 31 to 35, 50 to 65 and 95 to 102 (the CDRS) and
>
> at least residues 23, 24, 49, 71, 73 and 78 (in the framework regions)
>
> correspond to the equivalent residues in said donor antibody."

213. The claim has a similar structure to claim 1 and 2 in the issued patent but it is not the same in a number of ways. The language at the end "correspond to equivalent…" is not in the granted claims. There is no disclaimer of chimeric antibodies, rather the claim aims to distinguish from chimeric antibodies by providing that the variable domain comprises "predominantly human acceptor antibody heavy chain framework residues". The examiner objected to that language on clarity grounds, particularly the word predominantly. In the 29th February 2000 Office Action the examiner had asked:

> "What if the donor and acceptor residues are identical for a particular position, would that residue count as donor or acceptor for determining the predominance?"

214. The statement relied on by Chugai is the answer to that question.

215. UCB argues that the statement made in the answer was not about whether residues at the specified framework positions (or in the CDRs) counted as donor if they also matched acceptor (which is the issue on the claims as granted). Rather it was about whether residues were counted as acceptor (if they also matched donor) for the purpose of determining whether the variable domain comprised 'predominantly human acceptor' heavy chain framework residues. UCB supported by Dr Hale, contends that the person of ordinary skill in the art would appreciate that the technical objectives lying behind the two were different. The former which relates to the claims in issue is concerned with binding affinity (making residues donor to improve binding) while the latter, about claim 56, is concerned with limiting the HAMA response by making as much of the framework as human as possible.

216. I do not entirely accept this part of UCB's analysis. I agree that as a technical matter making framework regions donor is to improve binding affinity whereas the reason why the framework region is generally human is to reduce the HAMA response. However, as Dr Hale also recognised in paragraph 125 of his first report (and is stated in terms in the passage relied on), the patentee was telling the Examiner that this claim language (variable domain predominantly human acceptor) was to distinguish the claims from chimeric antibodies. The statement was being made in the context of patentability.

217. If the question was whether this amounted to a relevant disclaimer, then the answer would be clearly not. Prof Chisum explained that statements about a claim term have no disclaiming effect about a significantly different claim term.

218. However that is not the relevant question given the difficulty in construing the specification. In my judgment this statement lends clear support to Chugai's case on construction and is inconsistent with UCB's case.

Antibody hTNF1

219. In the letter of 29th August 2000 just referred to, the applicant also filed a declaration of Geoffrey Yarranton of Celltech. This was filed in response to another objection contained in the Office Action of 29th February 2000, about enablement. Amongst other things the examiner was asking detailed questions about individual residues in the heavy chain and making a point (for example) that residue 6 seemed to be necessary to retain antigen binding but was not listed in the claims as they then were. The applicant argued that the examiner was misreading the specification and also used the Yarranton declaration to show that molecules with the claimed features were functional. The declaration discussed Queen and the differences between that approach and the invention and also included tables showing the sequences of various antibodies' heavy and light chains as well as some assay data. The tables indicate by a D, A or c whether residues are donor, acceptor or conserved in the humanised form.

220. After introducing the Yarranton declaration (and after a comment made in the context of CDRs that no change is necessary if donor and acceptor are the same) the applicant sought to persuade the examiner that residue 6 (and 78) was not necessary to retain potency. Using the claim language in play at the time, they did not have to "correspond to equivalent residues in the donor antibody". The passage draws specific attention to antibodies 61E71 and hTNF1 in the tables. The letter states that neither of these antibodies has a donor residue at positions 6 or 78 and they are said both to have 100% of the potency of the parent (donor) antibody.

221. However, as Chugai points out, in the Yarranton tables hTNF1 has a "c" for conserved at position 6 and 78. So the statement by the patentee that hTNF1 does not have a donor residue at these positions is flatly contrary to the patentee's case now, that conserved residues count as donor. (In the tables antibody 61E71 does have an A for acceptor at 6 and 78.)

222. UCB contends, supported by Dr Hale, that the person of ordinary skill in the art would appreciate that the patentee intended to refer to a different antibody in the table, hTNF3, and not to hTNF1.

223. The mistake is said to be obvious for three reasons. First, the table shows that hTNF3, like 61E71, has acceptor residues at positions 6 and 78 and these are the only two antibodies to do so. Further, the assay results table shows that hTNF3 has exactly the same assay results as 61E71, with potency being given as 100%. Given that the patentee was trying to persuade the examiner that it was not necessary to have residues at positions 6 and 78 that correspond to the equivalent residues in the donor antibody in order to retain potency, hTNF3 would, like 61E71, have been a good example to use. UCB argues that it is inexplicable that the patentee would refer the examiner to hTNF1 rather than hTNF3 to support the point it was trying to make.

224. Second, the reference to hTNF1 having "potency of 100% of the parent antibody" would not fit with the assay results table because there is no potency result for hTNF1 in the table. It is therefore clear that the Applicant cannot be referring to hTNF1, which would have been a hopeless example to have chosen. Professor Rees suggested that on noticing that there was no potency result for hTNF1 in the table, the skilled person would look for binding data in the patent. However it is fair to say that binding data (which is in the patent for hTNF1 but not 61E71) is not the same thing as potency data and the data in the patent uses a different comparator.

225. Third, the reference to hTNF1 as not having donor residues at positions 6 and 78 is inconsistent with the other statements the patentee made to the examiner about the Yarranton antibodies, including hTNF1 in later correspondence.

226. Despite these points I am not persuaded the person of ordinary skill in the art would determine that the reference to hTNF1 was an error at all or that what should have been written was hTNF3. For one thing no-one at the time seems to have noticed if it was an error and, for example, the examiner replied to the letter in detail referring to hTNF1. The important thing is that the person of ordinary skill in the art will approach this with an open mind, not knowing what the right answer is to the question of construction of "non-human donor". Understandably perhaps Dr Hale approached this issue from a starting point in which he already formed the view that conserved sequences were donor. From that stand point the reference to hTNF1 stands out as anomalous but that is not the standpoint of the skilled person. The fact hTNF3 could be used to make the point is not a strong indication of an error. Using hTNF1 to make the point in this way would also be consistent with the earlier statement in the same document that conserved residues count as acceptor.

227. As for the assay results, the person of ordinary skill in the art would be confused. I note the examiner was also confused (e.g. p5 of the later 1st August 2001 Office Action). The assay data present by Yarranton does not fit with what is said in the applicant's letter (of 29th August 2000) but nevertheless at a broader level there is positive data for hTNF1 albeit it is binding data and it is in the patent. Although something has gone wrong it is not obvious that there is a wrong description of the antibody rather than a wrong reference to assay data. For what it is worth (and I believe it is irrelevant) I prefer Chugai's case on the L292 assay. Low numbers mean poor performance and the later 21 November 2001 letter from the applicant is wrong in that respect.

228. The third point made by UCB is a good point, that the reference to hTNF1 as not having donor residues at positions 6 and 78 is inconsistent with the other statements the patentee made to the examiner about the Yarranton antibodies, including hTNF1, in later correspondence. However that is not enough to make the reference in the applicant's letter of 29th August 2000 into an obvious mistake for the skilled person.

229. I conclude that, subject to the next point, the hTNF1 point helps Chugai.

Request for reconsideration of 21st May 2001

230. The next point is the applicant's request for reconsideration dated 21st May 2001. The sequence of events was that after the letter of 29th August 2000 enclosing Yarranton the examiner was not persuaded on all points and essentially maintained the objections. The examiner's objections are in an Office Action dated 21st November 2000. This included a concern about the word "corresponding". The applicant felt (I think rightly) that the examiner had misunderstood the point that amino acids are not actually mouse or human in nature but that the antibodies are being designed at a conceptual level taking sequences from human or murine sources. This explanation includes the following:

> "A skilled person will, thus, readily understand the use of the 'corresponding' language. It is no doubt the case that, at some positions, the amino acid in the expressed antibody will

> correspond to the amino acid at that position in both the donor and human sequence. However, this will not be a problem for the skilled person, especially in light of the passage on page 17, lines 1 to 5 of the specification as filed which teaches that the acceptor and donor residues may be identical at a particular position, and thus, no change of acceptor framework residue is required. It is not necessary for the skilled person to determine which "areas" of the variable domain are donor and which are human. All that a skilled person needs to determine is whether the "residues" specified as being donor in the relevant claims are donor in the antibody in question. Given this, it is submitted that the skilled person would have had no difficulty in understanding the claims."

231. UCB submit this is consistent with and supports its approach to construction. I agree.

232. The same letter then goes on to focus on the Yarranton declaration and addresses the "corresponding" language, stating that:

> "Of the 17 framework chimeric heavy chains shown in Table 1 of the Yarranton Declaration, 14 have residues that correspond to residues in all of the 23, 24, 49, 71 and 73 Kabat numbered positions as found in claim 56."

233. The only way that number 14 can be correct is if the table is approached using UCB's construction, in other words counting conserved framework sequences as donor. Notably hTNF1 is one of the 14 (and is mentioned expressly on the same page of the letter).

234. This also support's UCB's construction and tends to neutralise the point on hTNF1 arising from the letter of 29th August 2000.

235. UCB argues that one can then see that the corresponding to language remained in the claim afterwards through the file history, for example, in December 2005 with the examiner working on the basis that "correspond to the equivalent residues in the donor antibody" meant "are donor residues" and there was no significant change until the patent was allowed. The claim language as granted came in a letter dated 4th March 2008 which included a statement by the patentee that the scope of the claims was not changed by replacing the "corresponds to" language with the wording now in the claims.

236. Thus UCB is correct that the "corresponding to" language remained and the final form of words in the issued claims was represented to be the same. However, if it matters, I am not convinced it is possible to tell how the examiner understood the claims finally allowed were to be construed. That is because the Reasons for Allowance dated 5th May 2008 state in terms that "the art does not teach or suggest a humanized antibody where specific amino acids in the CDRs and in the framework regions, as claimed in claims […] are non-human donor". However as is common ground the claims in fact read onto the Queen anti-Tac sequence on UCB's construction and thus, for the purposes of this action, that statement is wrong. It is particularly odd since various Queen documents had been discussed as prior art at a much earlier stage and also given

that following a request made by the examiner at an interview in April 2002 (which I infer was made for patentability reasons), UCB had filed a comparison table between the Queen anti-Tac sequence and the claimed sequences in a letter dated 18th November 2002. The point being made at the time was about the differences in approaches as between Queen and the patent in question.

Conclusions on the prosecution file

237. The prosecution file contains material which supports each party's case. There are clear examples of statements consistent with both sides' constructions being made by the patentee.

Extrinsic evidence

238. Dr Rees gave evidence that the "ordinary and plain meaning in the art of antibody humanisation in 1989 was that an 'acceptor sequence' referred to the amino acid sequence that accepts residues from a donor amino acid sequence and a 'donor sequence' referred to an amino acid sequence that donates residues to an acceptor amino acid sequence".

239. UCB put a converse example to Dr Rees in which one imagines a skilled person starting from the donor sequence and bringing in further residues from the acceptor. Dr Hale said that in some work after the priority date some people he knew had taken that converse approach. I was not convinced by Dr Hale's evidence that this represented the thinking of the person of ordinary skill in the art at the relevant date and I find that the converse example put to Dr Rees does not represent the thinking of a person of ordinary skill in the art.

240. Chugai referred to examples in which the term "murine" (i.e. the donor) is used to refer to CDRs and to framework residue changes only and not to conserved residues in the framework regions. They were a witness statement by the inventor Dr Athwal and a project report to Ortho. Although these date from a period a few years after the relevant date, Dr Hale accepted (and I find) that the usage had not changed.

241. I refer back to the chimeric antibody diagram which is set out in the background section of this judgment. Dr Hale regarded the diagram as simplistic and at an undergraduate level and explained that the understanding of a person of ordinary skill in the art was more sophisticated. I agree that the person of ordinary skill in the art did indeed have a more sophisticated understanding than an undergraduate and would know, for example, that there were conserved residues in the variable region of a chimeric antibody. Nevertheless in my judgment it would be normal usage to refer to the variable region as donor and that is true even though, as the person of ordinary skill in the art would know, there may well in fact have been residues in the variable region which were conserved as between the donor and acceptor. This thinking is also illustrated by the diagram itself which seems to have been of a commonly used kind (e.g. the colouring in Riechmann fig 2) and represents the different sources in a clear way.

242. Dr Hale's view on what donor meant to the person of ordinary skill in the art at the relevant date supported UCB's case. He formed his view in the context of the patent and the prosecution history. Chugai submitted that Dr Hale accepted that in Winter-type CDR grafts normal usage would be that the CDRs were the donor part, and that

Dr Hale accepted that in Riechmann the framework residue which was changed and the CDRs would be described as donor and the rest would be acceptor. It is not accurate to say that Dr Hale accepted either point. On the Winter CDR grafts he agreed it was "something that may be said" and pointed out the terms take their meaning from their context. On Riechmann he did not say they would be described as donor, he said it might be one of the ways people talk about it.

243. In terms of the extrinsic sources, I find that in the art the term donor (and the term acceptor) were used as a reference to source. This usage was the same whether the term was applied to antibodies, parts of antibodies or residues. When applied to residues in a humanised antibody derived from a donor and acceptor (as the antibodies in this case are) this ordinary meaning of donor would have the result that a CDR sourced as a unit from the donor antibody would be "donor" regardless of conserved residues as between the donor CDR and the acceptor's CDR; and conversely a residue outside the CDR in the framework regions which was sourced from the human acceptor would be acceptor and not donor even if it was conserved as between the acceptor and the donor sequences. Only a residue changed from the human acceptor to a donor residue in the framework region would be called donor. In other words the extrinsic evidence firmly supports Chugai.

244. Overall, I preferred Prof Rees' evidence on these issues than that of Dr Hale.

Overall – the true construction of claim 2

245. The claims alone could be read either way. The specification, which is the single best guide and primary basis for construing the claims, is hard to interpret and contains some material which positively supports one side and some material which positively supports the other side. The prosecution file is similar, containing statements which support each side's case. The extrinsic evidence, albeit the least powerful source of evidence, is different. It firmly supports Chugai.

246. I am satisfied that approached purely as a matter of construction, I should not find in favour of UCB's construction. That is because overall, the case in support of UCB is not better than the case for Chugai's construction. Accordingly, looking ahead, it is tempting to say that the validity tie break is looming and on that basis claim 2 must be construed in the manner contended for by Chugai. That is because claim 2 does cover the anti-Tac antibody in Queen on UCB's construction and so, on the basis of the way the case has been put to me, the patent would be invalid over Queen.

247. However I do not think the construction issue is in fact so insoluble that only a tie breaker would do. Taking the extrinsic evidence into account, the patent can be construed in a reasonably coherent way using Chugai's approach provided one accepts that many of the statements which do support UCB are just not talking about the claims. They are talking about the wider work undertaken by the inventors. The claims and that wider description cannot be made to fit together on either party's case. The claims claim a particular kind of antibody which has the beneficial properties but the claims would not be understood as trying to claim every sort of antibody within the widest technical descriptions in the document. In the specification the "invention" is just not the same thing as what has been claimed in these claims nor are all the preferred embodiments. That has particular significance for the references using an acceptor with any degree of homology and the point that the impact on affinity is likely to be the same

whether the framework residues were conserved or changed to donor. On UCB's case the claim would cover an antibody for which no changes were made at all but, despite the breadth of the description, and the suggestion that one way to go is to go for high homology, the idea of no changes at all is not suggested anywhere and in my judgment the person of ordinary skill in the art would not understand the specification to go that far. It is also true that in order to fall within the claim one would have to use a human framework with lower homology than would be needed on UCB's construction but the specification by no means rules out using a relatively low homology acceptor. On Chugai's construction the claims use language in the same manner as the person of ordinary skill in the art would be familiar with from the wider art.

248. So my finding is that Chugai's construction is the right one.

Conclusion

249. Chugai's tocilizumab product does not infringe a Valid Claim of US patent 7,566,771. No royalties are due for tocilizumab under the patent licence between Chugai and UCB for product manufactured after 13th January 2016.