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Datasheet for the decision of 22 June 2017

Case Number: T 1784/15 - 3.3.04

Application Number: 07724105.7

Publication Number: 2007809

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Language of the proceedings: EN

Title of invention:
Glycosylated antibodies

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponents:
Novartis AG (appeal and opposition withdrawn)
Glaxo Group Limited

Headword:
Glycosylated antibodies/HOFFMANN-LA ROCHE

Relevant legal provisions:
EPC Art. 54, 56, 83, 87
EPC R. 115(2)
RPBA Art. 12(2), 12(4), 15(3)

Keyword:
Main request - requirements of the EPC met (yes)
Late-filed line of argument - admission into the appeal proceedings (no)

Decisions cited:
T 0277/95, T 0737/96

Catchword:

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Case Number: T 1784/15 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 22 June 2017

Appellant II: (Opponent 02)	Glaxo Group Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	Bhogal, Jasber Kaur GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent: (Patent Proprietor)	F. Hoffmann-La Roche AG Grenzacherstraße 124 4070 Basel (CH)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 13 July 2015 concerning maintenance of the European Patent No. 2007809 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	M. Blasi

Summary of Facts and Submissions

I. Appeals were lodged by opponent 01 (hereinafter "appellant I") and opponent 02 (hereinafter "appellant II") against the interlocutory decision of the opposition division that European patent No. 2 007 809, entitled "*Glycosylated antibodies*", could be maintained in amended form.

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty and inventive step and under Article 100(b) EPC.

III. In the impugned decision the opposition division held that auxiliary request II filed with the letter dated 5 June 2015, which was re-filed as main request during the oral proceedings, and a description adapted thereto met the requirements of the EPC.

IV. With their statements of grounds of appeal appellants I and II submitted *inter alia* arguments as to why the main request did not comply with the provisions of the EPC.

V. With its reply to the appellants' statements of grounds of appeal the patent proprietor (hereinafter the "respondent") submitted a main request (identical to the main request dealt with in the decision under appeal), claim sets of auxiliary requests and declarations D46 and D47.

Claims 1, 5 to 7 and 9 of the main request read:

"1. Monoclonal antibody of human IgGl or IgG3 type being glycosylated with a sugar chain at Asn297, said antibody being characterized in that

a) the amount of fucose within said sugar chain, related to the sum of G0, Gl, G2 without mannose 4 and mannose 5 as 100% and as analyzed by Liquid Chromatography/Mass Spectrometry (LCMS) peptide map analysis is at least 99%,

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

5. CHO cell line DSM ACC 2795.

6. Use of an antibody according to claims 1 to 4 for the manufacture of a medicament.

7. Pharmaceutical composition comprising an antibody according to claims 1 to 4.

9. Method for the recombinant production of a monoclonal antibody according to claims 1 to 4 in a CHO cell according to claim 5."

VI. Following a request for acceleration of the appeal proceedings submitted by appellant I, the board decided to deal with the case in an expedited manner. The parties were summoned to oral proceedings and were informed of the board's preliminary view in a communication pursuant to Article 15(1) RPBA.

VII. In reply, appellant II announced that it would not be attending the oral proceedings.

VIII. On the day before the oral proceedings appellant I withdrew its appeal.

IX. The following documents are cited in this decision:

D1: WO 2005/040221

D3: Shields R.L., *et al.*, (2002), J. Biol. Chem., 277: 26733-26740

D6: Chung S., *et al.*, (2012), mAbs, 4: 326-40

D14: Davies J., *et al.*, (2001), Biotech. Bioengin.-Combinatorial Chem., 74: 288-294

D18: Routier F. H., *et al.*, (1998), J. Immunol. Meth., 213: 113-130

D19: Raju T. S., *et al.*, (2000), Glycobiology, 10: 477-486

D20: Raju T. S., *et al.*, (2003), BioProcess Internat., 44-53

D21: Jefferis R., (2005), Biotechnol. Prog., 21: 11-16

D24: Bergwerff A. A., *et al.*, (1995), Glycoconjugate J., 12: 318-330

D25: Stadlman J., *et al.*, (2008), Proteomics, 8: 2858-2871

D33: Declaration of Dr. S. Hansen, dated 20 January 2014 (including Exhibit 1)

D38: Matsumiya S., *et al.*, (22 February 2007), J. Mol. Biol., 368: 767-779

D39: Shatz W., *et al.*, (2013), mAbs, 5: 872-881

D40: Declaration of M. Patel, Dr. H. Schuessler, and U. Aich, dated 16 April 2015 (including exhibits A-C)

D42: Shah B., *et al.*, (2014), J. Am. Soc. Mass. Spectrom., 25: 999-1011

D43: Declaration of Dr. D. Reusch, dated 2 June 2015 (including exhibit 1)

D46: Declaration of Dr. D. Reusch and Mr. M. Haberger, dated 7 April 2016

D47: Declaration of Dr. T. Schlothauer, dated 4 July 2016 (including exhibit 7)

X. Oral proceedings before the board were held on 22 June 2017. Appellant I's representative confirmed that appellant I's appeal and opposition were withdrawn. Appellant I's representative attended the oral proceedings as a member of the public. Appellant II was not present, as announced. During the oral proceedings the respondent withdrew all its previously filed 53 auxiliary requests. At the end of the oral proceedings the chairwoman announced the board's decision.

XI. Appellant II's arguments submitted in writing, where relevant for the present decision, may be summarised as follows:

Main request

Admission into the appeal proceedings of lines of arguments

The "*reasons of record (our written arguments set out in our grounds of opposition of 12 June 2013 and our Rule 116 EPC submissions of 16 April 2015, and the verbal arguments presented during the oral proceedings on 16 June 2015*" (see statement of grounds of appeal, point 2.1) should be taken into account by the board.

Sufficiency of disclosure (Article 83 EPC)

The key features of the monoclonal antibodies according to claim 1 relevant to insufficiency were that they were at least 99% fucosylated, contained 1% or less N-glycolylneuraminic acid (NGNA), and 1% or less α-1,3-galactose (α-1,3 Gal), all as determined by liquid chromatography/mass spectrometry (LCMS) peptide map analysis.

LCMS peptide mapping, as disclosed in Example 3, was not suitable for reliably determining the amounts of fucose, NGNA and α-1,3 Gal within the 1% ranges recited in claim 1, since it was inherently variable. This was shown by the significant standard deviations observed between measurements of the same antibody sample carried out with the same LCMS instrument on five consecutive days (see declaration D40, Tables 4 and 6).

Furthermore, the choice of the LCMS instrument for glycan determination was decisive. This was shown by the significantly deviating results obtained when LCMS measurements were carried out with two instruments of different manufacturers, although antibodies from the same sample lot were analysed and adequate system suitability tests were performed for each instrument (see declaration D40, Tables 1 and 2).

The deviations in the determined amounts of N-acetylglucosamine (GlcNac) - which was not part of the invention - did not cast doubts on the measurements with regard to fucose, NGNA and α-1,3 Gal disclosed in Tables 1 and 2 of declaration D40. These deviations were likely to be due to differences in the tuning conditions and source parameters of the two instruments. Indeed, the difference in the amounts of GlcNac was illustrative of the critical role the instrument played, especially when working within the small percentages recited in the claim.

Thus, the skilled person relying on LCMS peptide mapping could not determine consistent and accurate values for the glycosylation pattern of antibodies up to the limits in claim 1, which made it impossible to determine with sufficient certainty whether or not an antibody fell within the ambit of claim 1.

The patent provided neither information on the type of LCMS instrument used to determine the disclosed glycosylation pattern in the antibodies - which was necessary due to the different sensitivities of the instruments - nor information on the chromatographic separation conditions applied or on the internal standards used in its measurements.

Thus, the patent lacked essential technical information that would allow the skilled person to reproduce the data presented in Example 3.

The patent disclosed a single deposited cell line (clone 5) for the expression of an antibody binding to IGF-IR that fell within the claimed ambit. There was insufficient information allowing the skilled person, starting with that cell line, to obtain alternative antibodies falling within the ambit of claim 1 without undue burden. The patent disclosed neither technical information on how to genetically manipulate the DNA sequence of the deposited cells, nor details on their production, for example cell culture conditions, media or purification methods. Amino acid sequence, media or culture conditions all directly affected the glycosylation of antibodies (see documents D19 and D21). Thus, the generation of alternative antibodies amounted to a research project rather than routine experimentation.

The significance of the media was shown for example by the data relating to clones 3 and 5 reported in Tables 3a and 3b in the patent, which demonstrated that cells grown in different media produced antibodies with a different glycosylation pattern.

Thus, the invention of claim 1 and the corresponding dependent claims was not sufficiently disclosed in the patent.

Right of priority (Article 87 EPC)

The subject-matter of claims 1 to 9 did not enjoy the right of priority from the second priority application (hereinafter "P2" application), because the subject-matter claimed was not disclosed there in an enabling manner.

Although clone 5 was deposited on 21 June 2006, i.e. before the filing of the P2 application, Table 3b, disclosing detailed information on the levels of NGNA and α-1,3 Gal glycosylation of the antibody produced by clone 5, was only added when the European patent application was filed.

The glycosylation pattern in relation to fucose, NGNA and α-1,3 Gal as referred to in claim 1 was not an inherent feature of the deposited clone 5. The skilled person needed to genetically manipulate clone 5 to express an antibody of interest, followed by the culturing of the cell and the purification of the antibodies to analyse their glycosylation. Only the combination of the deposited clone with the glycosylation data disclosed in Table 3b provided the skilled person with the certainty that the glycosylation as defined in claim 1 would necessarily be found.

Decision T 277/95 supported the view that in the present case the right to priority could not be validly claimed. In that decision the board found that a claim to a method of producing a protein with a specific glycosylation pattern in CHO cells did not enjoy the right to priority from a priority application which made the cell line available but gave no information on

the specific glycosylation pattern. Novelty (Article 54 EPC)

The subject-matter of claims 1 to 4, 6 and 7 lacked novelty in view of the disclosure of documents D1 and D24.

Document D1 in Table 1 disclosed an antibody directed against human rhesus factor D, i.e. a human anti-D1 antibody, produced in CHO cells which was considered to be 100% fucosylated.

Document D24 disclosed chimeric human/mouse IgG1 monoclonal antibodies produced by SP2/0 subclones having N-glycans that were "*completely (α1→6)-fucosylated at the innermost GlcNAc residue*", (abstract), i.e. 100% fucosylated.

The fact that in both documents the glycosylation pattern was not determined by LCMS peptide mapping was irrelevant. If the LCMS method was indeed critical, then more information about the spectrometer type and conditions should have been given in the description of the patent.

Inventive step (Article 56 EPC)

Either of documents D20, D25 or D38 represented the closest prior art for the subject-matter of claim 1.

Document D20 disclosed keeping levels of NGNA and α-1,3 Gal low in therapeutic antibodies in order to reduce their immunogenicity. The document further reported that more than 95% of the oligosaccharides of human and CHO cell-derived antibodies were fucosylated and that there was a correlation between the level of

afucosylation in antibodies and improved antibody-dependent cell-mediated cytotoxicity (ADCC). Thus, document D20 suggested to the skilled person to produce recombinant therapeutic antibodies having a fucosylation level of above 95% - which more closely mimicked that of human antibodies - if ADCC was not desired.

The opposition division erred in the decision under appeal in finding that there was contradictory evidence as to whether there was a correlation between reduced ADCC activity and the fucosylation of antibodies in the range of 95% to 100%.

In fact, there was clear evidence that there was very little correlation, if any, that fucosylation levels above 95% had an effect on the reduction of the antibody's ADCC activity.

The alleged correlation was not derivable from the patent, which disclosed in example 4 and Figure 1 that there was no difference in the ADCC activity of antibodies generated in eight clones having fucosylation levels in the range of 99.4% to 99.9%.

Nor was evidence for such a correlation disclosed in documents D6 or D39. It was derivable from document D6 that there was a non-linear relationship between 7.5% to 0% afucosylated antibodies (92.5 and 100% fucosylated) and increased ADCC activity (Figures 7A, B and 8) and from document D39 that reducing the antibodies' afucosylation below 7.6% (increasing fucosylation above 92%) had little impact on ADCC activity. Thus, neither of the two documents disclosed evidence required in the present case, namely for a

correlation between the amount of fucosylated glycan and reduced ADCC in antibodies.
Thus, the opposition division was wrong to find that increasing the fucosylation above 95% had the technical effect of decreasing the antibodies' ADCC activity.

The opposition division was also wrong to find that there was no reasonable expectation of success in obtaining the claimed antibodies in view of the fact that the highest levels of fucosylation disclosed in the prior art were not reproducible. The patent too lacked teaching on how to modify CHO cells in order to increase the fucosylation of all secreted antibodies to at least 99% as referred to in claim 1. Therefore, the lack of reproducibility in the prior art could not be used in favour of the patent.

The glycosylation features of the claimed antibodies were a generalisation of the specific anti-IGF-IR antibody expressed by the deposited clone 5.

Declaration D33 provided evidence that clone 5 was obtained by chance. It was thus clear that the patent's contribution to the art was not a generic composition or a method allowing the skilled person to use any biological organism to reliably obtain antibodies characterised by the glycosylation features referred to in claim 1.

Therefore, in line with decision T 737/96, the technical contribution of the patent was limited to the provision of the deposited clone 5.

The selection of clone 5 appeared arbitrary, since the antibodies produced by all the other seven clones

disclosed in the patent exhibited higher fucosylation levels (see Table 2).

Alternatively, the subject-matter of claim 1 lacked an inventive step in view of document D38 as the closest prior art in combination with document D20. Document D38 was published on 22 February 2007, i.e. before the filing date of the patent but after the filing date of the second priority document, and in view of the submissions on the right of priority it constituted full prior art.

Finally, the subject-matter of claim 1 also lacked an inventive step in view of the disclosures of documents D25 in combination with D20.

XII. The respondent's arguments, where relevant for the present decision, may be summarised as follows:

Main request

Sufficiency of disclosure (Article 83 EPC)

The LCMS method, if correctly applied, reliably determined the levels of fucosylation, NGNA and α-1,3 Gal in antibodies in the ranges referred to in claim 1, as demonstrated by the experimental data reported in declaration D46 (see exhibit 3).

Significant deviations in the LCMS measurements between different instruments were avoided by applying art-established standards, in particular adequate system suitability tests (see declaration D43).

Example 3 disclosed evidence that antibodies falling within the ambit of claim 1 had been reliably obtained

from various transfected CHO cells, even if cultivated in different media.

This was confirmed by declaration D33.

Moreover, the subject-matter of claims 8 and 9 did not encompass antibodies produced in clone 5 from which the sequences of the anti-IGF-IR antibody had been replaced by sequences of other antibodies, since both claims were directed to the use or production of an anti-IGF-IR antibody.

Right of priority (Article 87 EPC)

The subject-matter of claims 1 to 9 was entitled to the priority date of the P2 application.

The opposition division correctly found that the P2 application sufficiently disclosed the deposited clone, as this document provided the same examples 1 to 3 as the application, giving detailed information on how to generate antibodies with the glycosylation pattern as claimed.

Should the disclosure of the glycosylation pattern indeed be necessary for acknowledging priority, then Table 2 of the P2 document provided the key features of this pattern for the clone 5 antibody. Thus, upon reproducing the antibody from clone 5, the skilled person had a reference pattern of its glycosylation at hand. Knowledge of the complete data disclosed in Table 3b was not required.

The fact that Table 3b was missing from the P2 application was thus immaterial for the enablement of the claimed subject-matter.

Furthermore, decision T 277/95 was not relevant for the present case, since in the case it dealt with the priority document did not disclose any glycosylation pattern at all. In the present case the P2 document (see claims on pages 22 and 23) disclosed literally the features relating to fucose, NGNA and α-1,3 Gal as recited in claims 1 to 3.

Novelty (Article 54 EPC)

The subject-matter of claims 1 to 4, 6 and 7 was novel over the disclosure of documents D1 and D24.

Neither of these two documents disclosed that LCMS peptide mapping was used to determine the relative amounts of fucose, NGNA and α-1,3 Gal referred to in claim 1.

Furthermore, as admitted by appellant II, document D24 disclosed that the antibodies contained NGNA in their glycosylation in amounts of <1.2% or <1.12%, which included values of above 1%, contrary to the antibodies claimed.

Inventive step (Article 56 EPC)

Admission into the appeal proceedings of a new lack of inventive step objection based on document D25 (Article 12(4) RPBA)

Appellant II's line of argument based on document D25 as the closest prior art submitted in its statement of grounds of appeal should not be admitted into the appeal proceedings. Although document D25 was on file from the outset of the opposition proceedings,

appellant II had not raised this line of argument at that stage. Therefore, the line of argument based on document D25 could have been raised by appellant II during the first-instance proceedings, whereas there was no justification for submitting it only at the appeal stage.

Closest prior art

Document D20 represented the closest prior art. Among other things it disclosed that 95% of the antibodies produced in CHO cells contained core fucosylated biantennary glycans terminating in 0, 1 or 2 Gal residues. It further reported that antibodies produced in mouse cells suffered from the disadvantages that they contained NGNA and α-1,3 Gal residues which both potentially caused adverse immunogenicity in humans and that non-fucosylated antibodies were characterised by improved ADCC activity.

The antibodies of claim 1 differed from the antibodies of the closest prior art, which had a fucosylation level of 95%, by having a fucosylation of at least 99%, i.e. 4% higher, which had the effect that the antibodies reliably lost their ADCC activity (see example 4 and Figure 1 of the patent).

Furthermore, as demonstrated by comparative experimental data, increasing the fucosylation of antibodies from 98.3% to 99% reduced the proportion of antibodies binding to the FcγRIIIa receptor from 12.43% to 5.98% (see declaration D47, exhibit 7). Since the affinity of the IgG1 and IgG3 antibodies to the FcγRIIIa receptor was a direct measurement of the antibodies' potential to induce ADCC, the data in exhibit 7 demonstrated that antibodies having a fucose

content of at least 99% likewise had a lower potential for inducing ADCC compared to the antibodies of the closest prior art.
This finding was also supported by documents D6 and D39, which both disclosed that there was a linear relationship between an increased level of fucosylation in antibodies and reduced ADCC activity.

The technical problem was thus how to provide monoclonal antibodies having a lower potential for inducing ADCC.

The problem was solved across the whole ambit of claim 1, since it was derivable from the patent, for example from Figure 1, that a fucose amount of at least 99% in the antibodies had the effect that the antibodies reliably lost their ADCC activity.

Moreover, the patent provided a novel and non-obvious process for preparing the claimed antibodies, and appellant II had not submitted evidence demonstrating that the process was not enabled to do so across the whole claimed ambit. Therefore, decision T 737/96 was not relevant in the present case, since the contribution of the present invention to the art corresponded to what was actually claimed.

The antibodies according to claim 1 were not an obvious solution to this problem for several reasons. Firstly, the teaching of document D20 provided no motivation for the skilled person to increase the fucose content of the antibodies to achieve a more reduced ADCC activity. Secondly, even if the skilled person had envisaged the generation of antibodies with an increased fucosylation above 95% in view of the teaching of document D20, there would have been no incentive to try to achieve

this goal by the approach disclosed in the patent in examples 1 to 3. Thirdly, even if the skilled person had envisaged this approach, it would not have been possible to derive from any of the cited prior-art documents a reasonable expectation that taking this approach would indeed have resulted in antibodies with an at least 99% fucose content.

XIII. Appellant II requested in writing that the decision under appeal be set aside and that European patent No. 2 007 809 be revoked.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. After withdrawing its opposition and appeal, the former appellant I ceased to be a party to the appeal proceedings. Its submissions were therefore disregarded for the purpose of this decision.

2. The duly summoned appellant II was not present at the oral proceedings, which therefore took place in its absence in accordance with Rule 115(2) EPC. Moreover, in accordance with Article 15(3) RPBA, for the purpose of this decision it was treated as relying on its written case.

Admission into the appeal proceedings of lines of arguments submitted by appellant II

3. Article 12(1) and (2) RPBA defines the basis for the appeal proceedings. Pursuant to Article 12(2) RPBA the statement of grounds of appeal and the reply shall

contain a party's complete case. They shall set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should specify expressly all the facts, arguments and evidence relied on.

4. Appellant II requested the board to take into account all the reasons of record submitted with its notice of opposition and its Rule 116 EPC submission or presented verbally during the oral proceedings before the opposition division.

5. A mere reference to all "*reasons of record*", which the board understands as covering all objections and arguments made by appellant II during the written and oral phase of the opposition proceedings, is generic to such an extent, that none of the other parties to the proceedings, including the board, can immediately understand to which specific objection or argument it relates. Furthermore, the lines of argument in these submissions were all raised by appellant II during the opposition proceedings before the opposition division took its final view on the individual issues in the decision under appeal. Therefore, it is not clear to which of the reasons in the decision under appeal the arguments are directed and neither the board nor any of the other parties to the proceedings can immediately understand why - based on these unspecified lines of argument - the decision under appeal should be reversed. Thus, the mere reference to all objections and arguments submitted by appellant II during the written and oral phase of the opposition proceedings lacks clarity and conciseness.

6. Consequently, the board decided not to consider any of these unspecified objections or arguments in the

present appeal proceedings pursuant to Article 12(2) RPBA.

Introduction to the invention

7. The invention concerns human monoclonal antibodies of the IgGl or IgG3 type, wherein the carbohydrate (glycan) structure attached to the antibodies' Fc region is almost completely fucosylated (by at least 99%), while it is almost free of N-glycolyneuraminic acid (NGNA) and N-terminal alpha-1,3 galactose (α-1,3 Gal) molecules (both are present in an amount of 1% or less) (see paragraph [0001] of the patent).

8. Antibody-dependent cytotoxicity (ADCC) activity relates to an antibody's ability to activate effector cells to lyse target cells. The underlying mechanism involved in this cytotoxic process relies on the binding of an antibody's Fc region to an Fc gamma receptor (FcγR), in particular FcγRIII, located on the surface of the effector cells. The binding affinity between the antibody and the receptor is affected by the level of fucosylation in the Fc region. The smaller the content of fucose is in the glycan structure of the Fc region, the higher the binding affinity. A high binding affinity correlates with increased ADCC activity (see paragraphs [0002], [0004] and [0006] and Figure 1 of the patent).

9. The low amount of NGNA and α-1,3 Gal molecules has the consequence that the antibodies of the invention have a low immunogenic potential in humans (see document D20, page 48, column 1, last paragraph, to column 2, second paragraph).

10. Parts (a) and (b) of claim 1 define the glycosylation of the monoclonal antibodies *inter alia* as the amount of fucose, NGNA or α-1,3 Gal, "*related to the sum of G0, Gl, G2 without mannose 4 and mannose 5 as 100%*".

11. The terms G0, G1 and G2 indicate that the antibodies are defined by a "*core fucosylated biantennary complex oligosaccharide glycosylation terminated with up to 2 galactose residues*" (see paragraph [0035] of the patent).

12. The terms "*mannose 4 and mannose 5*" (Man4 and Man5) describe a glycosylation type of "*High Mannose structures bearing four and five mannose residues respectively*" (see paragraph [0070] of the patent).

13. Finally, the term "*Asn297*" referred to in claim 1 denotes the conserved asparagine residue located at position 297 in the polypeptide chain of antibodies of the IgG1 and IgG3 type, which is the amino acid at which the sugar chain is linked to the antibody (see paragraphs [0026] and [0035] of the patent).

Sufficiency of disclosure (Article 83 EPC)

14. Claim 1 is directed to a monoclonal antibody of the human IgGl or IgG3 type being glycosylated with a sugar chain at Asn297, wherein the sugar chain (glycan) is further structurally characterised in that (1) the amount of fucose is at least 99%, (2) the amount of NGNA is ≤1%, and (3) the amount of α-1,3 Gal is ≤1%, all related to the sum of G0, Gl, G2 without Man4 and Man5 as 100%. The method by which these parameters are to be determined is indicated in the claim: "Liquid Chromatography/Mass Spectrometry (LCMS) peptide map analysis".

15. Thus, claim 1 is directed to human monoclonal antibodies of specific subtypes, which are *inter alia* structurally defined by the amounts of fucose, NGNA and α-1,3 Gal in the range of at least 99% and and less than or equal to 1%, respectively, relative to the sum of G0, Gl, G2 glycosylation types without Man4 and Man5 set as 100%, all as determined by LCMS peptide mapping. Thus, since the glycosylation types G0, Gl, G2, Man4 and Man5 represent only a subset of types found in antibodies, the amounts of fucose, NGNA and α-1,3 Gal recited in claim 1 are relative and not absolute.

16. It is established case law of the boards of appeal that a claimed invention must be disclosed in the application as a whole in a manner sufficiently clear and complete for it to be carried out by the skilled person, also taking his common general knowledge into account. Furthermore, sufficiency of disclosure presupposes that the skilled person is able to obtain substantially all embodiments falling within the ambit of the claims.

17. Moreover, the purpose of a parameter contained in a claim is to define an essential technical feature of the invention. Thus, the method specified for determining the parameter should produce consistent values, so that the skilled person is able to identify suitable compounds, here antibodies, necessary for solving the problem underlying the patent at issue (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016 (hereinafter "CLBA"), II.C, II.C.4.4, II.C.4.5).

18. An issue in the present case is whether or not LCMS peptide mapping is suitable for reliably determining

the relative amounts of fucose, NGNA and α-1,3 Gal in the ranges referred to in claim 1.

19. Appellant II argued during the first instance proceedings that this method was not reliable as demonstrated by the data disclosed in declaration D40. The opposition division was not convinced by this, primarily in the light of declaration D43, a document submitted by the respondent. In this context the opposition division held that it had "*no reason to doubt the declaration of P's technical expert in D43 that it is decisive to apply an adequate system suitability test to measure relative glycan quantities, while neither the use of different instruments nor the absolute sensitivity of the instrument is decisive. It is not derivable from D40 whether an adequate system suitability test has been done for both instruments used for comparison*" (see decision under appeal, point 16.4.3 and declaration D43, point 8).

20. In the appeal proceedings appellant II again relied solely on declaration D40 and essentially reiterated the arguments it submitted during the first-instance proceedings, which may be summarised as follows:
(i) although adequate system suitability tests were performed for both LCMS instruments disclosed in declaration D40, the amounts determined for the individual glycan molecules by the two LCMS instruments were significantly different; (ii) the deviating values with regard to N-acetylglucosamine (GlcNac) disclosed in Tables 1 and 2 of declaration D40 were most probably due to differences in the tuning conditions and source parameters applied in the two LCMS instruments used, and there was no reason to doubt the correctness of the data disclosed in Tables 1 and 2 for fucose, NGNA and α-1,3 Gal, simply because the values of GlcNac varied;

(iii) the standard deviations reported in Tables 3 to 6 of declaration D40 for the measurements carried out on five consecutive days were correct, since they were performed on the same antibody sample, which was stable at the storage conditions applied. Moreover, the measurements were carried out by the same technical expert.

21. With its reply to appellant II's statement of grounds of appeal the respondent submitted declaration D46. This declaration discloses that the amount of fucose in an anti-IGF-IR antibody (i.e. the antibody disclosed in examples 1 to 3 of the patent) being fucosylated by 99% can be reliably determined with an accuracy of +/-0.1%, relying on LCMS peptide mapping on consecutive days (see declaration D46, points 6 to 8, and exhibit 3).

22. Furthermore, the respondent reiterated its argument based on declaration D43 that the deviating amounts of GlcNac disclosed in Tables 1 and 2 of declaration D40 might be an indication that the LCMS measurements had not been carried out with the required thoroughness.

23. Thus, the board finds itself in a situation where the question at issue, i.e. whether or not LCMS peptide mapping is suitable for reliably determining the relative amounts of fucose, NGNA and α-1,3 Gal in the ranges referred to in claim 1, has to be decided on the basis of contradictory arguments and experimental data submitted by the parties. Moreover, none of the evidence and arguments submitted by either party seem to disprove the submissions of the other party.

24. Appellant II as opponent and appellant bears the burden of proof for the present objection of lack of sufficiency of disclosure and thus has to convince the

board that the opposition division's decision was wrong in order to obtain a favourable decision on this point.

25. The board in the present situation is unable to conclude that appellant II has discharged its burden of proof, in particular given the fact that the respondent's arguments and facts in relation to declaration D46 remain uncommented.

26. In a further line of argument with regard to sufficiency of disclosure, appellant II submitted that the teaching of the patent did not allow the skilled person to obtain substantially all antibodies falling within the ambit of claim 1. This was because the patent disclosed only a single deposited cell line (clone 5) which expressed the anti-IGF-IR antibody as an exemplary antibody of the invention. However, the patent disclosed neither details of how this cell clone could be genetically manipulated to replace the gene encoding the anti-IGF-IR antibody with genes encoding other antibodies, nor for example information on culture conditions, media and amino acid sequences of alternative antibodies, which were all known to crucially affect the glycosylation pattern of antibodies, see documents D19 and D21. In other words, the patent did not disclose a generic method that was suitable for obtaining antibodies of the invention other than the deposited anti-IGF-IR antibody.

27. The issue to be assessed is thus whether the patent discloses a method that is suitable for obtaining substantially all antibodies falling within the ambit of claim 1.

28. It was common ground between the parties that the CHO cell line DSM ACC 2795 (i.e. "clone 5") and the anti-

IGF-IR antibody produced by it were sufficiently disclosed in the patent. Moreover, it was common ground that the antibody produced by clone 5 including its glycosylation pattern was encompassed by the antibodies according to claim 1.

29. Regarding the generation of claimed antibodies other than those produced by clone 5, contrary to appellant II's view there is no teaching derivable from the patent that their production relies on the genetic manipulation of clone 5. Thus, to carry out the invention according to claim 1 it is not necessary to resort to the deposited clone 5.

30. Rather, in the context of how exemplary antibodies of the invention are generated, the patent discloses in paragraph [0062] that the "*parental cell line used for the generation of a cell line for recombinant IgG expression is a Chinese hamster ovarian (CHO) cell line, CHO-DG44*", in which the cells "*have lost both endogenous loci for the enzyme Dihydrofolate Reductase (DHFR)*". In the board's view, the skilled person would derive from this passage that the CHO-DG44 cell line is the starting point for obtaining the recombinant antibodies of the invention. Appellant II did not dispute the public availability of this cell line.

31. Example 1 further discloses that the CHO-DG44 cells are transfected with a plasmid carrying the gene for the anti-IGF-IR antibody ("*AK18*"). Subsequently, the cells are "*put under selection pressure consisting of MEM alpha Minus Medium, 10% dialysed FCS and 2 mmol/L L-Glutamine and 20nM Methotrexate (MTX)*", and three weeks later clones are picked and expanded (see paragraphs [0064] and [0065]). Supernatants of the transfected clones are analysed for the presence of human

antibodies, and the clones are adapted "*to growth in suspension culture and serum-free medium, HyQ SFM4 CHO-Utility (HyClone #SH30516) containing 20nM MTX. In parallel, the glycopattern profile* [i.e that of the antibodies, note added by the board] *was determined.*" Lastly, the example reports that: *"Subclones were selected providing defucosylation of 2.0% or lower (referring to total molar oligosaccharide amount)*" (see paragraph [0067]), or in other words, that clones are selected that express antibodies that are fucosylated by at least 98%.

32. Example 3 teaches that antibodies are purified and subsequently analysed by LCMS peptide mapping in relation to their glycosylation structure (see paragraph [0069]). Table 2 discloses that antibodies of eight clones (see column headed "*Clone No.*") contain glycans having relative amounts of fucose in the range of 99.4% to 99.9%, in relation to the G0, G1 and G2 glycosylation types without taking Man4 and Man5 into account (see Table 2, in particular the column headed "*Non-Fuc[%]*": a non-fucosylated ("Non-Fuc") value of "*0.1*" corresponds to a fucosylation of 99.9%, a value of "*0.6*" corresponds to a fucosylation of 99.4%, note added by the board). Furthermore, example 3 reports that NGNA is not detectable in the glycosylation of the antibodies, which indicates "*that the amount of NGNA is lower than 0.5%*" (see paragraph [0075]). It was common ground between the parties that the glycosylation of recombinant proteins produced in CHO cells lacked α-1,3 Gal, and Tables 3a and 3b in the patent seem to confirm this, since galactose is not detectable in the glycosylation pattern of antibodies produced by clones 3 and 5.

33. Example 3 further mentions that the cell clones disclosed in Table 2 are cultivated in two commercially available media, either "*obtained from Hyclone (HyQ SFM4 CHO-Utility, used for clone 4-6) or Sigma (C-8862, used for clone 1-3 and 7)*" (see paragraph [0072]). Moreover, since all antibodies expressed by clones 1 to 8 disclosed in Tables 2, 3a and 3b exhibit a glycosylation pattern falling within the ambit of claim 1, the patent discloses that various cell culture media are suitable for obtaining antibodies of the invention.

34. Therefore, the patent discloses that eight exemplary antibodies of the invention are obtained upon applying the cultivation and screening method reported in examples 1 to 3. That has not been disputed by appellant II.

35. Hence, the cultivation and screening method reported in examples 1 to 3 of the patent is a generic method allowing the skilled person to reliably obtain substantially all the antibodies of the invention. The skilled person would merely follow the instructions reported in these examples, starting with the transfection of a CHO-DG44 cell with genes encoding heavy and light chains of desired antibodies (see points 30 to 33 above).

36. Declaration D33 (see Table 1 on page 4) further illustrates the feasibility of the method disclosed in examples 1 to 3 in the patent, since it discloses that in order to obtain the eight exemplary antibodies disclosed in Table 2 only "*about 1320*" CHO-DG44 cells had to be transfected and subsequently screened for the desired glycosylation properties.

37. Thus, although the method described in examples 1 to 3 might be labour-intensive, its performance is considered to be a matter of routine for the skilled person. Moreover, in the board's view, since eight exemplary antibodies are obtained by this method, the skilled person would be confident that the antibodies disclosed in the patent are not obtained by a unique and therefore non-reproducible event.

38. Therefore, the board concludes that the main request meets the requirements of Article 83 EPC.

Right of priority (Article 87 EPC)

39. The assessment of inventive step hinges *inter alia* on whether or not the disclosure of document D38 constitutes prior art pursuant to Article 54(2) EPC. Appellant II submitted that it did, because the subject-matter of claims 1 to 9 was not entitled to the priority of the EP application No. 06 016 203.9, filed on 3 August 2006 (hereinafter "P2" application). It essentially argued that the P2 application did not disclose the invention claimed in the later European application in such a way that a skilled person could carry it out, or in other words that the claimed invention was not disclosed in an enabling manner in the P2 application.

40. It was common ground between the parties that clone 5 was deposited on 21 June 2006, i.e. before the filing date of the P2 application, and that the P2 application differed from the later application as filed only in that Table 3b was lacking.

41. Following established case law that a document must contain an "enabling" disclosure for it to be considered detrimental to the novelty of claimed subject-matter, it is likewise established by case law that the right to priority can only be validly claimed if the earlier application discloses the invention claimed in the later European application in such a way that a skilled person can carry it out (see for example CLBA, II.D.2.3).

42. The issue to be assessed is thus whether or not the subject-matter of claims 1 to 9 is disclosed in an enabling manner in the P2 application, despite the absence of Table 3b.

43. The board notes that the P2 application discloses the parental cell line CHO-DG44 for the generation of an exemplary antibody of the invention, examples 1 to 3 including Table 2 (see page 14, lines 3 to 9, page 16, line 3 to page 17, line 7), which are identical to the respective paragraph [0062], examples 1 to 3 and Table 2 in the patent. Furthermore, the P2 application discloses that NGNA is not detectable by LCMS peptide map analysis in the glycosylation of the eight clones disclosed in Table 2 and that therefore "*the amount of NGNA is 0.5% or lower*" (see page 17, lines 16 to 20). It further discloses "*that the amount of fucose within said sugar chain*" of the human IgG1 or IgG3 type antibodies "*is at least 99%, and in addition the amount of NGNA is 1% or less and/ or the amount of N-terminal alpha 1,3 galactose is 1% or less*" (see claim 1) and that the amounts of NGNA and α-1,3 Gal are "*0.5% or less*" (see claims 2 and 3).

44. Thus, for the reasons set out in points 30 to 37 above with regard to sufficiency of disclosure, the skilled

person finds all the necessary information for reliably obtaining the antibodies of the invention likewise in the P2 application. The information in Table 3b is not necessary for this task.

45. Appellant II submitted that the glycosylation properties of the antibodies referred to in claim 1 were not an inherent feature of cell clone 5 in line with decision T 277/95 of 16 April 1999, point 15 of the reasons. It further argued that without the information disclosed in Table 3b, the skilled person was not certain to obtain antibodies of the invention using clone 5 for their production.

46. However, firstly, as set out above, the P2 application discloses a method suitable for reliably obtaining antibodies of the invention (see point 44 above), and there is consequently no need to rely on clone 5 for carrying out the invention. Consequently, whether or not the glycosylation pattern of the clone 5 antibody is an inherent feature of the antibody is not relevant in judging the enablement of the disclosure in the P2 document, and consequently nor is the knowledge of the detailed glycosylation pattern of clone 5.

47. Secondly, the situation in the present case is not comparable with the situation dealt with in decision T 277/95. In that case the priority application was completely silent on the desired or achieved glycosylation pattern of the recombinant protein produced by the deposited CHO cell line (see decision T 277/95, point 15(b) of the reasons). In the present case, the P2 application literally discloses the key features of the antibodies of the invention, i.e. the desired amounts of fucose, NGNA and α-1,3 Gal in the glycan structure, for example in

claims 1 to 3. Thus, this decision cannot be relied on by appellant II in support of its case.

48. Appellant II has not submitted arguments showing that the subject-matter of claims 2 to 9 lacks an enabling disclosure in the P2 application.

49. Therefore, the board concludes that the P2 application provides a disclosure which is sufficient for the skilled person to carry out the invention according to claims 1 to 9. Thus, the requirements of Article 87 EPC are met and the subject-matter of claims 1 to 9 is entitled to the priority date of the P2 application pursuant to Article 89 EPC .

50. In view of the board's above finding on priority, document D38, published on 22 February 2007, does not constitute prior art pursuant to Article 54(2) EPC.

Novelty (Article 54 EPC)

51. Appellant II submitted that the disclosure of documents D1 and D24 anticipated the subject-matter of claims 1 to 4, 6 and 7.

52. Claim 1 is directed to a monoclonal antibody of human IgG1 or IgG3 type being glycosylated with a sugar chain at Asn297, requiring in claim 1(a) that the amount of fucose is at least 99%, related to the sum of G0, Gl, G2 without Man4 and Man5 as 100% and as determined by LCMS peptide map analysis.

53. It was common ground between the parties that the subject-matter of claim 1 differs from the disclosures in documents D1 and D24 at least in the feature whereby

the relative amount of fucose is at least 99% "*as analyzed by LCMS peptide map analysis*". Document D1 reports that an N-CHO capillary, separated and quantified by capillary electrophoresis with detection of laser-induced fluorescence (HPCE-LIF), is used for the determination of fucose (see document D1, page 22, line 28, to page 23, line 2), while document D24 mentions the combined use of fast protein liquid chromatography (FPLC) and high-pressure liquid chromatography (HPLC) for this purpose (see page 321, column 1, last paragraph, to column 2, first paragraph).

54. The board observes that the decision under appeal in the context of assessing novelty has held that "*it is evident from the disclosures of D18 and D42 that results obtained using different detection methods are not directly comparable, in particular in view of the clear determination of the fucose amount*" (see decision under appeal, point 16.6.4, emphasis added).

55. With regard to the fact that document D24 did not use LCMS peptide mapping, appellant II submitted that this was of "*no consequence*", since "*[i]f the method was critical to the claim then more information around the spectrometer type and conditions should have been given in the description. It is clear from D40 how results can vary using different instruments*" (see appellant II's statement of grounds of appeal, point 6.1.6).

56. However, this argument does not address the issue in the decision under appeal that the amounts of fucose as determined by HPCE-LIF, FPLC/HPLC and LCMS are not comparable, but relates to the issue of whether or not the measurements of the amount of fucose with LCMS instruments from two different manufacturers are

comparable. Hence, the board is not convinced by appellant II's argument.

57. The board therefore concludes that the disclosures of documents D1 and D24 do not directly and unambiguously disclose the feature in the subject-matter of claim 1 whereby the relative amount of fucose is at least 99% "*as analyzed by LCMS peptide map analysis*". Thus, the main request meets the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

Admission of a new lack of inventive step objection based on document D25 as closest prior art into the appeal proceedings (Article 12(4) RPBA)

58. An objection of a lack of inventive step of the subject-matter of the main request based on document D25 as the closest prior art has been submitted by appellant II with its statement of grounds of appeal (see point 7.8.1). According to Articles 12(1) and (2) RPBA, this line of argument is part of the appeal proceedings. The board, however, has pursuant to Article 12(4) RPBA, a discretion to hold inadmissible facts, evidence or requests, which could have been presented or were not admitted into the first instance proceedings.

59. Appellant II contested the novelty of the subject-matter of claim 1 as granted in the opposition proceedings *inter alia* on the basis of the disclosure of document D14 (see notice of opposition, point 6.2; note of the board: document D14 cited in the notice of opposition corresponds to document D25 in the consolidated lists of documents of the opposition

proceedings and the appeal proceedings). The subject-matter of claim 1 as granted is essentially identical to that of claim 1 of the present main request, since both differ only in that the "or" alternative in claim 1(b) as granted has been deleted. Furthermore, the opposition division in its annex to the summons informed the parties of its preliminary view that the arguments with regard to document D25 were not convincing (see communication of 14 October 2014, point 11.3.4).

60. With regard to lack of inventive step, appellant II relied during the opposition proceedings on a line of argument based on document D20 as the closest prior art for claim 1 as granted. The opposition division informed the parties of its preliminary view that it was not convinced by this line of argument either (see communication of 14 October 2014 annexed to the summons, point 11.4.2).

61. Thus, in the present case, the filing of an alternative line of argument with regard to lack of inventive step as a fall-back position would have been an appropriate reaction by appellant II, in view of the negative opinion of the opposition division expressed in the written phase of the first instance proceedings. Furthermore, the subject-matter of claim 1 in the appeal proceedings is essentially identical to that of claim 1 in the opposition proceedings. Thus in the board's view, the objection of lack of inventive step based on document D25 as the closest prior art could have been submitted during the opposition proceedings, and the board has not seen an amendment having occurred during the oral proceedings before the opposition division or in the decision under appeal that may have justified the late submission of this objection in the

appeal proceedings. Moreover, appellant II did not submit reasons why the new line of argument was filed only with its statement of grounds of appeal.

62. The board thus decided not to admit the line of argument with regard to inventive step based on document D25 into the appeal proceedings pursuant to Article 12(4) RPBA.

Closest prior art

63. Appellant II argued that either of documents D20 or D38 represented the closest prior art for the subject-matter of claim 1. Since it has been found that document D38 does not constitute prior art pursuant to Article 54(2) EPC (see point 50 above), document D38 is to be disregarded for the assessment of inventive step. Therefore document D20 is the closest prior art document for the subject-matter of claim 1, a choice to which the parties and the board likewise agree.

64. Document D20 summarises the common general knowledge of the skilled person in the year 2003 with regard to glycosylation variations in therapeutic antibodies resulting from several recombinant expression systems, including their impact on the antibodies' biological activities/effector functions, for example ADCC (see title, page 44, second column, last paragraph, to column 3, first paragraph, page 45, second column, first paragraph).

65. It is common ground between the parties that document D20 discloses that *"more than 95%*" of the core biantennary complex oligosaccharides of antibodies that are recombinantly expressed in CHO cells are fucosylated (see page 48, column 1, second paragraph,

and column 2, last paragraph). In other words this means that 95% of the antibodies within a population of CHO cell-produced antibodies are fucosylated.
The parties further agree that document D20 discloses that antibodies produced in CHO cells lack potentially immunogenic terminal α-1,3 Gal and NGNA molecules, due to the absence of specific enzymes catalysing either the transfer or the synthesis of these two molecules in CHO cells (see page 48, column 1, second paragraph, to column 2 second paragraph). Lastly, the parties agree that document D20 discloses that the fewer antibodies carry fucose, the more improved the ADCC activity is, or in other words that the amount of fucose in antibodies is inversely correlated with their ADCC activity (see page 48, column 2, last paragraph, to column 3, first paragraph).

66. Thus, antibodies fucosylated by 95% and in addition lacking α-1,3 Gal and NGNA molecules in their glycosylation as disclosed in document D20 represent the closest prior art for the subject-matter of claim 1.

Technical problem and solution

67. The antibodies according to claim 1 differ from the closest prior art antibodies in that their fucosylation level is at least 99%, compared to "*more than 95%*", i.e. in a level of fucosylation less than 4% higher.

68. Appellant II submitted that there was evidence on file that an increase in fucosylation to a level of above 95% exhibited "*very little correlation, if any*" with a reduction of the antibodies' ADCC activity, compared to antibodies that are fucosylated by 95%. In other words, antibodies fucosylated by either 95% or 99% exhibited

the same low ADCC activity. Thus, the increase in fucosylation was not associated with a technical effect.

69. Therefore, the issue under consideration in the present case is whether or not a technical effect in the form of reduced ADCC activity can be ascribed to the antibodies of the invention having an increased fucosylation of less than 4% compared to the closest prior art antibodies.

70. It is common ground between the parties that the patent discloses in example 4 and Figure 1 that all of the antibodies expressed in clones 1 to 8 and characterised by a fucosylation level varying between 99.4% and 99.9% exhibit no detectable ADCC activity (see page 10, Table 2, column headed "*Non-Fuc[%]*", paragraphs [0078] to [0081]); and that antibodies fucosylated by 99.9% compared to antibodies fucosylated by 99.4% as disclosed in Figure 1 do not exhibit lower ADCC activity, since the effector cell-based ADCC assay is not sensitive enough to resolve a 0.5% difference in fucosylation (99.4% to 99.9%).

71. The respondent submitted experimental data comparing the binding affinity of antibodies having a fucosylation level of 99.0% and 98.3% to the receptor FcγRIII (see declaration D47, point 12). It argued that it was established in the prior art before the relevant date of the patent that the antibodies' ADCC activity correlated with their binding affinity to the FcγRIII receptor (see e.g. document D3, abstract and title, document D14, page 292, second column, paragraph headed "*Increased ADCC correlates with Increased Binding to FcγRIII*", document D21, page 14, column 1, second paragraph). Thus, the affinity determined in this assay

allowed direct measurement of the antibodies' potential to induce an ADCC response in effector cells (see declaration D47, points 4 to 10).

72. Exhibit 7 in declaration D47 discloses that the proportion of antibodies binding to the FcγRIII receptor is reduced from 12.43% to 5.98%, i.e. by a factor of about 2, if fucosylation is increased from 98.3% to 99.0% (see also declaration D47, point 15). In view of documents D3, D14 and D21 the board considers it to be established that an increased binding affinity of antibodies to the FcγRIII receptor correlates with increased ADCC activity (see point 71 above). A consequence of this, in the board's view, is that conversely a reduced binding affinity of the antibodies to the FcγRIII receptor indicates that the antibodies likewise have a reduced potential for inducing ADCC.

73. Furthermore, in the board's view, the comparative data in exhibit 7 demonstrates that the effect of a reduced ADCC potential is associated with the distinguishing feature (see point 67 above), since (i) the two antibodies appear to differ from each other only in their level of fucosylation, and (ii) the level of 98.3% is comprised within the range of "*more than 95%*" of the closest prior art antibodies, while a level of 99.0% corresponds to the lower limit of the range referred to in claim 1. Moreover, (iii) since exhibit 7 discloses that a 0.7% difference in fucosylation (99.0% to 98.3%) reduces the binding affinity of the antibodies to the FcγRIII receptor, a reduction is likewise expected for the larger difference of about 4% (see point 67 above) between the antibodies of the invention and the antibodies of the closest prior art. Appellant II has disputed neither the correctness of

the data disclosed in exhibit 7 of declaration D47 nor the conclusions drawn therefrom by the respondent.

74. Since the comparative data in exhibit 7 supports an effect of at least 99% fucosylation in the antibodies of the invention on a reduced ADCC activity compared to the closest prior art antibodies, arguments relying on the disclosures in documents D6 and D39 for the purpose of formulating the technical problem in the present case need not be addressed by the board for the purposes of this decision.

75. Thus the technical problem to be solved is how to provide an antibody with a reduced potential for inducing ADCC.

76. The board is satisfied that this technical problem is solved by the subject-matter of claim 1 across the whole ambit claimed, in view of the data disclosed in exhibit 7 of declaration D47 and Figure 1 of the patent, disclosing that eight exemplary antibodies of the invention lack detectable ADCC activity.

77. Appellant II submitted that the skilled person had no reasonable expectation of success in arriving at the antibodies of the invention, since the amounts of fucose, NGNA and α-1,3 Gal recited in claim 1 were not reproducible, due to the fact that the eight clones disclosed in the patent were obtained by a chance event (see declaration D33). Furthermore, the patent disclosed neither a generic composition nor a method allowing the skilled person to rely on any biological organism for reliably obtaining antibodies characterised by the glycosylation features referred to in claim 1.

78. In the board's view, appellant II's objection seems to be directed to the issue that the technical problem defined above is not solved across the whole ambit of claim 1. However, as set out with regard to sufficiency of disclosure in point 35 above, examples 1 to 3 in the patent teach a generic method allowing the skilled person to reliably obtain substantially all antibodies falling within the ambit of claim 1. Thus, the board is not persuaded by appellant II's arguments.

Obviousness

79. In view of the parties' submissions, in the present case it remains to be assessed whether or not the person skilled in the art, starting from the antibodies being more than 95% fucosylated as disclosed in document D20 and faced with the technical problem defined above, would have been motivated to modify the teaching of the closest prior art to arrive at the antibodies of claim 1 in an obvious manner.

80. The respondent essentially submitted that the skilled person would not have derived a motivation from the teaching in document D20 to generate antibodies with an increased fucosylation to potentially reduce their ADCC activity, since document D20 was rather directed to the production of antibodies exhibiting increased ADCC activity due to a reduced fucosylation level, i.e. an aim opposite to that underlying the antibodies of the invention.

81. The board is not convinced by this argument for the following reasons. The skilled person derives from the disclosure in document D20 that a lack of fucose in antibodies increases their ADCC activity, which is due

to an increased binding affinity of the antibody to the FcγRIII receptor (see point 72 above). Therefore, since fucose's impact on receptor binding affinity was well established at the relevant date of the patent, the skilled person would derive from document D20 that an increase in fucosylation to a level above 95% likewise has the potential to reduce the antibody's affinity to the FcγRIII receptor, and consequently its potential in reducing ADCC in effector cells, if desired.

82. Therefore, the board concludes that the skilled person would derive a motivation from the teaching of document D20 to obtain antibodies with a fucosylation level of above 95% to reduce their potential in inducing ADCC.

83. The board, however, notes that the skilled person had no means at hand to reliably obtain antibodies that are fucosylated by at least 99%, since the available prior art documents do not disclose a suitable method for the generation of these antibodies. Nor do they disclose hints that either the method disclosed in examples 1 to 3 of the patent or any other alternative method might be suitable for this task. This has also not been argued by appellant II.

84. Therefore, in the absence of means to solve the technical problem by providing the antibodies according to claim 1, the board concludes that the skilled person would not have provided the antibodies according to claim 1 since he had no reasonable expectation of success in obtaining them.

85. Appellant II submitted that since the glycosylation features of the claimed antibodies were a generalisation of the specific anti-IGF-IR antibody expressed by the deposited clone 5, the technical

contribution of the patent was limited to the provision of the deposited clone 5, in line with decision T 737/96. Thus, for this reason too the claim should be limited to this subject-matter.

86. The board is not convinced by this argument for the following reasons. Firstly, the relevance of decision T 737/96 to the present case is not apparent. In that case the claim was directed to deposited microorganisms and mutants or variants thereof all characterised by improved properties. The question was whether the variants of that particular microorganism obtained by conventional mutagenesis techniques constituted a contribution to the art which deserved patent protection (see point 17 of the reasons). The board in that case came to the conclusion that it did. The present case is different in that claim 1 is not directed to deposited antibodies and variants thereof and in that there was no teaching in the prior art as to how to obtain the claimed antibodies. Secondly, with regard to the argument that the contribution of the patent to the art was clone 5 but not the generic subject-matter of claim 1, the board observes that the patentability of claimed subject-matter in general, and also specifically when the question of obviousness is addressed, is not determined according to what is deemed to be a patent's "contribution to the art". This may serve as an auxiliary consideration, but not as the decisive one. Rather, what is to be asked in the present context is whether or not the claimed subject-matter was obvious in the light of the teaching of the prior art.

87. Therefore, the board concludes that the antibodies of claim 1 are based on an inventive step. The same applies to the deposited CHO cell line according to claim 5, and to the dependent subject-matter of claims

2 to 4 and 6 to 9. The main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated