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**Datasheet for the decision of 9 September 2022**

**Case Number:** T 2164/21 - 3.3.08

**Application Number:** 19185595.6

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**Language of the proceedings:** EN

**Title of invention:**
Method for stabilizing proteins

**Applicant:**
Chugai Seiyaku Kabushiki Kaisha

**Headword:**
Method for producing a stabilised antibody/CHUGAI

**Relevant legal provisions:**
EPC Art. 56, 83
RPBA 2020 Art. 13(2)

**Keyword:**
Main request - inventive step (no)
auxiliary request 1 - sufficiency of disclosure (no)
amendment after summons - exceptional circumstances (no)

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European Patent Office
Office européen des brevets

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**Case Number: T 2164/21 - 3.3.08**

# D E C I S I O N
# of Technical Board of Appeal 3.3.08
# of 9 September 2022

| | |
|---|---|
| **Appellant:** (Applicant) | Chugai Seiyaku Kabushiki Kaisha<br>5-1, Ukima 5-chome<br>Kita-ku<br>Tokyo 115-8543 (JP) |
| **Representative:** | Leonard, Thomas Charles<br>Kilburn & Strode LLP<br>Lacon London<br>84 Theobalds Road<br>London WC1X 8NL (GB) |
| **Decision under appeal:** | **Decision of the Examining Division of the European Patent Office posted on 14 July 2021 refusing European patent application No. 19185595.6 pursuant to Article 97(2) EPC** |

**Composition of the Board:**

| | |
|---|---|
| **Chairwoman** | T. Sommerfeld |
| **Members:** | R. Morawetz |
| | P. de Heij |

## Summary of Facts and Submissions

I. The appeal by the applicant (appellant) is against the examining division's decision refusing European patent application No. 19 185 595.6, filed as a divisional application of European patent application No. 02 792 048.7, having a date of filing of 27 December 2002 and claiming priority from JP patent application 2001400895, filed on 28 December 2001.

II. The decision under appeal dealt with a main request and three auxiliary requests. The examining division held, *inter alia*, that the subject-matter of claim 1 of auxiliary request 2 lacked inventive step and that the invention claimed in claim 1 of auxiliary request 3 was not sufficiently disclosed for it to be carried out by the skilled person.

III. The following documents are referred to in this decision:

D1 Tomizawa H. *et al.*, Protein Engineering 8, 1995, 1023-1028

D2 Tyler-Cross R. and Schirch V., J. Biol. Chem. 266, 1991, 22549-22556

D7 Perkins M. *et al.*, Pharm. Res. 17, 2000, 1110-1117

D8 WO 2010/129904

D10 WO 2012/170607

D14 Presta L. *et al.*, Thromb. Haemost. 85, 2001, 379-389

D16 EP 3 020 812

D17 Root A.R. *et al.*, MABS 13, 2021, e1850395-1-e1850395-18

D18 WO 2017/093448

D20 WO 03/073982

D21 Declaration by Dr Beatriz Goyenechea and Dr Kevin Moulder, dated 24 November 2021

D22 Kabat E.A. *et al.*, Sequences of Proteins of Immunological Interest, 5th edition, 1991, National Institutes of Health, extract

IV. With the statement of grounds of appeal the appellant filed sets of claims of a main request and auxiliary requests 1 to 3. The main request and auxiliary request 1 were identical to auxiliary requests 2 and 3, respectively, considered in the decision under appeal. Auxiliary requests 2 and 3 were newly filed requests. The appellant furthermore submitted document D21.

Claim 1 of the main request reads as follows:

"1. A method of producing an antibody with reduced susceptibility to deamidation, wherein the method produces a mutant antibody, wherein the method comprises the step of substituting a glycine that is located adjacent to the C-terminal side of an asparagine of the original antibody with another amino acid, wherein the mutant antibody has a reduced

susceptibility to deamidation relative to the original antibody before the amino acid substitution, wherein the mutant antibody has the same binding specificity as the original antibody, and wherein the asparagine exists in the complementary determining region 2 (CDR2) of the heavy chain as determined by Kabat numbering."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the expression "and wherein the antigen-binding activity of the mutant antibody is 70% or more of the antigen-binding activity of the original antibody before the amino acid substitution" was added to the end of the claim.

V. By letter dated 14 December 2021, the appellant requested that the appeal proceedings be accelerated (Article 10(3) RPBA).

VI. The board granted the appellant's request for the appeal proceedings to be accelerated, scheduled oral proceedings and issued a communication pursuant to Article 15(1) RPBA in which it indicated its preliminary view with respect to, *inter alia*, the inventive step of claim 1 of the main request and the sufficiency of disclosure of claim 1 of auxiliary request 1.

VII. By letter dated 6 September 2022, the appellant withdrew auxiliary requests 2 and 3 and submitted document D22.

VIII. Oral proceedings were held as scheduled. At the end of the oral proceedings the Chairwoman announced the board's decision.

IX. The appellant's arguments, insofar as they are relevant to the decision, are summarised below.

*Article 113(1) EPC*

In the decision under appeal the examining division had interpreted the closest prior art, document D7, as teaching the substitution of a glycine residue. As this interpretation of document D7 had not been communicated to the appellant before, it had not been given the opportunity to respond. Accordingly, it was deprived of its right to be heard with respect to the examining division's decision on inventive step.

*Main request - claim 1*

*Inventive step*

*Closest prior art*

The disclosure in document D7 could be considered to represent the closest prior art. Document D7 suggested the substitution of an asparagine residue in the constant regions of the antibody to reduce susceptibility to deamidation. The examining division was incorrect to hold that document D7 taught the substitution of a glycine residue.

*Objective technical problem*

The claimed subject-matter differed from the disclosure in document D7 in that claim 1 required the substitution of a glycine residue adjacent to the C-terminal side of the asparagine located in the CDR2 of the heavy chain (HCDR2) of the antibody.

While the appellant had submitted in writing that the objective technical problem was to provide a method for improving the stability of an antibody whilst retaining antigen-binding activity, it submitted during the oral proceedings that the objective technical problem was to provide an alternative method of producing an antibody with reduced susceptibility to deamidation.

*Obviousness*

The method of the invention was not obvious in view of the disclosure of document D7, even when combined with the teaching in document D1 or document D2. The skilled person would not have substituted glycine residues of an antibody in order to suppress deamidation of the adjacent asparagine residue in the heavy chain CDR2. Despite the fact that retention of antigen-binding activity was not recited in the claim, the skilled person would have been reluctant to attempt substitution of amino acids in the CDRs of an antibody, as they would have wanted to avoid a loss in antigen binding. There was a complete absence of any teaching in the prior art that would have suggested that substitutions of amino acids in the CDRs of an antibody could be made without impacting antigen-binding activity.

Document D1 was directed towards a thermostable enzyme and investigated the effect of substituting glycine with alanine on the protection of lysozyme against irreversible thermoinactivation (see page 1023, left-hand column, first line of "Introduction" section, page 1023, right-hand column, first paragraph and page 1024, right-hand column, fourth paragraph). It dealt with an unrelated technical field, which the skilled person seeking to manufacture or optimise an antibody would

not have consulted. The authors of document D1 were familiar with document D2 and speculated that substitution of the glycine residue would have protected the enzyme against irreversible thermoinactivation (see page 1023, right-hand column, first paragraph), but they actually found that the substitution of the glycine residue resulted in reduced conformational stability of lysozyme (see abstract and page 1027, left-hand column, "Discussion" section, lines 1 to 5). For antibodies, reversible conformational stability at ambient temperature was important, and therefore the teaching of document D1 led away from the claimed method. Even if the skilled person had combined document D7 with document D1, they would still not have arrived at the subject-matter of the invention because D1 did not disclose the substitution of an amino acid in a CDR of an antibody.

The skilled person would not have consulted document D2 when faced with the objective technical problem either, because (i) it concerned deamidation in small peptides and hence a different technical field,
(ii) peptides had no tertiary structure and therefore the principles taught in document D2 would not have been expected to apply to antibodies and (iii) small peptides had no function and only the deamidation rate was measured in document D2.

Documents D1 and D2 had been available but their teaching had not been used by the authors of document D7.

*Document D22*

*Admittance (Article 13(2) RPBA)*

Document D22 provided evidence that the Asn-Gly motif in HCDR2 was a germ line motif, and thus appeared in a large number of antibodies. This fact, in combination with the post-published documents that showed the successful application of the claimed method to different antibodies (see e.g. documents D8, D10, D16, D17, D18 and D20), confirmed the broad applicability of the method of the invention to other antibodies besides the anti-TF antibody exemplified in the application.

The filing of document D22 did not represent a change to the appellant's case. The representative had only recently received the document from the appellant.

*Auxiliary request 1*

*Article 83 EPC*

The application provided at least one way of carrying out the claimed invention (see Example 2). It furthermore provided the skilled person with guidance for performing the invention with any antibody presenting an Asn-Gly dipeptide sequence in the HCDR2 for at least three reasons.

First, the steps of the method, mutating antibodies and the required testing for deamidation susceptibility and antigen-binding activity were well known and routine for the skilled person (see document D21, paragraphs 7, 12 to 22 and 26 to 28). Therefore, based on the content of the application as filed and the common general knowledge of the skilled person, the method of the

invention could be readily performed without undue burden.

Second, it was not reasonable to require the skilled person to be able to predict in advance which substituting amino acid could be used. A reasonable amount of trial and error was allowed (see Case Law of the Boards of Appeal, 10th edition 2022; II.C.6.7). Once the skilled person knew that a glycine in an Asn-Gly motif in HCDR2 of an antibody could be substituted to reduce deamidation, the claimed method could be easily performed by replacing the glycine with a range of replacement amino acids in parallel and screening for those substituted antibodies with the desired characteristics. This required only routine methods. Some amino acid substitutions would not work but an occasional failure was acceptable. Applying the general principle of the invention, the skilled person would at least have a reasonable expectation of success in obtaining an antibody with reduced susceptibility to deamidation whilst retaining antigen-binding activity. The case at hand was different from the case considered in decision T 32/85 (see Reasons, point 5) in that the number of options for the substituting amino acid was limited.

Third, the application provided a general principle that could be applied to any antibody having an Asn-Gly motif in HCDR2, and the skilled person would expect that the invention could be realised for most of, if not all of, such antibodies. The inventive contribution of the application was that, in cases in which an antibody had an Asn-Gly motif in HCDR2, substitution of the glycine for another amino acid could reduce susceptibility to deamidation whilst retaining antigen-binding activity. The skilled person was then able to

generate a library of mutant antibodies, in which the glycine was substituted for a different amino acid, and screen said mutant antibodies for the desired properties. The creation of the library and subsequent screening would all be part of the routine work of the skilled person. The claimed method was not dependent on an understanding of the molecular structure of the antigen-antibody complex, and as such, was readily applicable to different antibodies. This was confirmed by document D21 (see paragraphs 30, 31 and 34) and by the post-published evidence (see documents D8, D10, D16, D17, D18 and D20).

There were no serious doubts substantiated by verifiable facts that the claimed method could be applied to other antibodies without undue burden. The claimed invention met the requirements of Article 83 EPC.

X. As far as relevant to the present decision, the appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division with the order to grant a patent on the basis of the set of claims of the main request, or alternatively, on the basis of auxiliary request 1, both requests having been filed by letter dated 24 November 2021, and that document D22, filed by letter dated 6 September 2022, be admitted into the proceedings.

## Reasons for the Decision

1. The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC and is admissible.

*No remittal to the examining division*

2. The appellant submitted that it was deprived of its right to be heard (Article 113(1) EPC) with respect to the examining division's decision on inventive step of the subject-matter of claim 1 of the main request.

3. Under Article 11 RPBA the board will not remit a case to the department whose decision was appealed for further prosecution unless special reasons present themselves for doing so. As a rule, fundamental deficiencies which are apparent in the proceedings before that department constitute such special reasons.

4. According to established case law of the Boards of Appeal, the violation of the right to be heard under Article 113(1) EPC is a fundamental deficiency in the proceedings before the examining division that amounts to a special reason within the meaning of Article 11 RPBA.

5. However, when deciding whether or not to remit a case to the department of first instance, the Boards of Appeal also take further factors into account, such as the age of the application, the length of the proceedings and whether or not a party requested remittal.

6. In the case at hand, the application has a date of filing of 27 December 2002 (see section I. above) and the 20-year term (Article 63(1) EPC) of any patent resulting from the application would have been due to expire by 27 December 2022. Indeed, it was for this reason that the appellant had requested that the appeal proceedings be accelerated. Remitting the case to the examining division would have resulted in a further

delay. Finally, the appellant did not request that the case be remitted to the examining division.

7. Therefore, the board considered that, in the circumstances of the case at hand, remittal to the examining division would have been inappropriate even if the appellant's right to be heard had been violated. Accordingly, the board decided not to remit the case to the examining division, but to consider the issue of inventive step of the subject-matter of claim 1 of the main request in substance.

8. As nothing turns on it, there is no need for the board to decide on the alleged violation of the appellant's right to be heard (Article 113(1) EPC).

*Main request - claim 1*

*Inventive step*

*Closest prior art*

9. The examining division considered that document D7 represented the closest prior art, and this was not disputed by the appellant. The board sees no reason to differ.

10. Document D7 concerns determining the molecular basis of charge heterogeneity found in a murine monoclonal antibody (mAb) MMA383 (see page 1110, left-hand column, first paragraph) and it reports that deamidation of asparagine (Asn) residues in the heavy chain and the light chain are the major cause of MMA383 charge heterogeneity (see page 1110, left-hand column, fourth paragraph). Two deamidation sites are identified in mAb MMA383: an asparagine-serine (Asn-Ser) sequence in

the heavy chain and an asparagine-glycine (Asn-Gly) sequence in the light chain (see page 1116, left-hand column, last paragraph).

11. Document D7 also discloses that "[d]*eamidation of Asn at neutral to alkaline pH is facilitated if the side-chain of the subsequent residue is small or absent, like in Ser or Gly*" (see page 1116, left-hand column, last paragraph, lines 1 to 3) and that "*the only practical way to eliminate deamidation would be the replacement of the unstable amino acids by introducing point mutations*" (see page 1117, left-hand column, lines 3 to 6).

12. The examining division held that the unstable amino acids referred to in document D7 (see previous point) were asparagine, serine and glycine and that document D7 therefore already taught the replacement of the glycine residue.

13. However, the unstable amino acid in the deamidation sites of document D7 is not glycine or serine, but asparagine, as it is the residue that undergoes deamidation resulting in aspartic acid or isoaspartic acid (isoAsp), and isoAsp can distort the conformation of a protein and has been linked to loss of biological activity (see document D7, page 1116, right-hand column, first and fourth paragraphs).

14. Therefore the board considers in agreement with the appellant that document D7 suggests the replacement of the asparagine residue to eliminate deamidation but does not teach or suggest substitution of the glycine residue in an Asn-Gly sequence.

*Objective technical problem*

15. The claimed subject-matter differs from the disclosure in document D7 on account of the substitution of the glycine residue instead of the asparagine residue in a Asn-Gly motif located in the CDR2 of the heavy chain (HCDR2) of an antibody.

16. As regards the technical effect(s) of the distinguishing features, the experimental data provided in the application (see Example 2) demonstrate that, depending on the type of amino acid replacing the glycine, the antigen-binding activity of the antibody can be substantially lower than the antigen-binding activity of the antibody before the amino acid substitution (see Figure 11). Retention of the antigen-binding activity is therefore not a technical effect of the claimed method. Improved stability is not a necessary consequence of the method in claim 1 either; see Example 2 and Figure 16 of the application. Accordingly, the method in claim 1 does not necessarily result in an antibody that retains its antigen-binding activity or has improved stability, as asserted by the appellant in the written submissions.

17. The board concludes that the technical effect of the differences over document D7 is the same as that disclosed in document D7, i.e. a reduction in the susceptibility of the antibody to deamidation of the asparagine residue at an Asn-Gly motif.

18. Accordingly, the objective technical problem to be solved is to provide an alternative method of producing an antibody with reduced susceptibility to deamidation. During the oral proceedings the appellant agreed to

this formulation of the problem.

*Obviousness*

19. In the assessment of obviousness, the question to be answered is whether or not the skilled person starting from the disclosure in document D7 and seeking a solution to the above-formulated technical problem would have replaced the glycine in an Asn-Gly motif located in the HCDR2 of an antibody with another amino acid.

20. As explained in point 13. above, document D7 does not teach or suggest the replacement of the glycine residue in an Asn-Gly motif.

21. However, on the priority date of the application, it was already known in the art that deamidation of asparagine in an Asn-Gly motif can be suppressed by substituting the glycine residue in the Asn-Gly motif.

22. Document D1 discloses that it has been reported in the art that the deamidation of asparagine is dependent on the adjacent C-terminal residue and that substituting the glycine in an Asn-Gly motif in a peptide with another amino acid such as alanine will suppress the deamidation rate (see document D1, abstract and paragraph bridging pages 1024 and 1025). As regards the model protein studied in document D1, hen egg-white lysozyme (see page 1023, left-hand column, last paragraph), document D1 also discloses that it has been found that the suppression of the isomerisation of the Asp-Gly sequence achieved by the substitution Gly to Ala leads to enhanced stabilisation against irreversible thermoinactivation of lysozyme, despite a decrease in reversible conformational stability (see

page 1027, left-hand column, second paragraph).

23. Document D2 discloses that in short peptides the rate of deamidation decreased with the size and steric bulk of the residue located adjacent to the C-terminal side of the asparagine (see document D2, abstract and page 22549, right-hand column, first full paragraph). Document D2 also discloses that the characterisation of deamidation of asparagine residues has been primarily elucidated from studies of short Asn-containing peptides, but that the effects observed in these studies may be important in proteins as well (*ibid.*). Indeed, according to document D2, model peptide sequences were usually selected on the basis of amino acid sequences in proteins which were known to deamidate (see page 22550, left-hand column, first full paragraph).

24. An antibody is a protein and documents D1 and D2 concern the deamidation of asparagine in Asn-Gly sequences in enzymes, i.e. proteins, and in short model peptides selected on the basis of amino acid sequences in proteins which are known to deamidate, respectively. Therefore, the board considers that the skilled person would have consulted these documents when faced with the objective technical problem set out above. In the board's judgement, the teaching in these documents would have prompted the skilled person to replace the glycine in an Asn-Gly motif in an antibody with another amino acid, thus arriving at the claimed method in an obvious manner.

25. The appellant's submission to the effect that the teaching of document D1 led away from the claimed invention because it disclosed that the substitution Gly to Ala led to a decrease in reversible

conformational activity is not found to be persuasive.

26. Document D1 teaches that replacing the glycine with another amino acid residue will suppress the deamidation rate, i.e. provide a solution to the objective technical problem with which the skilled person is faced. The fact that such a substitution also affected the reversible conformational activity of the enzyme studied in document D1 would not have deterred the skilled person from applying the teaching of document D1 to an antibody, in particular, since claim 1 does not require that the antibody maintains any activity, conformational or otherwise.

27. The appellant's submissions that are based on the reluctance of the skilled person with respect to making amino acid substitutions in the CDRs of an antibody are not found to be persuasive for similar reasons. The skilled person, faced with the problem of merely providing an alternative method of producing an antibody with reduced susceptibility to deamidation, is not concerned with maintaining the binding activity of the antibody either. This would only be the case if maintaining binding activity were part of the objective technical problem; however, this is not the case as the claimed subject-matter does not result in this effect over the whole scope of the claim. For similar reasons, the argument that combining the disclosure of document D7 and document D1 would not result in the claimed subject-matter since there is no disclosure in document D1 of substitution of an amino acid in the CDR2 of the heavy chain is not convincing either. The location of the deamidation site in the CDR2 has no technical effect and is thus arbitrary.

28. Finally, the fact that the teaching of documents D1 and D2 was available but had not been used by the authors of document D7 cannot establish an inventive step either. The reason for this could be that replacing the unstable amino acids is another obvious solution to avoid deamidation, one that is recommended by the authors of document D7. According to the case law of the Boards of Appeal a selection from a number of obvious solutions to a technical problem does not generally involve an inventive step (cf. Case Law of the Boards of Appeal of the European Patent Office, 10th edition 2022 ("CLBA)"), I.D.9.21.9). Instead, to conclude that a proposed solution would have been obvious, it is sufficient for the board to be convinced that the skilled person would have considered the claimed subject-matter to be a solution to the technical problem.

29. The subject-matter of claim 1 of the main request does not meet the requirements of Article 56 EPC.

*Document D22*

*Admittance (Article 13(2) RPBA)*

30. Three days before the oral proceedings the appellant filed document D22 and submitted that, in combination with the post-published documents already on file, it confirmed the broad applicability of the claimed method to other antibodies.

31. The argument that the claimed method was applicable to a broad range of antibodies because the Asn-Gly motif is a germ line motif present in many antibodies had not been submitted before. The submission of document D22 and the appellant's line of argument that was based on

document D22 therefore constituted an amendment to its case made after notification of a summons to oral proceedings.

32. Pursuant to Article 13(2) RPBA, which applies in the case at hand, any amendment to a party's appeal case after notification of a summons to oral proceedings is, in principle, not to be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

33. Exceptional circumstances are new or unforeseen developments in the appeal proceedings which lie outside the sphere of influence of the party affected by them, e.g. a new line of argument raised by the board. In the case at hand, the appellant did not submit that document D22 was filed in response to an objection raised for the first time in the board's communication. Instead, the appellant's representative submitted that they had only recently come into possession of document D22 and had filed it as soon as it was made available to them by the appellant.

34. In the board's view, this line of argument is unsuitable for establishing extraordinary circumstances since the circumstances that led to the late filing of document D22 lay entirely within the appellant's control. Indeed, document D22 was published in 1991 and could thus have been provided with the statement of grounds of appeal should the appellant have wanted to rely on it in its submissions regarding sufficiency of disclosure during the appeal proceedings.

35. The appellant did not submit that there were any other exceptional circumstances which would have justified

admitting document D22.

36. The board therefore decided not to admit document D22 and the line of argument based on it into the appeal proceedings (Article 13(2) RPBA).

*Auxiliary request 1*

*Sufficiency of disclosure (Article 83 EPC)*

37. Claim 1 of auxiliary request 1 is based on claim 1 of the main request, which has been amended to require the antigen-binding activity of the mutant antibody to be 70% or more of the antigen-binding activity of the original antibody before the amino acid substitution.

38. Article 83 EPC requires that the application discloses the invention in a manner sufficiently clear and complete for it to be carried out by the skilled person. In interpreting Article 83 EPC it has been established in the case law of the Boards of Appeal that the claimed invention must be sufficiently disclosed on the filing date (CLBA, II.C.2.) based on the application as a whole (*ibid.*, II.C.3.1), in consideration of the common general knowledge of the skilled person (*ibid.*, II.C.4.1.). While at least one way of carrying out the claimed invention must be disclosed, this disclosure is sufficient only if it allows the invention to be performed in the whole range claimed (*ibid.*, II.C.5.2., II.C.5.4 and II.C.7.1.2).

39. The application discloses one way of carrying out the claimed invention (see Example 2), in which one specific amino acid in HCDR2 of an anti-TF antibody, namely glycine at position 55 (Gly55), is substituted with 18 different amino acids and the binding activity

of the resultant mutants is measured. The results are shown in Figure 11 of the application.

40. It is evident from Figure 11 that not all the replacements result in binding activity which is "*70% or higher than the antigen-binding activity of the antibody before the amino acid substitution*". In this particular example, the binding activity of 3 out of 18 mutants was significantly decreased compared with the non-substituted antibody. Consequently, the nature of the amino acid replacing the glycine residue in the HCDR2 seems to be critical.

41. What is at issue is whether the application, when considered alone or in combination with common general knowledge, provides guidance which allows the skilled person to obtain substantially all the embodiments falling within the ambit of the claim without undue burden.

42. In the section entitled "*Background Art*" on page 1 of the description, the application discloses that "*substitution of asparagine with another amino acid by site-directed mutagenesis is considered the most certain method to prevent deamidation of proteins*" (see page 1, lines 25 to 28); however, it also discloses that "*this substitution has the potential to influence protein activity*" and that it is known that "*when the asparagine is located in the complementary determining region (CDR) of an antibody, such substitution is reported to affect the antibody binding affinity (Presta L. et al., Tromb. Haemost. 85: 379-389, 2001)*" (see page 1, lines 28 to 33).

43. The application does not provide any further examples or technical guidance for substitutions of glycine

residues in Asn-Gly sequences occurring in HCDR2 regions of any other antibody that would help the skilled person find substitutions resulting in an antibody as claimed, i.e. an antibody with antigen-binding activity which is 70% or higher than the antigen-binding activity of the antibody before the amino acid substitution.

44. In addition, while the application states explicitly that "[g]*enerally, an antibody is inactivated by amino acid substitution in the CDR*" (see page 12, lines 32 to 33), no rationale or explanation is provided in the application to guide the skilled person to select a replacement for the glycine residue in Asn-Gly sequences occurring in HCDR2 regions of any other antibody that will not reduce the antigen-binding activity.

45. It was not argued by the appellant that the skilled person would know from their common general knowledge that, and how, substitution of the glycine residue instead of the asparagine residue of the Asn-Gly motif in HCDR2 regions of any antibody will not negatively affect the binding activity of the antibody either. To the contrary, the appellant submitted that "[t]*he skilled person would have been extremely reluctant to attempt substitution of amino acids in the CDRs, for fear of a potential loss in antigen binding activity. There is a complete absence of any teaching in the prior art that would have suggested such substitutions could be made without impacting binding*" (see statement of grounds of appeal, page 9, sixth paragraph) and "[*b]ased on the common general knowledge at the priority date in 2001, the skilled person would be wary of making changes to the CDRs of an antibody and would be reluctant to do so*" (*ibid*, page 12, second

paragraph). While these statements were made in the context of inventive step, the common general knowledge of the skilled person is taken to be one and the same in the assessment of inventive step and sufficiency of disclosure (see CLBA, I.D.8.3 and II.C.4).

46. In sum, neither the application as filed nor common general knowledge provides the skilled person with any information that would reliably guide them to the amino acid substitutions which result in an antibody fulfilling the functional requirements of the claim.

47. Accordingly, for each and every antibody comprising an Asn-Gly sequence in HCDR2, in the absence of any guidance as to which amino acid should replace the glycine in any given circumstance, other than to use all possible amino acids and to screen the substituted antibodies for those with the desired characteristics, the skilled person has to identify each time, by trial and error, which amino acid replacement will provide an antibody with the desired characteristics, without any guarantee that such a substitution will be found at all.

48. The fact that methods for generating an antibody with a specific mutation, methods for assessing deamidation and methods for antigen-binding activity were described in the application, were well known to the skilled person of the application and were routine on the priority date of the application does not mean that the invention can be put into practice without undue burden.

49. According to the settled case law of the Boards of Appeal, experimentation and testing is reasonable when the application or common general knowledge provides

the person skilled in the art with adequate information that leads necessarily and directly to success after evaluating initial failures; however, if the skilled person can only determine by experimenting whether they have selected a parameter (in this case, the amino acid replacing the glycine) in such a way that a satisfactory result will be achieved (in this case, an antibody with reduced susceptibility to deamidation and 70% or more of the antigen-binding activity of the original antibody) without the confidence that such result can be achieved at all, this constitutes an undue burden, even if it involves routine experimentation (see CLBA, II.C.6.7.). Therefore, the appellant's main line of argument cannot succeed.

50. Contrary to the appellant's submission, the case at hand is no different from the case considered in T 32/85 (see Reasons, point 5) as the only feature ascertaining the claimed effect is the functional feature of the claim relating to the antigen-binding activity of the mutant antibody, i.e. "*70% or more of the antigen-binding activity of the original antibody before the amino acid substitution*". No adequate information leading to success after initial failure is provided in the application. It has been established above (see point 47.) that the skilled person can only establish by trial and error whether or not their choice of amino acid substituting the glycine provides a satisfactory result without guarantee of success for any antibody other than the exemplified antibody. In such circumstances it is irrelevant that the number of options for the substituting amino acid is limited. The appellant's second line of argument thus also fails.

51. The appellant's submissions to the effect that the application provided a general principle that could be

applied to any antibody having an Asn-Gly motif in HCDR2 is not found to be persuasive either.

52. The appellant's argument hinges on the submission that the claimed method only required steps that were all within the routine work of the skilled person and was not dependent on an understanding of the molecular structure of the antigen-antibody complex, and as such, was readily applicable to different antibodies; however, it has been established above (see point 49.) that, in the circumstances of the case at hand, even performing routine work amounts to an undue burden.

53. Furthermore, the board considers that the statement relied on by the appellant to the effect that "*it would be expected the invention could be realised for most if not all antibodies having an NG motif in HCDR2 (or another CDR)*" (see document D21, paragraph 34) is an assertion devoid of evidential value. It has been established above (see points 44. and 45.) that, on the priority date of the application, it was part of the common general knowledge of the skilled person that substitution of an amino acid within a CDR of an antibody was likely to negatively affect the antigen-binding activity of the antibody. In these circumstances, providing a single example (see point 39.) which demonstrates that the antigen-binding activity of a specific antibody is retained after some particular substitutions cannot be considered to establish the existence of a general principle that can be applied to any other antibody having an Asn-Gly motif in HCDR2. Instead, on the priority date of the application, the skilled person would have considered that the successful substitutions of the exemplified antibody represented a lucky chance event.

54. Post-published evidence (see documents D8, D10, D16, D17, D18 and D20) is manifestly unsuitable for guiding the skilled person in carrying out the claimed invention on the priority date. Furthermore, consideration of these post-published documents only confirms that, for any given antibody, the skilled person has to test each and every amino acid substitution in order to determine whether and how it affects deamidation and binding affinity of the antibody.

55. Finally, in the case at hand serious doubts arise from the facts set out in points 39. to 46. above. Therefore, the appellant's argument that there were no serious doubts substantiated by verifiable facts that the claimed method could be applied to other antibodies without undue burden also fails.

56. The board concludes that the requirements of Article 83 EPC are not met because, while the application provides one way of putting the claimed invention into practice, the skilled person cannot put the invention into practice over the whole scope without undue burden.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated