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Datasheet for the decision of 16 April 2015

Case Number: T 2522/10 - 3.3.04

Application Number: 02029008.6

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Language of the proceedings: EN

Title of invention:
A composition comprising anti-HER2 antibodies

Patent Proprietor:
Genentech, Inc.

Opponent:
Synthon B.V.

Headword:
Anti-HER2 antibodies/GENENTECH

Relevant legal provisions:
EPC Art. 54, 56, 111
RPBA Art. 13(1)

Keyword:
Main request: novelty (yes), inventive step (yes)
Remittal to the department of first instance (no)

Decisions cited:
G 0002/88, T 1523/07

Catchword:

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Case Number: T 2522/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 April 2015

Appellant: (Patent Proprietor)	Genentech, Inc. 1 DNA Way South San Francisco CA 94080-4990 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Opponent)	Synthon B.V. Microweg 22 6545 CM Nijmegen (NL)
Representative:	Prins, Hendrik Willem Arnold & Siedsma PO Box 18558 2502 EN The Hague (NL)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 October 2010 revoking European patent No. 1308455 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: R. Morawetz
K. Garnett

Summary of Facts and Submissions

I. The appeal of the proprietor (hereinafter "appellant") lies against the decision of the opposition division whereby European patent No. EP 1 308 455 was revoked. The patent at issue has the title "A composition comprising anti-HER2 antibodies".

II. Claim 1 as granted reads:

"1. A composition comprising a mixture of anti-HER2 antibody and one or more acidic variants thereof, wherein the amount of the acidic variant(s) is less than about 25%,
and wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated,
and wherein the anti-HER2 antibody is humMAb4D5-8,
and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate."

Dependent claims 2 to 6 relate to preferred embodiments of the composition defined in claim 1.

III. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), under Article 100(b) EPC and under Article 100(c) EPC.

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

D4: WO92/22653

D6 WO97/04801

D7 Harris R., The Waterside Monoclonal Conference (1996), Chromatographic techniques for the characterisation of human monoclonal antibodies: rhuMAb HER2, pages 1 to 7

D13 Adachi T. et al., Journal of Chromatography (1997), vol. 763, pages 57 to 63

D20 Harris R., Journal of Chromatography (1995), vol. 705, pages 129 to 134

D22 Harris R. et al., Journal of Chromatography (2001), vol. 752, pages 233 to 245

D26 Declaration by Wang D. (2011)

V. The opposition division decided that the subject-matter of the main request (claims as granted) met the requirements of Article 83 EPC and was novel over documents D4, D7 and D20 but that claims 1, 2 and 4 lacked novelty vis-à-vis document D6. No decision on inventive step was taken.

VI. The appellant filed a statement of grounds of appeal maintaining the claims as granted as the main request and providing arguments as regards novelty of the claimed subject-matter vis-à-vis document D6. It requested remittal of the case to the opposition division for the consideration of inventive step once novelty was established.

VII. In its reply to the statement of grounds of appeal the respondent argued lack of novelty of the claimed subject-matter on the basis of documents D4, D6, D7 and

D20. In the context of the cation exchange chromatography disclosed in document D6 reference was made to document D22. As regards arguments of lack of inventive step reference was made to the notice of opposition. Arguments as regards lack of sufficiency of disclosure were also provided.

VIII. By letter dated 12 November 2014 the appellant provided further arguments as regards novelty vis-à-vis document D6 as well as arguments regarding inventive step of the claimed subject-matter.

IX. The parties were summoned to oral proceedings and were informed about the board's preliminary view in a communication pursuant to Article 15(1) RPBA. The board considered, *inter alia*, that the decision of the opposition division as regards novelty vis-à-vis document D20 was correct.

X. Oral proceedings before the board were held on 16 April 2015. During the oral proceedings the respondent stated that it no longer relied on document D22 in its argument regarding lack of novelty vis-à-vis document D6. Furthermore, the respondent withdrew its novelty objections based on documents D4, D7 and D20, and its objection of lack of sufficient disclosure. At the end of the oral proceedings the chairwoman announced the board's decision.

XI. The appellant's arguments may be summarised as follows:

Main request

Novelty

Document D6 did not provide a direct and unambiguous disclosure of the feature of claim 1 that the acidic variants are predominantly deamidated variants, wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate. Document D6 analysed on page 26 the loss of native protein due to deamidation or succinimide formation in four reconstituted, previously lyophilised, formulations. The document disclosed on page 19 that in the liquid state rhuMAb HER2 was observed to degrade by deamidation at position Asn30 of the light chain and isoaspartate formation via the intermediate succinimide at position Asp102 of the heavy chain. However, there was no basis in document D6 for the conclusion that degradation in the examined formulations resulted in the variants defined in the claim. In fact, the nature of the variants in these formulations had not been analysed, either at "time zero" or at any other point in time. Whether deamidation involved 30Asn let alone 30Asn in CDR1 of either or both VL regions of huMAb4D5-8 conversion to aspartate for the lyophilised formulations in figures 5 to 8 was not explained in document D6.

Remittal

The case should be remitted to the opposition division for consideration of inventive step. This would give the appellant the possibility to have its case decided by two instances. However, if required, it was prepared

to argue the case during the oral proceedings before the board.

Inventive step

The purpose of the invention was to provide means and methods which allowed the reduction of the amount of acidic variants occurring in anti-HER2 antibody preparations.

Document D6 did not have the same purpose, as it was concerned with the stabilisation of reconstituted lyophilised HER2 antibody formulations. Although document D6 disclosed the occurrence of deamidation, there was no disclosure as regards removal of acidic variants.

Document D7 represented the closest prior art. It disclosed that "25% of pool [of rhuMAb HER2] had deamidated Asn-30" and consideration was given as to whether or not to remove the deamidated material: see page 7, upper slide. Thus, it recognised the problem of the occurrence of deamidated/acidic variants.

The technical problem to be solved in view of document D7 was the provision of humMab4D5-8 compositions with improved properties. However, document D7 provided no motivation to remove the deamidated Asn30 since in the upper slide on page 7 it is stated that it was decided not to remove the deamidated material. Moreover, document D7 was silent as regards the conditions of the MonoS cation exchange chromatography resulting in the profile depicted in the lower slide on page 4 with a separation of acidic and basic variants from the native antibody. The skilled person was left with the challenge of finding the correct conditions which would

bring about the separation of the acidic variants from the non-deamidated antibody protein.

The question was whether the skilled person could have supplemented the missing information with his common general knowledge. Assuming that the disclosure in document D20 represented the common general knowledge, the respondent had itself provided experimental evidence in declaration D26 that when working according to the conditions of D20 it was unable to separate the acidic variants from the non-deamidated antibody molecule by MonoS cation exchange chromatography. According to declaration D26, a different column, namely a Bakerboard CSX column, and different conditions were required for the cation exchange chromatography than those described in document D20.

The skilled person had no reason to even consider document D13. Figure 7 reported the results of anion exchange chromatographic separation of recombinant human growth hormone (hGH) and its deamidated isoforms. HGH was much smaller than the rhuMAb HER2 antibody. There was no evidence that with the method of document D13 the skilled person would have separated the rhuMAb HER2 antibody and its acidic variants. This separation was particularly difficult because the deamidated antibody variants differed from the native antibody, which has a large net charge, only in one or two charges. Document D13 did not disclose the reverse wash step employed in the patent nor that the acidic variants could be separated without that step on the column material disclosed in document D13. It had not been shown that any approach was available to arrive at the claimed material. Even if the skilled person would have tried to separate the acidic variants from the native protein, he would have had no reasonable

expectation of success.

Amendment of the respondent's case

The opposition division had decided that document D20 did not anticipate the claimed subject-matter and the board had indicated in its preliminary opinion that it considered this decision to be correct. The respondent could thus have proposed document D20 earlier as closest prior art.

Document D20 was concerned with the processing of C-terminal lysine and arginine residues of proteins isolated from mammalian cell culture but not with the purification of the rhuMAb HER2 antibody.

XII. The respondent's arguments may be summarised as follows:

Main request

Novelty

Document D6 provided a disclosure of all the features of claim 1. Page 19, line 13 disclosed deamidation at Asn30 of the light chain and isoaspartate formation, via the intermediate succinimide, at Asp102 of the heavy chain. On page 26 it was repeated that the major degradation route for rhuMAb HER2 in aqueous solutions was deamidation or succinimide formation. The loss of native protein due to deamidation or succinimide formation was assessed for four reconstituted rhuMAb HER2 formulations using cation exchange chromatography. Although the nature of the variants was not analysed, based on the reference on page 26, line 14 to "previously", it was clear that the disclosure on

page 19 described the nature of the variants in the reconstituted rhuMAb HER2 formulations. Figures 5 to 8 of document D6 showed that at the start of the experiment the rhuMAb HER2 preparation comprised 82 or 81% native protein and therefore a maximum of 18 to 19% deamidated by-products. The deamidation was the result of deamidation of Asn30 in either one or both of the light chains of rhuMAb HER2. Figure 5 reported 82% native protein which implied 18% variants, and thus less than 25%. These variants could be acidic or basic. The only acidic variant disclosed in document D6 was the variant resulting from deamidation at Asn30. Document D6 thus anticipated the claimed subject-matter.

When the starting materials were clearly defined and the method by which these starting materials were reacted, processed or separated was clearly defined, then the result of that process was directly and unambiguously disclosed.

Remittal

The case should not be remitted to the opposition division. Both parties had provided their arguments as regards inventive step in writing during the appeal proceedings.

Inventive step

Document D6 represented the closest prior art because it disclosed a formulation comprising the same type of antibody and the same type of impurity, namely deamidation at position Asn30 of the light chain. It also disclosed a procedure, namely cation exchange

chromatography, to obtain the native protein (see page 26).

Document D7 related to chromatographic techniques for the characterisation of rhuMAb HER2 and also disclosed deamidation at Asn30. D7 disclosed on page 4 that a composition comprising rhuMAb HER2 could be resolved in five peaks by MonoS cation exchange chromatography. The acidic peaks were to the left of the native peak, which was peak 3, while the basic peaks were to the right of the native peak. On page 6 document D7 provided information on the composition of peaks 1 and 3. Peak 1 comprised deamidated light chain Asn30 while peak 3 did not.

Page 7 reported that peak 1 had 82% specific activity in a $p185^{HER2}$ binding assay while peak 3 showed 100% specific activity and corresponded to the native rhuMAb HER2. The determination of the activity for the individual peaks presupposed that these peaks had been isolated. D7 thus disclosed a fraction of the rhuMAb HER2 preparation which had been isolated by ion exchange chromatography and which was pure. If document D7 was considered as the closest prior art, the problem to be solved was to provide a purer or improved formulation comprising rhuMAb HER2.

Document D7 motivated the skilled person to remove the acidic variants: see page 7, upper slide. He would have performed a cation exchange chromatography and - knowing about the type of variants in the different peaks (see previous paragraph)- would have started collection of the peak 3 material after peak 2 had been eluted. This would have removed the acidic variants. The skilled person would have identified the

appropriate conditions for the MonoS cation exchange chromatography by routine experimentation.

If the skilled person would not have been able to separate the acidic variants by MonoS cation exchange chromatography he would have considered using a different cation exchange chromatography material. Thus, the skilled person trying to provide a purer formulation comprising rhuMAb HER2 would have turned to document D13, which dealt with novel stationary phases, termed MCI GEL ProtEx. Document D13 moreover disclosed on page 63, left hand column, that the ProtEx stationary phase was suitable for the separation of proteins with subtle differences and reported the effective separation of hGH from its deamidated isoforms. By using this material the skilled person would thus have been able to remove the acidic variants from a rhuMAb HER2 antibody preparation.

Amendment of its case

Document D20 had not been proposed earlier as closest prior art because only during the oral proceedings was it understood that a novelty attack based on this document would not be successful.

Document D20 could be taken to represent the closest prior art. It disclosed in section 2.2. on page 130 that a MonoS cation exchange chromatography could be used to determine the composition of a rhuMAb HER2 preparation. Figure 2 depicted the results of the cation exchange chromatography of three lots of rhuMAb HER2. The acidic peaks 1 and 2 were identified as comprising deamidated Asn30 in one light chain while the main peak, peak 3, contained native protein. The only difference to the claimed subject-matter was that

the amount of the acidic variants was not explicitly indicated.

XIII. The appellant requested that the decision under appeal be set aside and the opposition be rejected. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request

Introduction

1. The invention under consideration concerns a composition comprising the anti-HER2 antibody humMAb4D5-8 and one or more acidic variants thereof. Acidic - and basic - variants are contaminant molecules which can arise during storage of recombinantly produced humMAb4D5-8. Deamidation of e.g. an asparagine residue of the antibody resulting in an aspartate residue generates an acidic variant. Isoaspartate formation via the intermediate succinimide from an aspartate residue results in a basic variant of the antibody. These acidic and basic variants can be separated from the native anti-HER2 antibody on the basis of their different charges. In a cationic exchange chromatography the acidic variants are eluted earlier than the native antibody, while basic variants are eluted later.

Novelty (Article 54 EPC)

2. The subject-matter of claim 1 relates to a composition comprising a mixture of the anti-HER2 antibody humMAb4D5-8 and one or more acidic variants thereof, wherein the amount of the acidic variant(s) is less

than about 25%, and wherein the acidic variant(s) are predominantly deamidated variants, and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate.

3. Novelty of the claimed subject-matter was challenged by the respondent on the basis of the reconstituted, previously lyophilised, rhuMAb HER2 formulations disclosed in example 1 of document D6.

4. For an invention to lack novelty, all the claim's features must be disclosed in the prior art. If the prior art consists of a written description, as in the present case, what is made available to the public is the information content of the written description (see decision G 2/88, reasons, point 10). It is a generally accepted principle that for lack of novelty, there must be a direct and unambiguous disclosure, either explicit or implicit, in the state of the art which would inevitably lead the skilled person to subject-matter falling within the scope of what is claimed. In this context "implicit disclosure" means disclosure which any person skilled in the art would objectively consider as necessarily implied in the explicit content (see e.g. decision T 1523/07, reasons, point 2.4).

5. Example 1 of document D6 (see pages 18 to 27) reports the development of a lyophilized formulation comprising full length humanised antibody huMAb4D5-8, which is referred to as rhuMAb HER2 (see page 18, line 35 to page 19, line 2). It was undisputed that document D6 does not explicitly disclose the feature of claim 1 that the acidic variants are predominantly deamidated variants, wherein the deamidated variants have Asn30 in

CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate.

6. The question to be answered is thus whether or not this feature is implicitly disclosed in the sense that it can be directly and unambiguously derived from what is explicitly disclosed in document D6.

7. From page 19 to page 24, document D6 describes the various lyophilised formulations of the rhuMAb HER2 antibody. On page 19 document D6 discloses (see lines 13 to 15) that:

> "[i]n early screening studies, the stability of several lyophilized recombinant humanized anti-HER2 antibody (rhuMAb HER2) formulations was investigated after incubation at 5°C (proposed storage condition) and 40°C (accelerated stability condition). In the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain) and isoaspartate formation via a cyclic imide intermediate, succinimide (102Asp of heavy chain)."

8. From page 24, line 11 onwards document D6 describes experiments which address the stability of the antibody after reconstitution and during storage. For this purpose, four different types of reconstituted lyophilised formulations of rhuMAb HER2 were prepared and the stability of these reconstituted formulations in terms of deamidation or succinimide formation was determined. In this context document D6 discloses (see page 26, lines 14 to 18) that:

> "[a]s mentioned previously, the major degradation route for rhuMAb HER2 in aqueous solutions is

deamidation or succinimide formation. The loss of native protein due to deamidation or succinimide formation was assessed for the four reconstituted rhuMAb HER2 formulations. Analysis of rhuMAb HER2 deamidation and succinimide formation was performed using cation exchange chromatography."

9. Figures 5 to 8 depict the results of the cation exchange chromatography in terms of % native protein against time (days) for the different formulations at different temperatures. The % native protein is defined as the peak area of the native (not degraded) protein relative to the total area as measured by cation exchange chromatography (see legends of Figures 5 to 8 on page 4, lines 20 to 38). Pursuant to Figure 5 the amount of the native protein is around 82% at the beginning of the experiment (time zero).

10. The respondent argued that the value of 82% native protein reported in Figure 5 implied the presence of a maximum of 18% variants, i.e. less than about 25% as stipulated by claim 1. These variants could be either acidic or basic. As the only acidic variant disclosed in document D6 was the variant resulting from deamidation at Asn30 in the light chain of rhuMAb HER2, document D6 anticipated the claimed subject-matter.

11. In relation to this line of argument the board observes that the experiments described at page 26 of document D6 are concerned with comparing the properties of reconstituted, previously lyophilised, formulations over time. Document D6 is silent about the nature of the degraded antibody present in these reconstituted formulations of rhuMAb HER2.

12. Document D6 mentions on page 19 that in the liquid state rhuMAb HER2 was observed to degrade by deamidation at position Asn30 of the light chain and isoaspartate formation at position 102Asp of the heavy chain (see point 7 above). In the context of the studies performed on the reconstituted formulations document D6 refers back to this statement (see point 8 above). However, the statement on page 19 is made in the context of "early screening studies" and the skilled person has no reason to conclude that the same degradation takes necessarily place in the reconstituted formulations. From the statement on page 19 it is also not derivable that (i) deamidation in the reconstituted formulations of example 1 involves position Asn30 or (ii) that the result of the deamidation, if it is at position Asn30, is necessarily a conversion of Asn30 to Asp30. No conclusion can thus be drawn about the nature of any particular variant which might be present in the reconstituted formulation at time zero, or at any other point in time, from the written description of example 1 of document D6.

13. The board concludes from the above that the feature that the acidic variants are predominantly deamidated variants, wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate, is not directly and unambiguously disclosed in document D6.

14. In a second line of argument the respondent submitted that when the starting materials were clearly defined and the method by which these starting materials were reacted, processed or separated was clearly defined, then the result of that process was directly and unambiguously disclosed, although inherently.

15. As discussed above (see points 11 and 12), the starting material of the experiments conducted in example 1, i.e. the composition of the reconstituted formulations of rhuMAb HER2 at time zero of the study, and in particular the nature of the variants of the antibody present in the reconstituted formulation, is not clearly defined in document D6. Accordingly, the respondent's second argument fails for this reason alone.

16. It follows from the above, that document D6 does not directly and unambiguously disclose all the features of claim 1. Therefore, the subject-matter of this claim, and of dependent claims 2 to 6, is not anticipated by document D6. The main request fulfills the requirements of Article 54 EPC.

Remittal to the opposition division

17. In the present case, the decision under appeal did not deal with inventive step. Under Article 111(1) EPC the board of appeal may either decide on the appeal or remit the case to the opposition division. The board observes that there is no absolute right to have an issue considered by two instances. Both parties have submitted their arguments concerning inventive step in writing during the appeal proceedings. When asked at the oral proceedings by the board, the appellant stated that it was prepared to deal with the issue of inventive step. Taking also into consideration the requirement of procedural efficiency, the board decided to refuse the appellant's request for remittal and to decide the issue of inventive step.

Inventive step

Closest prior art

18. The closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the EPO, 7th edition 2013, section I.D.3.1).

19. The purpose of the claimed invention is the reduction of the amount of acidic variants occurring in anti-HER2 antibody preparations.

20. The respondent proposed that either document D6 or document D7 represented the closest prior art, while the appellant considered that document D7 represented the closest prior art.

21. Document D6 is concerned with providing stable lyophilized antibody formulations that contain specific excipients which protect against further physical and chemical degradation of the antibodies contained in the lyophilised reconstituted formulations (see page 1, lines 4 to 6; example 1). Although document D6 discloses (see page 19, lines 13 to 15) that rhuMAb HER2 may degrade in the liquid state by deamidation at Asn30 of the light chain and succinimide formation at Asp102 of the heavy chain, it is silent about removal of the resulting variants.

22. Document D7 is a collection of slides of a presentation given at a conference, The Waterside Monoclonal

Conference, relating to chromatographic techniques for the characterisation of rhuMAb HER2. Document D7 discloses that a composition comprising rhuMAb HER2 and charge variants thereof can be resolved by MonoS cation exchange chromatography (see lower slide on page 4). An analysis of the individual peaks with respect to the presence of Asn30 and/or Asp30 is shown in the lower slide on page 6. In the upper slide on page 7, document D7 reports that peak 1, which comprises the acidic variant, has 82% specific activity in a $p185^{HER2}$ binding assay while peak 3, which comprises the native rhuMAb HER2, shows 100% specific activity in the binding assay. In the same slide it is reported that 25% of the pool has deamidated Asn30 and that it was decided not to remove the deamidated material. Document D7 also discloses that deamidation increases when harvested cell culture fluid (HCCF) is held and that therefore harvests are taken straight through to purification (see page 7, upper slide).

23. The board concludes that document D6 does not have the same purpose as the claimed invention as it is concerned with the stabilisation of reconstituted lyophilised antibody preparations and does not aim at reducing the amount of undesired variants, such as acidic variants. Document D7 on the other hand recognises the issue of the occurrence of deamidated/ acidic variants and thus relates to same purpose as the invention. Accordingly document D7 represents the closest prior art.

Technical problem to be solved

24. The technical problem to be solved in view of document D7 is the provision of rhuMAb HER2 compositions with improved properties. The solution consists in the

provision of a composition as defined in claim 1 in which the level of a particular type of acidic charge variant is reduced to below 25%.

Obviousness

25. When considering whether or not the subject-matter constitutes an obvious solution to the technical problem, the question to be answered is whether or not the skilled person, in the expectation of solving the technical problem defined in point 24 above, would have modified the teaching in the closest prior art document D7 so as to arrive at the invention in an obvious manner.

26. In that context, the appellant argued that document D7 would not have provided any motivation to the skilled person to remove the deamidated material.

27. However, document D7 discloses that deamidation of Asn30 decreases the binding activity of rhuMAb HER2 in a $p185^{HER2}$ binding assay and that harvests are taken straight through to purification to avoid an increase in deamidation (see point 22 above). Thus, in the board's view, document D7 teaches that deamidation at position Asn30 has a negative impact on the activity of the rhuMAb HER2 antibody preparation and also that the occurrence of deamidation should be minimised. The skilled person would thus have been motivated to remove the deamidated material, i.e. the acidic variants, from the antibody preparation disclosed in document D7 in order to solve the problem formulated above. The question which remains to be answered is whether or not he would also have had a reasonable expectation of success.

28. The respondent submitted that the skilled person would have easily succeeded in the task by performing a MonoS cation exchange chromatography as disclosed in document D7 to resolve the acidic variants from the native antibody. By collecting the native rhuMAb HER2 only after elution of the acidic variants, the acidic variants would have been removed from the antibody preparation. Absent any disclosure of the conditions of the MonoS cation exchange chromatography in document D7, the skilled person would have used routine conditions which formed part of his common general knowledge.

29. In this context the board notes that it is undisputed that the skilled person, when trying to implement the teaching of document D7, would also have been aware of document D20. This document discloses the same profile for the cation exchange chromatography of rhuMAb HER2 (see Figure 2) as document D7. Document D20 moreover provides detailed instructions about the conditions for the MonoS cation exchange chromatography (see section 2.2. on page 130).

30. However, the respondent itself has provided evidence that it was unable to obtain the cation exchange profile as given in Figure 2 of document D20 by following these instructions: see point 5 of declaration D26. According to points 6 and 7 of declaration D26 a different column material, namely Bakerboard CSX, was required to actually obtain the cation exchange profile depicted in Figure 2 of document D20, which is the same as the one depicted in document D7. Thus, as shown by declaration D26, the skilled person aiming at solving the problem defined in point 24 above by following the teaching of document D7 and aware of routine conditions of MonoS cation

exchange chromatography of rhuMAb HER2 as disclosed in document D20 would not have succeeded in separating the acidic variants from the native antibody molecule.

31. The respondent further submitted that if the skilled person had found that he was not able to separate the acidic variants from the native antibody by MonoS cation exchange chromatography he would have found a suitable method in document D13. The respondent relied in particular on Figure 7, which depicts the results of an anion exchange chromatographic separation of recombinant human growth hormone (hGH) and its deamidated isoforms.

32. The board accepts that the skilled person looking for techniques to separate an antibody from its deamidated isoforms would have been aware of document D13. The board observes however that document D13 addresses the issues arising in the context of the separation of small amounts of proteins (see page 57, paragraph bridging the columns). It reports on separation studies performed with novel stationary phases, termed MCI GEL ProtEx, with *inter alia* standard protein mixtures and hGH and concludes that ProtEx stationary phases are suitable for the separation of proteins with subtle differences, such as variants and isoforms (see page 63, left hand column, last paragraph).

33. The board considers it at least questionable whether the skilled person, starting from document D7, which deals with the large scale production of rhuMAb HER2 (see page 4, upper slide), and faced with the problem set out above (see point 24), would have taken account of the separation techniques disclosed in document D13 for the separation of small amounts of proteins.

34. Assuming, in the respondent's favour, that the skilled person would have taken into account the techniques of document D13 he would, in the board's view, have had no reason to infer that a separation technique that worked for hGH would also work for the rhuMAb HER2 antibody preparation. The molecules separated in document D13, hGH and its deamidation isoforms, are considerably smaller than the rhuMAb HER2 antibody and its acidic variants. In the case of rhuMAb HER2 only one or two charges are changed in the acidic variant relative to the large net charge of the native antibody. The relative difference in charge between the native antibody and its variant is thus small and the skilled person would have had no reason to assume that the conditions disclosed in D13 for the separation of hGH and its isoforms would resolve rhuMAb HER2 and its isoforms. Indeed, pursuant to the patent, a wash step with an intermediate buffer of lower conductivity is necessary to separate the acidic variant from the native antibody in an cation exchange chromatography (see paragraph [0114]). This step is not disclosed in document D13.

35. In summary, the board is not persuaded that either of the two methods suggested by the respondent would have led the skilled person to the successful separation of the acidic variants from the native rhuMAb HER2 antibody. The skilled person would thus have had no reasonable expectation of success.

36. For these reasons, the board concludes that the subject-matter of claim 1 is not obvious. Accordingly, the subject-matter of claim 1, and by the same token that of dependent claims 2 to 6, involves an inventive step within the meaning of Article 52(1) and 56 EPC.

Amendment to the respondent's case (Article 13 RPBA)

37. During the written part of the appeal proceedings the respondent had submitted that either document D6 or document D7 represented the closest prior art. In the course of the oral proceedings before the board the respondent proposed document D20 as closest prior art. This represented an amendment to the respondent's case. Pursuant to Article 13 RPBA any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion.

38. The respondent had justified the amendment of its case at this late stage of the appeal proceedings by saying that it was only in the course of the discussion of document D6 during the oral proceedings that it had understood that the board did not consider document D20 as novelty destroying.

39. However, the board had indicated in its communication sent under Article 15(1) RPBA that is considered, albeit provisionally, that the opposition division had correctly decided that document D20 did not anticipate the claimed subject-matter. Accordingly, the respondent was aware of the board's opinion on document D20 well before the date of the oral proceedings.

40. Document D20 is concerned with the processing of C-terminal lysine and arginine residues of proteins isolated from mammalian cell culture. It discloses that C-terminal Lys residues are often absent in proteins isolated from mammalian cell culture and that incomplete removal of C-terminal Lys residues causes charge heterogeneity. Such charge variants can be resolved by cation-exchange chromatography. RhuMAb

HER2, for example, shows five charge species (see Figure 2) in cation-exchange chromatography. The acidic peaks 1 and 2 are deamidated at Asn30 in one light chain, peak 1 has no Lys450 residues, while peak 2 has one Lys450 residue. Although document D20 thus mentions deamidation of rhuMAb HER2, it is concerned with the identification of variants after the production of the antibody in culture and not with its purification. Thus it relates to a different purpose and does not qualify as the closest prior art.

41. The board concluded from the above that the amendment to the respondent's case was not only late but that also document D20 did not in fact qualify as closest prior art. For these reasons the board decided, in the exercise of its discretion pursuant to Article 13 RPBA, not to admit the amendment of the respondent's case in the appeal proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The opposition is rejected.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated