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**Datasheet for the decision
of 14 May 2014**

Case Number: T 2045/09 - 3.3.04

Application Number: 97908923.2

Publication Number: 0896586

IPC: C07K16/32, A61K39/395,
G01N33/577, C12N5/10, C12N5/20,
C07K17/00, C12N15/64

Language of the proceedings: EN

Title of invention:
ErbB3 antibodies

Patent Proprietor:
Genentech, Inc.

Opponents:
Amgen Inc.
U3 Pharma GmbH
Merrimack Pharmaceuticals, Inc.

Headword:
Anti-ErbB3 antibody/GENENTECH

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2), 123(3)
EPC R. 139
RPBA Art. 13(3)

Keyword:

Admissibility of appeal - appeal admissible after remedy of deficiencies
Inventive step - Main request (no)
Late-filed auxiliary requests - admitted (yes)
Amendment - added subject-matter - Auxiliary request 1 (yes)
Claims - unclear characterization of parameters -
Auxiliary request 2 (yes)
Amendment - added subject-matter - Auxiliary request 3 (no)
Inventive step - Auxiliary request 3 (yes)

Decisions cited:

G 0001/92, G 0001/93, G 0001/12, T 0735/00, T 0500/01

Catchword:



**Beschwerdekammern
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Case Number: T 2045/09 - 3.3.04

**D E C I S I O N
of Technical Board of Appeal 3.3.04
of 14 May 2014**

Appellant: Genentech, Inc.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted on
18 August 2009 concerning maintenance of the
European Patent No. 0896586 in amended form.

Composition of the Board:

Chairwoman G. Alt
Members: M. Montrone
K. Garnett

Summary of Facts and Submissions

- I. Appeals were filed by the patent proprietor (hereinafter "appellant-patentee"), by opponent 1 (hereinafter "appellant-opponent I") and by opponent 3 (hereinafter "appellant-opponent III") against the interlocutory decision of the opposition division dated August 2009 to maintain European patent 0896586 entitled "ErbB3 Antibodies" in amended form. A further opposition and appeal were also filed, as to which, see Points V to VII, below. The patent had been granted for European patent application No. 97908923.2 which was published as international application WO 97/35885 (hereinafter "application as filed").
- II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), under Article 100(b) EPC and under Article 100(c) EPC.
- III. In its decision the opposition division held that the subject-matter of claim 1 of the main request lacked an inventive step (Article 56 EPC) and that the same applied to the subject-matter of claim 1 of the auxiliary requests 1 to 3, and 6 because it was identical to that of claim 1 of the main request. The subject-matter of claim 1 of auxiliary requests 4 and 5 was held to lack clarity (Article 84 EPC). The patent was maintained on the basis of auxiliary request 7.
- IV. With its statement of grounds of appeal the appellant-patentee filed a main request corresponding to the patent as granted, and six auxiliary requests. The main and auxiliary request 1 differed from the other claim requests in that paragraph [0017] of the description was amended by deleting the phrase "but it is in any

- case disclaimed herein from the claims directed to the antibodies per se". In this decision this passage of the description will hereafter be referred to as the "Disclaimer".
- V. An opposition had also been filed in the name of U3 Pharma AG (opponent II), whose address was stated to be Bunsenstrasse 1, 82152 Martinsried. With a letter dated 9 June 2009 this party filed a request that the change of U3 Pharma AG's "corporate form" to U3 Pharma GmbH be recorded, its address still being Bunsenstrasse 1, 82152 Martinsried. In support of this request there was filed a copy of a letter from the Amtsgericht in Munich enclosing a copy of the relevant entry from the commercial register ("Handelsregister B"), recording the change ("*durch formwechselnde Umwandlung*").
- VI. Proceedings continued before the opposition division with U3 Pharma GmbH as opponent 2. This was also how the party was named in the minutes of the oral proceedings and in the appealed decision. No change in representation occurred.
- VII. On 1 October 2009 a notice of appeal was filed by the representatives who had represented U3 Pharma GmbH in the opposition division proceedings, saying as follows: "In the name of, and by authorisation of our client U3 Pharma AG[,] Bunsenstrasse 1, 82152 Martinsried, DE[,] we herewith lodge an appeal against the decision dated August 18, 2009." (This appellant party will hereafter be referred to as "appellant-opponent II"). Reversal of the decision and revocation of the patent was requested. The heading included a reference to the proprietor, Genentech, Inc., and to "OII", which was named as U3 Pharma AG. The notice cited the representative's file reference, which was the same as

that in the proceedings before the opposition division. The statement of grounds of appeal which was filed on 23 December 2009 on behalf of this party was in the same form. When the notice of appeal and statement of grounds of appeal were filed by the appellant-opponent II it was not noticed by the board or indeed anyone else that anything might be amiss with the notice of appeal.

- VIII. All parties requested oral proceedings as an auxiliary measure.
- IX. The appellant-patentee filed a reply to the appellant-opponents' statements of grounds of appeal and submitted auxiliary requests 7 to 12. An amended version of auxiliary request 9 was later filed.
- X. All of the appellant-opponents filed replies to the appellant-patentee's statement of grounds of appeal and the appellant-patentee filed a reply to these submissions.
- XI. With a further submission appellant-opponent III filed a second declaration of Mr. Totty (document D61, section XXII, *infra*), in response to which the appellant-patentee filed a second declaration of Mr. Arnott (document D62, section XXII, *infra*).
- XII. The board sent a summons to oral proceedings to be held on 13 and 14 May 2014.
- XIII. With its letter dated 3 April 2014 the appellant-patentee took the point that, subject to the pending decision of the Enlarged Board of Appeal in G 1/12, appellant-opponent II's appeal appeared to be inadmissible.

Subsequently, appellant-opponent II filed a request to correct its name in the notice of appeal to U3 Pharma GmbH in accordance with Rule 101(2) EPC.

- XIV. With its letter of 10 March 2014 the appellant-opponent I withdrew its request for oral proceedings. Appellant-opponent III announced in its letter of 23 April 2014 that it would not attend the oral proceedings.
- XV. Oral proceedings before the board took place on 13 and 14 May 2014. The appellant-patentee and appellant-opponent II were represented.

At the oral proceedings the board pointed out that in the light of decision in G 1/12 (which by then had been published), Rule 139 EPC might be a preferable basis for any correction of the appellant-opponents II's name. Appellant-opponent II accepted this. There were no further submissions on this issue from the appellant-patentee. The board then allowed appellant-opponent II's request to correct the name of U3 Pharma AG in its notice of appeal (and implicitly in the statement of grounds of appeal) to U3 Pharma GmbH, and declared its appeal to be admissible.

At the end of the oral proceedings the appellant-patentee's requests were that the decision under appeal be set aside and the patent be maintained on the basis of auxiliary request 1 as filed with its statement of grounds of appeal (hereinafter, the "main request"), alternatively on the basis of auxiliary requests 4 or 5 as filed with its grounds of appeal but with the same amendment to delete the Disclaimer as with the main request (hereinafter "auxiliary request 1" and "auxiliary request 2"), or alternatively that the appeals of the opponents be dismissed, *i.e.* that the patent be maintained on the basis of auxiliary request

6 as filed with its statement of grounds of appeal, which corresponded to auxiliary request 7 before the opposition division (hereinafter "auxiliary request 3").

At the oral proceedings appellant-opponent II requested that the decision under appeal be set aside and the patent be revoked. The appellant-opponents I and III had made the same request in writing.

XVI. The claims of the main request and of the auxiliary requests 1 to 3 which are relevant for this decision read as follows:

Main Request

"1. An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3.

2. The antibody of claim 1 which also increases the binding affinity of heregulin for ErbB3 protein.

8. An antibody which binds to the epitope bound by the 8B8 antibody obtainable from the hybridoma cell line ATCC no. HB-12070.

10. An antibody which has the complementarity determining regions of the 8B8 antibody obtainable from the hybridoma cell line ATCC no. HB-12070.

11. The antibody of any one of claims 1 to 10, which is labelled.

12. The antibody of any one of claims 1 to 10, which is immobilized on a solid phase.

16. The antibody of any one of claims 1 to 10 for use in a method of medical treatment.

17. Use of an antibody according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment of a condition in which excessive activation of the ErbB2-ErbB3 protein complex is occurring, such as benign and malignant tumours; leukaemias and lymphoid malignancies; neuronal, glial astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; and inflammatory, angiogenic and immunologic disorders."

Auxiliary request 1:

"1. An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3, wherein the reduction in (i) is at least 70% as determined by reflectance scanning densitometry of Western blots of the complex, and the reduction in (ii) is at least 70% as determined by reflectance scanning densitometry of Western blots of the complex probed with an anti-phosphotyrosine antibody."

Auxiliary request 2:

"1. An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2

activation in a cell which expresses ErbB2 and ErbB3, wherein the reduction in (i) is at least 70% of the number of ErbB2-ErbB3 complexes which form in a cell which has been exposed to the antibody and heregulin relative to an untreated control cell, as determined by reflectance scanning densitometry of Western blots of the complex, and the reduction in (ii) is at least 70% reduction of tyrosine phosphorylation activity of ErbB2 which occurs when heregulin binds to ErbB3 in the ErbB2-ErbB3 protein complex relative to an untreated control cell, as determined based on phosphotyrosine levels in the ErbB2-ErbB3 complex following exposure of the complex to heregulin and the antibody of interest, and as determined by reflectance scanning densitometry of Western blots of the complex probed with an anti-phosphotyrosine antibody and wherein the cell which expresses ErbB2 and ErbB3 is a Caov3 cell".

Auxiliary request 3:

"1. An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3, and (iii) increases the binding affinity of heregulin for ErbB3 protein".

XVII. The following documents are referred to in the present decision:

D1: C. H. Heldin, *Cell*, vol. 80, 1995, pg. 213-223

D5: Lewis et al., *Cancer Research*, vol. 56, 1996, pg. 1457-1465

- D6: Rajkumar et al., *The Breast*, vol. 4, 1995, pg. 84-91
- D7: Rajkumar et al., *Br. J. Cancer*, vol. 70, 1994, pg. 459-465
- D8: US 5,480,968
- D12: Declaration of Dr. Martin Tredder dated 10 July 2007
- D23: Carraway and Cantley, *Cell*, vol. 78, 1994, pg. 5-8
- D33: Second declaration of Dr. Nielsen dated 7 January 2008
- D35: Declaration of Dr. Marx dated 28 April 2009
- D43: Declaration of Dr. Kunst dated 27 April 2009
- D44: Declaration of Professor Koland dated 30 April 2009
- D45: Declaration of Mark X. Sliwkowski dated 22 December 2009
- D50: Declaration of Robert Akita dated 17 May 2010
- D53: Gassman et al., *Electrophoresis*, vol. 30, 2009, pg. 1845-1855
- D55: Declaration of Nicholas Totty dated 22 July 2010
- D58: Pham et al., *Anal. Biochem.*, vol. 352, 2006, pg. 77-86

- D61: Second declaration of Nicholas Totty dated
6 July 2012
- D62: Second declaration of David Arnott dated 12 July
2013
- D63: Henzel et al., JBC, 1989, 264, pg. 15905-15911
- D64: Soutar et al., PNAS, 89, pg. 7389-7393
- D65: Stahl et al., Biochemistry, 1993, 32, pg.
1991-2002
- D66: Bandeira et al., Nature Biotechnology, 2008, 26,
pg. 1336-1338

XVIII. The appellant-patentee's arguments, as far as they are relevant for the present decision, may be summarised as follows:

Main request

Amendments (Article 123(2) EPC)

A basis for the subject-matter of claim 1 was present on page 3, lines 23 to 26 of the application as filed.

The subject-matter of dependent claim 2 was disclosed on page 1, first paragraph and on page 3, lines 23 to 28 of the application as filed.

A basis for the subject-matter of claims 8 and 10 was present in original claims 15 and 16 and on page 30, lines 1 to 5 of the application as filed. The functional feature present in claims 15 and 16 by their dependency on claim 1 was an inherent feature of the

8B8 antibody of claim 8 and of the complementary determining regions (CDRs) of the 8B8 antibody of claim 10, respectively.

A basis for the subject-matter of claim 11 was present on page 9, lines 19 to 22 and page 26, line 30 of the application as filed in combination with original claim 9.

A basis for the subject-matter of claim 12 was present in original claim 10 in combination with the disclosure on page 3, lines 31, 32 and page 26, lines 20 to 26 of the application as filed.

A basis for the subject-matter of claim 16, *i.e.* the first medical use of the antibodies according to claims 1 to 15 was present on page 4, lines 3 to 5, page 8, lines 4 to 10, page 7, lines 37 to 39 and page 28, line 27 of the application as filed.

A basis for the subject-matter of claim 17, *i.e.* the heregulin independent activation of the ErbB2-ErbB3 complex, was present on page 28, lines 28 to 35.

Extension of protection (Article 123(3) EPC)

The deletion of the Disclaimer from the passage in the description relating to the background art and in particular document D8 had no effect on the scope of claim 1 because document D8 did not contain any novelty-destroying disclosure for the subject-matter of this claim. In addition, the Disclaimer was only present in the description and was therefore not part of the definition of a feature in any of the claims. Hence, this statement was devoid of any effect as

regards the claims and could be deleted in accordance with point 11 of the reasons in G 1/93.

Sufficiency of disclosure (Article 83 EPC)

The subject-matter of claim 8 met the requirements of Article 83 EPC because the person skilled in the art required nothing else than standard technology, such as epitope mapping, to obtain the claimed antibodies.

A therapeutic effect of the 8B8 antibody in the treatment of the diseases referred to in claim 17 was plausible in view of the experimental data disclosed in the application as filed for the 3-8D6 antibody. This antibody belonged, as did the 8B8 antibody, to a group of anti-ErbB3 antibodies that were selected in a screening assay because they all increased the binding affinity of heregulin to ErbB3. The 3-8D6 antibody was further tested and found to reduce the complex-formation of ErbB2 and ErbB3, and the activity of ErbB2. Since the 8B8 antibody had been retrieved in the same way as the 3-8D6 antibody, there was reason to assume that it had the same properties. This was then later confirmed by post-published data in document D33, which showed that the 8B8 antibody indeed had the functional properties as referred to in claim 1.

Novelty (Article 54 EPC)

According to the headnote in G 1/92, the Enlarged Board of Appeal concluded the chemical composition of a product was only state of the art when the product as such was available to the public and could be analysed and reproduced by the skilled person, irrespective of whether or not particular reasons could be identified for analysing the composition.

The prior, non-restricted sale of a 100µg sample of the antibody SGP-1 to Iowa State University was, in view of documents D43 and D44, not disputed. There was however no document available showing that a sample size of 100µg was sufficient to determine the complete amino acid sequence of the SGP-1 antibody by the technologies available in 1994 such that it could be considered as reproducible as required by G 1/92. Document D58 showed that the determination of the complete amino acid sequence of an antibody by Edman degradation in combination with mass spectroscopy was still a major scientific challenge in 2006. Moreover, the knowledge of the amino acid sequence alone was not sufficient for exact reproduction of the SGP-1 antibody. Its reproduction required in addition the back-translation of the amino acid sequence into cDNA followed by the recombinant production of the antibody in a mouse cell line adding exactly the same post-translational modifications on the SGP-1 antibody as the ones which were added when the antibody was produced by the specific SGP-1 hybridoma cell line. This hybridoma cell line was however not publicly available.

Document D8 disclosed the sequence of the ErbB3 receptor and fragments thereof including antibodies binding to it. However, the document did not disclose in an enabling manner an antagonising anti-ErbB3 antibody, *i.e.* an antibody that inhibited tumour cell growth and bound to the ligand-binding site of ErbB3, since neither the ligand nor its binding site on ErbB3 nor a screening assay for detecting and isolating antibodies competing with any ligand for its binding to ErbB3 was disclosed.

Inventive step (Article 56 EPC)

Document D8 was the closest prior art since it disclosed an antagonistic anti-ErbB3 antibody binding to the ligand-binding site of ErbB3. However, this antibody had not actually been provided. Also the ligand of ErbB3 and its binding site on ErbB3 were not disclosed. Moreover, the activity of ErbB3 was unknown and it was also no known whether a ligand binding to it activated or blocked its activity. Finally, the document did not disclose a screening assay to select antagonistic anti-ErbB3 antibodies. Document D5 was not a suitable starting point because it disclosed anti-ErbB2 antibodies.

ErbB2 and ErbB3 were functionally different subunits of the ErbB2-ErbB3 heterodimeric receptor complex. ErbB2 bound to and thereby activated ErbB3 but it did not bind to heregulin, whereas ErbB3 bound to heregulin, *i.e.* it was the receptor for the ligand heregulin. The functional asymmetry between the two receptor subunits in the complex formed upon heregulin-binding did therefore not allow a prediction about the activity of an anti-ErbB3 antibody on the basis an anti-ErbB2 antibody. Hence, the provision of an anti-ErbB3 antibody reducing the heregulin-induced receptor complex formation and the activity of the ErbB2 was not obvious. The requirements of Article 56 EPC were met.

Auxiliary Request 1

Admissibility

The present auxiliary request 1 differed from the corresponding request filed with the statement of grounds of appeal (auxiliary request 4) only in that

the Disclaimer was deleted. However, such an amendment to the description had already been made in relation to auxiliary request 1 as filed with the statement of grounds of appeal (now the main request). Thus, the present auxiliary request 1 was admissible.

Amendments (Article 123(2) EPC)

A basis for amended claim 1 was present on page 5, lines 10 to 30 and lines 28 to 30 of the application as filed.

Auxiliary Request 2

Admissibility

As for auxiliary request 1, the present auxiliary request 2 differed from the corresponding request filed with the statement of grounds of appeal (auxiliary request 5) only in that the Disclaimer was deleted. For the reason given in relation to auxiliary request 1, auxiliary request 2 was admissible.

Clarity, support (Article 84 EPC)

The amendment in claim 1 reading:

"wherein the reduction in (i) is at least 70% of the number of ErbB2-ErbB3 complexes which form in a cell which has been exposed to the antibody and heregulin relative to an untreated control cell, as determined by reflectance scanning densitometry of Western blots of the complex, and the reduction in (ii) is at least 70% reduction of tyrosine phosphorylation activity of ErbB2 which occurs when heregulin binds to ErbB3 in the ErbB2-ErbB3 protein complex relative to an untreated

control cell, as determined based on phosphotyrosine levels in the ErbB2-ErbB3 complex following exposure of the complex to heregulin and the antibody of interest, and as determined by reflectance scanning densitometry of Western blots of the complex probed with an anti-phosphotyrosine antibody and wherein the cell which expresses ErbB2 and ErbB3 is a Caov3 cell"

was aimed at improving the definition of the ErbB3 antibody by specifying its activity in a more detailed way. The recited feature was clear, because the skilled person could reliably determine if an antibody had the claimed functional properties by carrying out a reasonable number of experiments to arrive at statistically significant results.

Auxiliary Request 3

Amendments (Article 123(2) EPC)

The subject-matter of claim 1 had a basis on page 1, first paragraph and on page 3, lines 23 to 28 of the application as filed.

Inventive step (Article 56 EPC)

Either of documents D8 or D7 qualified as the closest prior art document because both related to anti-ErbB3 antibodies and thus at the same purpose as the present invention. However, the disclosure of an antagonistic anti-ErbB3 antibody in document D8 was speculative, *i.e.* the antibody had not actually been provided. The anti-ErbB3 antibody disclosed in document D7 acted agonistically rather than antagonistically upon binding to ErbB3, *i.e.* it stimulated tumour cell growth. The subject-matter of claim 1 differed from the antibodies

disclosed in these two documents in that the claimed antibodies not only had an antagonistic activity on the ErbB3/ErbB2 receptor complex formation and on ErbB2 activation but also at the same time increased the binding affinity of heregulin to ErbB3. This was unexpected and surprising. The antibodies of the invention thus provided a genuine alternative and an independent mechanism for inhibiting a heregulin-induced ErbB3-dependent cell proliferation and thus tumour cell growth.

- XIX. The appellant-opponents' arguments, as far as they are relevant for the present decision, may be summarised as follows:

Main Request

Amendments (Article 123(2) EPC)

An antibody with the functional features referred to in points (i) and (ii) of claim 1 was not disclosed in the application as filed. Moreover, even if this combination was disclosed, one of the embodiments of the subject-matter of claim 1 was not disclosed, namely that the antibody reduced the complex formation of ErbB2-ErbB3 and the activity of ErbB2 in **different** cells.

The subject-matter of dependent claim 2, *i.e.* an antibody which in addition to the functional features of claim 1 increased the binding activity of heregulin for ErbB3 protein, had no basis in the application as filed.

The subject-matter of claims 15 and 16 as filed could not form a basis for the subject-matter of claims 8 and

10. Claims 15 and 16 were dependent on claim 1 and thus their subject-matter was restricted by the feature "an antibody which binds to ErbB3 protein and reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3". Claims 8 and 10 were independent from claim 1 and thus lacked this restriction.

Claim 9 as filed was dependent only on claim 1 as filed and thus its subject-matter concerned antibodies according to claim 1 in labelled form. Present claim 11 was dependent on claims 1 to 10. The subject-matter of this claim generated, by virtue of its dependency on the subject-matter of claims 2 to 10 (*i.e.* the antibodies of these claims in labelled form), new subject-matter which had no basis in the application as filed. This reasoning applied *mutatis mutandis* to claim 10 as filed and present claim 12.

The application as filed did not provide a basis for the subject-matter of claim 16, *i.e.* the first medical use of the antibodies of claims 1 to 15.

The subject-matter of claim 17 referred to the treatment of disorders generally caused by an excessive activation of the ErbB2-ErbB3 complex formation. The application as filed, however, disclosed only the treatment of such disorders where the excessive activation of the complex formation was caused by heregulin. The omission of the feature "by heregulin" in claim 17 resulted in subject-matter which had no basis in the application as filed.

Extension of protection (Article 123(3) EPC)

In view of Article 69 EPC the Disclaimer in paragraph [0017] of the description of the patent "but it is in any case disclaimed herein from the claims directed to the antibodies per se" related to claim 1 as granted and restricted its scope. Its deletion from the description therefore extended the scope of the present claim beyond that of claim 1 as granted. Decision T 500/01 was a similar case.

Sufficiency of disclosure (Article 83 EPC)

The patent did not provide an enabling disclosure for the subject-matter of claim 8 because, having regard to document D35, the isolation of antibodies binding to the same epitope as the antibody 8B8 constituted an undue burden for the skilled person.

Moreover, a therapeutic effect of the 8B8 antibody in the treatment of the diseases according to claim 17 was not provided in the patent. In particular, the patent lacked any data showing that the 8B8 antibody reduced heregulin-induced ErbB2-ErbB3 complex formation and ErbB2 activation. However, the disclosure of these functional properties for the 8B8 antibody was essential to render the therapeutic effect of the 8B8 antibody credible in the treatment of the diseases referred to in the claim.

Novelty (Article 54 EPC)

The subject-matter of claim 1 was not novel in view of the prior use of the SGP-1 antibody as disclosed in documents D43 and D44 or the prior use of several other anti-ErbB3 antibodies as disclosed in documents D12 and

D33. The unrestricted sale of a sufficient quantity of the SGP-1 antibody before the relevant date allowed the determination of its amino acid sequence by Edman degradation and mass spectroscopy and thus its reproduction. In accordance with the criteria of G 1/92 the antibody therefore belonged to the state of the art.

In addition, the subject-matter of claim 1 was not novel over the antagonistic anti-ErbB3 antibodies disclosed in document D8. These antibodies were disclosed in an enabling manner in view of the disclosure provided in column 9, lines 16 to 26 and column 26, lines 39 to 42. Although heregulin was not disclosed as the ligand of ErbB3 in document D8, it belonged to the common general knowledge of the skilled person, as evidenced by documents D1 and D23, that heregulin was the ErbB3 ligand.

Inventive step (Article 56 EPC)

Documents D8 or D5 were the closest prior art. Starting from document D8 the problem to be solved was the provision of an alternative antagonistic anti-ErbB3 antibody reducing the biological activity of the ErbB3 receptor. Starting from document D5 the problem to be solved was the provision of an alternative antagonistic anti-ErbB2-ErbB3 receptor complex antibody reducing the heregulin-induced ErbB2-ErbB3 receptor complex formation and activation of ErbB2. The solution was the anti-ErbB3 antibody of claim 1 characterised by its property of reducing heregulin-induced ErbB2-ErbB3 receptor complex formation and of reducing ErbB2 activation. This solution was obvious in view of the teaching in either D5 or D8 when combined with the

common general knowledge concerning generation of alternative antibodies.

Auxiliary Request 1

Admissibility

The present request corresponded to auxiliary request 4 filed with the statement of grounds of appeal apart from the deletion of the Disclaimer. This resulted in an amendment of the appellant-patentee's case which put the admittance of auxiliary request 1 at the board's discretion.

Amendments (Article 123(2) EPC)

Page 5, lines 10 to 30 and lines 28 to 30 were not a basis for claim 1.

Auxiliary Request 2

Admissibility

The reasoning with regard to auxiliary request 1 applied *mutatis mutandis* to the present request.

Clarity, support (Article 84 EPC)

The amendment of claim 1 rendered the subject-matter of claim 1 unclear since the determination of the relative percentage in reduction achieved by the anti-ErbB3 antibody depended on too many variables, such as for example the number of Caov3 cells or the amount of heregulin used. Moreover, the reflectance scanning densitometry of Western blots used for determining the reduction produced inconsistent results. It was thus

impossible for the person skilled to reliably determine the claimed value of percentage in reduction.

Auxiliary Request 3

Amendments (Article 123(2) EPC)

The subject-matter of claim 1 had no basis in the application as filed.

Inventive step (Article 56 EPC)

Either of documents D8 or D5 could be considered as the closest prior art. The problem to be solved was the same as that formulated in relation to claim 1 of the main request since the presence of the feature "increases the binding affinity of heregulin for ErbB3 protein" had no limiting effect on the other two features of claim 1, namely the reduction of the heregulin-induced ErbB2-ErbB3 receptor complex formation and the ErbB2 activation. Moreover, the increased binding affinity of heregulin to its receptor induced by the antibody binding to ErbB3 was only achieved under artificial conditions. ErbB2 was not present in the cells used for testing the binding affinity of heregulin to ErbB3. This effect was thus devoid of any physiological relevance. However, the mere provision of a further alternative anti-ErbB3 antibody was obvious in view of the teaching of either documents D5 or D8 in combination with common general knowledge to produce this antibody. The circumstances underlying decision T 735/00 were similar to the present case, and in that case the subject-matter was found to lack an inventive step.

Reasons for the Decision

Admissibility of appellant-opponent II's appeal

1. The decision in G 1/12 confirms that Rule 139 EPC ("... mistakes in any document filed with the European Patent Office may be corrected on request") applies to notices of appeals and that an allowable correction under the rule has retrospective effect (and so in this case would date back to within the appeal period). An incorrect statement may be remedied to introduce what was originally intended but not to enable a person to give effect to a change of mind. What is relevant to consider is the party's actual rather than ostensible intention.

2. The board considers that the correction of the appellant-opponent II's name in the notice of appeal and statement of grounds of appeal is appropriate in the present case. Although according to G 1/12 the person requesting correction bears a heavy burden of proof where the original intention is not immediately apparent, the board considers that the original intention of appellant-opponent II is plainly apparent in this case. The evidence for this is found partly in the notice of appeal itself, which (a) refers to "OII", (b) requests revocation of the patent, (c) states as the address of the appellant-opponent II the address given in the European Patent Register for opponent 2 / U3 Pharma GmbH, (d) was filed by the same representative as had represented opponent 2 and U3 Pharma GmbH before the opposition division, and (e) refers to the same file number of the representative as before. Evidence is also available in the file explaining the earlier change of corporate form ("*formwechselnde Umwandlung*") of U3 Pharma AG into U3

Pharma GmbH and showing U3 Pharma GmbH's participation in the proceedings before the opposition division as opponent 2 thereafter.

3. During the oral proceedings the board therefore allowed appellant-opponent II's request for correction of its name in the notice of appeal and statement of grounds of appeal. Its appeal is admissible.

Main Request

Amendments (Article 123(2) EPC)

Claim 1

4. The subject-matter of claim 1 is literally disclosed on page 3, lines 23 to 26 of the application as filed:

"antibodies which bind to ErbB3 protein and further possess any one or more of the following properties: an ability to reduce heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3 [see feature (i) of the claim]; and the characteristic of reducing heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3" [see feature (ii) of the claim]

and thus has a basis in application as filed.

Claim 2

5. The subject-matter of claim 2 is disclosed on page 1, lines 4 to 7 of the application as filed having regard to the combination of the three features referred to by the conjunction "and":

"In particular, it relates to anti-ErbB3 antibodies which, surprisingly, increase the binding affinity of heregulin (HRG) for ErbB3 protein **and**/or reduce HRG-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses both these receptors **and**/or reduce heregulin-induced ErbB2 activation in such a cell." (Emphasis added by the board).

It thus has a basis in the application as filed.

Claims 8 and 10

6. The subject-matter of claims 15 and 16 as filed differs from the subject-matter of present claims 8 and 10 in that it explicitly recites the feature "reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3".
7. The antibodies in claim 8 are defined such that they bind to the same epitope as the 8B8 antibody which itself is obtainable from a specific hybridoma cell line.

The reduction of the heregulin-induced formation of an ErbB2-ErbB3 protein complex is an intrinsic property of the 8B8 antibody (see document D33, figure 2A and 2B) which is induced by its binding to its specific epitope on the ErbB3 protein. Consequently, the board considers that antibodies binding to the same epitope as the 8B8 antibody will also have this functional property. The feature "reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3" is therefore considered to be an implicit feature of the subject-matter of claim 8.

8. The subject-matter of claim 10 refers to antibodies having the complementary determining regions (CDRs) of the 8B8 antibody. It is well-known that the CDRs are responsible for the binding of an antibody to its epitope. Consequently, in the light of the observations given in relation to claim 8 above, the feature "reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3" is regarded as an implicit feature of the subject-matter of claim 10.

Claim 11

9. The subject-matter of present claim 11 differs from that of claim 9 as originally filed in that it refers to claims 1 to 10, and not just to claim 1. Claim 9 as filed reads "The antibody of claim 1 which is labelled." The appellant-opponents thus argued that the subject-matter of claim 11 generated, by its dependency on the subject-matter of claims 2 to 10 (*i.e.* the antibodies of these claims in labelled form), new subject-matter which had no basis in the application as filed.

The term antibody is defined in the description on page 6, lines 3 to 9 and 34 of the application as filed as follows:

"The term "antibody" is used in the broadest sense and specifically covers intact monoclonal antibodies. polyclonal antibodies. multispecific antibodies (e.g. bispecific antibodies) formed from at least two intact antibodies, and antibody fragments, ... , Fab..., humanized..."

Moreover, antibodies blocking the binding of the 8B8 antibody to ErbB3 are disclosed on page 16, lines 38 and 39 and page 30, line 5 of the application as filed.

The skilled person reading claim 9 as filed in the context of the whole application would, in the board's view, understand that the term "antibody" in claim 9 is used as an umbrella term for the individual antibody types, such as monoclonal, humanised or human antibodies and Fab fragments thereof including antibodies that bind to the same epitope as the 8B8 antibody, *i.e.* those antibodies referred to in present claims 2 to 10. Therefore the subject-matter of claim 11 does not contain added matter.

Claim 12

10. As with claim 11, the subject-matter of claim 12 differs from claim 10 as filed by referring to claims 1 to 10 and not only to claim 1. Claim 10 as filed reads "The antibody of claim 1 which is immobilized on a solid phase."

In the light of the reasons outlined above for claim 11 (see point 9), claim 12 is not considered to relate to subject-matter extending beyond the content of the application as filed.

Claim 16

11. The application as filed discloses on page 4, lines 3 to 5:

"The invention also provides a method for treating a mammal comprising administering a therapeutically effective amount of the antibody described herein to

the mammal, wherein the mammal has a disorder requiring treatment with the antibody",

and hence provides a direct and unambiguous basis for the first medical use of the antibodies according to claim 16.

Claim 17

12. The disclosure on page 28, lines 28 to 30 of the application as filed reads:

*"It is contemplated that the anti-ErbB3 antibody of the present invention may be used to treat conditions in which excessive activation of the ErbB2-ErbB3 complex is occurring, **particularly where such activation is mediated by a heregulin polypeptide.**"* (Emphasis added by the board).

The first half of this sentence provides a literal basis for the heregulin-independent activation of the ErbB2-ErbB3 receptor complex according to claim 17, in particular in view of the fact that a heregulin dependent activation of the ErbB2-ErbB3 receptor complex is disclosed in the second half of this sentence as a preferred embodiment. Thus, the subject-matter of claim 17 does not add matter.

13. There were no further objections pursuant to Article 123(2) EPC raised by any of the appellant-opponents against the remaining claims. Also the board has none. The subject-matter of claims 1 to 17 of the main request thus meets the requirements of Article 123(2) EPC.

Extension of scope of protection (Article 123(3) EPC)

14. Paragraph [0017] of the patent as granted contains the following statement: "US patent 5480968 discloses the erbB3 polypeptide, and antisera raised against specific peptides from that polypeptide, one of which comes from the extracellular domain. However, while it mentions possible uses of the antibodies in therapy and detection of erbB3, it does not mention any effect on the action of heregulin, and indeed does not recognize its existence. It is not known whether **the antiserum to the extracellular domain** would intrinsically have such a property, **but it is in any case disclaimed herein from the claims directed to the antibodies per se.**" (Emphasis added by the board, the last passage being the Disclaimer - see point VI, above).
15. This must be read in the context of granted claim 1 (which is identical to claim 1 of the main request before the board), which reads as follows: "1. An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3."
16. As part of the appellant-patentee's main request it is sought to delete the Disclaimer. The issue is whether, because of the Disclaimer, the scope of the granted claims, in particular claim 1, did not extend to the "antiserum to the extracellular domain" referred to in paragraph [0017] of the granted specification and, if did not do so, whether the removal of the Disclaimer from the description would have the effect of extending

the scope of protection conferred by the granted patent to include this subject-matter, contrary to Article 123(3) EPC.

17. The extent of the protection conferred by a European patent is to be determined by the claims (Article 69(1) EPC), which should define the matter for which protection is sought (Article 84 EPC). The description and drawings should be used to interpret the claims (Article 69(1) EPC). To "interpret" claims means to determine their meaning, something which is typically necessary in the case of an ambiguity.
18. In the present case, claim 1 of the granted patent is clear and would have presented no ambiguity to the skilled person when seeking to understand its scope. It is not suggested otherwise. Thus, there is no need to resort to the description to interpret claim 1.
19. The appellant-opponents referred to decision T 500/01 of 12 November 2003 to support the submission that claim 1 had to be interpreted in the light of paragraph [0017] of the description and that deleting the Disclaimer would therefore alter the meaning of the claim. In that case, however, the board noted that a patent might be its own dictionary and might define technical terms, and so determine how a skilled person has to interpret a specific word when used in the description or in the claims (point 6 of the reasons). The present board does not doubt this but the present case is different. The description does not purport to contain a definition of a term used in the claims.
20. The board therefore concludes that Article 123(3) EPC is not infringed by the amendment.

Sufficiency of disclosure (Article 83 EPC)

21. The subject-matter of claim 8 refers to antibodies binding to the epitope bound by the 8B8 antibody. The preparation of these antibodies requires the expression and purification of the ErbB3 antigen to immunise a mouse to obtain anti-ErbB3 antibodies by the hybridoma technology. Finally a cross-blocking assay is used to screen and to identify among the antibodies obtained those competing with the 8B8 antibody for the same binding site on ErbB3. The description of the patent in suit discloses sources for ErbB3 (see paragraph 4), the hybridoma technology (see paragraphs 62 to 66) and the cross-blocking assay (see paragraph 93). Hence, the patent in suit provides a complete teaching of the technology required for the skilled person to obtain further antibodies falling within the scope of present claim 8.

22. The appellant-opponents argued that the antibodies according to claim 8 could only be obtained with undue burden and referred to the declaration D35.

The declaration indeed emphasizes that several months would be necessary to produce these antibodies, but acknowledges (i) that nothing else than standard technology would be required for their production (see points 1 to 5 of document D35) and (ii) that the skilled person would be able to achieve this task (see page 2, last paragraph of document D35). In the board's view while this evidence may demonstrate that the preparation of antibodies binding to the epitope of the 8B8 antibody is time-consuming, it does not show that the amount of time needed for their generation is so

high that they could only be produced with undue burden.

23. The subject-matter of claim 17 refers to the second medical use of the antibodies of claims 1 to 10. The antibodies according to claims 8 and 10, *i.e.* antibodies binding to the same epitope as the 8B8 antibody or having the same CDRs as the 8B8 antibody therefore concern the same use as the antibodies of present claim 17. The appellant-opponents argued that the patent in suit did not show that the 8B8 antibody has all of the properties of the antibodies of the invention, *i.e.* in particular that it reduced a heregulin-induced complex formation between ErbB2 and ErbB3 and reduced ErbB2 activation. However, these properties were required to establish that the antibodies of claims 8 and 10 are suitable for the treatment of the disorders according to claim 17.
24. It is established jurisprudence of the Boards of Appeal that a claim to a second medical use meets the requirements of sufficiency of disclosure only if there is evidence either in the patent and/or in the available prior art showing that the product referred to in the claim is indeed suitable for its claimed therapeutic application (see Case Law of the Boards of Appeal, edition 7, chapter II.C.6.2, first paragraph).
25. While the patent in suit discloses data for the 8B8 antibody which show an increased binding affinity of heregulin to ErbB3 upon 8B8 binding (see figure 1), it does not in fact show that the 8B8 antibody also has the other properties of the antibodies of the invention (see point 23 above).
There are however, experimental data in the patent disclosing all these three functional properties for

the 3-8D6 antibody (see paragraphs 176 to 178 and figure 1 of the patent in suit). Both antibodies, 3-8D6 and 8B8, were initially screened and selected because they increased the binding affinity of heregulin to ErbB3 (see paragraph 178 and figure 1 of the patent).

For the board this is an indication that they bind to the same or at least to neighboring epitopes on ErbB3, which in turn suggests that the two antibodies also have the two other properties in common, *i.e.* the reduction of the heregulin-induced complex formation between ErbB2 and ErbB3 and the reduction of ErbB2 activation. This is indeed confirmed by document D33 for the 8B8 antibody (see figure 1B and figure 2B).

26. Thus on the basis of the available evidence the board considers that the 8B8 antibody is a suitable candidate for the treatment of the disorders according to claim 17. Consequently, antibodies binding to the same epitope as the 8B8 antibody (claim 8) and antibodies having the CDRs of the 8B8 antibody (claim 10) also have to be considered as suitable candidates.
27. Hence, the appellant-opponents' case is not persuasive.
28. The requirements of Article 83 EPC are therefore met.

Novelty (Article 54 EPC)

Prior use

29. In G 1/92 (published in OJ EPO, 1993, 277) the Enlarged Board of Appeal concluded that the chemical composition of a product is state of the art when the product as such is available to the public and can be analysed and

reproduced by the skilled person, irrespective of whether or not particular reasons can be identified for analysing the composition (see the conclusion).

30. The appellant-opponents argued that the subject-matter of claim 1 was not novel in view of different anti-ErbB3 antibodies known at the priority date, such as SGP-1, E3-1 or S3, S4 and S5 (see documents D12, page 6 to 11 and D33, figures 1A, 1B, 2A and 2B; D43 and D44).
31. As to the SGP-1 antibody, documents D43 and D44 show that this antibody was sold by Oncogene Science Inc. before the priority date of the patent in suit. There is no dispute that in 1994 Iowa State University received a 100µg sample of this antibody without any legal constraints. The parties also agreed that it could be analysed, because it was known that SGP-1 binds to the extracellular domain of ErbB3 (see document D6, page 88, column 1, second paragraph).

The appellant-patentee disputed however, that the 100µg protein sample was a sufficient quantity to reproduce the SGP-1 antibody and that the technologies available in 1994 were suitable for its reproduction.

32. The reproduction of the SGP-1 antibody would require as a first step the determination of the amino acid sequence of the antibody.
33. Based on declarations D55 and the documents referred to therein and D61 and the scientific publications annexed thereto (documents D63 to D66), the appellant-opponents argued that the skilled person was able to determine the amino acid sequence of the SGP-1 antibody by Edman degradation in 1994.

34. The board observes that all except two publications referred to in declarations D55 and D61 were published before 1994 and can thus be taken to reflect the knowledge of the skilled person concerning protein sequencing by Edman degradation. While documents D63 to D66 disclose the sequencing of proteins having a length comparable to that of the SGP-1 antibody, none of the documents referred to in the two declarations D55 and D61 disclose the full-length amino acid sequencing of an antibody.
35. Such sequencing was however shown in document D58, submitted by the appellant-patentee, in relation to the OX40L antibody. This document was published in 2006 and thus about 12 years after the relevant date, *i.e.* 1994. The authors of document D58 emphasize that the sequencing of the variable regions of antibodies comprising the CDRs constituted a major scientific challenge. In particular, the unique character of the CDRs renders an alignment and the comparison of the data to already existing antibody sequences in databases impossible. A complete and sufficiently correct amino acid sequence could only be achieved by complementing the data of the Edman sequencing with sequence data obtained independently from mass spectrometry (see document D58, page 77, abstract, page 77, column 1, third paragraph to column 2, third paragraph, page 78, column 2, first paragraph, page 82, column 2, third paragraph to page 83, column 2, first paragraph).
36. Therefore, only the combined use of Edman degradation together with mass spectroscopy would have generated enough complementary sequence data to provide a complete and correct amino acid sequence of the OX40L antibody. On balancing the evidence, the board is not

- persuaded that the skilled person could have correctly determined the amino acid sequence of the SGP-1 antibody with the knowledge and the technologies available in 1994 - even assuming 100µg were a sufficient quantity.
37. In addition, the board notes that for the reproduction of the SGP-1 antibody it would further be necessary to back-translate the obtained amino acid sequence into its corresponding nucleic acid sequence for the expression in a host cell. This host cell must be one which produces the same glycosylation pattern as the hybridoma cell line by which the SGP-1 antibody is produced. In this latter respect it is noted that the SGP-1 hybridoma cell line was not even publicly available in 1994.
38. In view of these observations, the board concludes that the SGP-1 antibody could not be reproduced in 1994 in the sense required by G 1/92. This conclusion also applies to the other anti-ErbB3 antibodies referred to by the appellant-opponents, such as E3-1, S3, S4 and S5.
39. Consequently, none of these antibodies is considered as belonging to the state of the art and these antibodies are not prejudicial to the novelty of the antibodies of present claim 1.
40. The appellant-opponents further argued that the antagonistic anti-ErbB3 antibodies of document D8 were disclosed in an enabling manner because (i) this document disclosed a process for the production of these antibodies and (ii) the skilled person knew from the common general knowledge at the priority date that heregulin was in fact the ligand for ErbB3.

41. The first passage cited by the appellant-opponents in support of their argument is in column 9, lines 16 to 26 of document D8 and reads as follows:

*"This invention additionally provides a method of decreasing a biochemical or biological activity mediated by the erbB-3 receptor, comprising blocking the binding of an erbB-3 activating ligand with the erbB-3 receptor. The blocking can be accomplished by an **antibody** reactive with the ligand binding domain of the erbB-3 receptor".* (Emphasis added by the board).

Thus, this passage refers indeed to an **antagonistic anti-ErbB3 antibody**.

The second passage referred to by the appellant-opponents is in column 26, lines 39 to 42 of document D8 and reads:

*"The triggering or blocking of erbB-3 activation can be detected by comparing the level of erbB-3 tyrosine phosphorylation in the cell line after exposure to the potential **ligand** source with the normal level, e.g., the level obtained after exposure to the control medium."* (Emphasis added by the board).

This disclosure refers to a binding assay having the purpose of identifying a **potential but yet unknown ligand** activating or blocking the ErbB3 receptor. Hence, this passage does not disclose a process for the preparation of an antagonistic anti-ErbB3 antibody. For this reason alone, document D8 cannot be considered as constituting an enabling disclosure for antagonistic anti-ErbB3 antibodies.

42. The question whether or not it was common general knowledge at the priority date that heregulin was the ErbB3 ligand need not therefore be considered. The board observes however that the information content of a document consists of what the skilled person would derive from it at its publication date (see Case Law of the Boards of Appeal, 7th edition 2013, I.C.1.1). At the publication date of document D8 it was neither explicitly nor implicitly derivable from its disclosure content that heregulin was the ErbB3 ligand. Thus, reading the information of documents D1 and/or D23 into document D8, as proposed by the appellant-opponents, would change its information content in an impermissible manner.

43. Hence the subject-matter of claims 1 to 17 is novel.

Inventive step (Article 56 EPC)

44. The present invention relates to anti-ErbB3 antibodies which are functionally defined by their ability to reduce (i) heregulin induced ErbB2-ErbB3 complex formation and (ii) ErbB2 activation.

Closest prior art

45. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal normally apply the "problem and solution" approach and this board will do the same in the present case. It requires as a first step the identification of the closest prior art. This is generally 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 technical

features in common, *i.e.* requiring a minimum of modifications (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.3.1).

46. The appellant-patentee considered document D8 and the appellant-opponents either document D5 or D8 as the closest prior art document.
47. Document D5 discloses antibodies binding to ErbB2 (page 1458, column 2, third paragraph). They reduce (i) heregulin-induced ErbB2-ErbB3 complex formation (page 1463, column 2, first paragraph) and (ii) ErbB2 activation (figure 1) and have thus the same functions as the anti-ErbB3 antibodies of claim 1.
48. Document D8 discloses antibodies binding to ErbB3, but does not disclose that they have either of the two functions (i) and (ii) of the antibodies of claim 1 (see also points 41 and 42 above).
49. Hence, in view of the criteria established by the case law for the determination of the closest prior art document, the board concludes that document D5 represents the closest prior art document.

Problem and solution

50. There is no evidence before the board that the anti-ErbB3 antibodies of the present invention have superior activities in reducing the heregulin-induced ErbB2-ErbB3 receptor heterodimerisation or ErbB2 activation compared to the anti-ErbB2 antibodies disclosed in the closest prior art document D5. The objective technical problem in view of document D5 can thus be seen as the provision of alternative antibodies interfering with

the formation of the ErbB2-ErbB3 receptor complex thereby reducing the activity of ErbB2.

51. The board considers the problem to be plausibly solved by the subject-matter of claim 1 in view of the data provided in the patent for the antibody 3-8D6 (see paragraphs 176 and 177 of the patent and point 23 above).

Obviousness

52. The question then is whether it would have been obvious to the skilled person, when faced with the problem of providing alternative antibodies interfering with the formation of the ErbB2-ErbB3 receptor complex, thereby reducing the activity of ErbB2, would have been motivated to provide antibodies directed to ErbB3 instead of ErbB2 as disclosed in document D5.
53. Document D5 discloses a study aimed at determining the responsiveness to heregulin ("*HRG*") of a panel of human breast and ovarian cell lines with known ErbB2 levels (see the Abstract). In the course of this study antibodies directed against ErbB2 were used to determine if ErbB2 was essential in mediating heregulin interactions with ErbB3 or ErbB4.

From the disclosure in document D5 the mechanism of how heregulin triggers ErbB2-ErbB3 receptor formation and ErbB2 activation is derivable. In an initial step heregulin binds to the medium-affinity ErbB3 receptor (and not to the ErbB2 receptor). Upon this binding, ErbB3 dimerises with ErbB2 to form a heregulin-receptor complex with high affinity for heregulin (see page 1458, column 2, lines 20 to 23; page 1463, column 1, first paragraph to column 2, second paragraph). The

formed complex activates the tyrosine kinase domain of ErbB2 which in a last step activates ErbB3 by trans-phosphorylation (see page 1463, column 2, second paragraph).

Thus, document D5 teaches that successful ErbB2-ErbB3 complex formation requires the presence of heregulin and that ErbB2 activation cannot occur without the previous complex formation between ErbB2 and ErbB3. It also teaches that the disclosed anti-ErbB2 antibodies act by inhibiting the recruitment of ErbB2 to the high-affinity ErbB2-ErbB3 complex thereby interrupting complex formation and preventing ErbB2 activation (see page 1463, column 2, lines 15 to 18).

54. The authors of document D5 conclude on page 1457, last sentence of the "introduction" that the studies reported "suggest that development of HRG antagonists or **compounds that target HRG receptors** may find clinical utility in the treatment of a number of important human cancers", and on page 1464 at the bottom of column 1 that "**antibodies**" interrupting the heregulin induced ErbB2-ErbB3 activation "will have growth inhibitory effects" (Emphasis added by the board).
55. In the board's opinion, the skilled person would understand from the passages referred to in points 53 and 54 above that the blocking of the ErbB2-ErbB3 activation pathway can be achieved not only by antibodies binding to ErbB2 but also by other compounds capable of interfering with steps in the ErbB2-ErbB3 receptor activation, such as, for example, antibodies interfering with the initial step of the receptor activation, namely the binding of heregulin to ErbB3. It follows that the skilled person would have been

motivated to solve the problem of providing alternative antibodies interfering with the formation of the ErbB2-ErbB3 receptor complex, thereby reducing the activity of ErbB2, by providing antibodies interfering with the binding of heregulin to ErbB3.

56. The appellant-patentee's argument that the different functions of ErbB2 and ErbB3 in the ErbB2-ErbB3 receptor complex did not allow a prediction about the effect of an anti-ErbB3 antibody is not considered as persuasive. The individual functions of ErbB2 and ErbB3 in heregulin-induced receptor complex formation and activation were known from document D5, knowledge which renders the consequences of an interference at each step of this process predictable.
57. It follows from the conclusions above that the skilled person would have arrived at the subject-matter of claim 1 in an obvious manner. Claim 1 does therefore not fulfil the requirements of Article 56 EPC.

Auxiliary Requests 1 to 3

Admissibility

58. These auxiliary requests correspond to auxiliary requests 4 to 6 filed with the statement of grounds of appeal with the exception that the present requests comprise an amended page 3 of the description from which the Disclaimer has been deleted. This amended page 3 of the description was only filed at the oral proceedings.
59. A correspondingly amended page 3 of the description was part of the appellant-patentee's first auxiliary

request (now the main request), which was filed with the statement of grounds of appeal. The board has decided in relation to the main request (see point 20 above) that the deletion of the Disclaimer does not have any effect on the interpretation of the claims (see points 17 and 18 above).

60. Hence, the amendment did not provoke unexpected or complex technical or legal issues. Consequently, the board decided to admit auxiliary requests 1 to 3 into the proceedings.

Auxiliary Request 1

Amendments (Article 123(2) EPC)

Claim 1

61. The subject-matter of claim 1 of auxiliary request 1 differs from claim 1 of the main request by the additional functional limitation "wherein the reduction in (i) is at least 70% as determined by reflectance scanning densitometry of Western blots of the complex, and the reduction in (ii) is at least 70% as determined by reflectance scanning densitometry of Western blots of the complex probed with an anti-phosphotyrosine antibody". The appellant-patentee indicated as a basis for this amendment page 5, lines 10 to 17 and lines 18 to 30 of the application as filed. These passages read as follows:

"The expression "reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3" refers to the ability of the antibody to statistically significantly reduce the

number of ErbB2-ErbB3 protein complexes which form in a cell which has been exposed to the antibody and HRG **relative to an untreated (control) cell**. The cell which expresses ErbB2 and ErbB3 can be a naturally occurring cell or cell line (e.g. Caov3 cell) or can be recombinantly produced by introducing nucleic acid encoding each of these proteins into a host cell. Preferably, the antibody will reduce formation of this complex by at least 50%, and more preferably at least 70%, as determined by reflectance scanning densitometry of Western blots of the complex (see the Example below)." (Emphasis added by the board).

"The antibody which "reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3" is one which statistically significantly reduces tyrosine phosphorylation activity of ErbB2 which occurs when HRG binds to ErbB3 in the ErbB2-ErbB3 protein complex (present at the surface of a cell which expresses the two receptors) **relative to an untreated (control) cell**. This can be determined based on phosphotyrosine levels in the ErbB2-ErbB3 complex following exposure of the complex to HRG and the antibody of interest. The cell which expresses ErbB2 and ErbB3 protein can be a naturally occurring cell or cell line (egg Caov3 cell) or can be recombinantly produced. ErbB2 activation can be determined by Western blotting followed by probing with an anti-phosphotyrosine antibody as described in the Example below. Alternatively, the kinase receptor activation assay described in WO 95/14930 and Sadick et al.. Analytical Biochemistry, 235:207-214 (1996) can be used to quantify ErbB2 activation. Preferably, the antibody will reduce heregulin-induced ErbB2 activation by at least 50%, and more preferably at least 70%, as determined by reflectance scanning densitometry of

Western blots of the complex probed with an anti-phosphotyrosine antibody (see the Example below)."

(Emphasis added by the board).

62. It is derivable from these passages that the determination of the percentage in reducing the ErbB2-ErbB3 complex formation and in reducing the ErbB2 activation is made in relation to a control sample - (see passages in bold above). Hence, the 70% reduction according to the description is a **relative** quantitative value determined by reflectance scanning densitometry of Western Blot signals. This is not so in the context of claim 1 where, due to the absence of a reference to a comparison with a control sample, the value is taken to be **absolute**.
63. The board's view that, depending on the experimental set up, the result of the determination by reflectance scanning densitometry of a Western blot may be expressed either in relative or in absolute quantitative terms, is confirmed by declaration D45 filed by the appellant-patentee in support of the reliability of this method. It stated that the assays disclosed in the patent only required the determination of a relative value by the scanning of the Western blot and not an absolute quantitative value (see declaration D45, points 6 and 17).
64. Consequently, the board concludes that claim 1 relates to subject-matter which extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

Auxiliary Request 2

Clarity, support (Article 84 EPC)

Claim 1

65. The ErbB3 antibody is defined in claim 1, *inter alia*, by the feature "wherein the reduction in (i) is at least 70% of the number of ErbB2-ErbB3 complexes which form in a cell which has been exposed to the antibody and heregulin relative to an untreated control cell, as determined by reflectance scanning densitometry of Western blots of the complex, and the reduction in (ii) is at least 70% reduction of tyrosine phosphorylation activity of ErbB2 which occurs when heregulin binds to ErbB3 in the ErbB2-ErbB3 protein complex relative to an untreated control cell, as determined based on phosphotyrosine levels in the ErbB2-ErbB3 complex following exposure of the complex to heregulin and the antibody of interest, and as determined by reflectance scanning densitometry of Western blots of the complex probed with an anti-phosphotyrosine antibody and wherein the cell which expresses ErbB2 and ErbB3 is a Caov3 cell".
66. Article 84 EPC stipulates that the claims shall define the matter for which protection is sought and that they shall be, *inter alia*, clear.
67. A claim defining a product by a parameter is, in accordance with the established jurisprudence of the Boards of Appeal, only clear if the parameter can be clearly and reliably determined - whether the method of determination is included in the claim or not (see Case Law of the Boards of Appeal, edition 7, chapters II.A.3.1, third paragraph and II.A.3.5, first paragraph). In

the present case the method of determination "as determined by reflectance scanning densitometry of Western blots of the complex probed with an anti-phosphotyrosine antibody and wherein the cell which expresses ErbB2 and ErbB3 is a Caov3 cell" is part of the claim.

68. There is statistically verified evidence before the board that in 2009, and thus 13 years after the relevant date, the method of claim 1 still produced contradictory results (see document D53, page 1853, column 1, second paragraph). This cannot only be attributed, as alleged by the appellant-patentee, to the varying amounts of Caov3 cells or heregulin used in the method. Also the different hardware and software of the reflectance scanning densitometry used for the determination of the results obtained is considered to be responsible for these variations (see document D53, page 1845, abstract, page 1853, column 2, first paragraph to page 1855, column 1, first paragraph).
69. The method recited in claim 1 does not define any of these relevant conditions.

Therefore, in view of this evidence, the board considers that the skilled person cannot clearly and reliably determine the parameters at issue, *i.e.* that "(i) the reduction is at least 70% of the number of ErbB2-ErbB3 complexes which form in a cell which has been exposed to the antibody and heregulin relative to an untreated control cell, as determined by reflectance scanning densitometry of Western blots of the complex, and that (ii) the reduction in is at least 70% reduction of tyrosine phosphorylation activity of ErbB2 which occurs when heregulin binds to ErbB3 in the ErbB2-ErbB3 protein complex relative to an untreated

control cell, as determined based on phosphotyrosine levels in the ErbB2-ErbB3 complex following exposure of the complex to heregulin and the antibody of interest, and as determined by reflectance scanning densitometry of Western blots of the complex probed with an anti-phosphotyrosine antibody".

70. Consequently, the subject-matter of claim 1 cannot be considered as defined in a clear way, contrary to the requirements of Article 84 EPC.

Auxiliary Request 3

Amendments (Article 123(2) EPC)

71. The subject-matter of claim 1 of auxiliary request 3 is a combination of the subject-matter of claim 1 of the main request and its dependent claim 2. The subject-matter of present claim 1 is thus the same as that of claim 2 of the main request. In point 5 above the board has decided that claim 2 of the main request does not contravene the requirements of Article 123(2) EPC. Hence, the same conclusion applies to claim 1 of the present request.

72. The subject-matter of claims 1 to 16 fulfils the requirements of Article 123(2) EPC

Clarity, support (Article 84 EPC), sufficiency of disclosure (Article 83 EPC) and novelty (Article 54 EPC)

73. The appellant-opponents did not raise objections pursuant to Articles 54, 83 or 84 EPC against any of

the sixteen claims of auxiliary request 3. The board also has no objections.

74. The subject-matter of claims 1 to 16 thus meets the requirements of Articles 84, 83 and 54 EPC.

Inventive step (Article 56 EPC)

Claim 1

Closest prior art, problem and solution

75. The subject-matter of claim 1 of this request differs from claim 1 of the main request by the inclusion of the additional feature "which further increases the binding affinity of heregulin for ErbB3 protein" (feature (iii)).

76. In the board's view, despite this difference, for the reasons given in points 45 to 51 above, the findings in relation to the main request with regard to the closest prior art, the problem to be solved and its solution apply equally to claim 1 of this request.

Obviousness

77. The question is then whether the skilled person, faced with the problem of providing alternative antibodies interfering with the formation of the ErbB2-ErbB3 receptor complex thereby reducing the ErbB2 activity, would have been motivated to provide antibodies directed to ErbB3 having the function of increasing the binding affinity of heregulin for ErbB3.

78. As outlined above, document D5 discloses not only a model of how heregulin-induced ErbB2-ErbB3 receptor dimerisation and activation works but also provides a motivation to look for alternative antibodies inhibiting this heregulin-induced receptor complex formation (see points 53 and 54).

Document D5 thereby suggests that antagonistic anti-ErbB2 antibodies inhibit ErbB2-ErbB3 receptor complex formation by preventing the recruitment of ErbB2. It also suggests that antibodies may be used that interfere with the the binding of heregulin to its receptor ErbB3 (see point 55 above).

79. The antibodies of present claim 1 interfere with the binding of heregulin to ErbB3. Yet they do not inhibit or reduce its binding but, on the contrary, they stimulate it by "increasing the binding affinity of heregulin for ErbB3".

Document D5 does not provide any hint for the skilled person that the provision of antibodies with this particular property could be a solution to the problem mentioned above.

80. In fact, in view of the model for heregulin-induced ErbB2-ErbB3 receptor complex formation in document D5, the skilled person would rather expect that antibodies **increasing** the binding affinity of heregulin to ErbB3 would promote receptor complex formation and ErbB2 activation rather than reducing the receptor complex formation and reducing ErbB2 activation.

81. The appellant-opponents argued that the property of the antibodies of claim 1 of increasing the binding affinity of heregulin for ErbB3 was unrelated to other

properties of the antibodies, *i.e.* the reduction of the formation of the ErbB2-ErbB3 complex and of ErbB2 activation. Therefore, the claimed subject-matter was obvious for the same reasons as that for the main request. Decision T 735/00 of 23 March 2004 was cited in support of this argument.

82. However, according to the model derivable from document D5 the binding of ErbB2 to ErbB3 increases the binding affinity of heregulin (see point 53 above). So far as concerns the functioning of the antibodies of claim 1 this implies, in the board's view, that: (a) on the one hand, they "mimic" the binding of ErbB2 to ErbB3, a conclusion which explains the increase in the binding affinity of heregulin, and (b) on the other hand, they prevent the binding of ErbB2 to ErbB3 to form the receptor complex which is responsible for the reduction of ErbB2 activation (see paragraph 183 of the patent). These observations show that the antibodies of claim 1 in fact have three distinct functions forming a functional unit, a common property which the antibodies of claim 1 of the main request do not have.

Antibodies with the functional properties of the claimed antibodies were not known from the prior art. The present situation thus differs from the one dealt with in decision T 735/00. In that case antibodies having the same unexpected property as that of the claimed antibodies were already known (see T 735/00, point 29 of the reasons). Hence, the appellant-opponent's argument that the subject-matter of claim 1 should be held obvious for the same reasons as that of the main request is not persuasive.

83. It was further asserted by the appellant-opponents that the anti-ErbB3 antibody-caused an increase in the binding affinity of heregulin to ErbB3 is an artificial effect because it was only detected in a cell system which lacked ErbB2 (see paragraph 178 of the patent in suit) which is in contrast to physiological conditions where ErbB2 is always present.

Document D50 shows that the antibody 8B8 and other antibodies binding to its epitope reduce ErbB2-ErbB3 receptor complex formation and ErbB2 activation in cells where ErbB2 is present, while at the same time increasing the binding affinity of heregulin to ErbB3 (see document D50, points 7, 8 and figure A). Hence, the board cannot agree with the appellant-opponents' argument.

84. With regard to the subject-matter of claim 7, the appellant-opponents argued that it related to antibodies which do not increase the binding affinity of heregulin to its receptor. An undefined sterical interference outside of the CDR binding region of these antibodies could prevent them from binding to the epitope of the antibody 8B8. Thus, the subject-matter of claim 7 related to antibodies which did not solve the problem formulated above.

85. Document D50 shows that all the antibodies competing with the 8B8 antibody for its binding site (epitope) at the same time increase the binding affinity of heregulin to its receptor (see points 7, 8 and figure A). In view of this fact and the generally accepted principle that the functional properties of an antibody are determined by the binding to its epitope (see point 7, above) the board cannot accept to the appellant-opponents' argument.

86. In conclusion, the board considers that the subject-matter of claim 1 and, for the same reasons, the subject-matter of claim 7 involve an inventive step. This applies equally to the subject-matter of the dependent claims 2 to 6, and 8 to 16.

87. The requirements of Article 56 EPC are thus met.

Conclusion

88. Since the appellant-patentee's main request and its first and second auxiliary requests have been found not to be allowable it follows that the appellant-patentee's appeal must be dismissed. Since the appellant-patentee's third auxiliary request has been found to be allowable it follows that the appellant-opponents' appeals must be dismissed.

Order

For these reasons it is decided that:

The appeals of all parties are dismissed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated