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Datasheet for the decision of 12 July 2022

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Application Number: 11802372.0

Publication Number: 2655412

IPC: C07K16/00, C07K16/32, C07K16/18, C07K16/30

Language of the proceedings: EN

Title of invention:
Isoform enriched antibody preparation and method for obtaining it

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponent:
Bayer Intellectual Property GmbH

Headword:
Antibody chromatography/ROCHE

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Main request and auxiliary requests 1 to 26: Amendments - added subject-matter (yes)

Decisions cited:
G 0009/91, G 0010/91

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Case Number: T 1683/20 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 July 2022

Appellant: (Opponent)	Bayer Intellectual Property GmbH Alfred-Nobel-Straße 10 40789 Monheim (DE)
Representative:	Viering, Jentschura & Partner mbB Patent- und Rechtsanwälte Hamborner Straße 53 40472 Düsseldorf (DE)
Respondent: (Patent Proprietor)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
Representative:	Boult Wade Tennant LLP Salisbury Square House 8 Salisbury Square London EC4Y 8AP (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 June 2020 concerning maintenance of the European Patent No. 2655412 in amended form**

Composition of the Board:

Chair	M. Blasi
Members:	O. Lechner
	B. Rutz

Summary of Facts and Submissions

I. The opponent's ("appellant") appeal lies from the opposition division's decision ("decision") that European patent No. 2 655 412 ("patent"), as amended in the form of the main request, and the invention to which it relates meet the requirements of the EPC.

II. The patent is based on European patent application No. 11 802 372.0 ("application as filed") filed on 19 December 2011.

III. An opposition had been filed invoking the grounds of lack of inventive step (Article 56 EPC) under Article 100(a) EPC, as well as the grounds under Article 100(b) and (c) EPC.

IV. With the statement of grounds of appeal, the appellant raised objections *inter alia* as to added subject-matter (Article 123(2) EPC), insufficiency of disclosure (Article 83 EPC), non-entitlement to the priority claimed (Article 89 EPC) and lack of inventive step (Article 56 EPC).

V. The patent proprietor ("respondent") replied and submitted sets of claims of a main request (identical to the claims of the main request considered in the decision under appeal) and of auxiliary requests 1 to 26, which are identical to those filed on 24 December 2019 during the opposition proceedings.

VI. The board summoned the parties to oral proceedings as requested and subsequently issued a communication pursuant to Article 15(1) RPBA providing the board's preliminary opinion *inter alia* on claim construction

and on added subject-matter in relation to the main request and auxiliary requests.

VII. The oral proceedings before the board took place on 12 July 2022 as a videoconference.

During the oral proceedings the respondent promoted auxiliary request 3 to auxiliary request 1 and auxiliary request 26 to auxiliary request 2, and renumbered the remaining requests accordingly.

At the end of the oral proceedings, the Chair announced the board's decision.

VIII. Claim requests

(a) Main request

Claim 1 reads as follows:

"1. A method for producing an antibody preparation comprising the following steps:

(a) applying a buffered solution comprising different isoforms of an antibody to a cation exchange chromatography material,

(b) applying a first solution with a first conductivity to the cation exchange chromatography material, whereby the antibody isoforms remain adsorbed to the cation exchange chromatography material,

(c) applying a second solution with a second conductivity to the cation exchange chromatography material and thereby obtaining the antibody preparation with enriched antibody isoforms,

wherein the conductivity of the second solution exceeds the conductivity of the first solution by not more than 10 %,
wherein the cation exchange chromatography material has a swellable matrix,
wherein the first solution is changed to the second solution in a single step,
wherein the conductivity of the first solution is of from 4 mS/cm to 5 mS/cm, and
wherein the buffered solution is a citrate buffered solution."

(b) Auxiliary request 1

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request, but with the following amendment (difference to the main request underlined by the board):

"[...] wherein the first solution is changed to the second solution in a single step that is a change from 100 vol% of the first solution to 100 vol% of the second solution, [...]"

(c) Auxiliary request 2 (one claim only; differences to claim 1 of the main request underlined by the board):

"1. A method for producing an antibody preparation comprising the following steps:
(a) applying a buffered solution comprising different isoforms of an antibody to a column having a cation exchange chromatography material,
(b) applying a first solution with a first conductivity to the cation exchange chromatography material, whereby the antibody isoforms remain

adsorbed to the cation exchange chromatography material,
(c) applying a second solution with a second conductivity to the cation exchange chromatography material and thereby obtaining the antibody preparation with enriched antibody isoforms,

wherein the antibody is the anti-HER2 antibody trastuzumab,
wherein the conductivity of the second solution exceeds the conductivity of the first solution by not more than 10 %,
wherein the first solution is 20 mM sodium citrate, adjusted to pH 6.2
wherein the second solution is 20 mM sodium citrate, adjusted to pH 6.2 and supplemented with 5 mM sodium chloride;
wherein the cation exchange chromatography material has a swellable matrix that is Highscreen SP-Sepharose,
wherein the first solution is changed to the second solution in a single step,
wherein the single step is a change from 100 vol% of the first solution to 100 vol% of the second solution,
wherein the second solution is used to elute the antibody preparation over 20 column volumes,
wherein the conductivity of the first solution is of from 4 mS/cm to 5 mS/cm, and
wherein the buffered solution is a citrate buffered solution consisting of 20 mM sodium citrate, adjusted to pH 6.2."

(d) Auxiliary request 3

Claim 1 of auxiliary request 3 is identical to claim 1 of the main request except for the following amendment

(difference to the main request underlined by the board):

"wherein the conductivity of the second solution exceeds the conductivity of the first solution by at least 1% but not more than 10%".

(e) Auxiliary request 4

Claim 1 of auxiliary request 4 is identical to claim 1 of the main request, but additionally specifies "wherein the antibody is an IgG,".

(f) Auxiliary request 5

Claim 1 of auxiliary request 5 is identical to claim 1 of the main request, but additionally specifies that "the cation exchange chromatography material has a swellable matrix that is agarose," (difference underlined by the board).

(g) Auxiliary request 6

Claim 1 of auxiliary request 6 is identical to claim 1 of the main request, but additionally specifies that the cation exchange chromatography material is a strong cation exchange chromatography material.

(h) Auxiliary request 7

Claim 1 of auxiliary request 7 is identical to claim 1 of the main request, but has been amended such that the method is defined as "consisting of" the recited steps, rather than "comprising" them.

(i) Auxiliary request 8

Claim 1 of auxiliary request 8 is identical to claim 1 of auxiliary request 3, but additionally specifies that "the antibody is an IgG,".

(j) Auxiliary request 9

Claim 1 of auxiliary request 9 is identical to claim 1 of auxiliary request 3 except for the following amendment (difference underlined by the board): "wherein the first solution is changed to the second solution in a single step that is a change from 100 vol% of the first solution to 100 vol% of the second solution,".

(k) Auxiliary request 10

Claim 1 of auxiliary request 10 is identical to claim 1 of auxiliary request 1, but additionally specifies that "the antibody is an IgG,".

(l) Auxiliary request 11

Claim 1 of auxiliary request 11 is identical to claim 1 of auxiliary request 10 except for the following amendment (difference underlined by the board): "wherein the conductivity of the second solution exceeds the conductivity of the first solution by at least 1% but not more than 10%".

(m) Auxiliary request 12

Claim 1 of auxiliary request 12 is identical to claim 1 of auxiliary request 8, but additionally specifies that "the cation exchange chromatography material has a

swellable matrix that is agarose," (difference underlined by the board).

(n) Auxiliary request 13

Claim 1 of auxiliary request 13 is identical to claim 1 of auxiliary request 3, but additionally specifies that the cation exchange chromatography material is a strong cation exchange chromatography material and that "the cation exchange chromatography material has a swellable matrix that is agarose," (difference underlined by the board).

(o) Auxiliary request 14

Claim 1 of auxiliary request 14 is identical to claim 1 of auxiliary request 1, but additionally specifies that the cation exchange chromatography material is a strong cation exchange chromatography material and that "the cation exchange chromatography material has a swellable matrix that is agarose," (difference underlined by the board).

(p) Auxiliary request 15

Claim 1 of auxiliary request 15 is identical to claim 1 of auxiliary request 9, but has been amended such that the method is defined as "consisting of" the recited steps, rather than "comprising" them.

(q) Auxiliary request 16

Claim 1 of auxiliary request 16 is identical to claim 1 of auxiliary request 9, but additionally specifies that the cation exchange chromatography material is a strong cation exchange chromatography material and that "the

cation exchange chromatography material has a swellable matrix that is agarose," (difference underlined by the board).

(r) Auxiliary request 17

Claim 1 of auxiliary request 17 is identical to claim 1 of auxiliary request 16, but additionally specifies that "the antibody is an IgG,".

(s) Auxiliary request 18

Claim 1 of auxiliary request 18 is identical to claim 1 of auxiliary request 16, but has been amended such that the method is defined as "consisting of" the recited steps, rather than "comprising" them.

(t) Auxiliary request 19

Claim 1 of auxiliary request 19 is identical to claim 1 of auxiliary request 18, but additionally specifies that "the antibody is an IgG,".

(u) Auxiliary request 20

Claim 1 of auxiliary request 20 is identical to claim 1 of the main request.

(v) Auxiliary request 21

Claim 1 of auxiliary request 21 is identical to claim 1 of auxiliary request 3.

(w) Auxiliary request 22

Claim 1 of auxiliary request 22 is identical to claim 1 of auxiliary request 3, but additionally specifies that "the antibody is an IgG,".

(x) Auxiliary request 23

Claim 1 of auxiliary request 23 is identical to claim 1 of auxiliary request 3, but with the following additional amendment (difference underlined by the board): "wherein the first solution is changed to the second solution in a single step that is a change from 100 vol% of the first solution to 100 vol% of the second solution,".

(y) Auxiliary request 24

Claim 1 of auxiliary request 24 is identical to claim 1 of auxiliary request 23, but additionally specifies that the cation exchange chromatography material is a strong cation exchange chromatography material and that "the strong cation exchange chromatography material has a swellable matrix that is agarose" (difference underlined by the board).

(z) Auxiliary request 25

Claim 1 of auxiliary request 25 is identical to claim 1 of auxiliary request 24, but additionally specifies that "the antibody is an IgG,".

(aa) Auxiliary request 26

Claim 1 of auxiliary request 26 is identical to claim 1 of auxiliary request 25, but has been amended such that the method is defined as "consisting of" the recited steps, rather than "comprising" them.

IX. The appellant's submissions relevant to this decision may be summarised as follows:

(a) Main request

Amendments - Article 123(2) EPC - claim 1

Independent claim 1 was based on independent claim 1 of the application as filed in which some arbitrarily selected features from dependent claims 4, 5 and 15 had been incorporated.

Citrate buffered solution

Citrate buffer was selected from a list of alternative buffers mentioned in the paragraph bridging pages 10 and 11 of the application as filed, none being labelled as preferred. None of the examples supported the selection of citrate buffer as loading buffer as claimed. The sample buffer was not defined in the examples, as evidenced by the last paragraph on page 26 of the application as filed.

The first solution is changed to the second solution in a single step

Single-step buffer exchange was disclosed in claim 10 as filed, but this was dependent on claim 9, which provided two options, i.e. a selection from among these

two options was necessary. It was evident that claim 10 of the application as filed only further defined one alternative of claim 9, but did not disclose a selection of that alternative.

It was not evident from the application as filed that a single-step buffer exchange was preferred.
The passage on page 22, lines 19 to 20 stated: "*The method is especially effective by using a gradient with a slight slope* [...]", thus clearly pointing away from using a single-step buffer exchange.

The skilled person would have derived that gradient elution was preferred. For example, page 5, paragraph 3 referred to the use of a gradient with an especially slight slope. The term "especially" was synonymous with "preferred".
Example 7 together with Figure 6 showed that the best separation could be achieved employing gradient elution chromatography. The single-step elution method according to Example 4 showed semi-detached peaks (see Figure 4), i.e. a mixture of isoforms. However, the overall aim of the method was to separate antibody isoforms.
The claimed single-step elution required the selection of a less-preferred, inferior, option.

Obtaining the antibody preparation with enriched isoforms (step (c))

A further selection had to be made between the two options, namely (partial) separation and enrichment, to arrive at the claimed feature "enriched antibody isoforms" (see page 2, paragraph 1 and page 5, lines 8 to 12).

Only a few passages of the application as filed related specifically to enrichment, i.e. page 2, paragraph 1 referred to "*separation and/or enrichment of antibody isoforms*", and page 5, line 8 stated that "*antibody isoforms can be enriched or partially separated*".

Moreover, the feature "enriched" had not been disclosed in the application as filed in combination with the other features of claims 1 and 2. Page 2, paragraph 1 and page 5, lines 8 to 12 of the application as filed disclosed enrichment only in the context of gradient elution and not of stepwise elution.

Furthermore, enrichment was only disclosed in the context of a salt or pH gradient, but not a step elution with a conductivity change. The only other passages disclosing enrichment methods, i.e. those on pages 21 to 22 of the application as filed, related to the enrichment or partial separation of different antibody isoforms from each other.

(b) Auxiliary request 1

Amendments - Article 123(2) EPC - claim 1

Claim 1 of auxiliary request 1 had the same deficiencies under Article 123(2) EPC as claim 1 of the main request. Incorporating the feature "that is a change from 100 vol% of the first solution to 100 vol% of the second solution" from claim 10 of the application as filed did not overcome the necessity of selecting from the two options, gradient elution or single-step elution. The experimental evidence and the description preferred gradient elution as providing better separation of the antibody isoforms.

(c) Auxiliary request 2

Consideration of Article 123(2) EPC

The opposition division's decision dealt only with the main request, which was considered allowable, thus there had been no reason to address the auxiliary requests in the statement of grounds of appeal.

The explanations provided by the respondent on page 48, point 5.10 of its reply to the statement of grounds of appeal for auxiliary request 2 (then auxiliary request 26) were identical to those provided when submitting auxiliary request 7 in March 2019 in the proceedings before the opposition division.
Auxiliary request 2 had not been substantiated since the respondent had never explained how this new claim request would overcome the objections raised in the context of the higher-ranking requests relating to added subject-matter, sufficiency, novelty and inventive step in the statement of grounds of appeal.

No basis in the application as filed had been been provided for the features of the claim.

All objections under Article 123(2) EPC raised against the higher-ranking claim requests essentially also applied in relation to this claim request.

These technical explanations should be considered by the board, and the case should not be remitted to the opposition division. It was for the respondent to provide a proper basis for the claimed subject-matter, and if the respondent's position was that some features of Example 4 could be omitted, the burden of showing

that the features were not linked lay on the respondent.

Amendments - Article 123(2) EPC - claim 1

The method of Example 4 could not be extrapolated to methods for enriching other antibody isoforms. There was, for example, no basis for "a citrate buffered solution consisting of 20 mM sodium citrate adjusted to pH 6.2" in Example 4, on page 28 or anywhere else in the application as filed. Moreover, only certain features of Example 4 had been picked out while other features of the method, such as the flow rate or the amount of protein loaded, had been omitted.
Contrary to the respondent's allegation, these omitted features were also essential since they influenced the resolution properties of the chromatographic method.
The selection of some but not all features from Example 4 represented an intermediate generalisation.
Example 4 did not specify which buffer had been used for loading the chromatographic column, so the citrate buffer solution from page 11, paragraph 1 had to be brought in.

(d) Auxiliary requests 3 to 26

Amendments - Article 123(2) EPC

The subject-matter of claim 1 of these requests extended the content of the application as filed for the same reasons as the main request and auxiliary requests 1 and 2.

X. The respondent's submissions relevant to this decision may be summarised as follows:

(a) Main request

Amendments - Article 123(2) EPC - claim 1

Basis for the features could be found in the application as filed as follows:

- claims 1 and 2 of the application as filed provided the general structure;
- "enriched antibody isoforms" in step (c) found basis on page 2, paragraph 1 and page 5, paragraphs 3 and 4, showing that this step together with a change in conductivity was an integral part of the method;
- "the conductivity of the second solution exceeds the conductivity of the first solution by not more than 10 %" found basis in claim 4 and on page 5, lines 19 to 23;
- the "swellable matrix" found basis in claim 5 and on page 5, lines 22 to 23;
- "is changed to the second solution in a single step" found basis in claims 9 and 10, on page 5, line 28, on page 22, lines 15 to 25 and in Examples 2 to 4, all of which gave preference to single-step elution;
- the "conductivity of the first solution is of from 4 mS/cm to 5 mS/cm" found basis in claim 15 and on page 4, lines 17 to 18;
- the buffered solution being a citrate buffered solution found basis in step (a) of claim 1 and step (b)i) of claim 2 of the application as filed, which already related to "a buffered solution", in combination with the "citrate buffered solution"

provided in the list of buffers on page 10, last paragraph to page 11, paragraph 1.

Citrate buffered solution

To arrive at the claimed subject-matter, it was necessary to select the citrate buffer from a single list of buffers on page 10, last paragraph to page 11, paragraph 1. The appellant was wrong that a selection between "crude and buffered solutions" was required, as both claims 1 and 2 of the application as filed already contained the feature that the solution applied in step (a) or step (b)i), respectively, was a "buffered solution".

No new technical teaching was created, as Examples 2 to 4 clearly related to a single-step buffer exchange and the only buffer being disclosed in these examples was a citrate buffer. Based on these examples, a skilled person would have contemplated using a citrate buffer. According to established case law, a single selection from a list was allowable (see Case Law of the Boards of Appeal, 9th edn., 2019, page 460, decision T 330/05, Reasons 2.3).

The first solution is changed to the second solution in a single step

Claim 9 of the application as filed presented two individualised options for changing the first solution to the second solution: in a single step, or in a linear gradient. A claim reciting two options could not be considered a "list" from which a feature had been artificially singled out.

It was clear from the application as filed that changing the first solution to the second solution in a single step referred to changing the buffer applied to the top of the column to 100% of the second buffer at once. Of course, the exchange of buffer conditions within the column was something different. Single-step buffer exchange was clearly disclosed, e.g. on page 5, lines 28 to 30 and page 22, lines 15 to 25.

Therefore, not only were the present claims directed to methods involving "step elution", but the switch from "wash" to "elute", i.e. from the first solution to the second solution, was carried out in a single step. This was clearly different from a stepped elution process, where the conditions leading to elution are changed via multiple incremental stepwise changes. It was also different from continuous gradient elution.
The application of the second solution was clearly the method step at which the antibodies were eluted.

Claim 10 of the application as filed disclosed a single-step buffer exchange as the single option. Being dependent on claim 9 of the application as filed, claim 10 also comprised all the embodiments of the higher-ranking claims on which it depended.

Even if, *arguendo*, the two options of claim 9 were considered a list that required "selection" of a single-step change, Examples 2 to 4 provided a clear pointer to the use of a single-step change between the first solution and the second solution. Any such "selection" of a single-step change from the features of claim 9 as filed was thus not arbitrary, as this feature was a preferred option in the examples of the application as filed.

Obtaining the antibody preparation with enriched isoforms (step (c))

Enrichment was part of the separation process and not an alternative option.
Page 2, paragraph 1 and page 5, lines 13 to 15 of the application as filed provided basis for this feature. Page 5, lines 13 to 15, reading "*It has been found that the enrichment of antibody isoforms in an antibody preparation is possible by column chromatography with a decent conductivity increase of the mobile phase*.", not only related to gradient elution methods. Page 5, lines 28 to 30 of the application as filed stated that "*The increase can be in form of a single step*", thus methods of the application whereby the conductivity was increased in a single step (including the claimed methods) were disclosed to be for the production of antibody preparations with enriched antibody isoforms.

The passages on pages 21 to 22 of the application as filed, and especially page 21, lines 18 to 28, disclosed a method for enriching antibody isoforms including the requirement "*thereby obtaining the antibody preparation with enriched antibody isoforms*". Since the methods in this passage and the methods of the claims each resulted in obtaining an antibody preparation with enriched antibody isoforms, there was no inconsistency in the application as filed between the claims and this passage in the description.

(b) Auxiliary request 1

Amendments - Article 123(2) EPC - claim 1

The set of claims of auxiliary request 1 differed from that of the main request in that the wording of claim

10 of the application as filed (claim 6 of the main request), i.e. "that the single step is a change from 100 vol% of the first solution to 100 vol% of the second solution", had been added to the feature "wherein the first solution is changed to the second solution in a single step" of claim 1.

The incorporation of claim 10 of the application as filed into claims 1 and 2 resulted in subject-matter that no longer required the elution method to be selected from claim 9 of the application as filed. Claim 10 of the application as filed was dependent on claim 9, which referred back to the method of any one of the preceding claims. Claim 10 made the choice between the two options provided in claim 9. The same embodiment was also individualised on page 5, last paragraph, which made it clear that "single step" referred to a complete change of the elution solution, i.e. from 100% of the first to 100% of the second (= elution) buffer solution. The other features were taken from claim 4 (conductivity of the second solution exceeds the conductivity of the first solution by not more than 10 %), claim 5 (swellable matrix), and claim 15 (the conductivity of the first solution is of from 4 mS/cm to 5 mS/cm) of the application as filed. Thus only one selection, i.e. that of the citrate buffer, from the list of buffers provided in paragraph 1 on page 11 of the application as filed was required, which was permissible under Article 123(2) EPC, as also highlighted in the catchwords of decision T 1621/16.

(c) Auxiliary request 2

Consideration of Article 123(2) EPC

Auxiliary request 2 was identical to auxiliary request 7 as filed in March 2019 in reply to the notice of opposition. The issue of added subject-matter should not be addressed at all because the appellant had not raised any objections under Article 123(2) EPC in relation to auxiliary request 2 either in opposition or in appeal proceedings.

It was only at the oral proceedings in appeal that the appellant had raised an objection under Article 123(2) EPC. The board had not raised an objection under Article 123(2) EPC against auxiliary request 2 in its communication under Article 15(1) RPBA either.

Regarding the appellant's allegation of a lack of substantiation, more explanation than that on page 48 was not required because the claim request had already been presented (as auxiliary request 7) in the opposition proceedings. The appellant had had the opportunity to raise the objections in time.

The objections under Article 123(2) EPC were raised late. The technical explanations presented by the appellant for the first time at the oral proceedings involved complex technical considerations with regard to the various technical features of Example 4 and their connection with each other. These technical explanations should therefore not be admitted into the appeal proceedings.

Amendments - Article 123(2) EPC - claim 1

The sole claim of auxiliary request 2 was directed to a method for producing an antibody preparation incorporating all the essential features taken from the method described in Example 4 (see page 28) of the application as filed.
Features such as the flow rate or the amount of protein loaded were not pertinent and thus not included in the claim.

The use of citrate buffer as loading/sample buffer was fully consistent with the method of Example 4, which also employed citrate buffered solutions for the washing and elution steps. It was evident to the skilled person to use the same buffer system throughout the entire procedure, and this did not create a new teaching.

(d) Auxiliary requests 3 to 26

Amendments - Article 123(2) EPC

The same arguments as for the main request and auxiliary requests 1 and 2 applied.

XI. Relevant requests of the parties for reaching this decision:

(a) The appellant requested that the decision under appeal be set aside and that the patent be revoked.

(b) The respondent requested that:
- the appeal be dismissed, i.e. that the patent be maintained as amended in the form of the main

request considered allowable by the opposition division;

- or alternatively that the patent be maintained in amended form on the basis of one of the sets of claims of
  - auxiliary request 1, filed as auxiliary request 3 with the reply to the statement of grounds of appeal,
  - auxiliary request 2, filed as auxiliary request 26 with the reply to the statement of grounds of appeal,
  - auxiliary request 3, filed as auxiliary request 1 with the reply to the statement of grounds of appeal,
  - auxiliary request 4, filed as auxiliary request 2 with the reply to the statement of grounds of appeal,
  - auxiliary requests 5 to 26, filed as auxiliary requests 4 to 25 respectively with the reply to the statement of grounds of appeal.

Reasons for the Decision

Main request

1. *Claim construction - claim 1*

1.1 In view of the "comprising" language used, the method according to claim 1 does not exclude further steps. The feature that the "conductivity of the second solution exceeds the conductivity of the first solution by not more than 10%" means that the increase in conductivity has to be greater than, but excluding, 0% ("exceeds") and smaller than or equal to 10% ("not more than").

1.2 The board interprets the further feature that the first solution is changed to the second solution in a single step such that the second solution is applied at once, and not in a series of small (i.e. multiple) steps as argued by the appellant. The application of the second solution is the method step at which the antibodies are eluted.

1.3 The claim defines only the "buffered solution", i.e. the loading solution (see claim 1 step (a)), as being a citrate buffered solution. Steps (b) and (c) of claim 1 refer to a first and a second solution but not to a "buffered solution". This is consistent with the wording of claims 7 and 8, which relate to a "first solution" and "second solution" comprising tris (hydroxymethyl) aminomethane TRIS and NaCl (and not a citrate buffered solution).

2. Amendments - Article 123(2) EPC - claim 1

2.1 The appellant submitted that claim 1 was directed to subject-matter extending beyond the content of the application as filed, contrary to Article 123(2) EPC, and referred in particular to the features "citrate buffered solution", "the first solution is changed to the second solution in a single step" and "obtaining the antibody preparation with enriched antibody isoforms".

2.2 With regard to the disclosure of the specific combination of features of claim 1, the respondent argued that the application as filed provided pointers in the form of preferred embodiments which the skilled person would combine in a direct and unambiguous manner.

2.3 The features "citrate buffered solution", "the first solution is changed to the second solution in a single step" and "obtaining the antibody preparation with enriched isoforms" are addressed separately and in combination in the following.

2.4 Citrate buffered solution

2.4.1 Claims 1 and 2 of the application as filed relate to a buffered solution. The paragraph bridging pages 10 and 11 of the application as filed provides a list of buffered solutions "*employed in the method as reported herein*" from which citrate buffer has been selected.

2.4.2 Contrary to what has been argued by the appellant, a further selection between "*crude and buffered solutions*" from the passage on page 10, last paragraph of the application as filed is not required, as feature a) of claim 1 of the application as filed was already directed to "applying a buffered solution".

2.4.3 The respondent argued that a "citrate buffered solution", which the skilled person would combine with other preferred features, was disclosed as preferred.

Examples 2 to 4 disclose a single-step buffer exchange using a citrate buffer for washing and elution. However, the loading/sample buffer to be applied is not specified in these examples.

In Example 6, an affinity chromatography-purified anti-HER2 antibody is used which was eluted from the protein A resin with 10 mM Na citrate buffer, pH 3.0 ± 0.5. Before filtration, the pH value of the antibody-containing fraction is adjusted to pH 5.6 with TRIS buffer. However, in the example a stepwise increase of

the conductivity is used (see also Figure 5) and it is concluded that "*No separation of monomeric and aggregated forms of the antibody was achieved*".

Thus the examples do not provide a pointer to the feature "*applying a buffered solution* [...] *wherein the buffered solution is a citrate buffered solution*" of claim 1 as a preferred feature. A selection of the citrate buffer from a (non-converging) list of alternative buffers provided in the paragraph bridging pages 10 and 11 of the application as filed is required.

2.5 The first solution is changed to the second solution in a single step

2.5.1 The application as filed discloses two options, i.e. the first solution being changed to the second solution in a single step or in a linear gradient (see claim 9 as filed). As set out in point 1.2 above, the board interprets the feature "wherein the first solution is changed to the second solution in a single step" as referring to a change of the buffer applied to the top of the chromatography column to 100% of the second buffer at once. This single-step buffer exchange is directly and unambiguously disclosed, e.g. on page 5, lines 28 to 30 and page 22, lines 15 to 25 of the application as filed.

2.5.2 A single-step buffer exchange is distinct from a stepped elution process, where the conditions leading to elution are changed via multiple incremental stepwise changes. It is also different from continuous gradient elution (see page 5, lines 15 to 21 of the application as filed).

2.5.3 Claim 9 of the application as filed presents two individualised options for changing the first solution to the second solution - in a single step, or in a linear gradient. Selection of the single-step change is required to arrive at the claimed subject-matter.

2.5.4 The respondent argued that the single-step buffer exchange was disclosed as a preferred method in the application as filed, e.g. in claim 10 of the application as filed, which refers to "change from 100 vol% of the first solution to 100 vol% of the second solution". However, this claim only defines more precisely how the "single step" according to claim 9 is to be carried out, and is therefore not an indication that the one-step elution would be a preferred embodiment.

2.5.5 The respondent further argued that Examples 2 to 4 provided a pointer to the use of a single-step exchange between the first solution and the second solution. The "selection" of single-step exchange from the alternatives of claim 9 as filed was thus not arbitrary, as it represented a preferred option in the examples of the application as filed.

The board, however, is not persuaded by this argument. Page 22, lines 17 to 22 of the application as filed explicitly states that enrichment or even partial separation of antibody isoforms by cation exchange chromatography "*can be achieved in a bind-and-elute method using a pH or salt gradient, either linear or step, for recovering of the antibody from the chromatography material. The method is especially effective by using a gradient with a slight slope* [...]". Comparing the results of the single-step elution protocols used in Examples 2 to 4 (see Figures

2 to 4) with those of gradient elution in Example 7 (see Figure 6) also reveals that the gradient elution protocol resulted in better separation of the different antibody isoforms.
Thus there is no pointer in the application as filed to single-step buffer exchange as being preferred over a gradient elution protocol.

2.6 Obtaining the antibody preparation with enriched isoforms (step (c))

2.6.1 The respondent argued that "enrichment" was part of the separation process and could not be considered as an alternative to "separation".

2.6.2 The board agrees with the appellant that "enrichment" and "separation" in the context of the application as filed are not synonyms, and define different results of the chromatographic method. Enrichment refers to the concentration of the antibody isoforms in a preparation, while separation refers to the isolation of the individual isoforms. In the application as filed, this difference has been underlined by using "or" or a slash (which is commonly used in English as a shorter substitute for the conjunction "or") when mentioning the two terms within the same sentence. Thus the selection of the feature "enrichment" requires a further selection from the options "*separation"* or *"enrichment*" disclosed on page 2, paragraph 1 or "*enriched" or "partially separated*" disclosed on page 5, lines 8 to 10, or "*can be enriched or even partially separated*" disclosed on page 22, lines 15 to 16.

2.7 Combination of features

Based on the above considerations, the board is of the opinion that, to arrive at the claimed subject-matter, at least the three features (i) citrate buffer as loading/sample buffer (see point 2.4 above), (ii) single-step buffer exchange (see point 2.5 above) and (iii) enrichment of antibody isoforms (see point 2.6 above) need to be selected and combined. Since none of these features is disclosed as a preferred embodiment, the resulting subject-matter is not directly and unambiguously disclosed in the application as filed. Thus claim 1 contains subject-matter which extends beyond the content of the application as filed, and the main request is not allowable under Article 123(2) EPC.

Auxiliary request 1

3. Amendments - Article 123(2) EPC - claim 1

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request, but additionally specifies that the first solution is exchanged for the second solution in a single step "that is a change from 100 vol% of the first solution to 100 vol% of the second solution". According to the respondent, this amendment addressed the appellant's argument that the conductivity of the second solution was arbitrary. However, the board considers that the wording "wherein the first solution is changed to the second solution in a single step" already implies that the buffer is exchanged at once, rendering the additional clarification "that is a change from 100 vol% of the first solution to 100 vol% of the second solution" redundant. That aside, this amendment does not remedy the lack of basis in the application as filed for the

remaining combination of features, as already established in the context of the main request (see point 2.7 above).
Therefore claim 1 is not allowable under Article 123(2) EPC for the same reasons as the main request.

Auxiliary request 2

4. Consideration of Article 123(2) EPC

4.1 The set of claims of auxiliary request 2 was filed in March 2019 during opposition proceedings, as what was then auxiliary request 7, and had never been addressed by the opposition division. In its decision, the opposition division only had to deal with the main request, which it considered allowable.

4.2 The board can thus accept that the appellant had no reason to address the set of claims of what was then auxiliary request 7 in its statement of grounds of appeal.

4.3 The set of claims of the former auxiliary request 7 (in opposition proceedings) was refiled with the respondent's reply to the statement of grounds of appeal as auxiliary request 26. Regarding this claim request, the respondent explained on page 48, in point 5.10 of its reply to the statement of grounds of appeal, that "*the method incorporates all of the features taken from the method described in Example 4 of the application as filed. Basis can be found on page 28 of the application as filed*". As submitted by the appellant, this is the same explanation as provided when submitting what was then auxiliary request 7 in March 2019. No further reference to the application as

filed was provided by the respondent as a possible basis for the amendments. While the appellant had raised the issue of whether auxiliary request 26 was sufficiently substantiated, the board considered the request on its merits.

4.4 The board does not agree with the respondent's view that Article 123(2) EPC could not or should not be considered in relation to (what is now) auxiliary request 2. As the objection under Article 123(2) EPC pursued by the appellant in the statement of grounds of appeal in relation to the main request turned out to be prejudicial to its allowability, it was for the respondent to demonstrate that this objection would be overcome by the amended claim set. According to the appellant this was not the case. Thus, in line with decisions G 9/91 and G 10/91 (see OJ EPO 1993, 408, 420, Reason 19), the board considered itself entitled to assess the respondent's submissions as to where basis for the set of claims of auxiliary request 2 was to be found and to establish whether or not the passages relied upon actually provided such a basis, in particular since the basis indicated was questioned by the other party.

5. Amendments - Article 123(2) EPC - claim 1

The board agrees with the appellant that neither the information given in Example 4 nor that in the remaining passages of page 28 of the application as filed provides a suitable basis for a loading/sample buffer being "a citrate buffered solution consisting of 20 mM sodium citrate, adjusted to pH 6.2".

In Example 4, the equilibration and wash buffers are disclosed as consisting of/comprising 20 mM sodium

citrate, adjusted to pH 6.2. However, the composition of the loading buffer, i.e. of the buffered solution comprising different isoforms of an antibody which is applied to the chromatographic column, is not specified.

In Example 4, a single-step elution method is used, while in the other examples (single-)step gradient elution (e.g. Examples 2 and 3), gradient elution (e.g. Examples 5 and 7) or a combination of step and linear gradient elution (Example 1) is used. Moreover, none of the examples in the application as filed discloses the nature of the loading buffer applied to the respective columns.

As set out in the context of claim construction (see point 1.3) above, the buffer systems used for the different steps in the method do not necessarily need to be the same. Thus the indication of the buffer systems used for the first and second solutions does not necessarily allow a conclusion as to the composition of the buffered solution used for loading the sample on the column (see e.g. claims 7 and 8 of the main request).

No other part of the application as filed was relied upon by the respondent as a basis for the claimed subject-matter.

Therefore claim 1 contains subject-matter which extends beyond the content of the application as filed. Hence the set of claims of auxiliary request 2 is not allowable under Article 123(2) EPC.

Auxiliary requests 3 to 26

6. *Amendments - Article 123(2) EPC*

Claim 1 of auxiliary requests 3 to 26 comprises the combination of features objected to in the context of the main request under Article 123(2) EPC:

- wherein the first solution is changed to the second solution in a single step (see point 2.5 above);
- wherein the buffered solution is a citrate buffered solution (see point 2.4 above); and
- the "enriched antibody isoforms" of feature (c) (see point 2.6 above).

Thus the considerations in the context of amendments to claim 1 of the main request (see points 2.4 to 2.7 above) apply *mutatis mutandis* to the sets of claims of auxiliary requests 3 to 26.
Claim 1 of these auxiliary requests contains subject-matter which extends beyond the content of the application as filed. Hence these claim requests are not allowable under Article 123(2) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

I. Aperribay M. Blasi

Decision electronically authenticated