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Datasheet for the decision of 9 August 2023

Case Number: T 1215/21 - 3.3.04

Application Number: 14777867.4

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Language of the proceedings: EN

Title of invention:
Purification process for monoclonal antibodies

Patent Proprietor:
Zydus Lifesciences Limited

Opponents:
AWA Sweden AB
Cytiva Sweden AB
F.Hoffmann-La Roche AG
Weinzierl, Gerhard
Neuefeind, Regina

Headword:
Antibody purification/ZYDUS

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:

Inventive step - main request, auxiliary requests 4, 5, 10 to 12 (no)
Amendments - auxiliary requests 1 to 3, 6 to 9 - added subject-matter (yes)

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1215/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 9 August 2023

Appellant: (Patent Proprietor)	Zydus Lifesciences Limited Zydus Corporate Park, Scheme No. 63 Survey No. 536, Khoraj (Gandhinagar) Nr. Vaishnodevi Circle Ahmedabad, Gandhinagar, Gujarat, 382481 (IN)
Representative:	Pohlman, Sandra M. df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)
Appellant: (Opponent 1)	AWA Sweden AB P.O. Box 5117 200 71 Malmö (SE)
Representative:	AWA Sweden AB Box 45086 104 30 Stockholm (SE)
Appellant: (Opponent 2)	Cytiva Sweden AB Björkgatan 30 751 84 Uppsala (SE)
Representative:	Démoulin, Eva Lotta Cytiva Sweden AB Björkgatan 30 751 84 Uppsala (SE)
Appellant: (Opponent 3)	F.Hoffmann-La Roche AG 124 Grenzacherstrasse 4070 Basel (CH)
Representative:	Boult Wade Tennant LLP Salisbury Square House

8 Salisbury Square
London EC4Y 8AP (GB)

Appellant: (Opponent 4)
Weinzierl, Gerhard
Schiweck Weinzierl Koch
European Patent Attorneys
Landsberger Straße 98
80339 München (DE)

Representative:
Schiweck Weinzierl Koch
Patentanwälte Partnerschaft mbB
Ganghoferstraße 68 B
80339 München (DE)

Party as of right: (Opponent 5)
Neuefeind, Regina
Maiwald GmbH
Elisenhof
Elisenstraße 3
80335 München (DE)

Representative:
Maiwald GmbH
Elisenhof
Elisenstraße 3
80335 München (DE)

Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 June 2021 concerning maintenance of the European Patent No. 3013849 in amended form

Composition of the Board:

Chair R. Hauss
Members: B. Rutz
M. Blasi

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietor (appellant-patent proprietor) and opponents 1 to 4 (appellant-opponents I to IV) against the interlocutory decision of the opposition division that European patent No. 3 013 849 in amended form according to auxiliary request 10 met the requirements of the EPC, while no higher-ranking request was allowable. The patent is entitled "*Purification process for monoclonal antibodies*" and is based on application EP 14 777 867.4. The latter had been filed as international application under the PCT, published as WO 2014/207763 (the application).

II. The patent had been opposed on the grounds of Article 100(a) EPC, for lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), and Article 100(b) and (c) EPC.

III. With the statement of grounds of appeal, the appellant-patent proprietor re-filed the same sets of claims of the main request and auxiliary requests 1 to 39 as previously filed during the opposition proceedings.

Claim 1 of the main request reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential steps
(a) Affinity chromatography
(b) Hydrophobic interaction chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF

antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody."

In the following, differences to claim 1 of the main request are highlighted by the board by underlining additions and strike-through of deletions.

Claim 1 of auxiliary request 1 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential steps
(a) Protein A affinity chromatography
(b) Hydrophobic interaction chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode, wherein step (a) comprises loading of a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak, wherein the wash comprises three steps and elution of the desired protein is carried out at a lower pH and a higher conductivity than that of the third wash step~~, wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 2 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential steps
(a) Affinity chromatography
(b) Hydrophobic interaction chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode, wherein step (a) comprises loading of

a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak and wherein column wash comprises:
(i) First wash with equilibration buffer at suitable conductivity
(ii) Second wash at a conductivity higher than the first wash buffer
(iii) Third wash at a conductivity lower than the second wash buffer
(iv) Elution of an antibody at a higher conductivity than [sic] third wash buffer~~, wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 3 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential chromatography steps
(a) Affinity chromatography
(b) Hydrophobic interaction chromatography
(c) Ion exchange chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody."

Claim 1 of auxiliary request 4 is identical to claim 1 of the main request.

Claim 1 of auxiliary request 5 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential chromatography steps
(a) Protein A affinity chromatography
(b) Hydrophobic interaction chromatography
(c) Anion exchange chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody.

Claim 1 of auxiliary request 6 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential steps
(a) Affinity chromatography
(b) Hydrophobic interaction chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode, wherein step (a) comprises loading of a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak and wherein column wash comprises:
(i) First wash with equilibration buffer at suitable pH and conductivity
(ii) Second wash at the same pH as the first wash buffer and a conductivity higher than the first wash buffer
(iii) Third wash at a pH and a conductivity lower than the second wash buffer

(iv) Elution of an antibody at lower pH and higher conductivity than [sic] third wash buffer~~, wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 7 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential chromatography steps
(a) Protein A affinity chromatography
(b) Hydrophobic interaction chromatography,
(c) Ion exchange chromatography optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode, wherein step (a) comprises loading of a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak, wherein the wash comprises three steps and elution of the desired protein is carried out at a lower pH and a higher conductivity than that of the third wash step~~, wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 8 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential chromatography steps
(a) Affinity chromatography
(b) Hydrophobic interaction chromatography,
(c) Ion exchange chromatography optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute

mode, wherein step (a) comprises loading of a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak and wherein column wash comprises:
(i) First wash with equilibration buffer at suitable conductivity
(ii) Second wash at a conductivity higher than the first wash buffer
(iii) Third wash at a conductivity lower than the second wash buffer
(iv) Elution of an antibody [sic] higher conductivity than [sic] third wash buffer~~, wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 9 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential chromatography steps
(a) Affinity chromatography
(b) Hydrophobic interaction chromatography,
(c) Ion exchange chromatography optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode, wherein step (a) comprises loading of a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak and wherein column wash comprises:
(i) First wash with equilibration buffer at suitable pH and conductivity

(ii) Second wash at the same pH as of the first wash buffer and a conductivity higher than the first wash buffer
(iii) Third wash at a pH and a conductivity lower than the second wash buffer
(iv) Elution of an antibody at lower pH and higher conductivity than [sic] third wash buffer~~, wherein the antibody is selected from anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 10 reads as follows.
"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential chromatography steps
(a) Protein A affinity chromatography
(b) Hydrophobic interaction chromatography,
(c) Anion exchange chromatography optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode, wherein step (a) comprises loading of a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak and wherein column wash comprises:
(i) First wash with equilibration buffer at suitable pH and conductivity
(ii) Second wash at the same pH as of the first wash buffer and a conductivity higher than the first wash buffer
(iii) Third wash at a pH and a conductivity lower than the second wash buffer
(iv) Elution of an antibody at lower pH and higher conductivity than [sic] third wash buffer~~, wherein the antibody is selected from anti-HER antibody, anti-TNF~~

~~antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 29, which was subsequently renamed auxiliary request 11 (see point VI. below), reads as follows.

"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential chromatography steps

(a) Protein A affinity chromatography

(b) Hydrophobic interaction chromatography

(c) Anion exchange chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode wherein the antibody is selected from adalimumab, rituximab, trastuzumab, pertuzumab and anti-RANKL ~~anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

Claim 1 of auxiliary request 38, which was subsequently renamed auxiliary request 12 (see point VI. below), reads as follows.

"1. A process for purification of monoclonal antibody from cell culture comprising the following sequential steps

(a) Protein A affinity chromatography

(b) Hydrophobic interaction chromatography, optionally followed by other suitable purification steps, wherein hydrophobic interaction chromatography is performed in bind-elute mode, wherein step (a) comprises loading of a crude mixture containing the desired antibody to the column at suitable pH and conductance for binding, followed by column wash prior to elution of the desired antibody in the form of a single peak and wherein column wash comprises:

(i) First wash with equilibration buffer at suitable pH and conductivity
(ii) Second wash at the same pH as the first wash buffer and a conductivity higher than the first wash buffer
(iii) Third wash at a pH and a conductivity lower than the second wash buffer
(iv) Elution of an antibody at lower pH and higher conductivity than third wash buffer, wherein the antibody is selected from is [sic] adalimumab, trastuzumab and rituximab ~~anti-HER antibody, anti-TNF antibody, anti-VEGF antibody, anti-CD20 antibody, anti-CD52 antibody, anti-RANKL, anti-IgE antibody~~."

IV. The appellant-patent proprietor replied to the appellant-opponents' statements of grounds of appeal. The appellant-opponents and opponent 5 replied to the appellant-patent proprietor's statement of grounds of appeal.

V. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

VI. Oral proceedings before the board took place on 8 and 9 August 2023 in the absence of opponent 5, who was treated as relying on its written case in accordance with Rule 115(2) EPC and Article 15(3) RPBA. During the oral proceedings, the appellant-patent proprietor withdrew auxiliary requests 11 to 28, 30 to 37 and 39 filed with the statement of grounds of appeal and confirmed that the main request and auxiliary requests 1 to 10, 29 (renamed as auxiliary request 11) and 38 (renamed as auxiliary request 12) filed with the statement of grounds of appeal remained as the claim

requests to be decided upon. At the end of the oral proceedings, the Chair announced the board's decision.

VII. The following documents are cited in the present decision:

D9 A. A. Shukla et al., "*Downstream processing of monoclonal antibodies—Application of platform approaches*", Journal of Chromatography B 848, 2007, 28-39.

D10 J. Chen et al., "*Comparison of standard and new generation hydrophobic interaction chromatography resins in the monoclonal antibody purification process*", Journal of Chromatography A 1177, 2008, 272-281.

D15 WO 2011/089212

D21 S. Ghose et al., "*Protein A Affinity Chromatography for Capture and Purification of Monoclonal Antibodies and Fc-Fusion Proteins: Practical Considerations for Process Development*", Process Scale Bioseparations for the Biopharmaceutical Industry, ed. A. A. Shukla et al., 2007, 463-489.

D22 S. Vunnum et al., "*Protein A-based affinity chromatography*", Process Scale Purification of Antibodies, ed. U. Gottschalk, 2009, 79-102.

D54b Annex I to the declaration of A. K. Singh, M.Sc. (17 March 2020)

D61 K. Bergemann et al., "*Production and Downstream Processing*" Handbook of Therapeutic Antibodies Volume I, ed. S. Dübel, 2007, 199-237.

VIII. The appellant-patent proprietor's arguments relevant to the decision may be summarised as follows.

Main request, auxiliary requests 4 and 5
Inventive step (Article 56 EPC)

Document D10 did not disclose the purification of any of the antibodies mentioned in claim 1 of these requests. The objective technical problem in view of D10 was thus the provision of a purification process with high yield and high purity for the antibodies recited in claim 1.

Starting from D10, it needed moreover to be assessed whether the skilled person would have selected the Protein A affinity chromatography (ProtA) - hydrophobic interaction chromatography (HIC) - anion exchange chromatography (AEX) process which was described in Table 3 as involving "*complex*" development efforts and "*significant*" sample manipulation.

The entire disclosure of D10 highlighted the many advantages of the mixed mode mercapto-ethyl-pyridine (MEP) resin compared to standard HIC as a purification process and thus provided a very strong teaching away from the claimed process.

There was a strong preference in the art to use a different order of chromatography steps and a different mode of downstream HIC. Indeed, no other document on file suggested the claimed process in a relevant

context. In view of this knowledge and the very negative teaching in D10, the skilled person would not have seriously contemplated the use of the ProtA-HIC-AEX process.

Auxiliary requests 1 and 7
Amendments (Article 123(2) EPC)

The feature of claim 1 "*wherein the wash comprises three steps and elution of the desired protein is carried out at a lower pH and a higher conductivity than that of the third wash step*" was disclosed on page 9, lines 20 to 22 of the application as filed. Given that this passage disclosed that "*elution of the desired protein is carried out at pH lower than that of the third wash step, but at higher conductance*", it was evident that the wash comprised three steps. Consistent with this teaching, the examples also demonstrated the use of three wash steps. Furthermore, it was clear from the passage on page 6, lines 21 to 24 that the elution step was considered an independent step. Indeed, this passage taught that how the elution step was performed (independent of the wash steps) could directly influence the purity of the antibody eluate. Claim 1 was not an intermediate generalisation.

Auxiliary requests 2 and 8
Amendments (Article 123(2) EPC)

The definition of the wash protocol was taken directly from claim 5 as filed, which specified that the wash protocol may be defined in terms of pH and/or conductivity. Accordingly, claim 5 presented the skilled person with a single selection from one list. Either the wash protocol was defined in terms of i) pH and conductivity; ii) pH; or iii) conductivity. To

arrive at the subject-matter of claim 1, the skilled person merely had to select conductivity from this one list of three options, a pointer to that selection was not necessary.

Auxiliary request 3
Amendments (Article 123(2) EPC)

The application as filed used the terms "*column chromatography*" and "*chromatography*" interchangeably. For example, on page 3, lines 13 to 15, a process comprising ion exchange column chromatography was disclosed. Shortly after this passage, the application disclosed that "*ion exchange chromatography according to the present invention is selected from cation exchange chromatography and anion exchange chromatography*" (page 3, lines 23 to 25; see also page 7, lines 13 to 15; and claim 15 as filed). In view of the overall disclosure of the application, it was clear to the skilled person that these terms were interchangeable. Accordingly, a process comprising affinity chromatography (AC), HIC and ion exchange chromatography (IEX) was directly and unambiguously disclosed to the skilled person.

Furthermore, the sequence of the three steps was demonstrated as the preferred order on pages 9 to 10 of the application as filed and in the examples. Although the examples used specific AC and IEX columns as one way of carrying out these steps, this did not mean the demonstrated order of steps would not apply to a process comprising AC, HIC and IEX in general. On the contrary, the skilled person understood that although different types of columns (such as ProtA instead of AC; and AEX instead of IEX) may be used to carry out the process, the order of the steps had to be followed.

Although a skilled person could, in principle, carry out the steps which follow AC in a different order (as in the prior art), that was not the teaching of the application as filed, which required "*employing the conventional column chromatography techniques in a unique manner to obtain a highly purified preparation of desired antibody*" (page 2, lines 17 to 20).

Auxiliary requests 6 and 9
Amendments (Article 123(2) EPC)

The feature relating to the wash protocol was taken directly from claim 5 as filed, which referred back to claim 1 and AC in general. Furthermore, claim 5 as filed merely presented the skilled person with a single selection from one list. Either the wash protocol was defined in terms of i) pH and conductivity; ii) pH; or iii) conductivity. To arrive at the subject-matter of claim 1, the skilled person merely had to select the "*and*" option from claim 5, a pointer to that selection was not necessary. Nevertheless, the examples (as well as the passage on page 9, lines 11 to 22) clearly pointed the skilled person to select the "*and*" option in claim 5 by demonstrating this as the preferred choice.

Auxiliary request 10
Inventive step (Article 56 EPC)

As could be derived from paragraph [0052] (Example 1) of the patent in suit and document D54b, an improvement in purity after the AC step (a) was achieved with the claimed method.

The process of D10 resulted in 94 or 95.9% purity after the ProtA step (see Table 1, after subtraction of the

high and low molecular weight impurities) and only achieved an overall yield of 50 to 60% (see Table 3). In contrast, the claimed process achieved purities of more than 99% and yields of more than 80% (see patent paragraph [0002], line 47 to 51; Figures 7 to 9 and the supplemental data provided in D54b, e.g. in Table 3). Since both the purity and yield of the claimed process were higher than what was reported in D10, the objective technical problem should be formulated as the provision of an improved process for purifying antibodies.

However, irrespective of whether an improvement could be seen in view of D10 (since the lack of information in D10 on the antibodies and Protein A wash protocol precluded a direct comparison), it had to be at least acknowledged that the claimed process provided very pure antibodies with high yields. Since this result was consistently achieved for numerous different antibodies (see the examples in the patent and the data provided in D54b), it could not be considered accidental but had to be attributed to the wash and elution protocol used.

Even if no improvement was acknowledged and the objective technical problem were to be formulated as providing an alternative, no combination of two prior-art documents led to the claimed solution.

Auxiliary request 11
Inventive step (Article 56 EPC)

Claim 1 of auxiliary request 11 was distinguished from D10 in that it specified the antibodies to be selected from adalimumab, rituximab, trastuzumab, pertuzumab and anti-RANKL. The difference in comparison with D10 was that a higher yield and purity were obtained. The

objective technical problem was the provision of a purification process which achieved higher yield and purity of the mentioned antibodies. It was common general knowledge (see e.g. D9, page 31 and D61, page 211) that antibodies differed in their physico-chemical characteristics and that it was difficult to devise a generic purification scheme. It was thus surprising that the claimed process worked for all antibodies mentioned in the claim. The antibodies had been chosen purposefully, and the purification had been successfully tested in the patent or the experiments reported in D54b. The skilled person had no guidance on how to achieve an exceptionally high purity and yield for these antibodies and no expectation of achieving it. The claimed process was thus inventive.

Auxiliary request 12
Inventive step (Article 56 EPC)

Claim 1 of auxiliary request 12 was distinguished from the process described in D10 in that it specified the antibodies to be selected from adalimumab, trastuzumab and rituximab. These were the antibodies for which examples were provided in the patent, supported by the supplementary evidence in D54b. Moreover, claim 1 related to a two-step process with a defined wash and elution protocol for the ProtA step. The claimed two-step process yielded about 75% product (see D54b), while the three-step process disclosed in D10 yielded only 50 to 60%. The use of the specific wash and elution protocol was neither taught nor suggested by the prior art. Rather, the prior art taught that elution should be performed at a lower conductivity than the wash step (see D22, Figure 4.2) and that the elution conditions needed to be chosen in a product-specific manner (see D21, page 479, lines 6 to 8). It

was thus surprising that all three antibodies were purified at high yield and purity with the claimed process.

IX. The appellant-opponents' and opponent 5's arguments relevant to the decision may be summarised as follows.

Main request, auxiliary requests 4 and 5
Inventive step (Article 56 EPC)

The asserted technical effect of higher yield and higher purity could not be associated with the distinguishing feature. The post-published data could not be relied upon. No direct and true comparison with the prior-art process was available. It was not credible that the effect would have been achieved for all antibodies. The objective technical problem should be defined as applying the process of document D10 to selected antibodies, the provision of a process for purification of an arbitrary list of alternative antibodies or the identification of antibodies that could be purified by the process of D10. Using the known process of D10 for commonly known therapeutic antibodies would have been obvious to the skilled person. Thus, the opposition division was correct in its decision that the subject-matter of claim 1 of auxiliary request 5 lacked an inventive step. This finding also applied to the more broadly defined process of claim 1 of the main request and the identical claim 1 of auxiliary request 4.

Auxiliary requests 1, 2, 3, 6 to 9
Amendments (Article 123(2) EPC)

The opposition division was correct in its decision that claim 1 of these requests added subject-matter.

Auxiliary request 10
Inventive step (Article 56 EPC)

Document D10 disclosed a purification train comprising the steps of ProtA-HIC-AEX.

Claim 1 of auxiliary request 10 differed from the disclosure in D10 in the wash steps used for the ProtA step. The description did not state any advantage provided by this difference. There was no function, effect or advantage attributed to any of the wash steps, in combination or each step separately. Nor had the appellant-patent proprietor provided any comparative data to show that the claimed wash and elution protocol had a better effect than an alternative protocol. Thus, the objective technical problem to be solved starting from D10 was to provide an alternative purification method with specific wash and elution steps for ProtA.

Document D15 disclosed the three wash steps defined in claim 1 as a typical embodiment of ProtA. By teaching that the composition of the third wash buffer was similar to that of the elution buffer, D15 implicitly disclosed the following three options. Compared to the conductivity of the third wash buffer, the conductivity of the elution buffer could be (1) similar but higher, (2) similar but lower or (3) identical.

The common general knowledge also disclosed the characteristics of the wash and elution buffers.

Document D22 (page 88, point 4.3.3, second to third paragraph) disclosed that a low pH for the elution buffer could induce aggregates but that this could be

counteracted by increasing the conductivity, which reduced the amount of aggregates.

The skilled person was aware of the need to optimise process conditions, including the washing steps. This optimisation formed part of a common adaptation that all persons skilled in the art were able to perform and evaluate, without the need of any inventive skills.

Modifying buffer conductivity was a standard optimisation measure in purification trains. In addition, the teaching of D15 that the third wash buffer was similar to the elution buffer would encourage the skilled person to test similar but slightly different buffer compositions. Such buffers would by implication also have similar but slightly different conductivities.

Consequently, a third wash buffer having a conductivity lower than that of the elution buffer would have been considered by the skilled person.

Thus, the skilled person would have arrived at the wash and elution protocol of claim 1, starting from D10, consulting D15 and in view of common general knowledge.

Auxiliary request 11
Inventive step (Article 56 EPC)

The same reasons as for auxiliary request 5 applied because the only difference to the disclosure of document D10 resided in the choice of the antibodies. This could not be considered inventive as the skilled person had no reason not to apply the process disclosed in D10 to therapeutic antibodies such as adalimumab. Moreover, no comparison to other antibodies, e.g.

against TNF-α, had been provided in the patent. The alleged technical effect of higher yield and purity could thus not be attributed to specific antibodies. Moreover, it was clear from D54b that specific wash and elution conditions had been chosen for each antibody which were not reflected in the claim.

Auxiliary request 12
Inventive step (Article 56 EPC)

The fact that the claimed process mentioned only two steps did not mean that it could not comprise further steps, such as an additional AEX step as in D10. The same reasons as for auxiliary request 10 applied to the wash and elution protocol defined in the claim because there was no technical effect of the selection of the specific antibodies compared to the more generically defined antibodies in claim 1 of auxiliary request 10.

X. The appellant-patent proprietor requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the set of claims of the main request or, alternatively, on the basis of one of the sets of claims of auxiliary requests 1 to 9 or, alternatively, that the opponents' appeals be dismissed and that the patent be maintained as amended in the version of auxiliary request 10 considered allowable by the opposition division or, in the further alternative, that the patent be maintained in amended form on the basis of the set of claims of auxiliary request 11, filed as auxiliary request 29 with its statement of grounds of appeal, or auxiliary requests 12, filed as auxiliary request 38 with its statement of grounds of appeal.

The appellant-patent proprietor also had requested non-

admittance of several documents and objections submitted by the other parties. However, as the board's decision was taken based on considerations not relating to documents or objections in relation to which the appellant-patent proprietor had requested non-admittance, these requests for non-admittance need not be dealt with in this decision. The same applies to documents D51 to D53 which relate to issues of clarity and claim interpretation that were not relevant for the decision.

Appellant-opponents 1 to 4 requested that the decision under appeal be set aside and the patent be revoked. Additionally, appellant-opponents 3 and 4 requested that auxiliary requests 11 and 12 not be admitted into the proceedings.

Reasons for the Decision

Main Request - claim 1
Inventive step (Article 56 EPC)

1. In comparison with claim 1 of the main request, claim 1 of auxiliary request 5 contains further restrictions, namely it refers to "*sequential chromatography steps*" and "*protein A affinity chromatography*" (in step (a)) and contains additional step (c) of "*Anion exchange chromatography*". The subject-matter of claim 1 of auxiliary request 5 is therefore comprised as a more limited embodiment within the subject-matter of claim 1 of the main request. As a consequence, the subject-matter of claim 1 of the main request lacks an inventive step for the same reasons as that of claim 1 of auxiliary request 5 (see points 10. to 21. below).

Auxiliary request 1 - claim 1
Amendments (Article 123(2) EPC)

2. The board agrees with the decision under appeal that the feature "*wherein the wash comprises three steps and elution of the desired protein is carried out at a lower pH and a higher conductivity than that of the third wash step*" extends beyond the content of the application as filed. This feature cannot be directly and unambiguously derived from the passages in the application as filed indicated by the appellant-patent proprietor (page 9, lines 20 to 22 and page 6, lines 21 to 24) because the passage on page 9, lines 20 to 22 must be read in the context of the immediately preceding lines 15 to 20 which indicate a more specific combination of pH and conductivity of the different wash and elution steps not present in claim 1 (see decision under appeal, points 59 to 68). Even if the appellant-patent proprietor's argument that the passage on page 6, lines 21 to 24 disclosed the elution step as independent could be accepted, this does not lead to the conclusion that the disclosure on page 9, lines 15 to 22 could be divided into separate parts which could be generalised independently of the rest of the method disclosed in this passage.

3. The subject-matter of claim 1 of auxiliary request 1 extends beyond the content of the application as filed (Article 123(2) EPC).

Auxiliary request 2 - claim 1
Amendments (Article 123(2) EPC)

4. The definition of wash steps (i) to (iii) and elution step (iv) adds subject-matter in comparison with the

disclosure in claim 5 or on page 6, lines 3 to 7 of the application as filed because each of steps (i) to (iv) in claim 1 is limited by criteria relating to conductivity only, rather than to "*pH and/or conductivity*". This amounts to a combination of several selections as one out of three options is selected for each of the four steps. The passage on page 9, lines 16 to 22 indicated by the appellant-patent proprietor as a possible pointer equally refers to both pH and conductivity. The same holds true for the examples (see decision under appeal, point 73).

5. The subject-matter of claim 1 of auxiliary request 2 extends beyond the content of the application as filed (Article 123(2) EPC).

Auxiliary request 3 - claim 1
Amendments (Article 123(2) EPC)

6. The board agrees with the decision under appeal (see points 86 and 87) that the application as filed does not disclose the sequence of affinity chromatography (AC) – hydrophobic interaction chromatography (HIC) – ion exchange chromatography (IEX) in that order but rather indicates that HIC and IEX after AC can be carried out in any order (see e.g. page 4, lines 2 to 3; page 7, lines 26 to 27; claim 15). The argument by the appellant-patent proprietor that the numbering of the sections on page 9 and 10 (i.e. "*I) Protein A column chromatography*", "*II) Hydrophobic interaction column chromatography*", "*III) Anion exchange column chromatography*") disclosed an order is not convincing because these sections instead represent detailed descriptions of the individual steps not connected in a particular order with each other. Moreover, this section refers to the more specific case of Protein A

column chromatography and anion exchange chromatography (AEX), while claim 1 of this request refers to the more general methods of AC and IEX. The order used in the examples can not serve as a pointer, either, because it relates to more specific method steps, namely Protein A affinity chromatography (ProtA) - HIC - AEX, where each step is carried out under specific conditions.

7. The omission of the word "*column*" from "*ion exchange column chromatography*" adds subject-matter (see decision under appeal, point 89). The appellant-patent proprietor's argument that the terms chromatography and column chromatography were used interchangeably in the application as filed is not convincing because types of chromatography other than column chromatography were commonly known at the relevant date. The skilled person would have interpreted the terms accordingly and not replaced one term with the other.

8. The subject-matter of claim 1 of auxiliary request 3 extends beyond the content of the application as filed (Article 123(2) EPC).

Auxiliary request 4
Inventive step (Article 56 EPC) - claim 1

9. The subject-matter of claim 1 of auxiliary request 4 is identical to that of claim 1 of the main request. Thus, it likewise lacks an inventive step for the same reasons as claim 1 of auxiliary request 5, which shares all features with claim 1 of auxiliary request 4 but is limited by additional features (see point 1. above and points 10. to 21. below).

Auxiliary request 5 - claim 1
Inventive step (Article 56 EPC)

10. It was common ground that document D10 represented the closest prior art. D10 discloses the purification of two model monoclonal antibodies (see page 273, left-hand column, point 2.1: "*IgG1 subclass, Kappa light chain and pI 9.0-9.2*") with a ProtA-HIC-AEX purification train, in that order (see Table 3, middle column).

11. The appellant-patent proprietor's argument that the skilled person would not have chosen "*standard HIC*" as a starting point in D10 because the equally disclosed "*new generation HIC*" was presented as preferable cannot be accepted. The selection of a starting point serves the purpose of assessing inventive step and is performed by the body deciding on inventive step from among the prior-art disclosures eligible under Article 56 EPC. These may include alternative disclosures within the same prior-art document. Inventive step can, in principle, be assessed starting from any prior-art disclosure. If the starting point is too remote from the claimed subject-matter in terms of purpose and technical features, the problem-solution approach will simply not result in a finding that the claimed subject-matter is obvious. A disclosure in a prior-art document cannot be disregarded as a potential starting point simply because there are other (even preferred) options disclosed in the same document. If inventive step is to be acknowledged, the claimed subject-matter must be inventive starting from any potential starting point in the prior art.

12. Moreover, the appellant-patent proprietor's assertion that D10 teaches away from "*standard HIC*" is also

incorrect. D10 explicitly states (page 280, right column, lines 6 to 11) that "*the standard HIC process remains as one of the attractive choices for the high-purity driven DSP of therapeutic mAb manufacturing, especially in high aggregation removal situations*".

13. To take account of the objections actually considered by the opposition division and raised by the opponents on appeal, the board found it appropriate to assess inventive step starting from the disclosure of D10, specifically the ProtA-HIC-AEX purification train in that document.

14. To find auxiliary request 5 allowable, the board must be convinced that an inventive step can be acknowledged in an assessment based on the same starting point as the opposition division's assessment that led to a negative conclusion on inventive step in the decision under appeal.

15. It was undisputed that HIC in D10 is performed in bind-elute mode (see e.g. page 278, point 3.4.2).
The parties agreed that the subject-matter of claim 1 of auxiliary request 5 differed from the disclosure in D10 only in the selection of antibodies with targets selected from HER, TNF, VEGF, CD20, CD52, RANKL and IgE.

16. The appellant-patent proprietor contended that the choice of antibodies with these targets resulted in improved yield and purity. This was evident from paragraph [0002] of the patent: "*a highly purified preparation of antibody with more than 80% recovery*" and from the examples and the post-filed test report D54b, which reported a purity of more than 99%.

17. The board is not aware of any technical reason - and was also not presented with any - why the choice of antibodies binding to these targets would have any influence on the recovery and/or purity of the antibody. The binding specificity of antibodies is mainly governed by their CDRs and not by the rest of the antibody molecule. The latter, however, strongly influences the purification behaviour of the molecule. It therefore does not make technical sense that the target alone could influence the purification of an antibody.

18. The appellant-patent proprietor further argued that specific conditions were required for each individual antibody (see e.g. document D9, page 31, right-hand column, first paragraph and document D61, page 211). However, neither are specific antibodies listed in the claim, only targets, nor does the claimed process involve specific conditions, e.g. in terms of buffer, pH, conductivity, etc. Moreover, the appellant-patent proprietor failed to present any comparative data to show that antibodies to the targets listed in claim 1, when purified with the process claimed, which is identical to the one disclosed in document D10, would be obtained with higher purity or in higher yield compared to antibodies directed to other targets. The alleged effect of higher purity or higher yield can therefore not be taken into account to formulate the objective technical problem.

19. The objective technical problem can be formulated as the selection of antibodies to be purified with a ProtA-HIC-AEX purification train.

20. Document D10 focuses on the large-scale production of pharmaceutical-grade therapeutic monoclonal antibodies

(see e.g. page 272, left-hand column). The antibody targets listed in claim 1 include targets of commonly known commercial antibodies approved for therapeutic use (e.g. rituximab, which is anti-CD20; adalimumab, which is anti-TNF-α; trastuzumab, which is anti-HER). Neither document D10 nor any other cited document indicates to the skilled person that antibodies having one of the targets listed in claim 1 would not be amenable to purification with the process of D10. The selection of antibodies to the targets listed in claim 1 is thus an arbitrary choice from the many therapeutic antibodies commonly known to the skilled person. Applying the purification train disclosed in document D10 to antibodies with these targets is therefore obvious.

21. For these reasons, the subject-matter of claim 1 of auxiliary request 5 lacks an inventive step over the disclosure of document D10 (Article 56 EPC).

Auxiliary request 6 - claim 1
Amendments (Article 123(2) EPC)

22. The board agrees with the decision under appeal (see points 124 to 127) that the application as filed does not disclose wash and elution steps (i) to (iv) defined in claim 1 of auxiliary request 6 for affinity chromatography in general. The examples, which the appellant-patent proprietor considered to serve as a pointer for the selection of "*and*" from "*and/or*" as disclosed in claim 5 as filed, exclusively relate to Protein A affinity chromatography. The relative pH and conductivity adaptations of the wash and elution steps during Protein A affinity chromatography in the examples can therefore not serve as a pointer for conditions of affinity chromatography in general. The

same applies to the disclosure of the wash and elution steps on page 9, lines 16 to 22 which is also limited to Protein A column chromatography.

23. The subject-matter of claim 1 of auxiliary request 6 extends beyond the content of the application as filed (Article 123(2) EPC).

Auxiliary request 7 - claim 1
Amendments (Article 123(2) EPC)

24. The reasons for added subject-matter in claim 1 of auxiliary request 1 apply equally to this request because it also contains the feature "*wherein the wash comprises three steps and elution of the desired protein is carried out at a lower pH and a higher conductivity than that of the third wash step*".

25. The subject-matter of claim 1 of auxiliary request 7 extends beyond the content of the application as filed (Article 123(2) EPC).

Auxiliary request 8 - claim 1
Amendments (Article 123(2) EPC)

26. The reasons for added subject-matter in claim 1 of auxiliary request 2 apply equally to this request because each of steps (i) to (iv) in claim 1 is also limited by criteria relating to conductivity only, rather than to "*pH and/or conductivity*". The reasons for added subject-matter in claim 1 of auxiliary request 3 apply equally to this request because it also contains the sequence of affinity chromatography (AC) – hydrophobic interaction chromatography (HIC) – ion exchange chromatography (IEX) in that order.

27. The subject-matter of claim 1 of auxiliary request 8 extends beyond the content of the application as filed (Article 123(2) EPC).

Auxiliary request 9 - claim 1
Amendments (Article 123(2) EPC)

28. The reasons for added subject-matter in claim 1 of auxiliary request 3 apply equally to this request because it also contains the sequence of affinity chromatography (AC) – hydrophobic interaction chromatography (HIC) – ion exchange chromatography (IEX) in that order. The reasons for added subject-matter in claim 1 of auxiliary request 6 apply equally to this request because it also defines wash and elution steps (i) to (iv) for affinity chromatography in general.

29. The subject-matter of claim 1 of auxiliary request 9 extends beyond the content of the application as filed (Article 123(2) EPC).

Auxiliary request 10 - claim 1
Inventive step (Article 56 EPC)

30. The difference of the subject-matter of claim 1 to the disclosure in document D10 resides in the further definition of the wash and elution steps for ProtA. According to the appellant-patent proprietor, the effect achieved by this difference was a higher purity after the ProtA step. This was apparent from paragraph [0052] and figure 2 of the patent, which reported 98% purity, and was supported also by the post-filed data in document D54b, which showed an average purity after the ProtA step of close to 99% (see Table 2 of D54b). This had to be compared to Table 1 in D10 in which

impurities of 5.5 and 2.6% for high molecular weight aggregates and 0.5 and 1.5% for low molecular weight aggregates were reported, i.e. the overall purity was only 94 and 95.9% for the two model antibodies.

31. The board agrees with the opposition division and appellant-opponent 3 that such an effect of higher purity is not shown, because the patent does not provide comparative experiments relating to the chosen wash and elution conditions (see decision under appeal, paragraphs 158 and 159 and appellant-opponent 3's grounds of appeal, 6.7-6.8). The board also agrees with appellant-opponent 3 that any technical effect in connection with the wash and elution protocol could not be credibly achieved over the whole scope of the claimed process, because the wash and elution steps are limited only by relative pH and conductivity values in relation to each preceding step, and no absolute values or ranges for pH and conductivity are given for any of the steps (see statement of grounds of appeal of appellant-opponent III, point 7.16).

32. The first wash is "*with equilibration buffer at suitable pH and conductivity*". It is common general knowledge (see e.g. D9, page 31, right-hand column, first paragraph; D22, page 92, first full paragraph) that "*suitable pH and conductivity*" can be different for each antibody. The starting pH and conductivity of the wash steps is therefore undefined. The second wash step is only defined with reference to the first wash step ("*same pH*" and "*conductivity higher*"). The third wash step is only defined with reference to the second wash step ("*pH and conductivity lower*"), so the conductivity can be the same or lower or higher than in the first wash step (i.e. equilibration buffer), while the pH is always lower than in the first step because

it is the same in the first and second step. Likewise, the elution is only defined with reference to the third wash step ("*lower pH and higher conductivity*"). Furthermore, the relative changes ("*higher*", "*lower*") in pH and conductivity may be very small and thus in a range which makes no technical difference. The claim encompasses a wide variety of pH and conductivity conditions for each step, depending only on the conditions of the respective preceding step.

33. In contrast, the wash and elution steps in all examples were carried out at defined pH and conductivity values or within limited ranges (see Example 1, Step 2 in the application as filed and D54b, Table 1). Given the sensitivity of Protein A affinity purification to both pH and conductivity changes (see e.g. D9, page 35, left-hand column, first full paragraph and Table 3; D21, page 478 to 480, points 16.4.2.2 and 16.4.2.3; D22, pages 87 to 88, points 4.3.2 and 4.3.3), it is not credible that all those combinations would achieve the alleged higher purity after the ProtA step. In any case, the appellant-patent proprietor did not provide any data showing a comparison of purification of the same antibody using different wash and elution protocols.

34. In conclusion, the relative definitions of pH and conductivities allow for such a variety of pH and conductivity changes that the alleged effect of an improved purity after the ProtA step is not credibly achieved over the whole scope of the claimed process by the technical teaching of the application as filed, even if the post-published evidence (D54b) were to be considered. The effect of improved purity can therefore not be taken into account when formulating the objective technical problem.

35. The board thus agrees with the decision under appeal that the objective technical problem starting from the disclosure of document D10 is the provision of an alternative purification train with specific wash and elution steps for ProtA (see decision, point 159).

36. This alternative method was obvious to the skilled person when starting from the disclosure of document D10 for the following reasons.

37. In the absence of a technical effect, any wash and elution protocol available to the skilled person by the prior art is an alternative which the skilled person would take into consideration. A particular pointer or advantage of such a protocol need not be indicated in the prior art for it to be taken into account. If there are no prejudices or indications to the contrary against modifying the conditions, the skilled person would adopt the modifications within the ambit of routine optimisation of purification protocols.

38. The skilled person would have found a possible wash and elution protocol in document D15, which discloses Protein A affinity purification of monoclonal antibodies (see, pages 12 to 15, Examples and Figures 1 and 2).

39. A typical embodiment of the Protein A chromatography of D15 is described on page 12, line 18 to page 13, line 19. After loading, the column is washed with an equilibration buffer, which is PBS pH 7.4 (page 14, lines 27 to 29). Following equilibration, the column is washed with a wash buffer based on PBS pH 7.4 with 1 M NaCl (page 15, lines 1 to 9). As the equilibration buffer only comprises 140 mM NaCl, the wash buffer has

the same pH but a higher conductivity than the equilibration buffer. D15 further describes an additional wash step (page 13, lines 2 to 8) using a buffer which must have a pH that is lower than that of the previous washing buffer but higher than that of the elution buffer and that is similar to the elution buffer in terms of buffer salt and composition.

40. The option disclosed in document D15 thus contains steps (i) to (iii) as in claim 1 and also the lower pH of the elution step but does not explicitly disclose the higher conductivity of the elution buffer. However, D15 also suggests using buffers suitable for reducing the binding between the Fc-domain of the antibody and Protein A for elution (see page 13, lines 18 to 21). Even if the conductivity in step (iv) (elution) of the purification disclosed in D15 was the same or even lower than in the third wash step (e.g. because a buffer similar in salt and composition was used), it also belonged to the skilled person's common general knowledge that elution at low pH could result in higher aggregation. One commonly known solution to this was to add high concentrations of inorganic salt, such as NaCl (see D22, page 88, second paragraph). Increasing the conductivity of the elution buffer would thus also have been within the ambit of routine development of a wash and elution protocol that the skilled person would have integrated into the purification train disclosed in document D10. The argument by the appellant-patent proprietor that the "*typical*" Protein A elution step involved a lower conductivity compared to the previous wash buffer and that the skilled person therefore would have avoided higher conductivities (see Figure 4.2 in D22) is not convincing. Although Figure 4.2 is labelled "*A typical Protein A chromatogram*", D22 makes clear that the elution conditions have to be adapted to the

antibody (see page 88, second paragraph, cited above). In any case, the board cannot recognise a technical prejudice which would have prevented the skilled person from making routine modifications to the protocol in D10 to arrive at an alternative purification method falling under the terms of claim 1.

41. The subject-matter of claim 1 of auxiliary request 10 lacks an inventive step over the disclosure of document D10 in combination with D15 and common general knowledge (Article 56 EPC).

Auxiliary request 11
Admittance (Article 12(4) RPBA)

42. For deciding on this auxiliary request as to its merits, the board admitted it into the proceedings based on considerations of procedural economy. In view of the negative finding with regard to inventive step of the subject-matter of claim 1 (see below), the appellant-opponents and opponent 5 were not adversely affected and it was not necessary to further address the issue of admittance of auxiliary request 11.

Inventive step (Article 56 EPC) - claim 1

43. In comparison to the process of claim 1 of auxiliary request 5, this claim, apart from the generic antibody group "*anti-RANKL*" defined by its target, contains a list of four commercial antibodies (adalimumab, rituximab, trastuzumab and pertuzumab).

44. The reasoning on inventive step provided for claim 1 of auxiliary request 5 (see points 10. to 21. above) applies accordingly since the selection of antibodies, be it specific ones or generic groups, does not result

in any particular effect. The appellant-patent proprietor has also not provided comparative data to show a difference in this regard between the antibodies in the claim and other (not claimed) antibodies. The selection of the recited antibodies from the host of possible choices is arbitrary and therefore obvious.

45. The subject-matter of claim 1 of auxiliary request 11 lacks an inventive step starting from the disclosure of document D10 (Article 56 EPC).

Auxiliary request 12
Admittance (Article 12(4) RPBA)

46. For deciding on this auxiliary request as to its merits, the board admitted it into the proceedings based on considerations of procedural economy. In view of the negative finding with regard to inventive step of the subject-matter of claim 1 (see below), the appellant-opponents and opponent 5 were not adversely affected and it was not necessary to further address the issue of admittance of auxiliary request 12.

Inventive step (Article 56 EPC) - claim 1

47. In addition to the features of the process in claim 1 of auxiliary request 10, claim 1 of auxiliary request 12 contains a list of three antibodies (adalimumab, trastuzumab and rituximab). Furthermore, only ProtA and HIC are mandatory purification steps, AEX is not mentioned.

48. As set out for claim 1 of auxiliary request 10 (see points 30. to 41. above), the data in the patent application, even if supplemented by the post-published evidence D54b, does not make it credible that an

improvement in purity after the ProtA step is achieved across the scope of possible process conditions when applying the wash and elution steps as defined in the claim. To reach this conclusion, the additional presence of AEX in claim 1 of auxiliary request 10 was not decisive. Moreover, the absence of the AEX step in claim 1 of auxiliary request 12 is not a difference compared to the disclosure of document D10 because the claim comprises "*optionally further purification steps*", i.e. it also includes methods comprising an AEX step. This conclusion was also reached independently of the nature of the antibody. I.e. also for specific antibodies such as adalimumab, which was purified in Example 1 of the patent, it is not credible that applying the wash elution protocol as defined in the claim would achieve an improvement in purity in comparison with a different protocol. As outlined in point 31. above, the wash and elution steps, for which pH and conductivity are only defined relative to each preceding step, do not provide the skilled person with sufficient guidance to achieve improved purity. As is apparent from the post-filed data in D54b, adjustments were needed, even for the antibodies tested, to achieve optimal purification (compare pH and conductivity values for different antibodies in Table 1 of D54b).

49. Since document D10 discloses a general protocol for monoclonal antibody purification, the skilled person would have applied this to commonly known therapeutic antibodies such as the ones listed in the claim and would have implemented a suitable wash and elution protocol for the ProtA step, for instance, in accordance with the teaching of document D15 and common general knowledge. Also, D15, which relates to the purification of monoclonal antibodies, would not have given the skilled person a reason not to apply the

disclosed Protein A wash and elution conditions to a given therapeutic antibody.

50. The subject-matter of claim 1 of auxiliary request 12 lacks an inventive step over the disclosure of document D10 in combination with D15 and common general knowledge (Article 56 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 R. Hauss

Decision electronically authenticated