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Datasheet for the decision of 26 February 2020

Case Number: T 1077/17 - 3.3.06

Application Number: 08758815.8

Publication Number: 2152745

IPC: C07K16/00, C07K16/24, C07K16/32

Language of the proceedings: EN

Title of invention:
IMMUNOGLOBULIN PURIFICATION

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponents:
1) ---(the opposition of Steglich, Gregor has been withdrawn)
2) Potter Clarkson LLP
3) Baxter Innovations GmbH

Headword:
Immunoglobulin purification/Hoffmann-La Roche

Relevant legal provisions:
EPC Art. 100(b), 100(c), 111(1)
RPBA Art. 12(4)
RPBA 2020 Art. 11

Keyword:
Late-filed evidence - justification for late filing (yes)
Sufficiency of disclosure - main request (yes)
Amendments - extension beyond the content of the application as filed (no)
Remittal to the department of first instance - (yes)

Decisions cited:
G 0001/03, T 0609/02, T 0386/08, T 1966/16

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

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Case Number: T 1077/17 - 3.3.06

D E C I S I O N
of Technical Board of Appeal 3.3.06
of 26 February 2020

Appellant: (Patent Proprietor)	F. Hoffmann-La Roche AG Grenzacherstraße 124 4070 Basel (CH)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
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Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 February 2017 revoking European patent No. 2152745 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	J.-M. Schwaller
Members:	G. Santavicca
	C. Brandt

Summary of Facts and Submissions

I. The appeal lies from the decision of the Opposition Division revoking European patent No. 2 152 745 on the ground that the disclosure of the invention was insufficient (Article 100(b) EPC).

II. The patent comprises 10 claims, whereby the sole independent claim reads as follows:

"*1. Method for obtaining an immunoglobulin in monomeric form from a solution comprising the immunoglobulin in monomeric and in aggregated form, characterized in that said method comprises the following step:*

a) applying an aqueous, buffered solution comprising said immunoglobulin in monomeric and in aggregated form to a membrane cation exchange material under conditions whereby at least 90 % of said immunoglobulin in monomeric form does not bind to said membrane cation exchange material, and recovering said immunoglobulin in monomeric form from said aqueous, buffered solution after the contact with said membrane cation exchange material,

whereby said step a) is a chromatography step operated in flow-through mode and said aqueous, buffered solution has a pH value of from pH 4 to pH 8 and said aqueous, buffered solution of step a) has a conductivity of from 1.0 to 15.0 mS/cm and the sum of pH value and conductivity in mS/cm of the aqueous, buffered solution in step a) is in the range of from 10 to 15."

Claims 2 to 10 concern preferred embodiments of the method defined in claim 1.

III. The following items of evidence, relied upon in opposition proceedings, are relevant for the decision:

D4: W0 2006/024497 A1

D7: Lutkemeyer et al., "*Membrane chromatography for rapid purification of recombinant antithrombin III and monoclonal antibodies from cell culture supernatant*", 1993, J. Chromat., 57-66

D10: "*Strategies for protein purification and characterization - a laboratory cause manual*", Marshak et al, 1996, Cold Spring Harbor Laboratory Press, 54-58

D11: Josie & Lim, "*Analytical and preparative methods for purification of antibodies*", 2001, Food Technol. Biotechnol. 39(3), 215-226

D37: Deutscher, M.P. (Editor), Guide to Protein Purification in Methods in Enzymology (Vol. 182) (1990, Acad. Press), pages 9-15, 19-39, 309-317

D38: Scopes, R. (Editor), Protein Purification Principles and Practice (3rd Ed, 1993, Springer), pages 135-136, 146-171, 185-186, 324-3M

D39: Cutler, P. (Editor), Protein Purification Protocols (2nd Ed., 2004, Humana Press), pages 6-7, 91-99, 125-131, 455-462, 476-477

D40: First Declaration of the inventor, Dr. Roberto Falkenstein.

IV. With its grounds of appeal, the Patent Proprietor (Appellant) defended the patent as granted and submitted ten sets of amended claims as auxiliary requests I to X. Moreover, it filed a second declaration of the inventor (D45).

V. With its reply, (the then) Respondent 1/Opponent 1 requested to reject the appeal because the subject-matter of claim 1 as granted did not comply with the requirements of Articles 83 and 123(2) EPC. Furthermore D40 and D45 should not be admitted into the appeal proceedings. In case they were admitted, it requested for a different apportionment of costs.

VI. With a letter dated 19 December 2017 the Appellant submitted a third declaration of the inventor (D46), which in essence rectified an incorrect date in D45.

VII. After the parties had been summoned to oral proceedings, Opponents 2 and 3 announced that they would not attend.

VIII. In a communication the Board expressed its preliminary opinion that it was inclined to admit D40, D45 and D46 into the appeal proceedings and that it held the disclosure of the invention to be sufficient. It also saw no reason to deviate from the decision under appeal on the ground of opposition under Article 100(c) EPC.

IX. In its reply, (the then) Respondent 1 announced that it would not participate to the oral proceedings either. Also the Appellant withdrew its request for oral proceedings provided that the Board confirmed its opinion that the main request complied with Articles 100(c)/123(2) EPC and 100(b)/83 EPC.

X. With letter of 21 April 2020, Respondent 1/Opponent 1 withdrew its opposition, thus ceasing to be a party to the opposition proceedings.

XI. Final requests of the parties

The Appellant requested in writing that the decision under appeal be set aside and the patent be maintained on the basis of the claims according to the main request or, auxiliarly, of any of auxiliary requests I to IX filed with its grounds of appeal dated 4 July 2017. Further, it requested that declarations D40, D45 and D46 be admitted into the appeal proceedings.

Former Respondent/Opponent 1 had requested in writing that the appeal be dismissed. Further, it had requested not to admit declarations D40 and D45. If they were admitted, apportionment of the costs was requested.

Respondents/Opponents 2 and 3 did not submit any request during the appeal proceedings.

Reasons for the Decision

1. *Procedural aspects*

The grounds of appeal having been filed before 1 January 2020 and the replies thereto in due time, Articles 12(4) to (6) RPBA 2020 do not apply, whilst Article 12(4) RPBA 2007 applies to both the grounds of appeal and the replies.

2. Admittance of declarations D40, D45 and D46

Under Article 12(4) RPBA 2007, the admittance of such late filed documents is at the Board's discretion.

2.1 D40 was submitted before the Rule 116(1) EPC deadline for making submissions, but not admitted by the opposition division, because it contained *"a summary of the general knowledge of D37-D39, a representation of the skilled person's view of the teaching of the patent, an explanation of the method of calculating the monomer yield in the examples and section 35 which discloses the pH and conductivity conditions at which the experiments of example 3 were carried out. The OD holds that this information is essential to establish that the method can be carried out at a different pH and conductivity as those given in example 1. If the information in section 35 were admitted into the proceedings the situation from the Opponents' point of view would be changed drastically regarding the experimental evidence supporting the sufficiency of disclosure of the patent. If further data or evidence is allowed into the proceedings the Opponents would need to have the possibility to react by providing experimental data of their own. [...]. The OD decided not to admit D40 into the proceedings because part of it is not prima facie relevant and can be addressed in writing or orally in the arguments of the applicant's representative and the remainder is considered to be late filed, even though it was filed before the Rule 116(1) EPC deadline because it does not give the Opponents enough time to react by submitting experimental data. The information must have been in patent proprietor's possession since the filing of the application and could easily have been filed with the patent proprietor's reply to the notice of opposition in which objections under Article 83 EPC were raised."*

2.2 The Board cannot share this discretionary decision because D40 was filed along with D37, D38 and D39 with proprietor's letter of 18 November 2016 in reply to the

preliminary opinion of the Opposition Division, in which objections were raised against the obtention of a more than 90% recovery of the monomeric form across the whole breadth of the method of claim 1, in view of the results of table 2 of the patent and the alleged lack of information on operating conditions such as temperature, flow-rate and pI of the antibody.
Thus, not only D37 to 39 but also D40 was filed **in direct reaction** to the preliminary opinion within the given time limit, so that its filing was as justified as that of D37 to D39.

Furthermore, D40 makes this reaction apparent in that:
- points 7 to 15 thereof illustrate the common general knowledge of the skilled person based on D37 to D39, which was in dispute;
- points 19 to 30 give the response of the patent proprietor to the objections raised by the Opposition Division; and
- points 32, 37 and 38 show how to calculate the "at least 90% recovery of the monomeric form", and so concern the calculation of the effect defined in claim 1, which calculation is only based on data disclosed in the examples and tables 2, 5 and 6 of the patent.

Hence, at least these parts of D40 were relevant to the proceedings and should have been admitted.

The fact that point 35 in D40 mentions for the first time the operating conditions, such as the pH and conductivity used in example 3 of the patent was not decisive for the Board's decision for admitting D40, in so far as the example cannot be supplemented by these late filed operating conditions.

2.2.1 It follows that the late filing of D40 was justifiable and its content *prima facie* relevant, since it sheds light not only on essential features of the claimed method, but also on common general knowledge and on the way of calculation of the recovery given in claim 1 at issue. D40 is thus admissible.

2.3 D45 too is admissible, at least to the extent that its Point II represents a reaction to the decision under appeal on how to calculate the condition "at least 90% ..." defined in claim 1 at issue from the data mentioned in the examples of the patent in suit.

2.4 As regards the experimental items of evidence shown in point 35 of D40 or in point III and Annex A of D45, they may be considered in relation to sufficiency only to the extent that they merely confirm the findings in the application in relation to the recovery of immunoglobulins after purification, not however to establish sufficiency of disclosure on their own (see T 609/02, reasons, 9). Hence, these data may be used as post-published evidence to confirm that the application as filed and common general knowledge at the relevant date teach a plausible technical concept enabling the skilled person to carry out the claimed method so as to obtain the claimed recovery across the whole breadth of claim 1 without undue burden.

2.5 D46 merely concerns a rectification of a date mentioned in D45, its admissibility is thus not at stake.

2.6 The request for a different apportionment of costs (submitted by former Respondent/Opponent 1) is rejected because D40 was submitted in direct reaction to the preliminary opinion and within the time limits set by the Opposition Division. Moreover, its late filing was

the result of a legitimate desire to supplement, before the oral proceedings, the line of argument which was unsuccessful before the Opposition Division, rather than a procedural abuse. D45 was filed with the grounds of appeal to counter the decision under appeal, *inter alia* on the not admittance of D40. Hence, also the late filing of D45 was not abusive.

3. Sufficiency of the disclosure

3.1 The present invention (claim 1 as granted) concerns a method for purifying an immunoglobulin whereby its monomeric form is separated from aggregates, which method should be carried out on a cation exchange membrane material "*under conditions whereby at least 90% of said immunoglobulin in monomeric form does not bind to said membrane cation exchange material*".

Thus the effect to be achieved, namely that at least 90% of the monomeric form does not bind, depends on the choice of the operating conditions, such as the "*chromatographic step operated in flow-through mode*", *"the aqueous, buffered solution of step a) having a pH value of from pH 5 to pH 8" and the "conductivity of from 4.0 to 10.0 mS/cm", with the proviso that "the sum of pH value and conductivity value in mS/cm of the aqueous, buffered solution in step a) is in the range of from 10 to 15*" defined in claim 1 at issue.

It is in particular apparent from claim 1 that the term "*cation exchange membrane material*" encompasses any membrane material, with any density of ligands suitable for the cationic exchange. Furthermore the feature "*at least 90% of said immunoglobulin in monomeric form does not bind to said membrane cation exchange material*" implies that said defined amount of monomeric form

flows through the membrane material and exits with the effluent; whereby this functional feature defines the only effect to be achieved by the flow-through mode under operating conditions chosen within the window defined in claim 1 at issue, so that an effluent is recovered which contains at least 90% of the monomeric form of the loaded sample, irrespective of any purity, e.g. of the content of aggregated forms in the effluent.

3.2 In the decision under appeal, the invention was found to be insufficiently disclosed because:

(1) the evidence provided in the patent in respect of the variations of the claimed operating conditions pH and conductivity was not sufficient;

(2) a proof of insufficiency, based on verifiable facts, had been brought up by the Opponents;

(3) undue burden and trial and error of multiple parameters were required to reproduce the invention.

3.3 The Board cannot share these conclusions for the following reasons:

3.3.1 As regards the operating conditions defined in claim 1 at issue, the crucial issue is whether the determination of these conditions within the defined ranges for a specific immunoglobulin, such that at least 90% of the monomeric form does not bind to the cation exchange membrane, and so flows through the column, irrespective of its purity. For this, not only the explicit disclosure in the patent is to be considered but also:

- the documents referred to e.g. in paragraphs [0008] (Knudsen), [0009] (second sentence), [0012] (last sentence) and [0025] of the patent;
- the common general knowledge of the person skilled in the relevant field of chromatography applied to immunoglobulin (e.g. as acknowledged in paragraph [0029] of the patent dealing with principles and practice of protein purification).

3.3.2 The skilled person is a (bio)chemical engineer who is fully aware of the common general knowledge, in particular:

(a) D37, in particular:
- page 309, third paragraph, that the net charge on a protein will be a function of the pH of its environment;
- page 310, Principles of operation;
- page 314, first full paragraph, that "cation exchanger would generally be used below the pI" and "in cases where the amino acid composition (of the protein) is unknown, it will be necessary to try both anion and cation exchangers and various pH values to find the best conditions for separation";
- page 316, first full paragraph, that the measure of the salt concentration can be accomplished with a conductivity meter (hence, D37 shows that conductibility is not an unusual parameter in ion exchange separation);

(b) D38, in particular:
- page 135, heading "Ion Exchangers", that "Ion exchangers exploit the different net charges on proteins at a given pH, and interact with the proteins principally by electrostatic interaction";

- Chapter 6, page 146, point 6.1, that "Proteins bind to ion exchangers by electrostatic forces between the proteins' surface charges (mainly) and the dense clusters of charged groups on the exchangers" and "A protein must displace the counterions and become attached";
- Chapter 6, page 147, last paragraph, and page 154, last paragraph), according to which changes in pH and ionic strength affect the adsorption, and in particular that "two general methods for eluting proteins are available, are (1) to change the buffer pH - i.e. higher pH for a cation exchanger; and (2) to increase ionic strength, thereby weakening the electrostatic interaction between protein and adsorbent". Hence, it was generally known that two operating conditions were vital to the non-binding of a protein onto the adsorbent, i.e. the buffer pH and the ionic strength, so that for a cation exchanger an increase of the buffer pH or of the ionic strength weakens the electrostatic interaction between protein and adsorbent;
- Chapter 6, pages 158, table 6.3, showing some examples of choice of ion exchange and buffer pH depending on the pI; and pages 159-160, concerning the trials to determine ion-exchange behaviour.

(c) D39, in particular page 6 heading "Charge"; page 7 for the selection of a buffer, see points 1 to 6; page 126, last paragraph; pages 128 (preparation) and 129 (Point 4, Notes 1, 2) to 130 (Notes 4 and 5); page 159; page 458, Figure 1; page 462, note 10), according to which the skilled person knows how to determine the pI of a protein), at which temperature the method is to be carried out, and in particular confirming that pH and ionic strength are essential operating conditions.

3.3.3 The decision under appeal does not deal with the above common general knowledge, let alone does it show that it could not supplement the allegedly insufficiently disclosed "amount of evidence provided in the patent in respect of the variations of the claimed operating conditions pH and conductivity" (page 7 of the decision).

3.3.4 Instead, the contested decision held that claim 1 was broad, that the recovery defined therein was achieved only for some operating conditions, that the examples were anyhow not reproducible, relying only on allegedly proven failure apparent only from the patent itself, hence without however relying on experimental evidence of the Opponents themselves on non-working embodiments, or on embodiments carried out under operating conditions lying outside of the claimed window e.g. to show that the claimed window was set arbitrarily.

3.3.5 Concerning the point that the patent in suit showed that the at least 90% recovery of the monomeric form was achieved for one mAB (IL13) only at a pH of 6.5 (which is at the center of the range proposed in claim 1) and at 3 conductivity values (4.8, 5.8 and 6.8 mS/cm) which cover the lower half of the range of claim 1, the Board notes that it is established case law (9th edition, 2019, II.C.7.1.4 (regarding "broad claims") and II.C.7.3 (regarding "level of disclosure required for antibodies", e.g. T 386/08) that

- an invention may be objected for lack of sufficiency disclosure if there are serious doubts, substantiated by verifiable facts. The mere fact that a claim is broad is not in itself a ground for considering a non-compliance with the requirement of sufficiency under Article 83 EPC;

- the concept of sufficiency of disclosure over the whole scope of the claim does not mean that it has to be demonstrated that each and every conceivable embodiment of a claim could be obtained; in line with G 1/03 (OJ 2004, 413), there may be situations where the specification contains sufficient information on the relevant criteria for finding appropriate alternatives ("variants") over the claimed range with reasonable effort. Under these circumstances the non-availability of certain variants encompassed by the claim at the priority date is considered immaterial for sufficiency .

Moreover, claim 1 at issue does not require that at least 90% of the monomeric form of any specific immunoglobulin has to be obtained at any pH conductivity and sum thereof within the given ranges.

3.3.6 For the Board, the fact that not all exemplified pH and conductibility conditions defined in claim 1 can be applied to the specific antibody of e.g. example 1 for obtaining the claimed recovery does not mean that a failure is encountered in large part of the claimed window of operating conditions.

Instead, tables 1 and 2 of example 1 show how to scout for pH and ionic strength, by creating simple matrices of conditions, which do not appear to go beyond the trials (to be undertaken by the skilled person) mentioned e.g. in D37 to D39.

It is thus not apparent either that the operating conditions (ranges) defined in claim 1 are arbitrary.

Instead, as Example 1 shows at least two or three specific sets of operating pH and conductivity values

permitting the recovery as defined in claim 1 for a mAB, at least one way of carrying out the claimed invention is therein disclosed.

3.3.7 Concerning the objection that Example 2 did not show the achievement of the claimed recovery of at least 90%, and that example 3 dealt with an undefined mAB Her2 (no pI disclosed) which was treated according to a method with undefined pH and conductivity, the Board concurs with Appellant's explanation (D40, IV.33), that Example 2 does not show the achievement of at least 90% recovery of the monomeric form, because the same mAB of example 1 - albeit with a different monomer/aggregate - was fed to columns comprising cationic membranes different from that of example 1 but under the same best pH and conductivity conditions as in example 1. Thus, example 2 does not fall under claim 1 at issue, and the fact that such example does not achieve the sought-for recovery does not mean that it shows that the technical teaching of the patent in suit on the essential operating conditions is insufficient, but that it has to be optimised for each membrane.

Example 3 lacks the information of pH and conductivity, hence it does not fall under claim 1 at issue either. However, as it shows that the effect is achieved, despite being incomplete, it cannot show that the invention does not work. In any case, even if example 3 were non-reproducible, this would not mean an insufficiency of disclosure of the claimed invention.

3.3.8 Thus, former Opponent 1 has cast doubts referring to the examples in the patent in suit, without providing any evidence of its own substantiated with verifiable facts of the alleged insufficiency.

3.3.9 Summing up, the alleged insufficient guidance in the patent fails to convince the Board because:
- it did not consider common general knowledge,
- it does not disprove that at least example 1 shows how to scout for the defined operating conditions, and
- it is only based on allegedly failing examples of the patent in suit, and not on "serious" doubts backed by verifiable facts.

Therefore, the Board does not need to further consider the post-published evidence, apart from the way of carrying out the calculation filed by the Appellant, to assess the plausibility of the technical effect across the whole breadth of claim 1 without undue burden, e.g. in favour of the Appellant.

3.4 As regards the objection that the proprietor's late-filed calculation to determine the recovery from the data of examples was not derivable from the patent, the Board agrees with proprietor's arguments, insofar as the table of the examples only mention an overall and/or percent yield (i.e. the amount of the purified immunoglobulin compared to that of the immunoglobulin present in the loaded sample), whilst the recovery defined in claim 1 concerns the relative amount of the monomeric form of the immunoglobulin retrieved after purification from the aggregates compared with the amount loaded on the column, and is calculated only on the basis of data in the examples (so it is at least implicit from these latter).

As a case in point, the fact that the yield rather than the recovery was tabulated, i.e. the implicit character of the proposed calculation, is apparent e.g. from the values disclosed in Table 3 for Sample 1, comprising 14.71 mg of mAB IL13 (and having a volume of 11 ml,

i.e. a concentration of 1.34 mg/ml, whereby the concentration of the monomeric form is 94.8%), the effluent of which amounts to 1.02 mg which, when divided by the loaded amount (14.71 mg), gives a percent yield of mAB IL13 immunoglobulin as low as (1.02/14.71)x100 = 6.9%, as indicated in table 3. The same calculation can be done for all the samples and yields the same result. Hence, the yield indicated in Table 3, and correspondingly in the other tables such as Tables 4, 5 and 6, does not refer to the amount of monomeric form of the immunoglobulin and does not represent the recovery rate defined in claim 1 at issue. This applies *mutatis mutandis* to the data of Table 2, as pointed out by the Appellant. As a consequence, the calculation of the (implicitly disclosed) recovery is necessary, and Example 1 and Table 2 implicitly show at least three sets of specific conditions under which the claimed recovery is obtained, as argued by the Appellant (D40, IV.32 and D45, II.1).

3.5 Furthermore, contrary to the decision under appeal, no proof of insufficiency, based on verifiable facts, has been brought up by any of the (former) Opponents, not even in support of the objection that the invention cannot be carried out across its whole breadth.

3.5.1 The objection is only based on the argument that the experimental data in the patent provided substantial evidence that the method of obtaining an immunoglobulin in a monomeric form could not be carried out over the entire scope of claim 1, as they showed that repeated failure was encountered in a substantial part of the claimed ranges and that this was not an occasional failure. The objection fails to convince the Board, as already dealt above, in so far as it merely casts doubt

without any substantiated evidence with verifiable facts.

3.5.2 The respondents further filed (during the opposition proceedings) prior art disclosing the strategies according to which the common general knowledge on cation exchangers was applied to the particular purification of proteins, namely:

D4: e.g. pages 15 and 16 on the predictability of the binding of the immunoglobulins or e.g. of the aggregates, as dependent on e.g. the pI thereof. It has not been shown that guidance on the determination of the pI of an immunoglobulin was not (generally) known and/or required undue burden.

D7: page 61, right column, first full paragraph and Figure 5, which albeit concerning a disclosure for "binding" mABs shows that pH and ionic strength given in terms of conductivity (without indication of the temperature) were important operating conditions in ion exchange purification of mABs.

D10: page 58, first full paragraph, disclosing that flow-through mode in ion exchange chromatography was a known useful strategy.

D11: page 219, left column, Ion-exchange chromatography, to page 220, left column, which discloses the general strategies in relation to pI and pH of operation for (not)binding mABs on the exchange media as well as the necessity for the determination of the appropriate pH for optimal separation therefrom.

Therefore, whilst the alleged insufficiency across the whole breadth has not been proven with verifiable facts, the above documents invoked by the (former) Respondents appear to show that
- the skilled person knew how to determine the pI of mABs, eg to predict the binding of the mAB or of its aggregates;
- ion-exchange chromatography operated in through-flow mode was a known strategy; and
- also this strategy was based on pH and conductivity, as defined in claim 1 at issue.

As the skilled person could determine the pI, when not available, and scout for pH and conductivity, as shown in tables 1 and 2 of the patent, also these/further grounds/objections of insufficiency do not succeed.

3.6 It thus remains to decide on the further argument that undue burden and trial and error of multiple parameters were required to reproduce the invention.

3.6.1 In this respect, the (former) Respondents argued that:

- neither the patent nor common general knowledge provided any experimental support or reasoning justifying the choice of the limits of the ranges for pH and conductivity. Furthermore, the choice of the sum of pH and conductivity and its range was arbitrary;

- according to the general principle of purification with cation exchange material, the separation occurred due to charge interactions between the antibody and the material, which was also influenced by an (in the patent) unknown factor,

the isoelectric point of the antibodies tested, which varied between 5.5 and 9.5;

- the claimed method was not the separation of two different molecules with different charges but the monomeric form from the aggregated forms of the same immunoglobulin, whereby the behaviour of the aggregates in comparison to their monomers regarding the separation by a cation exchange membrane was not predictable, and the patent did not provide any guidance in this regard, so that the skilled person was not able to draw any conclusions regarding the conditions of pH and conductivity for a particular antibody to purify;

- it was not sufficient for the skilled person to test any antibody having any pI under the pH and conductivity conditions defined in the claim in order to achieve a yield of more than 90% of monomer, because the limits of the ranges were chosen randomly and the range of the possible isoelectric points was wider than the range of pH allowed in the claim;

- it was not plausible that for an antibody with a high isoelectric point, which is clearly negatively charged at the highest pH of 8 allowed by the claim and at conductivity of maximum 7 mS/sec and for an antibody with a low pI close to the lower end of the pH range which might be only weakly charged that the same effect on the separation of monomers from aggregates could be obtained with any cation-exchange membrane;

- the unpredictability was shown in examples 1 and 2 of the patent, with in example 1 the "strong"

cation exchange membrane Mustang™S being able to separate the monomers from the aggregates whereas in example 2 another "strong" cation exchange membrane Sartobind™ did not allow to separate the monomers under same conditions;

- hence, the patent did not generally disclose the suitable membranes to be used with each antibody, nor a mechanism which could guide the skilled person towards the selection of the operating conditions;

- furthermore not only the pH, the conductivity and the cation-exchange membrane were features influencing the yield of monomers but also the flow rate (see § 32 of patent) played a role;

- as trial and error experiments of multiple parameters were required for possibly achieving a more than 90% yield of monomers the skilled person was faced with a complete research program which went beyond a limited amount of routine trial and error experiments.

3.6.2 The Board cannot accept these arguments for the reasons already detailed *supra* for the operating conditions, as well as because it is generally known e.g. from D37 to D39 (*supra*) that the essential operating conditions for carrying out a cation exchange chromatographic separation, be it flow-through or bind and elute, are pH and ionic strength or actual ionic strength as measured by conductivity. Moreover, it was known before the priority date that these essential operating conditions were to be optimised to the specific protein/antibody and ion exchange membrane material (D38, D7, D11, *supra*), whereby information concerning

the membrane is obtainable from the manufacturer (i.e. this information is somehow implicit from the indication of membrane type/model) and the pI of the antibody can be determined by standard methods (e.g. D39, *supra*). Hence, pH and conductivity cannot be arbitrary conditions.

Moreover, the skilled person has already some information on the antibody to be purified, in e.g. paragraphs [0060] to [0062], [0066] and [0073] of the patent, and on the membranes, the value of which has not be dealt with by the Opponents.

For the Board, the (former) Opponents have not proven with verifiable facts that these determinations could not be carried out, nor that scouting for pH and ionic strength, as shown in tables 1 and 2 of the patent in suit, required undue burden. Again, already for these reasons, there is no need to go further into detail with the post-published data of the Appellant.

3.7 Finally, concerning the objection that the determination of the % of monomeric form had been carried out on the basis of its relevant content in the protein A eluate before the further treatments described in the examples, which treatments changed the content of the monomeric form, and so the yield of monomeric form mentioned in the examples, the Board notes that no evidence is on file showing that any of the conditions mentioned in the examples is likely to increase the relative content of monomeric form before applying the samples to the column. Hence the Board sees no reason not to follow the arguments given by the Appellant in D45 (point II.2) in this respect.

3.8 The Board thus concludes that the disclosure of the invention in the patent in suit as granted is sufficient, in particular as regards the defined minimum recovery of the monomeric form, contrary to the findings in the decision under appeal.

4. Amendments

For the Board, the claimed subject-matter is based on at least original claims 1, 2, 9, 12, 14, 18 and 23. Each of these claims referring back to any one of the preceding claims, their combination is at least implicitly and unambiguously disclosed thereby. It follows that there is no reason to deviate from the decision under appeal on this ground.

5. Remittal

Under Article 11 RPBA 2020 the Board may remit the case to the department whose decision was appealed if there are special reasons for doing so.

In the present case, substantive issues (such as novelty and inventive step) raised in opposition proceedings are not dealt with in the decision under appeal nor have the parties submitted their case on these issues in the appeal proceedings.

Under these circumstances, the Board holds that such special reasons are apparent in the present case.

As recalled in Article 12(2) RPBA 2020, the primary object of the appeal proceedings is to review the decision under appeal in a judicial manner. This principle would not be respected if the Board were to conduct a complete examination of the patent for

compliance with the requirements of Articles 54 and 56 EPC for which no decision of the first instance exists yet. Therefore, the Board considers it appropriate to remit the case to the opposition division (see also T 1966/16, point 2.2 of the reasons).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution.

The Registrar: The Chairman:

A. Pinna J.-M. Schwaller

Decision electronically authenticated