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Datasheet for the decision of 22 April 2022

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Application Number: 10760856.4

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Language of the proceedings: EN

Title of invention:
CATION EXCHANGE CHROMATOGRAPHY

Patent Proprietor:
E. R. Squibb & Sons, L.L.C.

Opponents:
GlaxoSmithKline Intellectual Property Development Limited
F. HOFFMANN-LA ROCHE

Headword:

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2), 25(1)

Keyword:
Inventive step - (no)
Late-filed auxiliary request - admitted (no)

Decisions cited:
T 0248/13, T 1904/16

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 0314/19 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 22 April 2022

Appellant: (Patent Proprietor)	E. R. Squibb & Sons, L.L.C. Route 206 and Province Line Road Princeton, NJ 08540 (US)
Representative:	Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Appellant: (Opponent 1)	GlaxoSmithKline Intellectual Property Development Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	Telfer, Ruth Marie GlaxoSmithKline Global Patents, CN9.25.1 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Appellant: (Opponent 2)	F. HOFFMANN-LA ROCHE Grenzacherstrasse 124 CH-4070 Basel (CH)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 November 2018 concerning maintenance of the European Patent No. 2480561 in amended form.**

Composition of the Board:

Chairman	M. Maremonti
Members:	S. Bertrand
	R. Romandini

Summary of Facts and Submissions

I. The appeals by opponents 1 and 2 and the patent proprietor lie from the interlocutory decision of the opposition division that European patent No. 2 480 561 in amended form according to auxiliary request 2b comprising the set of claims filed on 13 August 2018 met the requirements of the EPC.

II. Claim 1 according to auxiliary request 2b considered allowable by the opposition division reads as follows:

"*1. A method of purifying a protein of interest from a mixture comprising the protein of interest and one or more contaminants, comprising:*

(a) determining the pI of the most acidic isoform of the protein of interest in the mixture, wherein the mixture is produced from culturing a host cell that expresses the protein of interest;

(b) contacting the protein of interest with a cation exchange resin at a first pH that is less than the pI of the most acidic isoform of the protein of interest, such that the protein of interest binds to the resin;

(c) washing the cation exchange resin at a second pH that is greater than the first pH, but 0.1 to 0.6 pH units less than the pI of the most acidic isoform of the protein of interest; and

(d) eluting the protein of interest from the resin at a third pH that is equal to or less than the first pH, thereby purifying the protein of interest."

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

D1 WO 2009/058812 A1

D3 M. Vlckova et al., Journal of Chromatography A, 1181, 2008, 145-52

D9 Ion Exchange Chromatography & Chromatofocusing, Amersham Biosciences, 2004

D13 Y.Y. Zhao et al., Plos One, 2016, 1-13

IV. In the impugned decision, the opposition division's conclusions on the then pending requests included that the subject-matter of claim 1 of auxiliary request 2a lacked clarity and that the subject-matter of the claims according to auxiliary request 2b was novel and involved an inventive step over D1 taken as the closest prior art.

V. In their statements setting out the grounds of appeal, opponents 1 and 2 contested the reasoning of the opposition division and submitted, *inter alia*, that the subject-matter of the claims of auxiliary request 2b did not involve an inventive step starting from D1 as the closest prior art.

VI. In its statement setting out the grounds of appeal, the patent proprietor submitted, *inter alia*, that, contrary to the conclusion of the opposition division, claim 1 of auxiliary request 2a complied with Article 84 EPC.

VII. In their replies to the statements of grounds of appeal, opponents 1 and 2 and the patent proprietor rebutted the arguments of the adverse party.

VIII. Since the patent proprietor and the opponents are both appellants and respondents in these appeal proceedings,

they are referred to as "proprietor", "opponent 1" and "opponent 2" in the following.

IX. The board issued a communication pursuant to Article 15(1) RPBA in preparation for the oral proceedings.

X. In a further letter, the proprietor withdrew its previously filed main request and auxiliary request 1.

XI. Oral proceedings before the board were held on 22 April 2022 by videoconference. During the oral proceedings, the proprietor filed a new set of claims as auxiliary request 2c.

XII. The parties' final relevant requests are as follows.

Opponents 1 and 2 request that the decision under appeal be set aside and that the patent be revoked in its entirety.

The proprietor requests:

- as its main request, that the patent be maintained on the basis of the set of claims filed on 13 August 2018 as auxiliary request 2a;

- alternatively, that the patent be maintained on the basis of one of the sets of claims of auxiliary requests 2b, 2c, 3a and 3b. Auxiliary requests 2b, 3a and 3b were filed on 13 August 2018, while auxiliary request 2c was filed during the oral proceedings before the board.

XIII. The patent proprietor's case, where relevant to the present decision, may be summarised as follows.

- Main request - inventive step

  - The subject-matter of claim 1 involved an inventive step in view of example 2 of D1.

  - Example 2 of D1 disclosed a purification method comprising removing contaminants from Bevacizumab using cation exchange chromatography.

  - The distinguishing features of claim 1 were the washing pH of step (c) and the eluting pH of step (d).

  - The objective technical problem was the provision of an improved protein purification method.

  - The solution proposed by claim 1 was not obvious in view of D1 or the remaining documents invoked by the opponents.

- Auxiliary request 2c - admittance

  - The claim set according to auxiliary request 2c was filed in response to the board's conclusion that the eluting pH was not a distinguishing feature of claim 1 of the main request. In claim 1 of auxiliary request 2c, merely one alternative was deleted. The opponents should have been prepared for this possibility.

  - The request could not have been filed earlier since the representative took over the proprietor's case at a late stage of the appeal proceedings.

XIV. Opponents 1 and 2's case, where relevant to the present decision, may be summarised as follows.

- Main request - inventive step

  - The subject-matter of claim 1 did not involve an inventive step in view of example 2 of D1.

  - The distinguishing feature of claim 1 was only the washing pH of step (c), i.e. the pH used for washing the cation exchange resin.

  - The objective technical problem was at most the provision of a method for purifying a protein of interest resulting in higher contaminant removal.

  - The solution proposed by claim 1 was obvious in view of D1. The passage of D1 on page 27, lines 16 to 25, taught that the efficacy of purification was significantly improved by conducting the washing step of D1 at a pH of 7.0 or 7.8. Furthermore, the passage on page 4, line 29 to page 5, line 10, of D1 taught a washing pH of 6.8 to 8.0 for the purification of Bevacizumab. Finally, D9 evidenced that scouting for optimum pH was to be made at 0.5 to 1 pH unit away from the pI of the protein of interest.

- Auxiliary requests 2b, 3a and 3b - claim 1

  - The subject-matter of claim 1 of auxiliary requests 2b, 3a and 3b lacked an inventive step for the same reasons as for claim 1 of the main request.

- Auxiliary request 2c - admittance

  - Claim 1 of auxiliary request 2c comprised subject-matter which changed the direction of the discussion on inventive step. This was an amendment of the proprietor's case. Auxiliary request 2c was not to be admitted into the proceedings pursuant to Article 13(2) RPBA 2020.

Reasons for the Decision

Main request (set of claims filed on 13 August 2018 as auxiliary request 2a)

1. Claim 1 of the main request reads as follows:

"*1. A method of purifying a protein of interest from a mixture comprising the protein of interest and one or more contaminants, comprising:*

(a) determining the pI of the most acidic isoform of the protein of interest in the mixture, wherein the mixture is produced from culturing a host cell that expresses the protein of interest;

(b) contacting the protein of interest with a cation exchange resin at a first pH that is less than the pI of the most acidic isoform of the protein of interest, such that the protein of interest binds to the resin;

(c) washing the cation exchange resin at a second pH that is greater than the first pH, but about 0.1 to about 0.6 pH units less than the pI of the most acidic isoform of the protein of interest; and

(d) eluting the protein of interest from the resin at a third pH that is equal to or less than the first pH, thereby purifying the protein of interest."

The pI is the isoelectric point. The isoelectric point of a molecule (e.g. a protein) is the pH at which the molecule carries no net electrical charge.

In the following, the first, second and third pHs as mentioned in claim 1 are referred to as the loading pH, the washing pH and the eluting pH, respectively.

Inventive step - claim 1

2. Opponents 1 and 2 objected to inventive step in view of D1, example 2, as the closest prior art. The proprietor also argued inventive step starting from D1, example 2.

2.1 Example 2 of D1 (pages 34 to 37) discloses a purification method comprising removing contaminants from Bevacizumab using cation exchange chromatography (page 34, lines 25 to 28). Bevacizumab is an antibody (page 34, lines 11 to 13). The conditions for the cation exchange chromatography of example 2 of D1 are described as follows (table 3 of D1): loading pH of 5.5 ± 0.2, washing pH of 7.0 ("Wash 1" in table 3 of D1), eluting pH of 5.5. The pI of the most acidic form of Bevacizumab is not stated in D1. However, its value can be found in D3 or D13. According to D3 (table 1, page 150), this pI is 8.26 or 8.27. According to D13, the pI of the most acidic form of "Avastin" (the brand name of Bevacizumab) is 7.8 to 8.4 (last paragraph on page 7/13).

2.2 Distinguishing features

As set out above, Bevacizumab is an antibody and thus represents a protein of interest as required by claim 1

of the main request. The purification method of example 2 of D1 (table 3) comprises the step of contacting Bevacizumab with a loading pH of 5.5 ± 0.2, i.e. a loading pH less than the pI of Bevacizumab, as required by step (b) of claim 1 of the main request. Then a washing step ("Wash 1") is carried out at a washing pH of 7.0, i.e. greater than the loading pH (5.5 ± 0.2) and less than the pI of the most acidic isoform of Bevacizumab (8.26 or 8.27 according to D3 or 7.8 to 8.4 according to D13). A final step of eluting Bevacizumab is done at an eluting pH of 5.5, which is equal to the loading pH, as required by step (d) of claim 1 of the main request.

It was common ground that the step of determining the pI of the most acidic isoform of Bevacizumab (step (a) of claim 1) was implicitly disclosed in example 2 of D1.

Thus, the subject-matter of claim 1 of the main request differs from example 2 of D1 only in the washing pH of step (c), i.e. the pH used for washing the cation exchange resin. In example 2 of D1, this washing pH is 7.0 while it should be, according to step (c) of claim 1 of the main request, within the range of 7.66 to 8.16 or 7.67 to 8.17 considering a range of 0.1 to 0.6 pH units less than the pI of Bevacizumab as disclosed in D3 (8.26 or 8.27) or within the range of 7.2 to 8.3 if the pI of Bevacizumab as disclosed in D13 (7.8 to 8.4) is considered.

The proprietor submitted that the eluting pH (referred to in step (d) of claim 1 of the main request) was also a distinguishing feature of claim 1 of the main request since the eluting pH disclosed in example 2 of D1 (5.5) could also be higher than the loading pH. In D1, the

latter was not a specific pH but a range of pH values from 5.3 to 5.7.

The board does not agree. As submitted by the opponents, the value disclosed in D1 for the loading pH ("5.5 ± 0.2") is considered by the skilled person to be an experimental value corrected by error margins since the value is disclosed in an embodiment of D1 (example 2) and not a general teaching in a claim or the description of the invention. Thus, the skilled person would not consider this disclosed value a range as submitted by the proprietor. Thus, this argument of the proprietor must fail.

2.3 Technical effect and objective technical problem

The proprietor relied on the results of examples 1 and 2 and Figure 3a and 3B of the patent. It argued that the effect achieved by the higher washing pH according to claim 1 of the main request (i.e. 0.1 to 0.6 pH units less than the pI of the most acidic isoform of the protein to be separated) was increased contaminant removal in comparison to the process disclosed in example 2 of D1.

Therefore, the objective technical problem had to be seen in the provision of an improved protein purification method.

In the following, the board, for the sake of argument and in the proprietor's favour, accepts this formulation of the objective technical problem.

2.4 Obviousness

As submitted by opponents 1 and 2, D1 teaches the solution proposed by claim 1 of the main request. The passage of D1 on page 27, lines 16 to 25, teaches that

the efficacy of purification can be significantly improved by conducting the washing step at a high pH. This passage further teaches that by "*using a wash buffer with a pH of 6.8 to 9.0 (e.g. from about 7.0 to 8.0)**, such as, for example, about 7.8** or about 7.0 contaminants as described above are removed more efficiently than using the conventional lower pH range of about 5.0 to about 5.5*" (emphasis added by the board). Thus, the skilled person faced with the above objective technical problem would have considered carrying out the washing step disclosed in example 2 of D1 at a higher pH, e.g. at a pH of 7.8, to remove more contaminants. In doing this, the skilled person would have thus arrived at the subject-matter of claim 1 of the main request without exercising any inventive skill.

The patent proprietor submitted that there was no teaching in D1 prompting the skilled person to change the washing pH of example 2 of D1 (7.0) to a value of 7.8. The passage on page 27 disclosed only the preferred pH values (7.8 or 7.0) used in the examples. A pH of 7.0 corresponded to the washing pH in example 2 of D1, and a pH of 7.8 was the washing pH of example 1 of D1.

The board does not agree. There is no link between the general teaching of the two preferred washing pH values referred to on page 27 (7.8 and 7.0) and the values used in examples 1 and 2 of D1. Furthermore, even if this argument were accepted, the skilled person would not disregard the teaching on page 4, line 29 to page 5, line 10 of D1. This passage refers to the purification of Bevacizumab by cation exchange chromatography (as in example 2) and teaches a washing pH of 6.8 to 8.0. Thus, the skilled person would not be

inclined to exclude any pH from that range when trying to solve the objective technical problem.

2.5 In view of the above, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step in view of D1 taken as the closest prior art (Article 56 EPC).

Thus, the main request is not allowable.

Auxiliary requests 2b, 3a and 3b

3. Claim 1 of auxiliary request 2b differs from claim 1 of the main request in that the term "about" in step (c) was deleted. The washing pH is greater than the loading pH but 0.1 to 0.6 units less than the pI of the most acidic isoform of the protein of interest.

4. Claim 1 of auxiliary request 3a differs from claim 1 of main request in that the range from 0.1 to 0.6 pH units defining the washing pH of step (c) was replaced by the values "about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 pH units".

5. Claim 1 of auxiliary request 3b differs from claim 1 of auxiliary request 3a in that the term "about" was deleted. The washing pH is greater than the loading pH but "0.1, 0.2, 0.3, 0.4, 0.5, 0.6 pH units less than the pI of the most acidic isoform of the protein of interest".

6. The proprietor did not indicate any technical effect of the amendments made in claim 1 of auxiliary requests 2b, 3a and 3b going beyond the technical effect put forward for claim 1 of the main request (see above). It follows that the same board's observations on lack of inventive step of the subject-matter of claim 1 of the main request apply *mutatis mutandis* to the subject-

matter of claim 1 of auxiliary requests 2b, 3a and 3b. This conclusion was not disputed by the proprietor during the oral proceedings.

Thus, the board concludes that the subject-matter of claim 1 of each of auxiliary requests 2b, 3a and 3b does not involve an inventive step in view of D1 for the same reasons as those given for the subject-matter of claim 1 of the main request (Article 56 EPC).

Therefore, auxiliary requests 2b, 3a and 3b are not allowable.

Admittance of auxiliary request 2c into the proceedings

7. During the oral proceedings, the proprietor submitted a claim set according to auxiliary request 2c.

Claim 1 of auxiliary request 2c corresponds to claim 1 of auxiliary request 2b except that in step (d), the term "equal to or" was deleted, i.e. the eluting pH is required to be less than the loading pH.

7.1 The opponents requested that auxiliary request 2c not be admitted into the appeal proceedings.

7.2 The admittance of this request is subject to the criteria set out in Article 13(2) RPBA 2020, which applies to the case at hand in accordance with the transitional provisions set out in Article 25(1) RPBA 2020. Under this provision, any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances justified with cogent reasons by the party concerned.

7.3 According to the proprietor, the claim set according to auxiliary request 2c was filed in response to the

board's conclusion at the oral proceedings that the eluting pH was not a distinguishing feature of claim 1 of the main request. Moreover, in claim 1 of auxiliary request 2c, only one alternative was deleted; the opponents should have been prepared for this possibility. Claim 1 of auxiliary request 2c was not amended by inserting any feature from the description. Therefore, no delay of proceedings was to be expected.

7.4 The board does not agree. First, the eluting pH of claim 1 of the main request corresponds to the eluting pH of claim 1 as granted. In the impugned decision (points 4.1.2 to 4.1.5, pages 8 to 11), the opposition division concluded that claim 1 as granted was not novel in view of example 2 of D1, meaning that the eluting pH of claim 1 of the main request was disclosed in example 2 of D1 and did not represent a distinguishing feature. The same was argued by opponent 1 in its statement of grounds of appeal (point 38, page 10) and by opponent 2 in its statement of grounds of appeal (point 99, page 24). This conclusion was confirmed by the board in its communication pursuant to Article 15(1) RPBA 2020. In this communication (point 15.1), the board gave the preliminary view that the eluting pH of claim 1 as granted was disclosed in example 2 of D1. Thus, the board's conclusion during the oral proceedings that the eluting pH was not a distinguishing feature of claim 1 of the main request was merely a reiteration of what had been concluded by the opposition division and objected to by the opponents at the beginning of the appeal proceedings. As such, this conclusion cannot be surprising for the proprietor that could and should have filed an appropriate claim request with an eluting pH different from that disclosed in example 2 of D1 with its statement of grounds of appeal or its reply to the

appeals of the opponents. The proprietor did not even file this request as a prompt response to the board's preliminary opinion but instead waited until the oral proceedings, i.e. the latest possible stage of the appeal proceedings.

Even if only one alternative was deleted from claim 1 of the main request and no feature of the description was incorporated into claim 1 of auxiliary request 2c, this deletion amounts to a substantial amendment of the claimed subject-matter since it inserts an additional distinguishing feature and thus changes the case on inventive step. This would be surprising for the opponents. It is not the task of an opponent (or the board) to speculate about what amendments a proprietor might make at a very late stage of the proceedings and prepare pre-emptively for all of them (T 0248/13, reasons, 4.5).

Furthermore, the proprietor submitted that the request could not have been filed earlier since the representative had taken over the proprietor's case at a late stage of the appeal proceedings.

The board does not agree.

A change of representative belongs to the sphere of the party affected (here the proprietor) and, being extraneous to the proceedings, cannot influence whether a procedural action is considered done in a timely manner. On the contrary, a new representative is bound by the procedural actions performed by its predecessor and continues the proceedings from the point its predecessor reached when it takes over. Thus, a change of representative is not sufficient justification for

late filing of a request that could and should have been filed earlier (T 1904/16, reasons, 16.4).

For the reasons set out above, there are no exceptional circumstances justified by cogent reasons for the filing of auxiliary request 2c only at the oral proceedings.

7.5 Therefore, the board decided not to admit auxiliary request 2c into the appeal proceedings in accordance with Article 13(2) RPBA 2020.

8. Conclusion

None of the proprietor's requests is allowable and admissible.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow M. Maremonti

Decision electronically authenticated