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Datasheet for the decision of 6 December 2011

Case Number: T 0949/10 - 3.3.06

Application Number: 05722175.6

Publication Number: 1718386

IPC: B01D 15/08, C07K 16/00

Language of the proceedings: EN

Title of invention:
A process for the purification of antibodies

Applicant:
GE Healthcare Bio-Sciences AB

Opponent:
-

Headword:
Multimodal ion exchange resins/GE HEALTHCARE

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step: no-obvious combination of known technical means"

Decisions cited:
-

Catchword:
-

Case Number: T 0949/10 - 3.3.06

D E C I S I O N
of the Technical Board of Appeal 3.3.06
of 6 December 2011

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 21 December 2009 refusing European patent application No. 05722175.6 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: P. Ammendola
Members: L. Li Voti
J. Geschwind

Summary of Facts and Submissions

I. This appeal lies from the decision of the Examining Division to refuse European patent application No. 05 722 175.6, relating to a process for the purification of antibodies.

II. As regards the then pending sets of amended claims, the Examining Division, by referring *inter alia* to documents:

(3): WO 02/05959 and
(6): US-B-6498236,

found in its decision that

- the technical problem underlying the invention consisted in the further purification of an antibody material obtained from a first multimodal chromatographic step;

- the claimed subject-matter differed from the chromatographic methods disclosed in documents (3) or (6) only insofar as the eluate from the first chromatographic step was passed through a second chromatography resin;

- since multi-step chromatography was known to the skilled person, it would have been obvious for the skilled person to try to purify further the eluate from the chromatographic step of the known methods by passing it through another chromatography resin having multimodal ligands or a conventional chromatography resin;

- therefore, the claimed subject-matter lacked an inventive step.

III. An appeal was filed against this decision by the Applicant (Appellant).

The Board cited in its communication of 6 May 2011 documents (8): **US-A-2002/0002271** and (9): **Protein Purification Handbook**, pages 1 to 97, by Amersham Pharmacia Biotech AB 1999.

The Appellant submitted with letter of 27 June 2011 an experimental report. Moreover, following the summons to oral proceedings, it submitted with letter of 7 October 2011 an amended set of claims and document (10): **Antibody Purification Handbook,** Chapter 7, Large-scale purification, pages 77 to 80, by Amersham Biosciences AB 2002.

With the letter of 31 October 2011 the Appellant communicated to the Board that it would not attend the oral proceedings scheduled for 6 December 2011 and requested a decision based on the current state of the file, in particular based on the amended claims submitted on 7 October 2011.

Oral proceedings were held on 6 December 2011 in the absence of the Appellant.

IV. Claim 1 of the sets of claims of 7 October 2011 reads as follows:

"1. A process for the purification of one or more antibodies from a liquid, which process comprises contacting said liquid, which is a cell culture liquid or a fermentation broth, with a first chromatography resin comprised of a support to which multi-modal ligands have been immobilised to adsorb the antibodies to the resin, wherein each multi-modal ligand comprises at least one cation-exchanging group and at least one aromatic or heteroaromatic ring system; adding an eluent to release the antibodies from the resin; characterised by contacting the eluate so obtained with a second chromatography resin, which is a multimodal anion exchange resin, and recovering the antibodies from the flow-through of said chromatography resin, wherein the second chromatography step is a polishing step."

V. The Appellant argued in writing substantially that

- the amended claim 1 relates to a two-step process since it is known that a polishing step, the second step of the process of claim 1, is in chromatography the final step of a multistep process, used for obtaining a highly pure product;

- document (6), representing the closest prior art, did not disclose a second chromatographic polishing step operated in flow-through mode, subsequent to the first multimodal chromatographic step, as required in claim 1;

- the technical problem underlying the invention thus could be formulated as the provision of a simplified process for the production of high pure antibodies suitable for therapeutic applications, which process results in high throughput of liquid and an efficient overall process economy;

- even though document (6) suggested in general that the immunoglobulin solution resulting from the multimodal chromatographic step could be purified in a further processing step, this document did not contain any suggestion about how to obtain a high recovery of highly pure antibodies;

- therefore, the skilled person, faced with the technical problem underlying the invention, would have been led from the teaching of document (6) to add detergent in order to increase the recovery of pure antibodies, which step would require an additional removal step for the detergent and would increase the complexity of the process;

- moreover, even though he could have chosen to try a further known method of purification, for example an additional chromatographic step, he would have had to choose among a large number of commercially available chromatography resins which could be operated in many different modes and would have rather selected a three steps process involving capture, intermediate purification and polishing as suggested in the prior art (see e.g. document (10));

- in this respect, the skilled person would have thought that the use of a chromatography resin in flow-

through mode would have been economically acceptable only if the level of residual impurities from the first chromatographic step were sufficiently low, fact that was not guaranteed by the process of document (6);

- therefore, by considering the whole teaching of document (6), the skilled person would have rather chosen an additional more selective chromatographic step in bind-elute mode rather than one in flow-through mode;

- the claimed subject-matter thus involved an inventive step.

VI. The Appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 5, submitted with letter of 7 October 2011.

Reasons for the Decision

1. Inventive step

1.1 The present invention regards a process for the purification of antibodies, such as monoclonal antibodies (see page 1, lines 4 to 5 of the published WO application 2005/082483 to which is referred hereinafter).

As explained in the application, a known method for the isolation of antibodies such as immunoglobulins is chromatography (page 2, lines 14 to 15). Industrial chromatography processes often involve more than one

step, starting with a capture step, which is the initial purification of the target molecule from either crude or clarified feed, followed by an intermediate purification step and a final polishing step (page 3, lines 1 to 3).

Examples of chromatography processes used in the prior art are ion exchange chromatography (IEX), hydrophobic interaction chromatography (HIC) and affinity chromatography (page 3, lines 4, 11 to 12 and 25 to 27). In particular, Protein A and Protein G affinity chromatography have become, in combination with IEC, HIC, hydroxyapatite and/or gel filtration steps, the antibody capture method of choice for many biopharmaceutical companies (page 3, lines 25 to 30).

However, HIC requires the addition of lyotropic salts to the raw material to make the immunoglobulin bind efficiently. A disadvantage of this procedure is the increased cost to the large-scale user in terms of lyotropic salt to be used and of the disposal of several thousand litres of waste (page 3, lines 12 to 13 and 16 to 23).

The technical problem underlying the invention thus is defined in the present application as the provision of a further efficient method of purification of antibodies capable of purifying antibodies from smaller volumes of feed than prior art methods without a dilution step for the salt concentration in process feed (see page 6, lines 2 to 3 and 8 to 11).

1.2 It is undisputed that document (6), concerning the same technical problem addressed to in the present

application (see column 2, line 31 to column 3, line 8 and column 3, line 65 to column 4, line 6), represents the most suitable starting point for the evaluation of inventive step.

Since document (6) already solved the technical problem explicitly addressed to in the present application, the Appellant submitted in writing that the technical problem underlying the invention had to be formulated as the provision of a simplified process for the production of highly pure antibodies suitable for therapeutic applications, which process results in high throughput of liquid and an efficient overall process economy.

In the Appellant's view, the experimental results contained in the letter of 27 June 2011 show that the two steps process of claim 1 submitted with the letter of 7 October 2011 provides surprisingly a high recovery of highly pure antibodies and hence solves the above formulated technical problem.

1.3 The Board remarks that said claim 1 does not specify the degree of purity of the obtained antibodies or the antibody recovery to be achieved; moreover, the indication of the second chromatographic step as a polishing one is not sufficient by itself to precise the height of the purity of the recovered antibody. In fact, even though a polishing step is one carried out for achieving high purity by removing trace impurities or closely related substances (see document (9), page 10, second full paragraph from the bottom, and page 40, definition and goal), a purity of only 95% is already considered to be high in this technical field

(see document (9), page 13, table at the bottom page) and further purification steps after the polishing step can be needed to achieve a very high purity (see document (9), page 20, lines 13 to 15).

Therefore, the invention of claim 1 is not limited to the recovery of a high amount of antibodies having a very high purity suitable for therapeutic applications.

As regards the experimental results submitted by the Appellant, they concern only a single process and, precisely, the combination of the capture step of example 3 (erroneously indicated as example 2 on page 26, line 31 of the present application) and the polishing step of example 4 of the present application (see page 27, lines 12 to 17). In such a process a specific combination of multimodal chromatography resins (those of examples 1(b) and 2) were used under specific conditions (see page 24, lines 24 to 29 and page 26, line 31 to page 27, line 3).

However, it was known that for any chromatographic separation, the specific properties of the sample to be purified and the optimisation of the critical parameters and the selection of the most suitable media affect the result to be achieved in terms of level of purification and recovery (see e.g. document (9), page 21, second full paragraph above table 3 as well as page 23, second full paragraph, as well as document (10), page 77, last 10 lines).

Moreover, claim 1 of the present application does not specify any particular process conditions for the first and second chromatographic steps and identifies only

the two generic classes of resins to be used in said first and second step, respectively.

Therefore, the Board concludes that the single example provided by the Appellant cannot be taken as credible evidence that the alleged technical advantages not specified in the present application, i.e. the provision of a simplified process for the production of highly pure antibodies suitable for therapeutic applications, a high throughput of liquid and an efficient overall process economy are achieved by means of any combination of steps involving the use of multimodal chromatographic resins encompassed by the broad wording of claim 1.

The Board thus finds that, starting from the disclosure of document (6), the technical problem underlying the invention can only be formulated as the provision of an alternative chromatographic process for increasing the purity of the recovered antibodies.

The Board is convinced that this technical problem was solved by means of the process of claim 1.

1.4 It is undisputed that document (6) discloses explicitly the first multimodal chromatographic step of the process of claim 1 and discloses a process for the purification of antibodies, which differs from the claimed subject-matter only insofar as it does not disclose a second chromatographic polishing step operated in flow-through mode with a multimodal anionic resin, subsequent to the first multimodal chromatographic step (see e.g. column 4, line 10 to column 5, line 67). In particular, document (6)

discloses a process wherein an anionic surfactant is added to the initial cell culture liquid containing the antibody (see column 36, lines 26 to 29 in combination with column 25, lines 41 to 53), a step not explicitly excluded in present claim 1, and the recovered antibody has a purity greater than 95% (column 36, line 49); moreover, an antibody having a high purity of 95% can be recovered even without addition of the surfactant to the initial liquid, as shown in column 36, lines 1 to 17.

Therefore, even though document (6) teaches that the addition of a detergent to the initial immunoglobulin solution may increase the purity of the recovered antibody (see column 9, lines 27 to 30), it is clear from the overall teaching of document (6) that outstanding purity is also achieved without adding any detergent to the initial solution but by selecting the multimodal exchange resin and the chromatographic conditions (see column 6, lines 22 to 28 as well as the above mentioned passages from column 4, line 10 to column 5, line 67, disclosing the objects of the invention and not mentioning the addition of a detergent).

Since the disclosure of document (6) aimed at obtaining immunoglobulins of high purity, for example of at least 99% (column 8, line 34 and column 10, lines 15 to 19) and taught that the recovered immunoglobulins may be further purified in an additional step (column 7, lines 45 to 47), it would have been obvious for the skilled person to apply any known process of purification of antibodies after the multimodal

chromatographic step disclosed in this document for increasing the purity of the recovered antibodies.

1.5 It was known from the prior art that ion exchange chromatography (IEX), for example anion exchange chromatography, was a suitable polishing step in a purification process (see document (9), page 22, table 4; page 24, lines 5 to 11 under figure 5 and document (10), table 22 on page 78).
Moreover, it was known that a three steps purification, i.e. the combination of capture, intermediate purification and polishing steps, was not necessary if the capture and intermediate purification were achieved in a single step (see document (9), page 20, lines 8 to 10 and page 45, lines 5 to 8); for example, document (9) describes on pages 54 to 56 a two steps purification of a monoclonal antibody.

It thus would have been obvious for the skilled person to omit an intermediate purification in the further purification of the high pure antibodies of document (6) and to try anion exchange resins in the further polishing step.

1.6 Furthermore, it was also known that chromatographic methods used as polishing steps in the purification of antibodies could be operated in flow-through mode (see e.g. document (8) relating to a HIC polishing step, paragraphs 9 to 12, 31, 72 to 75, 113 to 118 and 127); similarly, it was known that IEX used for the purification of antibodies should not be used necessarily in bind-elute mode but it can also be used in flow-through mode by binding the impurities on the

column (see document (9), page 73, lines 3 to 8 below figure 31; document (3), page 1, lines 29 to 33).

Since document (6) disclosed the recovery of antibodies having high purity after one chromatographic step (see point 1.4 above), which purity was by the way even higher than that indicated in the Appellant's own experimental results of 27 June 2011 after the first chromatographic step, the skilled person would have considered a further purification step in flow-through mode to be applicable to such high purity antibodies. No evidence to the contrary was submitted by the Appellant.

Therefore, it would have been obvious for the skilled person to try a second multimodal chromatographic step for further purification of the already high pure antibodies disclosed in document (6) by using in flow-through mode commercially available multimodal anion exchange resins known in the prior art, e.g. those mentioned in the present application (see page 14, lines 9 to 10).

1.7 The Board concludes that the subject-matter of claim 1 submitted with letter of 7 October 2011 amounts to an obvious combination of known technical means and hence does not involve an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

D. Magliano P. Ammendola