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D E C I S I O N
of 24 July 2003

Case Number: T 0731/00 - 3.3.4

Application Number: 90917874.1

Publication Number: 0484464

IPC: C12P 21/00

Language of the proceedings: EN

Title of invention:
Method of cleansing proteins

Patentee:
Octapharma AG

Opponent:
01 Baxter Aktiengesellschaft
02 ZLB Bioplasma AG
03 Baxter Healthcare Corporation
04 COMMON SERVICES AGENCY

Headword:
Cleansing proteins/OCTAPHARMA

Relevant legal provisions:
EPC Art. 56, 83

Keyword:
"Inventive step (no)"

Decisions cited:
T 0301/87, G 0009/92

Catchword:
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Case Number: T 0731/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 24 July 2003

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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 22 May 2000 concerning maintenance of European patent No. 0484464 in amended form.**

Composition of the Board:

Chairman: U. Kinkeldey
Members: M. Wieser
R. Moufang

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietors (appellants) against the interlocutory decision of the opposition division, whereby the European Patent No. 484 464 was maintained in amended form. The patent had been opposed by four parties under Article 100(a) on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), Article 100(b) on the ground of lack of sufficient disclosure (Article 83 EPC) and Article 100(c) on the ground of unallowable amendments (Article 123(2) EPC).

II. Claim 1 of the main request before the opposition division, filed on 10 August 1998, read:

"A method of cleansing an albumin from multivalent metal ions bound thereto, wherein the multivalent metal ions are selected from one or more of the metals aluminium, iron, lead, chromium, mercury, nickel and copper, characterized in that the multivalent metal ions are released from the albumin by substituting them with monovalent metal ions, consisting of alkali metal or ammonium ions, by subjecting the albumin with multivalent metal ions bound thereto to a diafiltration process against an aqueous solution which contains the monovalent metal ions in a concentration from 0.15 M up to saturation, such that said multivalent metal ions are displaced from the albumin and are obtained in a filtrate, after which the multivalent metal ions released from the albumin are removed in a way known per se, and in that after the substitution of the multivalent metal ions with the monovalent metal ions, said monovalent metal ions are removed from the albumin by subjecting said albumin to a renewed diafiltration against a solution which essentially does not contain any metal ions."

III. The opposition division decided that this claim, and also claim 1 of auxiliary request 1 before them, did not involve an inventive step under Article 56 EPC in the light of document

(3) A.G.Welch et al., poster abstract P-M-4-08, International Congress ISBT-BBTS, London 11-15 July 1988.

The decision was based on the finding that no improvement with regard to document (3) was demonstrated and that the skilled person would not stick "slavishly" to the salt concentration disclosed in document (3).

The opposition division decided that the grounds for opposition did not prejudice the maintenance of the patent as amended according to auxiliary request 2 before them.

IV. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 5 filed on 10 August 1998.

The opponents 01 to 04 (respondents I to IV) requested that the appeal be dismissed.

V. With a first letter dated 29 November 2000, and a second letter dated 12 October 2001, the board was informed that the original opponents 02 (Rotkreuzstiftung Zentrallaboratorium Blutspendedienst SRK) had transferred their business assets relating to the development, production and distribution of plasma products to ZLB Bioplasma AG. Copies of the commercial registers of Bern and Zug were added to the letters.

VI. Oral proceedings took place on 24 July 2003 in the absence of respondents I who were duly summoned but informed the board in a letter dated 23 April 2003 that they will not attend.

VII. The submissions made by the appellants may be summarized as follows:

It was not obvious from document (3) or any other prior art document to raise the ionic concentration of the eluent to improve the removal of metal ions from albumin as it was the patent in suit which was the first to recognize that metal ions may be removed from albumin based on the ion-exchange principle. The demonstration of a surprising effect was no precondition for the existence of inventive step if the invention was not prima facie obvious. The inventive merit of the claimed process had been established by experiments showing that the amount of aluminium removed was proportional to the NaCl concentration. The invention was disclosed according to the requirements of Article 83 EPC, as the claims had to be read on workable embodiments which a skilled reader was able to find by routine experiments, not on unworkable embodiments which had to be construed artificially.

VIII. Respondents I did not make any submissions in the appeal procedure.

IX. The submissions of respondents II may be summarised as follows:

The salt concentrations used in document (3) and in the patent in suit were essentially the same and

corresponded both with the lower limit of the physiological conditions. Slight variations within the physiological range were obvious for the skilled person, all the more as the relationship between salt concentration and aluminium removal was known from document (3). It was denied that it were the present inventors who first found that aluminium could be removed from albumin by the ion exchange principle.

X. The submissions of respondents III and IV were as follows:

The claimed process was a routine workshop-variation of the disclosure in document (3). A skilled person, while not being bound exactly to the salt concentration of document (3), would obviously consider to vary this parameter, as it was the only possibility to change or improve the prior art process. The kind of binding between aluminium and albumin was known before the relevant date of the patent in suit. To remove the metal ions from albumin by an ion exchange process was therefore obvious. No significant improvement was seen over document (3) and the invention did not solve the posed problem over the whole scope of the claims. Moreover, claim 1 embraced unworkable embodiments wherein the used high salt concentrations would have caused albumin to precipitate and to clog the filters.

XI. In addition to document (3), the present decision refers to documents

(12) Protein Purification, R.K.Scopes, 2nd edition, Springer Verlag, 1987, pages 19 to 20

(18) Membrane Separations in Biotechnology, Edited by W.Courtney McGregor, M.Dekker Inc., New York and Basel, 1986, Chapter 6, pages 115 to 134

(29) J. of Trace Elem. Electrolytes Health Dis., Vol.3, No.1, 1989, pages 39 to 42

(35) Methods of Plasma Protein Fractionation, Edited by J.M.Curling, Academic Press London, 1980; pages 43 to 44

(39) Biochemical and Biophysical Research Communications, Vol.125, No.3, 1984, pages 1020 to 1024

(40) The Plasma Proteins, Vol. I (Isolation, Characterization and Function), Edited by F.W.Putnam, Academic Press New York and London 1960; Chapter 6, pages 179 to 239

(41) Chambers Dictionary of Science and Technology, Edited since 1940 by Chambers, New York, pages 271 to 272.

Reasons for the Decision

1. The transfer of the opposition indicated by respondents II (see paragraph VI above) was not objected to by the appellants and respondents I, III and IV. The board is satisfied on the basis of the evidence before them that the reported transfer of the relevant business assets and hence of the opposition has in fact taken place.

Article 83 EPC

2. Claim 1 refers to "... a diafiltration process against an aqueous solution which contains the monovalent metal ions in a concentration from 0.15 M up to saturation, ...".

Respondents III and IV argued, by referring to document (35) that a saturated solution of ammonium sulphate corresponds to an approximately 4.06 M solution (page 43, last paragraph). According to figure 10, on page 44, albumin precipitates in a 2.55 M solution of ammonium sulphate.

Therefore, claim 1 is regarded to refer to a number of unworkable embodiments, since due to clogging of filters by precipitated protein, a diafiltration process according to claim 1 is not possible within the entire range of salt concentrations claimed.

3. The board does not agree. The skilled reader is informed on page 3, lines 7 to 10 of the patent in suit, that "... the upper limit (of the salt concentration of claim 1; added by the board) is decided, in principle, by the saturation content of the salt concerned in the solution, although other factors may have significance. For instance some albumins can be denatured by high salt contents. The person skilled in the art, however, will have no difficulty in finding an operable salt content on the basis of simple experiments."

Thus, the person skilled in the art gets instruction what to consider to avoid process parameters that would

be a hindrance for carrying out the invention according to claim 1.

In such a situation, where a skilled person is able to distinguish between workable and non-workable embodiments covered by a claim with the help of simple, routine experiments, addressed in the description, there is no basis to find a claim unallowable under Article 83 EPC because of lack of disclosure.

As the competent board decided in the decision T 301/87 (OJ EPO 1990, 335), the requirement for sufficiency is not a matter of satisfying the perfectionist but to enable the skilled person to handle the invention in normal practice (see point 4.13 of the reasons for the decision).

4. Accordingly, the board decides that the requirements of Article 83 EPC are met.

Article 56 EPC

5. The board agrees with the opinion shared by all parties, namely that document (3) represents the closest state of the art.

This document refers to a method for improving the quality of albumin products. The removal of ethanol and of multivalent metal ions from said products by diafiltration against 0.13 M NaCl is examined. It is found that 98.8 +/- 0.5% ethanol and 90 to 95% aluminium, chromium and manganese, but very little nickel is removed by the method disclosed. Document (3) contains a graph, showing the development of ethanol-

and aluminium removal in dependency of increasing diafiltration volumes. While the ethanol concentration seems to decrease constantly with increasing diafiltration volumes, the aluminium concentration reaches a plateau after four volumes. Further increasing of diafiltration volumes does not have an influence on aluminium removal.

6. In the light of this teaching in the closest prior art, the problem to be solved by the present invention is seen to be the provision of an improved method for the removal of multivalent metal ions from albumin.

This is in agreement with the appellants, who stated in a letter dated 27 January 2000, that for "...high levels of aluminium contamination the method disclosed in D3 is clearly inadequate and requires improvement".

The problem is known in the art and is addressed for instance in document (29), where, by reference to the European Pharmacopoeia Commission, a limit for plasma aluminium of 200 µ/l is found to be a reasonable value (see page 41, left paragraph).

7. The method of claim 1 is distinguished from the disclosure in document (3) in that the salt concentration of the aqueous solution against which the albumin is diafiltrated, is raised from 0.13 M to 0.15 M up to saturation.

Moreover, monovalent metal ions bound to albumin after a first diafiltration step are removed therefrom by a further diafiltration against a solution not containing any metal ions. This feature, which is described in the

description of the patent (page 2, lines 53 to 54) as being purely optional, is well known in the art (see for instance document (18), pages 127 to 129) and cannot contribute to an inventive step.

8. Increasing the salt concentration of the eluent from 0.13 M, as disclosed in document (3), to 0.15 M, the lower threshold given in claim 1, seems to be a minor amendment only. However, for the question of inventive step this alone cannot be a reason to deny its existence. Rather an answer has to be found whether or not a skilled person reading document (3) and being aware of the problem to be solved would have amended its teaching in the way disclosed in claim 1 in an obvious way.

9. It is known that proteins are very soluble in physiological salt conditions, an ionic strength generally around 0.15 and 0.2 M (see document (12), page 42). Thus, both concentrations, 0.13 M and 0.15 M, are considered to be physiological. This is not only beneficial for the easy realisation of a diafiltration process, but also an advantage when considering that the processed albumin preparations are to be used for pharmaceutical purposes, and a salt content outside the physiological range would make mandatory a further, laborious and costly working step.

10. An important point, controversially discussed by the parties, is whether a skilled person when trying to improve the method of document (3) has a number of different parameters at hand from which he can chose, or is in fact left with the salt concentration of the

eluent as being the only possible way to reach an improvement.

While the appellants mentioned temperature, addition of non-polar solvents or of stationary phases as further possible working points to improve the teaching of document (3), without however providing any evidence disclosing the effect of these parameters on the efficiency of a diafiltration process, the respondents considered the salt concentration as being the only possible way to influence the result of the prior art process.

11. The board, taking account the graph shown in document (3), (see paragraph 5 above), takes the view that a skilled person would have learned therefrom that the aluminium content of albumin cannot be further reduced by increasing the number of diafiltration volumes.

When asking which process parameters the skilled person would have considered being promising candidates for achieving better results than document (3), one has to bear in mind that the aim of the process under consideration is the achievement of the maximum removal rate of multivalent metal ions from albumin. Thus, in other words, it is the goal of the method to break up the binding by which these metal ions are bound to albumin.

The knowledge of the binding mechanism between albumin and metal ions will provide the skilled person with valuable findings concerning useful parameters influencing these bonds.

12. The appellants repeatedly stressed that it were the present inventors who found for the first time that albumin acts as an ion exchanger for polyvalent cations, and that these ions therefore can be removed from albumin on an ion exchange principle. They argued that in principle, up to the publication of the patent in suit, other binding mechanisms, like for instance lipophilic binding, would have been considered possible by a skilled person.

13. The board does not agree. The state of the art contains convincing evidence showing that it was known before the relevant date of the patent in suit that aluminium ions are bound to albumin by electrostatic bonds and that they can be removed therefrom by an ion exchange process.

Document (39) reports on page 1021 (Materials and Methods, last sentence, first paragraph) that albumin standards contaminated with aluminium, prepared in a buffer containing 0.14 M Na^+, were passed through a Chelex column, a cation exchange resin, to remove the aluminium.

Document (40) states on page 180, last paragraph, that albumin contamination with heavy metal ions can be reduced to very low levels by ion-exchange procedures. Several of the metals mentioned in claim 1 belong to the group of heavy metals.

On page 190, first full paragraph, document (40) reads:

"Divalent and polyvalent metal ions are more strongly bound than monovalent cations, not only by serum

albumin but by proteins in general. In part, this is doubtless due to the enhanced charge interaction....The attraction of the anionic protein for a di- or tri-valent cation is expected to be greater than for univalent cations by simple application of Coloumb's law."

14. Coloumb's law (see document (41), pages 271 to 272) is a fundamental physical law, stating that the electric force for attraction of particles with different charge and repulsion of particles with the same charge is proportional to the product of the charges and inversely proportional to the square of the distance between them. The force, which is the bigger the bigger the charge is, is also dependent from the permittivity of the medium (ε). As can be seen from the formula on page 272 of document (41), increasing the permittivity (ε) reduces the electric force. Since, in the present case, permittivity (ε) is greater the greater the salt concentration of the eluent is, increasing said salt concentration weakens the electric force by which multivalent metal ions are bound to albumin.

15. The skilled person, at the relevant date of the patent in suit, was aware of the fact that multivalent metal ions are bound to albumin by electrostatic binding (see document (39) and (40)). As the board is convinced that an average person skilled in the field of protein purification is aware of the fundamental physical laws regulating the binding mechanism between chemical entities, it was obvious in order to solve the problem underlying the patent in suit, to further proceed on the basis of the teaching of document (3) by increasing

the salt concentration used in the diafiltration process and to arrive at the subject-matter of claim 1.

The subject-matter of claim 1 does not involve an inventive step and hence does not meet the requirements of Article 56 EPC.

16. Since none of the opponents have filed an appeal the subject-matter of the claims as maintained by the Opposition Division cannot be challenged (see Decision of the Enlarged Board of Appeal G 9/92, OJ EPO 1994, 875, point 14).

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey