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D E C I S I O N
of 19 January 2006

Case Number: T 1007/04 - 3.3.08

Application Number: 93108099.8

Publication Number: 0570916

IPC: C12N 15/14

Language of the proceedings: EN

Title of invention:
Process for the purification of human recombinant serum albumin

Patentee:
Mitsubishi Pharma Corporation

Opponent:
Delta Biotechnology Limited

Headword:
Serum albumin/MITSUBISHI

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1007/04 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 19 January 2006

Appellant: (Opponent)	Delta Biotechnology Limited Castle Court Castle Boulevard Nottingham NG7 1FD (GB)
Representative:	Bassett, Richard Simon Eric Potter Clarkson LLP Park View House 58 The Ropewalk Nottingham NG1 5DD (GB)
Respondent: (Proprietor of the patent)	Mitsubishi Pharma Corporation 6-9, Hiranomachi 2-chome Chuo-ku Osaka-shi Osaka 541-0046 (JP)
Representative:	Polz, Leo Dr. Hoffmann Eitle Patent- und Rechtsanwälte Postfach 81 04 20 D-81904 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 8 June 2004 rejecting the opposition filed against European patent No. 0570916 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the decision of the opposition division dated 8 June 2004, whereby the opposition against the European patent No. 0 570 916, entitled "Process for the purification of human recombinant serum albumin" and granted on the application No 93 108 099.8, was rejected.

II. The patent had been opposed on the grounds of Articles 100(a) and (b) EPC that the invention was not new and did not involve an inventive step. The objection of lack of novelty had not been taken further by the opponent.

III. In the decision under appeal it was considered by the opposition division that the claimed subject-matter as a whole involved an inventive step.

IV. In the statement of grounds of appeal, lack of inventive step of the subject-matter of claim 1 was the only reason why the decision under appeal was challenged by the appellant. In support of its views the appellant filed three additional documents (D5 to D7). In reply, the respondent (patent proprietor) filed observations.

V. The Board issued a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal containing provisional and non-binding opinions.

VI. Oral proceedings took place on 19 January 2006. They were not attended by the appellant as announced in advance in its letter of 9 January 2006.

VII. The set of granted claims consisted of nine claims.

Claim 1 read:

"1. A process for producing a recombinant human serum albumin comprising the steps of:

(1) treating a culture supernatant of a host which expresses human serum albumin, with a first ultrafiltration membrane having a molecular weight exclusive limit of from 100,000 to 500,000 and then with a second ultrafiltration membrane having a molecular weight exclusive limit of from 1,000 to 50,000 to yield a first filtrate;

(2) heat-treating the first filtrate at 50 to 70°C for 30 minutes to 5 hours to yield a heated sample;

(3) acid-treating the heated sample at a pH of from 3 to 5 to yield an acid-treated sample;

(4) treating the acid-treated sample using an ultrafiltration membrane having a molecular weight exclusive limit of from 100,000 to 500,000 to yield a second filtrate;

(5) exposing the second filtrate to a cation exchanger at a pH of 3 to 5 and a salt concentration of 0.01 to 0.2 M, and then exposing said cation exchanger to a pH

of 8 to 10 and a salt concentration of 0.2 to 0.5 M to yield a first eluate;

(6) allowing the first eluate to contact with a carrier for hydrophobic chromatography at a pH of 6 to 8 and a salt concentration of 0.01 to 0.5 M, and recovering non-adsorbed fractions to yield a second eluate; and

(7) allowing the second eluate to contact with an anion exchanger at a pH of 6 to 8 and a salt concentration of 0.01 to 0.1 M, and recovering non-adsorbed fractions to yield said albumin."

Claims 2 to 9 were dependent on claim 1 and were directed to particular embodiments thereof.

VIII. The following documents are referred to in the present decision:

(D1A) Japanese document dated 1991 with pages 229 to 243

(D1) English translation of document D1A, "Study Reports of Anti-AIDS Drug Development", Japan Health Sciences Foundation, Pages 1 to 15

(D2) EP-A-0 422 769 (published on 17 April 1991)

(D5) J. Janatova et al., Preparative Biochemistry, Vol. 10, No. 4, 1980, Pages 405 to 430

IX. The submissions made by the appellant (opponent) in writing, insofar as they are relevant to the present decision, may be summarised as follows:

Starting from document D1, the technical problem to be solved was identified as the provision of a process for the production of recombinant human serum albumin with a higher degree of purity.

Acid treatment was a well known protein purification procedure in the art (see, for example, documents D2 and D5), and its use as an additional step to try to improve the purity of the product of document D1's method was an obvious additional step to take.

Anion exchange was a well known albumin purification procedure in the art (see, for example, documents D2 and D5), and its use as an additional step to improve the purity of the product of document D1's method was a further obvious additional step to take.

There was no evidence to suggest that the increased elution pH in the cation exchange step of claim 1 contributed to the overall product purity.

Even though the cation exchange step had been made predictably less effective by the increase in the elution pH, the two additional purification steps (acid treatment and anion exchange) would have both been expected to contribute to an increase in albumin purity.

In the absence of evidence that all process parameters falling within the scope of claim 1 resulted in a product having an increased level of purity compared to document D1, the claim could not be said to solve the technical problem fully across its breadth.

Accordingly, claim 1 encompassed subject-matter that lacked inventive step.

X. The submissions made by the respondent (patent proprietor), insofar as they are relevant to the present decision, may be summarised as follows:

Document D1 was regarded as the closest state of the art. There was neither an acid treatment step nor an anion exchanger step (respectively steps 3 and 7 of claim 1) in the process of document D1. Using an acid treatment step as step 3 of claim 1, impurities were removed easily, thus allowing a reduction in the capacity of the subsequent steps for removing remaining impurities. In the process of document D1, the elution pH in the cation exchange step was not that of the corresponding step 5 in claim 1.

Moreover, document D1 did not suggest using such steps for further purification of the rHSA.

In the process of document D1, the rHSA dimers were observed after the cation exchange chromatography treatment (see page 6, Section 3-4). The subsequent hydrophobic chromatography demonstrated only a low rate of removal of rHSA dimers (see page 11, Section 4-4).

The HPLC pattern after the hydrophobic chromatography treatment in Figure 7 of document D1A showed a small peak besides the peak of monomer which might be a peak of rHSA dimers. In contrast thereto, Figure 1 of the patent showed that the HPLC pattern after the hydrophobic chromatography treatment was free of such a

small peak indicating that the rHSA dimers had been removed.

XI. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 570 916 be revoked.

XII. The respondent (patentee) requested that the appeal be dismissed.

Reasons for the Decision

Inventive step (Article 56 EPC)

1. For the assessment of whether claim 1 involves an inventive step, document D1 (together with the tables and figures of the original Japanese document D1A) represents the closest state of the art. It describes a purification method for recombinant human serum albumin (rHSA). That method is comprised of four steps, namely a first ultrafiltration step, a heat-treatment step, a second ultrafiltration step, and a cation exchange step (see pages 8 to 10, section 4-3, and Table 4). It was found that the resulting rHSA contained **dimers** (see page 11, third line). An attempt to remove said **dimers** by adding a fifth step consisting in a hydrophobic chromatography was unsuccessful (see page 11, section 4-4, second paragraph). It was concluded that there was a need for an additional procedure for removal of the **rHSA dimers** (see page 13, second full paragraph, fourth sentence).

2. Starting from document D1, the technical problem solved by the patent may be identified as the provision of a process for producing a highly purified recombinant human serum albumin wherein rHSA dimers are reduced. The solution to that problem is a seven step process as defined in claim 1 which differs from the attempted five step process of document D1 in that, in claim 1, (i) an acid-treatment step is added between the heat-treatment step and the second ultrafiltration step, (ii) the cation exchange step proceeds by elution of the bound albumin at a higher pH than that described in document D1, and (iii) an anion exchanger step is added after the hydrophobic chromatography step. The efficiency of the process of claim 1 is illustrated by Figure 1 of the patent which shows that after the hydrophobic chromatography no **rHSA dimers** were detected, compared with Figure 7 of document D1A which, as assumed by the respondent in its reply to the statement of grounds of appeal and not denied by the appellant, shows a peak indicating the presence of **rHSA dimers** in the rHSA of document D1 after the hydrophobic chromatography.

3. The question to be answered is whether any of the other cited prior art documents would have suggested that the method of document D1 might be modified into the method of claim 1.

4. As none of the said documents, including documents D2 and D5, specifically investigate how serum albumin dimers could be removed in the course of a process for preparing a recombinant human serum albumin, it has to be concluded that the skilled person would have found no guidance at all in the prior art to solve the

afore-mentioned technical problem. Regarding document D2, it is to be noted that "recombinant-DNA-derived materials containing albumin" are cited once in passing (see page 3, line 46 and 47), whereas the method of purification actually described and illustrated in the examples has been designed for the treatment of blood/plasma-derived albumin fractions such as the Fraction V from the Cohn method. As to document D5, it describes a procedure for the isolation of fractions from a lyophilised **bovine** serum albumin Fraction V and fresh **bovine** serum albumin isolated from bovine blood.

5. The Board is not convinced by the appellant's reasoning that inserting an acid-treatment step between the heat-treatment step and the second ultrafiltration step of the process of document D1, or changing the pH conditions for the elution of the cation exchange step of that process, or adding an anion exchanger step after the hydrophobic chromatography step of that process, each change being considered independently from the other two, was not inventive in view of the particular state of the art. In fact, because the outcome of a particular step of a particular process is largely dependent on the previous step, such reasoning would have had to show that performing all three changes in claim 1 at the same time was not inventive.

6. Therefore, the subject-matter of claim 1 involves an inventive step. The same conclusion applies *de facto* to claims 2 to 9 as they are dependent on claim 1. Thus, the requirements of Article 56 EPC are met. As lack of inventive step was the only ground for challenging the decision of the opposition division, the appeal should be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani