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D E C I S I O N
of 27 April 2000

Case Number: T 0378/95 - 3.3.4

Application Number: 85100223.8

Publication Number: 0150735

IPC: C12P 21/00

Language of the proceedings: EN

Title of invention:
Protein composition exhibiting coagulation activity and method for the preparation thereof

Patentee:
CHIRON CORPORATION, et al

Opponent:
Rhone-Poulenc Rorer, Inc

Headword:
Factor VIIIC/CHIRON CO.

Relevant legal provisions:
EPC Art. 123(2), 54, 56

Keyword:
"Main request: added matter (no)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0378/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 27 April 2000

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 20 March 1995 revoking European patent No. 0 150 735 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
C. Holtz

Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No. 0 150 735 (application No. 85100223.8). The patent had been granted on the basis of 7 claims for all designated Contracting States, except AT (hereafter: non-AT Contracting States) and 5 claims for the Contracting State AT. Claim 1 for the non-AT Contracting States read as follows:

"1. An isolated protein composition comprising a complex of a 77/80 kd doublet polypeptide fragment calcium bridged with a 92.5 kd polypeptide fragment, exhibiting a coagulation activity similar to that of human Factor VIIIC; and having a purity of at least 90%, based on complex plus precursor species".

II. There are three documents cited in the present appeal proceedings:

(A) EP-A-0 123 945;

(B) Fulcher C.A. et al, Blood, Vol. 61, No 4, pages 807-811 (April 1983);

(C) Fulcher C.A. et al., Proc. Natl. Acad. Sci. USA, Vol. 79, pages 1648-1652 (March 1982).

Document (A) is a European patent application enjoying a priority date earlier than (but published after) the earliest priority date of the patent in suit and constitutes prior art for the purpose of novelty (Article 54(3)(4) EPC). Document (B) is a pre-published journal report issued from the same authors of document

(A) relating to the same work described in patent application (A).

III. The board issued a communication pursuant to Article 11(2) of the Procedure before the Boards of Appeal expressing its provisional opinion.

IV. Oral proceedings were held on 27 April 2000, during which the appellant submitted a new main request and a first auxiliary request in replacement of any preceding requests. The sole claim of the main request read as follows (the changes vis-à-vis granted claim 1 are shown by way of deletions and in bold):

"1. An isolated protein composition comprising:
a complex of a 77/80 kd doublet polypeptide fragment calcium bridged with a 92.5 kd polypeptide fragment;
and precursor species;
said ~~composition~~ **complex** exhibiting a coagulation activity similar to that of human Factor VIIIC;
wherein said complex and precursor species have a purity of at least 90%, based on **total protein** ~~complex plus precursor species~~", and
wherein the complex has a purity of at least 30% based on total protein."

V. As regards the main request, the arguments submitted by the appellant were essentially as follows:

Article 123(2) and (3) EPC

- All the amendments satisfied the requirements of Article 123(2) and (3) EPC.

Novelty

- The features "at least 30% based on the total protein" and "at least 90% based on the total protein" in the claim were distinguishing features vis-à-vis the prior art since it was a purity that enabled the amino acid sequence of the complex to be obtained. In one experiment (see page 8, section IIA of the patent in suit), use was made of a further chromatographic step of gel filtration to increase the concentration of the desired complex in the Factor VIIIC preparation.

- The table on page 24 of document (A) showed that the amount of 1:1 complex of a 77/80 kd doublet polypeptide fragment calcium bridged with a 92.5 kd polypeptide fragment was at most 23% of the total proteins and that the maximum percentage of complex plus precursor was 50% of the total proteins.

Inventive step

- The problem to be solved by the patent in suit was to provide a preparation which contained a large proportion of the active complex (a stoichiometrically defined 1:1 complex of a 77/80 kd doublet polypeptide fragment calcium- bridged with a 92.5 kd polypeptide fragment complex).

- Document (B) was inconclusive as to the identity of the biologically active species. The authors of document (B) came to the conclusion that the 92 kd peptide was responsible for coagulant activity. No suggestion could be derived from this document that the active species was the 1:1 complex of a 77/80 kd doublet polypeptide fragment calcium-

bridged with a 92.5 kd polypeptide fragment. Document (B) thus was misleading as to what species had to be purified.

- There was in the prior art no suggestion as to how to degrade Factor VIIIC in a more specific manner so as to obtain a high proportion of the active 77/80-92.5 kd calcium-bridged complex. Document (B) did not give any hint as to how to obtain this without thrombin treatment.

VI. The arguments submitted by the respondent were essentially as follows:

Article 123(2) EPC

- On page 8, line 13 of the application as filed, the term "at least" related to 20%, not to 30%. Therefore, the wording "at least 30%" in the claim infringed Article 123(2) EPC.

Novelty

- Document (A) disclosed a composition according to the claim at issue wherein either the complex alone or the complex plus precursors exhibited the required purity. According to the table on page 24 of document (A), the complex alone was 20-30% of the total protein.

- The passage on page 11, line 30 to page 12, line 1 of this document stated that preparations of at least 90% purity could be obtained. This was further confirmed by the figures of 7,500 U/mg to 10,000 U/mg for the specific activity (page 12,

lines 27 to 28) which corresponded to a fold purification from plasma greater than 500,000, assuming the specific activity of plasma as 0.014 U/mg. Moreover, specific activities of 7,500 U/mg to 10,000 U/mg could be derived by dividing the "activity of the digestion mixture" in U/ml (1300, 1350, 1400, 1250) reported in the Table on page 24 of document (A) by the final protein concentration of 167 µg/ml of the purified Factor VIIIC subjected to thrombin activation (see page 16, line 11).

Inventive step

- Document (B) suggested that a non-covalently bound complex of the 92 kd peptide and the 79-80 kd peptide was the active species of Factor VIIIC.

- The Factor VIIIC preparations of the prior art were contaminated with fibronectin (see document (C), page 1649, right-hand column, under the heading "Results"). The skilled person only had to further purify this Factor VIIIC by means of an additional purification step on an anti-fibronectin affinity column in order to obtain the claimed preparation.

VII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the single claim of either the main request or the first auxiliary request, both submitted in the oral proceedings.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main request
Article 123(2) and (3) EPC

2. The expression "and precursor species" is to be found on page 8, line 11 of the application as filed. The wording "said complex exhibiting a coagulation activity similar to that of human Factor VIIIC" finds a basis in claim 1 of the application as filed. The expressions "based on total protein" and "purity of at least 30% based on the total protein" can be based on page 8, lines 13 to 14 of the application as filed. Contrary to the respondent's view, the board considers the expression "at least" of lines 13 to 14: "at least 20%, more usually 30%" as "distributive" in the sense that it can be interpreted as meaning "at least 20%, more usually, at least 30%". Furthermore, the claim is not broader in scope than the granted claims so that it does not infringe Article 123(2) and (3) EPC.

Novelty

3. It is argued by the respondent that document (A) discloses a composition according to the claim at issue wherein both the complex alone (at least 30% of the total proteins) and the complex plus precursors (at least 90% of the total proteins) exhibited the required purity. As for the degree of purity of the complex alone, based on the total proteins, the board observes that the Table on page 24 of document (A) describes the relative amounts of Factor VIIIC fragments at various

times after treatment with thrombin. At time zero (untreated sample), there are 29.2%, based on the total proteins (7.3% of fragment with Mr = 92,000 + 21.9% fragment with Mr = 79-80,000) of fragments which make up the complex stated in the claim at issue. However, since this complex has to be present in the mixture as a 1:1 complex, only 7.3% of these 21.9% of the fragment with Mr = 79-80,000 will bind to the 7.3% of fragment with Mr = 92,000 (ie, 7.3% is a limiting factor), thus yielding at most 7.3% + 7.3% = 14.6%, based on the total proteins, of the complex. Following thrombin treatment (see the Table on page 24 of document (A)), the maximum (11.5% + 12.9% = 24.4%) of fragments which make up the complex is reached after 2 minutes. But since a 1:1 complex has to form, 11.5% of the fragment with Mr = 92,000 can only bind at most 11.5% of the fragment with Mr = 79-80,000, thus yielding **at most 23%**, based on the total proteins, of the 1:1 complex. In conclusion, document (A) does **not** disclose a preparation wherein the complex represents **at least 30%** of the total proteins.

4. As regards the degree of purity of the complex plus precursors, based on total proteins, the board is not in a position to establish whether or not a preparation exhibiting a specific activity of 10,000 U/mg or a 500,000-fold purification over plasma corresponds to a preparation having more than 90% complex plus precursors, based on total proteins. This is because it is neither possible to calculate the relative purity in % from a specific activity (10,000 U/mg), nor is it possible to do so by departing from the figure of 500,000-fold purification over plasma without knowing the percentage of Factor VIIIC of the total proteins in plasma: this critical data is indeed not before the

board.

5. It can rather be deduced from the Table on page 24 of document (A) that the sum of the percentages of all fragments after 5, 10, 20, 30 and 40 min reaches a plateau around about 50% of the total proteins. This experimental result does not support the respondent's proposition that document (A) discloses a composition according to the claim at issue wherein the complex plus precursors represent at least 90% of the total proteins.

6. In conclusion, the subject-matter of the claim of the main request is novel over document (A).

Inventive step

7. The closest prior art is represented by document (B), a journal report issued from the same authors of document (A) relating to the same work described therein, albeit with less details. Figures 2 and 3 of document (B) report the same data as presented in the Table on page 24 of document (A), pertaining to the time course analysis of thrombin activated Factor VIIIC having a specific activity of 2000 U/mg (see page 808, left-hand column, under the heading "Results") at a final concentration of 167 µg/ml (ibidem, first full paragraph).

8. The problem to be solved by the patent in suit in the light of document (B) is to provide a preparation which contains at least 30%, based on the total proteins, of a biologically active complex (a stoichiometrically defined 1:1 complex of a 77/80 kd doublet polypeptide fragment calcium-bridged with a 92.5 kd polypeptide

fragment) and in which the complex and the precursor species account for at least 90% of the total protein. This problem is solved by, inter alia, the introduction in the purification scheme of a further chromatographic step of gel filtration to increase the concentration of the desired complex in the Factor VIIIC preparation (see page 8, section IIA of the patent in suit). That the disclosure of patent in suit leads to a complex exhibiting the purity stated in the claim, has never been disputed by the respondent. Further, there is evidence before the board (see Section D on page 10 of the patent in suit) that the high degree of purity of the claimed complex enabled amino acid sequence analysis of the fragments. Therefore, the board is satisfied that the patent in suit solves the above problem.

9. It has to be decided whether or not document (B) comprises a pointer towards the claimed subject-matter. The board observes that the last paragraph of document (B) analogizes the 92 kd and 79/80 kd fragments of Factor VIIIC with the 105 kd and 71/74 kd peptides of bovine and human Factor V, which form a non-covalently bound complex. In spite of this, the document is inconclusive as to the identity of the biologically active species. The authors of document (B) come to the conclusion that it is the 92 kd peptide that is responsible for coagulant activity (see page 810, right-hand column, lines 3 to 5). The function of the 79-80 kd doublet is still unknown to them (ibidem, lines 6 to 7). No suggestion can be derived either from document (B) that the 77/80 kd doublet polypeptide fragment and the 92.5 kd polypeptide fragment form a 1:1 calcium-bridged complex, **let alone** that such complex is responsible for coagulant activity. Document

(B) would, if anything, mislead the skilled person as to what species has to be purified (the 92 kd peptide).

10. There is also no suggestion in the prior art, including document (B), as to how to degrade Factor VIIIC in a more specific manner so as to obtain the high proportion of the active 77/80-92.5 kd calcium-bridged complex stated in the claim under consideration.

11. In view of the above findings, it must be concluded that document (B) does not lead in an obvious manner to the subject-matter of the claim at issue, which thus involve an inventive step (Article 56 EPC).

12. The board is thus satisfied that the sole claim of the main request meets the requirements of the Convention. No need arises to consider the auxiliary request.

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 with the order to maintain the patent on the basis of the main request as submitted in the oral proceedings and a description to be adapted thereto.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey