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D E C I S I O N
of 27 October 1998

Case Number: T 0367/95 - 3.3.4

Application Number: 86850067.9

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Language of the proceedings: EN

Title of invention:
Biologically active fragments of the human antihemophilic factor and method for their preparation and pharmaceutical preparations

Applicant/Patentee:
Pharmacia & Upjohn Aktiebolag

Opponent:
Immuno Aktiengesellschaft
Rhone-Poulenc Rorer, Inc
Novo Nordisk A/S

Headword:
Antihemophilic factor/PHARMACIA

Relevant legal provisions:
EPC Art. 123(2)(3), 54, 111(1)

Keyword:
"Amendment - extension of protection conferred (no)"
"Amendment - added subject-matter (no)"
"Novelty (yes)"
"Remittal"

Decisions cited:
G 0004/92

Catchword:
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Case Number: T 0367/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 27 October 1998

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 6 March 1995 revoking European patent No. 0 197 901 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
C. Holtz

Summary of Facts and Submissions

I. The appellants (patentees) lodged an appeal against the decision of the opposition division issued on 6 March 1995 whereby the European patent No. 0 197 901, which had been opposed by all the respondents (opponents 01 to 03) under Article 100(a) EPC and by respondents III (opponents 03) also under Article 100(c) EPC, was revoked pursuant to Article 102(1) EPC.

II. Claim 1 as granted in the version for all contracting states except AT (non-AT states) read as follows:

"Active fragment of human Factor VIII:C characterized by containing two peptide chains having molecular weights 90 000 and 80 000 daltons, respectively and having the aminoterminal amino acid sequences Ala-Thr-Arg-Arg-Tyr-Tyr and Glu-Ile-Thr-Arg-Thr-Thr, respectively and having the aminoacid composition: [Table with aminoacid composition is given]."

III. The opposition division considered that the subject-matter of the granted claim 1 for all non-AT states lacked novelty having regard to either one of the following documents:

(5) EP-A-0 150 735, this being prior art under Article 54(3)(4) EPC;

(7) EP-A-0 123 945.

In the view of the opposition division, claim 1 did not

relate to subject-matter which was selectively different from the active 92,000/79-80,000 daltons Factor VIII:C complex described in document (7), notwithstanding its higher purity in comparison to the latter. Furthermore, also the 77-80 kD/92.5 kD Factor VIII:C complex disclosed in document (5) was identical to the subject-matter of claim 1. In both instances the teaching of the documents in questions was considered to be enabling.

Neither the novelty of granted claim 1 for Austria nor the novelty of the subject-matter of all other claims (claims 2 to 17 for non-AT states and claims 2 to 11 for AT) were discussed. Nor was the inventive step issue treated in the decision, where it was stated that this had not been at issue at oral proceedings before the opposition division (see page 3 of the decision under appeal, item 2.10, first paragraph as well as page 7, second sentence).

IV. On 29 June 1995, with the statement of grounds of appeal the appellants filed a new main request and two auxiliary requests, each in the two versions, one for the non-AT and one for AT.

Claim 1 the **main request** (non-AT states) differed from claim 1 as granted only in that the wording "An active fragment of human factor VIII:C characterized by **consisting of**" (emphasis added) replaced the wording "Active fragment of human Factor VIII:C characterized by **containing**" (emphasis added).

Claim 1 (non-AT states) of the **first auxiliary request**

further specified that the two peptide chains were held together, while claim 1 (non-AT states) of the **second auxiliary request** specified that the two peptide chains were held together by one or several metal ion bridges.

V. All the respondents (opponents) replied to the statement of grounds of appeal.

VI. On 15 July 1998, the board issued a communication pursuant to Article 11(2) of the rules of procedure with an outline of the issues to be discussed at oral proceedings and some provisional remarks.

VII. With letter dated 3 September 1998, respondents III informed the board that they would not attend oral proceedings.

VIII. Oral proceedings took place on 27 October 1998.

IX. The appellants essentially submitted that:

- The flaw in the decision under appeal and in the respondents' arguments was that they read into documents (5) and (7) the disclosure of the further prior art document

  (1) Nature, vol. 312, 22 November 1984, pages 337 to 342.

  However, this document, which had been published after the filing date of documents (5) and (7), could not be considered as part of their disclosure. It was not permissible to combine two

documents for assessing novelty.

- Another flaw in the decision of the opposition division and in the respondents' submissions was that the doublets referred to in documents (5) and (7), by which two chains were meant, were considered to be equal to the single peptide chain of 80 kD of claim 1 at issue.

- The active fragment of claim 1 was not identified in any of documents (5) or (7) and thus was novel. Document (5) related to a composition containing 77 kD/80 kD doublets (cf claim 1 therein) which had amino acid compositions (cf page 29) different from the one given in claim 1 of the patent in suit for the 80 kD peptide. Document (7) concerned either the 92 kD polypeptide alone or its combination with one or more doublets (cf claim 1). The existence of doublets, possibly caused by differences in glycosylation, was an undeniable fact and had thus to be taken into account.

- The subject-matter of claim 1 corresponded to the product isolated from peak II which, as described in the specification (cf page 5 lines 3 to 8), was composed only of a 90 kD and a 80 kD peptide chain. This product, as discussed in the patent specification (cf page 2, line 45 to page 3 line 13), was well distinct from the known products of the prior art.

X. The respondents objected under Article 123(2) and (3)

EPC against amended claim 1 because in their view the change in wording from "containing" to "consisting" implied that the claimed fragment could now be active also in absence of metal ion bridges between the two peptide chains. This aspect was subject-matter different from the one previously claimed and found no support in the application as filed.

As for novelty, the respondents argued that an active Factor VIII:C fragment consisting of a polypeptide of about 92 kD and a polypeptide of 77-79/80 kD had been described in individualised form in the prior art (cf document (5), page 6, lines 24 to 31 and claim 1 as well as document (7), page 8, lines 21 to 29, page 11, lines 23 to 31). A greater purity or additional information about the amino acid composition, whereby the fragment of the patent in suit was characterised, could not per se contribute to novelty especially in view of the fact that the peptide fragments of 90 kD and 80 kD and their amino acid sequences were known in the art (cf document (1), see Figures 3 and 6 as well as page 342, left-hand column, first paragraph). The appellants had not made reference to any structural technical features which could justify novelty over said prior art. As for the doublet issue, a later publication by the inventors, namely document

(17) Proc. Natl. Acad. Sci. USA, vol. 83, May 1986, pages 2979 to 2983

demonstrated that the product of peak II also contained a doublet chain. In Figure 2 of the patent in suit, this was "hidden" in the broad band corresponding to

the electrophoretic run of the 80 kD peptide. Thus, no distinction could be made on the basis of an alleged absence of doublets (see also declaration of Dr Peter Turecek dated 12 December 1995 filed by respondents I).

XI. The appellants requested that the decision under appeal be set aside and the patent be maintained on the basis of either of the requests filed on 29 June 1995.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

Claim 1 of the main request

Article 123(2)(3) EPC

1. The board does not agree with the respondents' view that the change in wording from "containing" to "consisting" necessarily implies excluding the presence of a metal ion bridge between the two peptide chains of which the claimed active fragment is said to consist. The wording of the granted claim and of the claim here at issue evidently relates to polypeptide chains. Thus, the change of "containing" to "consisting" can only mean that no other peptide chains are present in the isolated active fragment of human Factor VIII:C and leaves completely open whether, and if, how the said two chains are held together. Thus, the presence of e.g. one or several metal ion bridges - this being a possibility indicated in the description - is not excluded by the claim. Thus, the amendment results neither in the creation of any fresh subject-matter nor in an extension of the protection conferred. For these reasons, there is no objection under Article 123(3) EPC against claim 1.

2. The amendment in claim 1 finds support in the application as filed where it is stated that "the peak II material contained only two peptide chains of molecular weights 90,000 daltons and 80,000 daltons" (cf page 7, lines 31 to 33) and that fragmentation of Factor VIII:C resulted inter alia in the formation of an active fragment "composed of a 90 000 daltons and a 80 000 daltons peptide chain" (cf page 8, lines 9 to 17). The aminoterminal amino acid sequence and the amino acid compositions of said chains are reported, respectively, on page 8, lines 23 to 28 and in Table II on page 12. Thus, there is no objection under Article 123(2) EPC against claim 1.

Novelty (Article 54 EPC)

3. At issue is only the novelty of the subject-matter of claim 1 over the disclosures of documents (1), (5) and (7).

4. Document (1) reports the deduced amino acid sequence of Factor VIII:C and indicates therein the potential position of the protease cleavage of the M_r 90,000 and 80,000 proteins (cf Figure 6). In respect of the latter proteins, the document draws an analogy with Factor V, of which - as it is stated - the corresponding fragments D and E "can be separated from the activation peptides and isolated as a functional two-subunit protein" (cf page 342, left-hand column, lines 1 to 5). The document further states (loc.cit. lines 6 to 10): "Both subunits are required for factor V activity and both **may** be required for factor VIII activity. A highly glycosylated intermediate region is cleaved from both

proteins. Therefore, both factors V and VIII **seem** to be highly similar in structure, thrombin cleavage pattern and, **presumably**, function." (emphasis added). Such statements are merely conjectural and as such do not amount to a clear and unmistakable disclosure of the active fragment of claim 1. For this reason, document (1) cannot be considered to be novelty-destroying.

5. Document (5), which is prior art under Article 54(3)(4) EPC, specifically refers inter alia to a Factor VIII:C complex containing the 77 kD and/**or** 80 kD species and the 92.5 kD polypeptide bridged by calcium (cf page 6, lines 24 to 31 as well page 8 lines 8 to 9). However, the amino acid compositions reported for the 77/80 kD peptides, which are said to have been determined by standard methods (cf page 29, lines 1 to 24), differ in many respects from the amino acid composition reported in claim 1 for the 80,000 daltons peptide (cf the table of comparison in the respondents' letter dated 28 September 1998). The respondents argue that these discrepancies have to be considered irrelevant because the amino acid composition of a peptide is a poor indicator of the structure of a protein, it is subject to errors of determination and it is merely information which cannot per se contribute to the novelty of a known individualised complex 80 kD/92.5 kD, the amino acid sequence of which was also known (cf document (1), Figures 3 and 6; cf also Appendix B in document (5)). In their view, since there is only one human Factor VIII:C, reference to the same specific complex could only imply that the fragment was the same.

5.1 The board observes firstly that the disclosure of

document (1) cannot be considered to form part of the disclosure of document (5), which contains no reference to the former (as matter of fact the former was published after the filing of the latter). Thus, any information contained in document (1) cannot be read into document (5). Secondly, the amino acid sequence information reported in Appendix B of document (5) is incomplete so that the theoretical percentage molar amino acid composition of the 77/80 kD peptides cannot be calculated therefrom.

In document (5) the 80 kD peptide is essentially identified in terms of its molecular weight, its partial amino acid sequence and the amino acid composition reported on page 29. Although there might be only one human Factor VIII:C, its fragmentation by proteolysis generates a number of different fragments which have to be purified. This does not always necessarily result in identical fragments as fragmentation could, for example, occur at different sites and generate fragments of similar or even identical molecular weight but slightly or completely different structure. Thus, other parameters, such as inter alia the amino acid composition, become of relevance for the identification of the peptide fragments. The board does not agree that amino acid composition data represent irrelevant information which can be disregarded. As a matter of fact, amino acid composition analysis, although not providing information on the sequence of the protein, bears a relationship to the chemistry of a protein and provides relevant information on the types of amino acids which are present as well as on their relative proportions. If by comparing the amino acid composition of two peptides it is found - like in the present case - that some amino acids are either absent or present in a different molar percentage, it can be concluded that the two peptides, although being possibly similar, are not identical. Of course, the occurrence of errors of determination cannot be excluded. However, in the present case, there is no evidence whatsoever that such errors occurred. Thus, the respondents' allegation that the discrepancies are likely to be due to errors of determination is unsubstantiated.

5.2 Due to the above mentioned difference in a relevant parameter, the board concludes that the Factor VIII:C complex described in document (5) **is not the same** as the active Factor VIII:C fragment of claim 1. Novelty of the latter over document (5) can thus be acknowledged.

6. Document (7) refers inter alia to a Factor VIII:C coagulant containing a polypeptide of about 92,000 daltons accompanied by a doublet of about 79,000 **and** about 80,000 (cf page 8, lines 21 to 29, page 11, lines 24 to 30, claim 1). Neither amino acid sequence data nor amino acid composition data are reported. Also in this case, it is not possible to read into the disclosure of this document information contained in document (1). This is again because document (7) contains no reference to the document (1), which in any case was published after its filing.

6.1 The respondents argue that the peptide chain of 80 kD referred to in claim 1 is the same as the doublet of 79/80 kD of document (7) as demonstrated also by a later publication by the inventors (cf document (17), cited as expert opinion).

6.2 The board observes that, while it is true that document (17) refers to a doublet chain at 80 kD of peak 2, it is also a fact that the elution profile from the high pressure liquid chromatography (HPLC) reported in document (17) (cf Figure 1) differs from that reported in the patent in suit (cf Figure 3), the main differences being observed precisely at the level of

peak 2 (peak II in the patent in suit). It is also noted that there are some differences in the experimental protocol for the purification of Factor VIII:C, which is the starting material for the fragmentation (compare Example 1 in the patent in suit with page 2979, right-hand column, paragraph at the bottom). Thus, document (17) cannot be used to support the contention that the peak II material which according to the present specification was found to contain only two peptide chains, one of 90 kD, the other of 80 kD (cf patent specification, page 5, lines 3 to 4), also contained a doublet at 80 kD.

6.3 Moreover, both the peptide chains referred to in claim 1 at issue are additionally characterized by their amino acid composition (molar percentages), fixed single values being given for each amino acid. This is relevant technical information which contributes to verify the identity of the claimed fragment (cf also point 5.1 supra) and which cannot be derived directly or by way of implication from document (7). Consequently this document cannot affect the novelty of claim 1.

7. In conclusion, in the board's view, the subject-matter of claim 1 was not inherent or "hidden" in any of the cited prior art documents and its novelty over them can therefore be acknowledged.

Procedural matters

8. The opposition division decided to revoke the patent in suit only on the basis of a finding of lack of novelty of the claim 1 then at issue for non-AT states, all further substantive objections raised by the opponents-respondents being left unexamined (cf Section III, last paragraph supra). Now that it has been found that claim 1 of the main request on file for the non-AT is novel, the board is obliged to make use of its power under Article 111(1) EPC to remit the case to the first instance for further prosecution of the main request.

9. In view of the above finding there is no need to examine the auxiliary requests.

10. Although duly summoned, the respondents III decided not attend oral proceedings (cf Section VII supra). According to decision G 4/92 (OJ EPO 1994, 149), a decision against a party who has been duly summoned but who does not appear at oral proceedings may not be based on facts put forward for the first time during those oral proceedings. In the present case, the board overruled the decision of the opposition division on the basis of a claim request and evidence which were already on file before the oral proceedings. Therefore, the respondents have had ample opportunity to comment on them in the written phase of the appeal. Thus, there is no conflict with the quoted decision of the Enlarged Board of Appeal.

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 for further prosecution of the main request for non-AT states, as filed on 29 June 1995.

The Registrar: The Chairperson:

D. Spigarelli U. M. Kinkeldey