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D E C I S I O N
of 2 October 1996

Case Number: T 0396/93 - 3.3.4

Application Number: 84107985.8

Publication Number: 0168506

IPC: A61K 39/395

Language of the proceedings: EN

Title of invention:
Process for preparing gamma globulin suitable for intravenous administration

Patentee:
Armour Pharma GmbH

Opponent:
IMMUNO Aktiengesellschaft

Headword:
Gamma Globulin/ARMOUR

Relevant legal provisions:
EPC Art. 54

Keyword:
"Main request - Novelty of a narrower range over a broader ranged disclosed by a prior art document (no)"
"Auxiliary request - allowable"

Decisions cited:
T 0245/91, T 0666/89, T 0198/84

Catchword:
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Case Number: T 0396/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 2 October 1996

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 12 March 1993 rejecting the opposition filed against European patent No. 0 168 506 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. European Patent No. 0 168 506 based on patent application No. 84 107 985.8 was granted with 13 claims. Claim 1 read as follows:

"1. An improved process for preparing gamma globulin suitable for intravenous administration comprising

(a) dissolving gamma globulin precipitated from blood or blood products in a solution;

(b) separating non-dissolved precipitate from the solution;

(c) adding polyethylene glycol to the separated solution;

(d) separating precipitate from the polyethylene glycol solution;

(e) increasing the polyethylene glycol concentration in the solution;

(f) separating precipitated purified gamma globulin from the higher concentrated polyethylene glycol solution;

(g) dissolving the purified gamma globulin in a solution suitable for intravenous administration wherein the improvement comprises

(1) the gamma globulin precipitated from blood or blood products is dissolved in a solution having a neutral pH;

(2) in the first polyethylene glycol addition step, adding the polyethylene glycol to a concentration of 4.0-5.5% by weight;

(3) in the second polyethylene addition step, increasing the polyethylene glycol concentration to at least 9%, but not more than 16% by weight;

(4) adding a citrate buffer to the solution just prior to adding the polyethylene glycol in one of the polyethylene glycol addition steps."

Claims 2 to 10 were specific embodiments of the process of claim 1.

Claims 11 and 12 were product-by-process claims directed to a product suitable for intravenous administration made by the process of claim 1 or 9, respectively.

Independent claim 13 read as follows:

"13. A product suitable for intravenous administration containing 2-10% native gamma globulin, optionally, buffer, optionally, sugar and water for injection; wherein the product has a pH of 7.00 ± 0.05, osmolarity of 300-330 mosmol/l, anticomplement activity of 10 u/ml or less, based on a protein concentration of 5% and the gamma globulin has a purity as judged by HPLC of about 99% or more."

II. Notice of opposition was filed solely against claims 11 to 13 by the opponent (appellant) requesting the revocation of the patent on the grounds that product claims 11 to 13 lacked novelty and inventive step (Articles 54 and 56 EPC) having regard to

(1) EP-A-0 122 558;

(2) J. Römer et al., Vox Sang. Vol. 42, pages 62 to 73 (1982);

(3) J. Römer et al., Vox Sang. Vol. 42, pages 74 to 80 (1982);

(4) US-A-4 276 283 and

(5) EP-B-0 092 186.

III. By its decision issued in writing on 12 March 1993, the opposition division rejected the opposition.

IV. The appellant (opponent) filed a notice of appeal against this decision and filed a statement of grounds of appeal. The respondent (proprietor of the patent in suit) filed counterarguments.

V. The appellant only argued with regard to novelty and inventive step of independent claim 13 which covered a preparation identical with the one disclosed by document (1), with the exception that the pH range was 7.00 ± 0.05 (claim 13) instead of 6.9 ± 0.4 (document (1)). Such restriction of the pH range did not fulfil any of the requirements necessary for leading to an invention of selection. In particular, the respondent did not show that the selection of the narrower pH range recited in claim 13 brought about advantageous effects. A test report provided by the appellant showed no variation of the product properties within the pH range of 7.00 ± 0.05.

VI. The respondent maintained that the narrower pH range of 7.00 ± 0.05 of claim 13 fulfilled the requirements for an invention of selection because the selected range was very narrow, there was a sufficient distance

between the claimed range and the pH of 6.8 recited in the examples of document (1), and the selection of the range of claim 13 was critical for the improved properties of the product. These were (1) a low anticomplement activity (hereafter: ACA) value; (2) the absence of prekallikrein activator (hereafter: PKA) and (3) a purity as judged by HPLC of more than 99%. The appellant's test report was contested in part (see point 8, *infra*).

VII. In a communication accompanying a summons to oral proceedings, the Board expressed its provisional opinion.

VIII. At the oral proceedings held on 2 October 1996, the respondent also relied on and was prepared to file late evidence as to the stability of the preparation of claim 13 as a hitherto not mentioned advantageous and surprising effect brought about by the selection of the narrow pH range of 7.00 ± 0.05. The respondent then submitted a new main request and a first auxiliary request. The claims of the main request differed from the claims as granted in that independent claim 13 comprised the additional feature that the product should not contain serum albumin. It was explained by the respondent that said amendment was made in order to better distinguish the claimed product from the one disclosed in document (1). The appellant further argued that claim 13 of the main request lacked novelty over document (4). The first auxiliary request did not include claim 13.

IX. The appellant (opponent) requested that the decision under appeal be set aside and that the main request submitted at the oral proceedings on 2 October 1996 be refused.

The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or the auxiliary request both submitted at the oral proceedings on 2 October 1996.

Reasons for the Decision

Late-filed evidence (Article 114(2) EPC)

1. At the oral proceedings, the respondent relied on and was prepared to file evidence as to the stability of the preparation of claim 13 as a hitherto not mentioned advantageous and surprising effect brought about by the selection of the narrow pH range of 7.00 ± 0.05 for the gamma globulin preparation of claim 1. Yet submitting only at the oral proceedings before the Board of Appeals a new line of argument accompanied by new experimental evidence, thus not allowing the other party to consider and to respond to it prior to the oral proceedings, and, if necessary, to file countertests, is not acceptable conduct on the part of the submitting party. The Board, in the exercise of its discretion provided by Article 114(2) EPC, thus refuses to take account of the late filed evidence.

Main request

Articles 123(2) and (3) EPC

2. The wording in claim 13 "but not containing serum albumin" finds a basis in the Examples which disclose only a product devoid of serum albumin and in column 2, lines 54 to 56 of the original description ("Also present in the solution may be albumin") implying that albumin may be absent. This expression moreover

represents a restriction of the scope of granted claim 13. Therefore claim 13 infringes neither Article 123(2) nor Article 123(3) EPC.

Article 83 EPC

3. It was argued by the appellant that, owing to the process of claim 1, it could not be excluded that some human serum albumin present in the starting material could be co-precipitated with the gamma globulins. Should this be the case, the preparation of claim 13 would include some albumin and the skilled person would not be able to arrive at the claimed composition devoid of albumin (Article 83 EPC). Whether serum albumin would necessarily be precipitated is a matter for evidence, and no such evidence is before the Board. In view of the conclusion that the Board reaches on novelty the matter can be left unresolved.

Novelty

4. Novelty (Article 54 EPC) and inventive step (Article 56 EPC) are at issue, relating to claim 13. The limitation "but not containing serum albumin" establishes formal novelty of claim 13 over document (1) disclosing compositions which always comprise human serum albumin as a stabilizer added in a ratio IgG/albumin of 1/1 to 5/1 (see page 11, step g).

5. The appellant argued at the oral proceedings that claim 13 lacked novelty over the composition of document (4). This discloses the following features:

(a) it comprises 0.5 to 20% of native gamma globulin (see column 3, line 54)

(b) it is dissolved in a buffer or a sugar solution (see the Examples)

(c) it has a pH between 7.0 and 7.5 (see column 3, line 19)

(d) it has an osmolarity of 300-330 mosmol/l (see column 3, line 56)

(e) it has an ACA value of 10 U/ml based on a protein concentration of 5% (see Table I, Example 3), and

(f) it has a purity of about 99% or more as judged by HPLC (see Table II, Example 3).

The respondent did not dispute that features (a), (b), (d) and (e) were common in this preparation and the claimed composition (see claim 13, Section I above) and the Board has no valid reasons for doing so. It was argued by the respondent that it was the absence of PKA and parameters (f) and (c) that rendered the composition of claim 13 novel over the one disclosed by document (4).

6. As regards the absence of PKA as a possible distinguishing feature, the Board observes that Endobulin® is, as admitted by the appellant, a preparation made according to the process of document (4). According to document (2) (see page 64, Table I and page 70, Table V) preparation No. 11 (i.e Endobulin®) exhibits indeed a high PKA value. However, as to the absence of PKA from the preparation of claim 13, this feature is **missing** in the claim and thus it cannot serve as a distinguishing feature.

7. With a view to feature (f), namely the purity of 99% or more as judged by HPLC, it was emphasized by the respondent that the purity of the preparations made according to document (4) is between 88.0 to 98.4 % (see Table II), the remaining representing polymers and

PKA. However, in the Board's view, the figure 99% in the patent in suit relates to the sum monomer + dimer (see column 4, line 39 and column 5, line 5), while the range 88.0 to 98.4% relates to the 7-S component, ie, the monomer only (see document (4), column 5, line 46 and Table II). There remains to be established how much dimer is contained in the preparation of the patent in suit. The appellant submitted on 6 July 1993 a test report as Anlage "A" (page 11 of the appeal file) showing the HPLC analysis of Purimmun®, a product covered by the patent in suit. Purimmun® turned out to include about 6% dimer. In reply to the test report, the respondent stated that "the experiments made and submitted by the appellant are **partly** doubtful" (emphasis added). The validity of the ACA values and the presence of fragments were contested. Yet the presence of about 6% dimer remained unchallenged. In view of this, the Board has to conclude that, once the content of dimers is not taken into consideration in both compositions, the purity of the preparation disclosed by document (4) is the same as the one covered by claim 13 and thus feature (f) cannot be considered as a distinguishing feature.

8. There remains to be decided whether feature (c), namely the pH range of 7.00 ± 0.05 exhibited by the preparation of claim 13, is able to establish novelty over the preparation of document (4) characterized by a pH range of 7.0 to 7.5.

The respondent maintained that the narrower pH range of 7.00 ± 0.05 of claim 13 fulfilled the requirements for an invention of selection. Much emphasis was placed by the parties on the question whether a particular technical effect was associated with the narrow pH range of 7.00 ± 0.05 recited in claim 13.

9. However, the Board disagrees. As has been stressed in decision T 666/89 (OJ EPO 1993, 495, point 8) such a particular technical effect is neither a prerequisite for novelty, nor can it as such confer novelty: its existence can merely serve to confirm a finding of novelty already achieved (following decision T 198/84, OJ EPO 1985, 209, point 7). Rather, for assessing the novelty of a claim in a case where overlapping numerical ranges of certain parameters exist between a claim and a prior art document, the correct approach is, according to decision T 666/89 (*loc. cit.*, point 7), to establish whether a person skilled in the art would, in the light of all the technical facts at his disposal, **seriously contemplate** applying the technical teaching of the prior art document in the range of overlap. In the present case, the question thus arises of whether a skilled person, having been taught by document (4) (see column 3, line 19) to carry out the last precipitation step of the immune globulins at a pH of 7.0 to 7.5, would seriously contemplate doing so in the range of overlap, namely in the pH range of 7.00 to 7.05.

10. In order to find an answer to this question, it should be noted that the process disclosed by document (4) for preparing pure immune globulin comprises five precipitation steps (a), (b), (d), (e) and (f) (see claim 4) occurring at pH 5.9 to 6.5, 7.2 to 8.0, 5.8 to 6.4, 6.4 to 7.0 and 7.0 to 7.5, respectively. These pH ranges are by themselves already very narrow since they extend less than one pH unit, and are very precisely defined. The selection of **all** the above pH ranges seems *inter alia* to be critical for obtaining high yields of a product devoid of extraneous proteins. There remains to be established whether document (4) would provide to the skilled person a technical basis to seriously contemplate considering the boundary values of the

above pH ranges as valid precipitation conditions. The Board observes that not only document (4) comprises no teaching that such boundary values are less interesting or that they should be excluded, but it rather shows that boundary values can seriously be taken into account by the skilled person since they are either exemplified (see column 4, line 30: pH = 7.2, i.e, the lower boundary values of step (b)) or explicitly recommended (see column 3, line 4: pH = 8.0, i.e., the upper boundary value of step (b)).

Under these circumstances, the Board must conclude that there is no new technical teaching and that nothing would prevent the skilled person from considering the lower boundary value of pH = 7.0 as a suitable pH for carrying out the last precipitation of the gamma globulin, and thus from arriving at a product falling under claim 13 of the patent in suit.

11. As the decided case closest to that in suit, the respondent cited the one dealt with in decision T 0245/91 of 21 June 1994 (not published in the OJ EPO), wherein the Board saw an invention of selection. However, it should be noted that in case T 0245/91 (*loc. cit.*, points 2.4 and 2.9) the question at issue was to decide whether a **combination** of more than ten overlapping parameters was available as a technical teaching to the skilled person. This situation is in no way comparable with present claim 13 involving only one overlap and thus the present case is more similar to the one dealt with in decision T 666/89 (*loc. cit.*), where the Board denied the novelty of a narrow range over a broader range disclosed by a prior art document.

12. Claim 13 of the main request thus does not fulfil the requirement of novelty (Article 54 EPC) and this request comprising a non allowable claim has to be rejected.

13. The auxiliary request no longer including claim 13 is allowable.

14. The description has to be amended so as to be in conformity with the now claimed subject-matter.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The matter is remitted to the first instance with the order to maintain the patent on the basis of the auxiliary request as filed at the oral proceedings on 2 October 1996.

The Registrar: The Chairwoman:

A. Townend U. Kinkeldey

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE ★ CHAMBRES DE RECOURS DE L'OFFICE EUROPÉEN DES BREVETS ★ BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

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