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D E C I S I O N
of 12 November 1997

Case Number: T 0710/94 - 3.4.2

Application Number: 87108296.2

Publication Number: 0249189

IPC: A61M 1/16

Language of the proceedings: EN

Title of invention:
Membrane for hemodialysis

Patentee:
TORAY INDUSTRIES, INC.

Opponent:
Akzo Nobel Faser AG
Fresenius AG

Headword:
-

Relevant legal provisions:
EPC Art. 100(b)
EPC R. 67

Keyword:
"Disclosure - sufficiency (no)"
"Reimbursement of the appeal fee (no)"

Decisions cited:
T 0585/92

Catchword:
-

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Case Number: T 0710/94 - 3.4.2

D E C I S I O N
of the Technical Board of Appeal 3.4.2
of 12 November 1997

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 1 July 1994 revoking European patent No. 0 249 189 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: E. Turrini
Members: R. Zottmann
M. Lewenton

Summary of Facts and Submissions

I. The Appellant (Patentee) lodged an appeal against the decision of the Opposition Division on the revocation of the patent No. 0 249 189 with the application No. 87 108 296.2.

The opposition was based on Article 100(a) and (b) EPC.

The Opposition Division held that the grounds for opposition mentioned in Article 100(b) EPC prejudiced the maintenance of the patent.

II. The following documents will be cited in this appeal decision:

D4: DE-A-3 426 331;

D7: Contr. Nephrol., vol. 46, pages 69 to 74 (Karger, Basel 1985);

D9: R. E. Kesting: "Synthetic polymeric membranes", J. Wiley & Sons Inc. USA, 1985, pages 237 to 286 (Chapter 7 Phase-Inversion Membranes);

D12: "Membranes and membrane processes", ed. by E. Drioli and M. Nakagaki, 18 June 1986, Plenum Press, New York and London, pages 507 to 513;

D13: English translation of "Testing Methods For Man-Made Yarns Filament Yarns JIS L 1013-1981, (Reaffirmed 1987)", pages 1 to 16 and Figure 2, as filed by the Appellant;

D14: ISO 62-1980(E), foreword and pages 1 to 4, first edition 1980-09-15, corrected and reprinted 1990-10-01.

The publisher informed the Board that D12 had been published on 18 June 1986.

III. Oral proceedings were held at the end of which the Appellant requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of a main request or two auxiliary requests. Furthermore, he requested reimbursement of the appeal fee.

Respondent I (Opponent I) requested that the appeal be dismissed, auxiliarily that the case be remitted to the first instance for further prosecution.

Respondent II (Opponent II) requested that the appeal be dismissed.

IV. Claim 1 according to the main request reads as follows:

"1. A symmetrical membrane for hemodialysis which, for a blood flow of 200 ml/min and a dialysate flow of 500 ml/min, has a total protein permeability of 0.2% or less and a β_2-microglobulin reduction rate of about 5-50% and which membrane has (i) a pore radius, as measured by Differential Scanning Calorimetry (DSC), of 4 nm to 15 nm, (ii) a total volume porosity of 35-75% and (iii) a pore volume porosity, as measured by DSC, of 25 % or more."

Claims 2 to 6 of the main request are dependent on claim 1 of said request.

Claim 1 according the first auxiliary request differs from claim 1 according to the main request in that "4 nm to 15 nm" is replaced by "5.5 to 15 nm".

Claims 2 to 5 of the first auxiliary request are dependent on claim 1 of said request.

Claim 1 according to the second auxiliary request differs from claim 1 according to the main request in that "4 nm to 15 nm" is replaced by "5.5 to 9.5 nm".

Claims 2 to 4 of the second auxiliary request are dependent on claim 1 of said request.

V. The Appellant's arguing with respect to the requirements of Articles 123 and 100(b) EPC is summarized as follows:

It is abundantly clear to the skilled reader from the last paragraph of page 2 to paragraph 2 of page 3 of the patent-in-suit that the hemodialysis conditions are employed when measuring both total protein permeability and β_2-microglobulin reduction rate. It is inconceivable that the skilled reader, after conducting a hemodialysis operation and measuring total protein permeability, would think it necessary to perform a separate hemodialysis operation to measure β_2-microglobulin reduction rate in order to be able to make that measurement at flow rates different from those used to measure total protein permeability. The measurements according to Example 3 are taken under non-operating conditions. From this follows in particular that the insertion of the flow conditions for measuring β_2-microglobulin reduction rate into claim 1 complies with Article 123(2) EPC.

If only the membrane has the properties as defined by the last three parameters (pore radius R, total volume porosity V_T and pore volume porosity V_P), of claim 1, the first two parameters of claim 1 (β_2-microglobulin reduction rate and total protein permeability) would be inevitably fulfilled.

The skilled person, at the filing date of the patent, was able to vary the manufacturing conditions and to select the polymeric materials such that said last three parameters of the finished membrane lie within the ranges of claim 1. Document D12 is cited in the patent and describes the DSC method which is suitable to determine R and the amount of pore water. D9 shows that the skilled person at the filing date of the patent was able to obtain a membrane having characteristics within the claim by accordingly altering the membrane production method.

Moreover, all conditions necessary for a reliable measurement of all parameters of claim 1 can be taken from the patent by the skilled person. Above all the fact that the measurements are to be carried out under conventional hemodialysis conditions enables the skilled person to obtain reliable measurement values. The water loss during dialysis has no influence on the determination of β_2-microglobulin reduction rate and total protein permeability. In Example 3 of D4 varying β_2-microglobulin reduction rate values were obtained with the same membrane. However, said tests were not carried out under conventional hemodialysis conditions with a minimal transmembrane pressure but under hemofiltration conditions with varying and higher transmembrane pressures. For the relatively large pore size membranes of the invention the maximum transmembrane pressures are so low that the β_2-microglobulin reduction rate and total protein permeability are not affected significantly by changes in said pressure. The deviations due to pressure variations within conventional hemodialysis were found to be at the utmost 4%.

The skilled person has no difficulties to determine V_T by using the absolute drying method mentioned in the patent. Guidance to the skilled reader as to which

drying method to adopt is given in international standards D13 and D14. The results of the tests of Experimental Report 1 carried out by the Patentee (annex of his letter dated 7 August 1996) show that several ways of removing water from the membrane and several ways of drying bring about almost the same results.

VI. The arguing of Respondent I with respect to the requirements of Articles 123 and 100(b) EPC is summarized as follows:

The skilled person is unable to measure and examine the parameters which are used in the claims to define their subject-matter.

The insertion of the flow rates into claim 1 is insufficient since the transmembrane pressure which defines the convection is missing.

The measuring of V_T is indefinite since the starting point as well as the end point of the drying method is not disclosed in the patent. A hint at a drying method, in particular a standard drying method, or a description of such a method would have been the minimum to obtain repeatable measuring points. According to the Appellant (reference was made to B)(2)(c)1. of his letter dated 7 August 1996), the absolute drying method starts with a saturated membrane which - according to the definition of W_T given by the design "DSC EVALUATION" of the Appellant - comprises chemically bound water. The latter requires particular drying methods. D13 describes a Japanese norm which is not applicable to membranes. On page 6 it is stated that the particular conditions for absolute drying should be appended. According to section 1.2 of D14, the Japanese standard described there is not applicable to cellular plastics and thus not to porous membranes.

The conditions for removing excess water of Experimental Report 1 of the Appellant cannot be taken from the patent.

The examples of the patent contain so little information about the manufacturing of the membranes that they cannot be carried out.

VII. The arguments of Respondent II with respect to the requirements of Articles 123 and 100(b) EPC are summarized as follows:

The introduction of the flow rates for the determination of β_2-microglobulin reduction rate into claim 1 clearly infringes Article 123(2). The patent contains only one value of the flow rate of the blood for the determination of the amount of β_2-microglobulin reduction rate reaching the dialysate. This value is mentioned in Example 3 and is considerably lower than the value of claim 1. The determination of β_2-microglobulin reduction rate is disclosed in a separate paragraph such that the conditions for determining total protein permeability described in the preceding paragraph cannot be applied to the determination of β_2-microglobulin reduction rate.

The measured β_2-microglobulin reduction rate value is dependent on the hemoconcentration of the blood which is in turn dependent on the constitution of the blood of the patient which can vary considerably. Above all the hemoconcentrations and the loss of water during dialysis should have been indicated in the patent to enable the skilled person to measure said parameter. *In vivo* measurements such as dialysis are dependent on the constitution of the test persons, such that different amounts of β_2-microglobulin reduction rate and proteins can be introduced into the blood by the test person's

body during the many hours' duration of the dialysis. This leads to different measurement results with the same membrane. Example 3 of D4 shows that β_2-microglobulin reduction rate is strongly dependent on the ultrafiltration rate and thus on the transmembrane pressure. The patent does not contain any information about the value of said pressure.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments (requirements of Article 123(2) and (3) EPC)*

In view of the fact that in paragraph 2 of page 3 where the determination of β_2-microglobulin reduction rate is described no measuring conditions are disclosed, it is clear to the skilled person that the hemodialysis conditions for measuring total protein permeability as set out in the preceding paragraph of the patent are valid also for β_2-microglobulin reduction rate. Example 3 makes no reference to measurement of either total protein permeability or β_2-microglobulin reduction rate as such. The measurements are taken remote from the operating conditions of dialysis. In particular, a small sample of blood is taken, contacted with the membrane and subjected to 20 minutes stationary incubation in the presence of dialysate liquid on the other side of the membrane. This contrasts with practical hemodialysis conditions where all of the blood of a patient is circulated and dialysate is also circulated continuously. The insertion of the flow conditions for measuring β_2-microglobulin reduction rate into claim 1 as granted complies with Article 123(2) EPC.

The Board is satisfied that the other amendments of the claims comply with Article 123(2) EPC and that all amendments of the claims do not infringe Article 123(3).

3. *Sufficiency (requirements of Article 100(b) EPC)*

3.1 The wording of the independent claims is only of importance in so far as it serves to define the subject-matter of the patent. The differences between the independent claims of the three requests are unimportant with respect to insufficiency considerations since the independent claims of the three requests differ from each other only in that the ranges for the pore radius (R) vary to a moderate extent. Moreover, the following considerations do no concern the limits of said range.

3.2 In the oral proceedings, the Appellant alleged that observance of the β_2-microglobulin reduction rate and total protein permeability ranges is unnecessary to define the subject-matter of the patent if only the remaining three parameters R, V_T and V_P lie within the indicated ranges. This would mean that the definition and measuring conditions for these parameters are not essential for judging sufficiency of the patent.

This point of view is, however, contrary to the teaching of the patent. The single independent claim of the application as originally filed, namely claim 1, contains said first two parameters (including their ranges) but not the parameters R, V_T and V_P. The latter are contained only in the dependent claims. From the description as originally filed (see for example page 8 lines 11 to 14: "The membrane of the invention **preferably** has a total volume porosity ... " [emphasis added by the Board], and page 9 second half) follows

that the β_2-microglobulin reduction rate and total protein permeability ranges are essential features of the subject-matter of the patent whereas the ranges of the last three parameters are optional. Nowhere in the description it is stated that said first two parameters are superfluous if only the last three parameters of claim 1 are within the indicated ranges.

3.3 The measurements of β_2-microglobulin reduction rate and total protein permeability are not defined by a repeatable or standardized method. The expression "conventional hemodialysis" used in the description does not comprise a definition of the blood or, respectively, test person used for the dialysis tests. In such *in vivo* measurements said parameters depend on the composition of the blood or, respectively, on the test person. For instance, if different test persons produce different amounts of β_2-microglobulin and/or proteins during dialysis tests of many hours' duration or if the blood of different test persons has considerably differing hemoconcentrations, β_2-microglobulin and/or of proteins, this would have an unneglectable influence on the measured values of β_2-microglobulin reduction rate and total protein permeability. The Appellant has not shown that such variations are unimportant.

Moreover, the transmembrane pressure during the determination of β_2-microglobulin reduction rate and total protein permeability and/or the filtration rate and/or fluid loss per test is/are not indicated in the patent (compare e. g. the very detailed information about the conditions of hemofiltration and hemodialysis tests on page 70 first half of document D7). Respondent II refers to Example 3 of D4 according to which, when stepping up the filtrate rate from 0 to 50 ml/min, the increase in clearance for β_2-microglobulin at a blood

flow of 200 ml/min was 40% and thus considerably. In the oral proceedings, the Appellant alleged that, due to the low pressure differences in hemodialysis, the deviation during the hemodialysis tests could be at the utmost 4%. However, the Appellant has not shown that the range of transmembrane pressures occurring at conventional hemodialysis is very low and its influence on the measuring results of β_2-microglobulin reduction rate is neglectable when using different membrane materials. It has moreover to be taken into account that low transmembrane operating pressures would cause back flow which would reduce the reliability of the method. Even if said pressure range in conventional hemodialysis were not very high and had no great influence on β_2-microglobulin reduction rate and total protein permeability, it would be nevertheless not neglectable since it adds to the uncertainties mentioned above and those set forth below.

Hence, β_2-microglobulin reduction rate and total protein permeability cannot be determined sufficiently exactly on the basis of the disclosure of the patent.

3.4 According to the attacked patent, an essential parameter of V_T and V_P is the total amount of water (W_T) which is to be determined by the "absolute drying method" (see page 4 lines 29 to 49). Said drying method is neither defined in the patent including D12 which is cited in the description nor in D9. The Appellant refers further to D13 and D14 and his Experimental Report 1.

Document D13 concerns testing methods applicable to man-made filament yarns but not to porous yarns or porous membranes. Moreover, D13 states that the conditions of "absolute drying" - which are indicated there in a very detailed manner (see sections (4) on page 2 to page 3 in the middle and page 5 last

paragraph to page 6) - such as drying means and temperature should be appended (see page 6). This means that the mention of "absolute drying method" alone - as in the patent-in-suit - is insufficient for the purpose of reproducibly measuring W_T.

Since the International Standard (ISO) according to D14 is a first edition of 1980 being corrected and reprinted 1990 (see cover sheet) it is unclear when the cited pages were published. Setting aside this aspect, D14 cannot be used for defining the conditions of "absolute drying" because it is applicable to compact plastics but expressly not to cellular plastics (see section 1.2 on page 1). Thus the skilled person would not take into account this document when seeking to determine the drying conditions of porous membranes. Moreover, D14 describes only one of several known standard methods.

The tests of Experimental Report 1 were carried out with only one material, namely that of Example 1 of the patent-in-suit (polymethylmetacrylate). It cannot be assumed that membranes consisting of a material different from that used in Example 1 (see claim 6 of the main request: polyacrylonitrile, cellulose, cellulose acetate, polysulfone, polyvinyl alcohol etc.) leads to such modest errors of V_T as mentioned in said report (ca. 2%) when using the different test methods for removing superficial water ("excess water"). Furthermore, the conditions of the tests cannot be derived from the patent-in-suit. The conditions for "several ways of drying" (test 2) are incompletely indicated; e. g. the method for removing superficial water and details of the convection are missing. The V_T values of the membrane (of Example 1) obtained with

different drying methods (test 2) are not indicated such that the possible error when varying the test method by using the different methods for removing superficial water (test 1) and the three drying methods (test 2) is unknown.

The Appellant, on the basis of the paper "DSC EVALUATION", put forward that the water content of a membrane according to the patent-in-suit typically consists of 35% of water in pores up to 15 nm ("pore volume porosity"), 30% of water in pores of more than 15 nm ("large volume porosity") and 35% of water "desolved in polymer chains" and that the latter water fraction leads to swelling of the polymer. Said water fraction is physically and/or chemically bound and thus is, apparently, no pore water. Such an interpretation of the quantity total volume **porosity** W_T cannot be derived from the patent-in-suit and thus cannot attribute to a clearer definition of the patent's expression "absolute drying method". A detailed definition of the drying method would be all the more necessary for an unambiguous definition of W_T.

Hence, W_T and thus V_T and V_P cannot be reliably determined on the basis of the disclosure of the patent.

3.5 In the proceedings before the Opposition Division, the burden of proving that the objections raised under Article 100 EPC have been substantiated lay with the Opponents. However, after revocation of the patent by the Opposition Division, the burden shifted to the Appellant (Patentee), who must demonstrate on appeal that the reasons for revoking the patent were not sound, that is that the Opposition Division's decision was wrong as to the merits (following decision T 0585/92, OJ EPO 1996, 129). Since it follows from the foregoing that considerable doubts remain whether the

patent discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, the Appellant does not succeed in demonstrating that the attacked decision was deficient as to its substance.

4. *Reimbursement of the appeal fee*

According to Rule 67 EPC the reimbursement of the appeal fee shall be ordered only if the Board of Appeal deems the appeal to be allowable. However, this requirement is not met.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana E. Turrini