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D E C I S I O N
of 16 September 1998

Case Number: T 0132/96 - 3.4.2

Application Number: 89105890.1

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Language of the proceedings: EN

Title of invention:
An adsorber module and adsorber apparatus for whole blood treatment

Patentee:
Asahi Medical Co., Ltd.

Opponent:
Akzo Nobel Faser AG

Headword:
-

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"After amendments: novelty (yes), inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0132/96 - 3.4.2

D E C I S I O N
of the Technical Board of Appeal 3.4.2
of 16 September 1998

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 1 December 1995 revoking European patent No. 0 341 413 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: E. Turrini
Members: M. Chomentowski
V. Di Cerbo

Summary of Facts and Submissions

I. The appellant is proprietor of European patent No. 0 341 413, which was granted with 11 claims on the basis of European patent application No. 89 105 890.1, wherein D1: WO-A-80/02805 was cited. Granted claim 1 read as follows:

"1. An adsorber module for whole blood treatment comprising:

a casing provided with a blood introduction means (2) and a blood withdrawal means (3), and

a plurality of porous hollow fibers (1) substantially equal in length arranged substantially in parallel relationship and bonded together at both end portions thereof to form a bundle, each porous hollow fiber of said bundle having openings at both terminal ends thereof,

said bundle being disposed in said casing along the length of said casing,

said both end portions of the hollow fibers of said bundle being fluid-tightly connected to said blood introduction means and said blood withdrawal means, respectively, thereby establishing communication between said blood introduction means and said blood withdrawal means through said bundle of hollow fibers,

each porous hollow fiber comprising a membranous porous resin matrix having pores which open at least at the inner wall of the hollow fiber and a plurality of ligands (8) attached to the overall surface of said porous resin matrix,

said ligands being capable of interacting with a substance to be adsorbed,

said ligands having low antigenicity,

said porous resin matrix having an average pore diameter of from 0.005 to 3 μm,

said porous hollow fibers having an average effective length (L mm) and an average inner diameter (D mm) which satisfy the inequality:

L/D^2 (mm^{-1}) > or = 2000

said average effective length being defined as an average of the lengths of said porous hollow fibers minus the lengths of said both end portions of said porous hollow fibers at which the fibers are bonded together and fluid-tightly connected to said whole blood introduction means and said blood withdrawal means, respectively."

Claim 9, although drafted as an independent claim, concerned an adsorber apparatus comprising inter alia an adsorber module with the same features as those recited in claim 1. The further claims were dependent claims.

II. An opposition was filed by the respondent (opponent) in particular on the grounds that the subject-matter of the claims was not patentable having regard to, inter alia, D1.

III. The European patent was revoked for lack of inventive step having regard to the combination of D1 with D16: EP-A-0143369.

The decision concerned an amended text of claim 1 wherein, inter alia, the porous hollow fiber had pores with openings at both surfaces thereof, said pores cooperating with said openings to form throughpaths running between both the surfaces of the fibers.

The opposition division, which had taken D17: WO-A-85/03011 into consideration but did not retain it in the decision, took the following view:

The closest prior art was D1. The claimed module was distinguished therefrom in that

(i) the ligands were attached to the overall surface of the porous resin matrix,

(ii) the ligands had low antigenicity, and

(iii) the porous hollow fibers had dimensions which satisfy the inequality L/D^2 (mm^{-1}) > or = 2000.

The person skilled in the art, starting from D1, was faced with the problem of improving the adsorbent capacity of the known module. A solution of this problem was known from D16, which was concerned with adsorption of malignant substance from blood using ligands which had no negative effect on blood; it was thus obvious to apply to D1 the distinguishing features (i) and (ii). As regards the distinguishing feature (iii), it was derivable from the results of comparative measurements provided by the patentee that they had no technical effect since acceptable results could also be obtained with values of dimensions which fall outside of the range determined by the inequality. Therefore, the claimed module lacked an inventive step.

III. The patent proprietor lodged an appeal against this decision.

IV. During the oral proceedings of 16 September 1998, which had been requested auxiliarily by both parties, the appellant filed a new set of 10 claims and requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of said set of claims, of the description to be adapted and of the drawings of the patent specification.

Claim 1 of appellant's request specifies additionally that the ligands, which have low antigenicity, are such that, when they are in contact with blood corpuscles, they do not cause hemolysis of erythrocyte, sensitization of leukocyte, or adherence and/or aggregation of platelet, and that the porous hollow fibers have an average effective length (L mm) and an average inner diameter (D mm) which satisfy the further inequality: 150 μm < or equal D < or equal 400 μm. This claim reads as follows:

"1. An adsorber module for removing malignant components of whole blood by adsorption, comprising:

a casing provided with a blood introduction means (2) and a blood withdrawal means (3), and

a plurality of porous hollow fibers (1) substantially equal in length arranged substantially in parallel relationship and bonded together at both end portions thereof to form a bundle, each porous hollow fiber of said bundle having openings at both terminal ends thereof,

said bundle being disposed in said casing along the length of said casing,

said both end portions of the hollow fibers of said bundle being fluid-tightly connected to said blood introduction means and said blood withdrawal means, respectively, thereby establishing communication between said blood introduction means and said blood withdrawal means through said bundle of hollow fibers,

each porous hollow fiber comprising a membranous porous resin matrix having pores therewithin and openings on both surfaces thereof, said pores cooperating with said openings to form throughpaths running between both the surfaces of said resin matrix, and a plurality of ligands (8) attached to the overall surface of said porous resin matrix,

each of said ligands being capable of selectively interacting with the malignant components to be adsorbed on said hollow fibers,

said ligands having low antigenicity such that when the ligands are in contact with blood corpuscles, the ligands do not cause hemolysis of erythrocyte, sensitization of leukocyte, or adherence and/or aggregation of platelet,

said porous resin matrix having an average pore diameter of from 0.005 to 3 μm,

said porous hollow fibers having an average effective length (L mm) and an average inner diameter (D mm) which satisfy the inequalities:

L/D^2 (mm^{-1}) > or = 2000, and

150 μm < or equal D < or equal 400 μm

said average effective length being defined as an average of the lengths of said porous hollow fibers minus the lengths of said both end portions of said porous hollow fibers at which the fibers are bonded together and fluid-tightly connected to said whole blood introduction means and said blood withdrawal means, respectively."

The only other independent claim is claim 8, which concerns an adsorber apparatus for removing malignant components of whole blood by adsorption, comprising an adsorber module comprising in substance the same features as those recited in claim 1.

V. The appellant submitted the following arguments in support of his request:

The filed amendments of the claims are admissible. As an outcome of said amendments, the claims define unambiguously the features of the invention, for instance the ligands with low antigenicity, and they are thus clear for the skilled person.

The module of D1 is the closest prior art because it concerns a module of the same type and problems related to high antigenicity of ligands when in contact with the corpuscles of whole blood. Therein, said ligands have high antigenicity and, for this reasons, they are restricted to the surface of the hollow fibers which is not faced with the blood. The invention intends to increase the limited adsorption capability of the module resulting from this restricted contact surface between blood and ligands. D16 gives information about unrestricted contact of blood with ligands which can have low antigenicity. However, D1 and D16 do not lead to the claimed adsorber module, which is a compromise between low antigenicity ligands which are safe but have low adsorption capability, on the one hand, and a

distribution of said ligands on the overall surface of the fibers with moreover specific dimensions of said fibers, whereby satisfactory results are obtained, on the other hand. Therefore, the inequalities of claim 1, which are not known in the art, can be considered as contributing to this compromise and thus to an inventive step of the claimed module.

D17 does not concern problems related to high antigenicity of ligands in contact with whole blood, and the inequalities relating to the dimensions of the fibers are not derivable therefrom.

Therefore, the subject-matter of the claims involves an inventive step.

VI. The respondent argued in substance as follows in support of his request that the appeal be dismissed and that patent remain revoked in its entirety:

The amendments having led to the present claims are not admissible for the reasons mentioned in the annex to the summons to oral proceedings. Moreover, the claims define the ligands with low antigenicity in an ambiguous way and thus lack clarity.

Starting from the module of D1, the skilled person is aware of problems related to high antigenicity of ligands when in contact with the corpuscles of whole blood. Moreover, D1 already indicates that said ligands are not restricted to the surface of the hollow fibers which is not faced with the blood, but can also be present in the pores of said fibers. For increasing the adsorption capability of the known module, the skilled person can increase the distribution of ligands by providing it on the overall surface of the fibers. For doing this, he only needs to take into account the teaching of D16, which he knows because it belongs to

the same technical field, and from which he can derive that there are ligands which are safe for using with whole blood and which are present in an unrestricted manner in fibers of the module; indeed, said ligands of D16 are in substance the same as those which are recited in the patent in suit. Concerning the further feature which distinguishes the module in dispute from the module known from D1, i.e. the inequalities relating to dimensions of the fibers, they are not critical for the result, as can be seen from the available results of comparative measurements, and in any case would be arrived at by the skilled person when carrying into practice a module resulting from the combination of D1 and D16. This last remark also applies to the module of D17, which is for doing the same operations as the module in dispute, and which is distinguished therefrom only by this additional feature relating to the fiber dimensions. Therefore, the module in dispute lacks an inventive step.

Reasons for the Decision

1. The appeal is admissible.

2. *Disclosure of the invention*

The notice of opposition indicated that the opposition was based inter alia on the grounds of Article 100(b) EPC. However, this objection has not been substantiated later by any argument concerning the sufficiency of disclosure of the invention. The respondent has admitted that his objection, which was based on the results of comparative measurements provided by the appellant, was primarily directed against inventive step, and that it was not doubtful that the invention was disclosed in a manner sufficiently clear and

complete for it to be carried out by a person skilled in the art. Therefore, since sufficiency has not been otherwise objected, appellant's request is considered as satisfying the requirement of Article 100(b) EPC.

3. *Formal requirements*

The claims of appellant's request contain amendments which, in the opinion of the Board, meet objections which had been mentioned in the annex to the summons and which related to the admissibility of the amendments having led to former texts of said claims. The respondent has argued that these objections are still valid against appellant's present request, but he has not substantiated this in any manner. Therefore, the present request does not infringe Article 123(3) and (2) EPC, which require that the claims of the European patent should not be amended in such a way as to extend the protection conferred and that the European patent should not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed, respectively.

The respondent has also objected that the ligands in the independent claims, which are mentioned as having low antigenicity such that when the ligands are in contact with blood corpuscles, the ligands do not cause hemolysis of erythrocyte, sensitization of leukocyte, or adherence and/or aggregation of platelet, are not correctly defined, so that the claims lack clarity. However, the claims of the granted specification only mentioned that said ligands had low antigenicity, and the respondent has not submitted any substantive argument showing that the addition by amendment of the feature that said low antigenicity is such that when the ligands are in contact with blood corpuscles, the ligands do not cause hemolysis of erythrocyte,

sensitization of leukocyte, or adherence and/or aggregation of platelet, introduces any ambiguity, i.e. any lack of clarity as compared to the claims as granted. Therefore, the claims of appellant's request satisfy the requirement of clarity of Article 84 EPC, and at least in this respect, a requirement of the Convention for maintaining a European patent in amended form pursuant to Article 102(3) EPC.

4. *Novelty*

4.1 The respondent has not contested that, contrary to the adsorber module of claim 1 in dispute, in the module known from D1 (see page 1, lines 8 to 25; page 2, lines 13 to 27; page 2, line 37 to page 6, line 15; page 9, line 20 to page 11, line 8; page 13, line 7 to page 14, line 8; Figures 1 to 4),

(i) the ligands are **not** attached to the overall surface of the porous resin matrix of the porous hollow fibers, but are only on the surface not in contact with the whole blood.

The respondent has argued that the passage of page 3, lines 21 to 24 of D1, according to which the biologically active material is immobilized in the pores and/or on the surface of the side of the membrane which is adapted to be faced away from the liquid, could mean that the ligands are also immobilized in the pores, i.e. not on the surface of the side of said membrane that faces away from the whole blood and thus in contact with whole blood. However, this cannot convince insofar as it is specified in D1 (see page 5, line 33 to page 6, line 15) that, irrespective of the outer shape or chemical or mechanical constitution of said membrane, said

biologically active material must be asymmetrically immobilized in said membrane in such a way that the surface of said membrane that faces towards the whole blood is free of "reagent", this being to avoid contact between blood corpuscles and the reagent and thereby pyrogen and/or anaphylactic reactions and that, thus, it is a form of asymmetric immobilization, where on one surface of said membrane as well in the pores thereof said biological active material has been immobilized.

Moreover, in the module known from D1,

(ii) said ligands are not specified as having low antigenicity such that when the ligands are in contact with blood corpuscules, the ligands do not cause hemolysis of erythrocyte, sensitization of leukocyte, or adherence and/or aggregation of platelet,

and,

(iii) the porous hollow fibers are not specified as having an average effective length (L mm) and an average inner diameter (D mm) which satisfy the inequalities:

L/D^2 (mm-1) > or = 2000, and

150 μm < or equal D < or equal 400 μm

said average effective length being defined as an average of the lengths of said porous hollow fibers minus the lengths of said both end

portions of said porous hollow fibers at which the fibers are bonded together and fluid-tightly connected to said whole blood introduction means and said blood withdrawal means, respectively.

4.2 The respondent has admitted that D16 does not show any specific constructional features of an adsorber module with bundles of hollow fibers and that another device, known from D17, does not comprise the feature of claim 1 of appellant's request about the inequalities concerning the length and the diameter of the fibers. The respondent has not contested that the other prior art documents are less relevant.

Therefore, since the module of claim 1 in dispute is not comprised in the state of the art, it is new in the sense of Article 54 EPC.

5. *Inventive step*

5.1 The adsorber module of D1 (see the text locations indicated here above) comprises microporous semipermeable membranes; whole blood is treated in said module, this treatment being done through adsorption by the membrane, more in particular by a biologically active material which is immobilized in the pores and/or on the surface of the side of said membrane that faces away from the whole blood. It is derivable from Figure 1 of D1 (see also page 9, lines 20 to 26) that the known system is concerned in particular with an extracorporeal system for the treatment of whole blood from a patient. It has not been disputed that said active material has the same function as the ligands of the patent in suit.

As set forth here above with respect to novelty, in the known module, the ligands are not attached to the overall surface of the porous resin matrix of the porous hollow fibers, but are only on the surface not in contact with the whole blood.

Starting from the adsorber module of D1, which concerns the same technique and which stresses the problems which are related with contacts of ligands and blood corpuscles and which is thus in any case an adequate starting point, there is according to the patent in suit (see page 3, lines 1 to 9; see also page 6, lines 36 to 40, page 11, line 51 to page 12, line 5 and page 12, lines 38 to 43) inter alia a problem due to the fact that the active material for the treatment of whole blood is present only at the outer surface of the hollow fibers, this resulting in their adsorbing capability being rather low. Therefore, an object of the invention is to provide an adsorber module having an increased adsorbing capacity for malignant substances by which it is easy to accomplish effective, efficient removal of the malignant components of whole blood without the danger of blood coagulation and hollow clogging so that the malignant components of the blood can be effectively removed by adsorption.

5.2 It has not been contested that the person skilled in the art of D1 is aware of the porous adsorbent of D16 (see page 2, printed numbering at the bottom of the page; page 4, lines 3 to 26; page 5, lines 14 to 28; page 8, line 15 to page 10, line 29; page 28, lines 10 to 14; page 29, lines 22 to 24 and page 30, lines 4 to 7; page 31, lines 12 to 16), which belongs to the same technical field and which allows in particular to purify and regenerate fluids such as whole blood by adsorbing in particular low density lipoproteins from said blood; the porous adsorbent can be in the form of hollow fibrous and filmy form, and it comprises, linked

with the surface of a carrier body, inter alia, a synthetic polyanion member having a molecular weight of 600 or more; said synthetic polyanion member has the capability of bonding and adsorbing low density lipoproteins to its surface; devices using such adsorber modules are mentioned in relation to extracorporeal circulation.

Because of this last information, the person skilled in the art of D1 can derive that, when the treatment of whole blood with direct contact to the surface of the adsorber is concerned in D16 (see also page 4, lines 3 to 12), non toxic ligands can be used for safety reasons. As conceded by the appellant, compounds mentioned in D16 as examples of the synthetic polyanion member fall within the definition of the ligands having low antigenicity in the sense of the patent in suit.

5.3 The question, whether the person skilled in the art of D1, taking into account the requirements of safety mentioned therein, and, in view of increasing the adsorbing capacity of this known adsorber module, the teaching of D16, would arrive in an obvious way to a module with ligands having low antigenicity on both surfaces of the membranes, said ligands being the same as those of the patent in suit (see in particular page 7, lines 16 to 25 and page 8, lines 21 to 47), can be left undecided for the following reasons:

The appellant has credibly argued as follows: people skilled in the relevant art generally know that ligands having low antigenicity also have limited adsorption capability; however, even if the number or density of ligands of the membrane can be increased by immobilizing the ligands on both surfaces and pores thereof and not only on one surface and pores thereof, there may remain a need to increase the adsorption capability of said ligands by providing a structure of

the module which allows such an increase; indeed, the results of comparative measurements which have been provided show that, at least for the values of the average effective length (L) and average inner diameter (D) of the fibers corresponding to the inequalities of claim 1 in dispute, a positive result is shown.

Concerning said feature additionally distinguishing the invention with respect to D1, i.e. that the porous hollow fibers have an average effective length (L mm) and an average inner diameter (D mm) which satisfy the inequalities L/D^2 (mm^{-1}) > or = 2000, and 150 μm < or equal D < or equal 400 μm, it is to be noted that, as convincingly argued by the appellant, this feature as such is not directly derivable from the relevant prior art and, moreover, it results in an increase in adsorption capability of the module; this increase is obtained, as derivable from the results of comparative measurements on file, without a direct relation to an increasing average effective length and/or a decreasing average inner diameter of the fibers, which the skilled person could derive from his general knowledge. Indeed, this feature is only partially critical in the sense that, as credibly argued by the respondent, satisfactory results can also be obtained with values which are outside of the range determined by said inequalities.

However, as convincingly argued by the appellant, the invention provides an adsorber module with **a compromise** between low antigenicity ligands which are safe but have low adsorption capability, on the one hand, and a distribution of said ligands on the whole surface of the fibers with moreover specific dimensions of said fibers, whereby satisfactory results are obtained, on the other hand. Therefore, the inequalities of claim 1,

which are not known in the art, can be considered as contributing to this compromise and thus to an inventive step of the claimed module.

5.4 D17 (see page 6, first paragraph to page 7, second paragraph; see also page 31, last paragraph to page 32, first paragraph) concerns a technique for the cross-flow filtration of a liquid, for instance blood, comprising circulating the liquid tangential to a charge modified organic polymeric microporous filter membrane, for instance in the form of hollow fibers, containing charge modifying agents, whereby adsorption may be effected. However, neither problems related to high antigenicity of ligands in contact with whole blood nor the inequalities relating to the dimensions of the fibers are derivable from this document; therefore, with respect to the present invention, it is appropriate neither as a starting point nor for completing the teaching of, inter alia, D1.

5.5 Consequently, having regard to the state of the art, the subject-matter of claim 1 of appellant's request is not obvious to a person skilled in the art and, thus, it involves an inventive step in the sense of Article 56 EPC.

Claim 8 of appellant's request is an apparatus claim with the same module features as claim 1 and involves thus an inventive step for the same reasons.

6. Therefore, the claims of appellant's request are allowable and the European patent can be maintained in amended form on this basis (Articles 52(1) and 102(3) EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of claims 1 to 10 presented at the oral proceedings of 16 September 1998 with the description to be adapted and the drawings of the European patent specification.

The Registrar:

P. Martorana

The Chairman:

E. Turrini