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D E C I S I O N
of 13 April 1999

Case Number: T 0581/96 - 3.3.5

Application Number: 86902225.1

Publication Number: 0218639

IPC: B01D 61/00

Language of the proceedings: EN

Title of invention:
Plasmapheresis System and Method

Patentee:
McLaughlin, William Francis

Opponent:
Akzo Nobel Faser AG
Dideco SpA

Headword:
-

Relevant legal provisions:
EPC Art. 114(2), 54(1), 56

Keyword:
"Novelty (yes) no implicit disclosure"
"Selection from a range"
"Inventive step (yes) - exclusion of hindsight"
"Late submitted ground of opposition (not admitted)"

Decisions cited:
-

Catchword:

-

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Beschwerdekammern | Boards of Appeal

Case Number: T 0581/96 - 3.3.5

D E C I S I O N
of the Technical Board of Appeal 3.3.5
of 13 April 1999

Appellant: (Opponent 01)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 5 June 1996**

concerning maintenance of European patent No. 0 218 639 in amended form.

Composition of the Board:

Chairman: R. K. Spangenberg
Members: A. Liu
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 218 639 was granted upon the European patent application No. 86 902 225.1, with a method claim 1 and further method claims 2 to 7 dependent thereon and an apparatus claim 8 and further apparatus claims 9 and 10 dependent thereon.

II. Upon two notices of opposition, the opposition division has taken the interlocutory decision of maintaining the patent in amended form (Article 106(3) EPC). The decision, posted on 5 June 1996, was based on the patentee's second auxiliary request consisting of claims 1 to 7 as granted. Claim 1 reads as follows:

"The method of membrane filtration of at least one lighter density component from a whole blood flow derived from a donor passing adjacent a filtration membrane, comprising the steps of:

maintaining the blood derived from the donor in a pH range of 6.8 to 7.2 and mixing anticoagulant with the blood derived from the donor in the proportion of 1:6 to 1:25 relative to the whole blood, and

passing the blood derived from the donor with the mixed anticoagulant adjacent the filtration membrane while filtering the lighter density component through the membrane".

III. Having taken ten citations into consideration, the opposition division held that the process of claim 1 was novel since none of the cited documents disclosed a membrane filtration process wherein the blood derived from the donor is maintained within the pH range of 6.8 to 7.2.

With respect to the closest prior art teaching, the distinguishing feature of maintaining the pH range was accepted as solving the problem of flow rate reduction encountered in a subpopulation of donors during whole blood filtration. Since the solution could not be derived from the available prior art documents, the claimed process was also considered to involve an inventive step.

The decision further mentioned that the opponents introduced a new ground of opposition under Article 100(b) late in the proceedings, which was therefore disregarded, pursuant to Article 114(2).

IV. Both opponents appealed against the decision of the opposition decision.

V. Appellant I (opponent I) argued that claim 1 of the patent-in-suit was so broadly defined that it went far beyond the problem addressed by the invention which was in fact restricted to cyclic plasmapheresis processes. This would lead to a contradiction between the problem to be solved as described and the solution as defined in claim 1.

In addition, he argued that the subject-matter of claim 1 was not novel or at least lacked an inventive step with regard to any one of the following newly cited documents:

D4: Artificial organs 7(4) 443-449 (1983)

D5: Conference paper at 1st International meeting on Hemapheresis, Dijon, 14 to 17 November 1984

D6: Transfusion 23(2) 143-147 (1983)

In essence, it was submitted that, since the same anticoagulant (ACD-A) was used in the same ratio in D4, D5 and D6, the resulting pH, even where not expressly disclosed, would necessarily fall into the claimed range. Furthermore, D5 revealed a mean pH value for the collected plasma at 7.359. In the appellant's view, the disclosed pH value was practically the same as the upper limit defined in claim 1 when the standard deviation from the mean pH value as indicated in D5 was taken into account.

VI. Appellant II (opponent II) submitted that the requirements of Article 83 EPC were not met since claim 1 was extremely broad although the description only disclosed one way of carrying out the invention.

Furthermore, it was asserted that the claimed processes lacked novelty with regard to D4. A new document was cited which was to complement the information disclosed in D4:

D4A: USP 23 Standard for "Anticoagulant citrate dextrose solution"

VII. The respondent submitted that none of the available prior art documents taught or suggested that the pH range of the whole blood should be maintained in the specific range from 6.8 to 7.2 during filtration. According to the invention, it might be necessary to use a more acidic anticoagulant to achieve the relatively low pH than would normally be required to simply achieve an acceptable level of anticoagulant in

normal whole blood.

VIII. At the end of the oral proceedings held on 13 April 1999, the appellants (opponents) requested that the decision under appeal be set aside and that the European patent No. 0 218 639 be revoked. The respondent (patentee) requested as main request that the appeals be dismissed and as auxiliary requests that the decision under appeal be set aside and that the patent be maintained on the basis of one of the sets of claims 1 to 7 or claims 1 to 6 submitted at the oral proceedings on 13 April 1999 as Auxiliary Requests I, II and III, respectively, with an opportunity to adapt the description appropriately.

Reasons for the Decision

1. The appeal is admissible

Main Request

2. *Sufficiency of disclosure*

Appellant I has criticised that claim 1 is inconsistent with certain passages of the description. The Board notes that this objection is based on Article 84 EPC which is not a ground for opposition under Article 100 EPC. Since the indicated passages and the claims are part of the patent specification as granted, even if such inconsistency should exist, the objection cannot be taken into consideration at this stage of the procedure.

Both appellants have also argued that the wording of claim 1 directed to a "method of membrane filtration of at least one lighter density component from a whole blood flow" encompasses the filtration from whole blood of components other than plasma. It has therefore been alleged that since the description does not give a clear teaching for such a process not involving the filtration of plasma, the requirements of Article 83 EPC are not met. The appellants, however, have not further substantiated the objection. They have neither provided any evidence that the nature of the components to be filtered would influence the filtration process as claimed nor shown that the claimed process could not be carried out in some situations within the ambit of the claim. The Board therefore considers that the opposition division has correctly exercised their discretionary power in disregarding this late filed ground of opposition.

3. *Novelty*

The appellants have raised the objection that the process of claim 1 lacks novelty with regard to D4, D5 and D6.

3.1 D4 is directed to membrane plasma separation employing citrate as anticoagulant, wherein citrate is added continuously in a ratio of 1 part acid citrate dextrose ACD-A to 10 parts blood derived from a donor (D4, page 444, left hand column, last paragraph). D5 is a report on procedures of continuous needle donor plasma filtration; the blood drawn from the donor is normally anticoagulated with 1/15 - 1/16 ACD-A. In D6, membrane plasma separation is conducted with the anticoagulant

ACD-A incorporated into blood in the ratio of 1 part to 9 parts blood (D6, page 145, right hand column, first paragraph).

The appellants have contended that the prior art processes use the same type of anticoagulant (ACD-A) and the disclosed ratios of anticoagulant to blood are within the range of 1:6 to 1:25 specified in claim 1 of the patent-in-suit. The resulting pH, although not explicitly indicated in D4 and D6, therefore necessarily would be within the claimed range. As a consequence, the citations are implicitly novelty-destroying to the subject-matter of claim 1.

The Board agrees with the appellants insofar as the use of identical anticoagulants in identical amounts should result in identical pH-values of the treated blood. However, it is uncontested that the name of the anticoagulant (ACD-A) used in both the prior art and in the patent-in-suit is not attributed to a composition having a specific, well-defined pH value. On the contrary, as indicated in D4A, the pH of a standard ACD-A solution may vary within the range of between 4.5 and 5.5. There is no hint in D4, D5 or D6 as to the pH value of the particular ACD-A solution used in the experiment described therein. The appellants, who carry the burden of proof, have failed to give evidence or convincing arguments that a pH as specified in claim 1 for the whole blood would ineluctably be obtained with any ACD-A standard solution, irrespective of its acidity, as long as it is used in the ratio to blood as in D4, D5 or D6. Furthermore, the respondent has stated that there is no specific concentration or acidity within the range defined in D4A which should be

considered "usual" for a standard ACD-A solution. This is not contested by the appellants. The Board therefore considers that, when carrying out the process of claim 1, a selection of anticoagulant with an appropriate pH would be necessary in order to deliberately maintain the pH of the blood within the specified range of 6.8 to 7.2 (see also patent-in-suit, column 7, lines 40 to 47).

3.2 The Board considers that the above finding is also in agreement with the disclosure of D5 which mentions a mean pH value of 7.359, albeit measured for the collected plasma and not the whole blood. The appellants have argued that, considering the standard deviation of 0.15, the true pH value of plasma is practically the same as the upper limit of 7.2 defined in claim 1. The appellants have in particular asserted that the standard deviation is more realistically to be subtracted from rather than to be added to the mean pH value and that the indicated pH of the collected plasma should therefore be read to be from 7.359 down to 7.209 but not as high as 7.509. The Board is, however, unable to share the appellants' interpretation which is not to be brought into line with the usual definition of a standard deviation. Furthermore, even when taking the lowest value into consideration, the pH value of the collected plasma is still outside the range as specified for the blood in claim 1. The appellants have not put forward any reason, let alone evidence, to support the view that the standard deviation in D5 should be broadened even further so that the pH value of the collected plasma falls within the range defined in claim 1.

3.3 The appellants have also submitted that the pH value of the whole blood is in reality lower than the value measured for plasma. The reason given in this respect is that carbon dioxide would be produced on the addition of acidic anticoagulant ACD-A to blood. The carbon dioxide however would remain dissolved in the blood during the transport to the filtration membrane and would only be released at the filtration, thereby raising the pH of the filtrate (plasma). The extrapolation of the pH value of plasma to the pH value of blood is, however, strongly disputed by the respondent who has contended that a categorical proof for a relationship between a specific pH of plasma and the corresponding pH of blood does not exist.

The Board remarks that the appellants' analysis of the prior art process according to D5 is based on a theory which may or may not be correct but it is in no way verified by facts or evidence. In the present case, any doubt about the true pH value of the whole blood prior to the plasma separation could have been rapidly dispelled by a reproduction of the tests described in D5. The Board considers that the onus is on the appellants to prove their point. In the absence of any evidence to the contrary, the Board therefore concludes that the requirement of maintaining the blood derived from the donor in a pH range of 6.8 to 7.2 as specified in claim 1 of the patent-in-suit is not disclosed in D5.

3.4 As a consequence, the process of claim 1 is new since the feature of maintaining the blood derived from the donor in the specified pH range is neither explicitly nor implicitly disclosed in D4, D5 and D6, or any of

the other available prior art documents.

4. *Inventive step*

4.1 D5 is considered to be the closest prior art document as it also relates to continuous single-needle plasmapheresis procedures for collecting plasma from a donor. This is in agreement with the submissions of all the parties.

4.2 The respondent has submitted that the problem to be solved with regard to D5 is the reaction of blood with filter during the dwell periods of the cycles, which would significantly reduce the blood flow rate. This flow reduction is said to occur with ca. 10% of the donor population (column 1, line 47 to column 2, line 28 of the patent-in-suit). The appellants, however, have queried that any filtration problem existed in the prior art. Although D5 mentions that in 2% of the cases the procedures have not been completed because of insufficient blood flow, this disruption of the filtration is attributed to the fact that some donors do not have a sufficient blood flow. The complications would thus be solely donor specific and not related to the filtration procedure itself.

The respondent has not challenged the appellants' above interpretation of D5 but has argued that the problem addressed by the invention has not been recognised in, let alone solved by the prior art. In the document in question, a relatively big difference in blood flow, corresponding to a plasma collection of 500 ml within 30 to 45 minutes, is tolerated. Moreover, it is unpredictable as to which donor will cause the problem

and this is more likely to happen when the system is pushed to limits. In view of this, the Board accepts that the relevant technical problem can be seen in the provision of a standard method which ensures a high blood flow from practically all the donors, including the problematic donor subpopulation.

4.3. The solution proposed by the invention is to maintain the pH of the anticoagulated blood within the range of 6.8 to 7.2.

4.4 The respondent has filed experimental data showing that the use of anticoagulant of sufficient quantity and sufficiently low starting pH leads to a marked decrease in the percentage of donors with whom the low plasma take problem arises (see patent-in-suit, column 7, lines 17 to 47). The allegation that this problem does not exist or is not credibly solved in respect of the separation of components other than blood plasma, has not been substantiated. Thus, the Board accepts that it is credible that the said filtration problem exists in the whole ambit of the claim and that it is solved by the selection of pH parameters for the process as claimed.

4.5 The question as to whether the claimed solution is obvious in view of the available prior art is answered in the negative. The Board considers that, at the priority date of the patent-in-suit, the general teaching concerning the use of ACD-A was that it should be added to blood in sufficient quantity to be effective as an anticoagulant. There was no hint as to the significance of its acidity. From the data given in D5, the Board rather infers that the skilled person did

not have interest in the resulting pH of the blood to be filtered and that only the pH of the plasma was considered relevant since it was returned to the donor, in which case, it would be abnormal to go to lower pH than needed. On that basis, the measurement of the plasma pH merely reflects the concern for keeping the pH close to the natural pH value of blood which, according to the parties, is between 7.5 and 7.35. Therefore, the Board holds that the skilled person, a priori, does not have any incentive in lowering the pH when carrying out the process of D5.

4.6 The appellants have argued that the proposed solution including the characterising feature of claim 1 is suggested by D6 which investigates the effect of anticoagulants on complement activation by membranes. It has been surmised that it is this activation by the surface of the membrane which causes blood clotting and thereby a decrease in plasma flow. The results of the experiments in D6 show that activation by the filtration membrane occurs in heparinised plasma but is almost completely inhibited in citrate plasma at citrate levels which are commonly used to anticoagulate blood in separators (D6, page 145, right hand column, first paragraph). Since it is common knowledge that heparin is slightly alkaline whereas the anticoagulant ACD-A is acidic, it has been concluded that D6 teaches lowering the pH value of blood for the membrane filtration. This finding would corroborate with the data in D5 which describe plasmapheresis conducted successfully without disruption when the plasma has a pH of 7.359.

The fact that ACD-A is the preferred anticoagulant in the relevant prior art processes and that its addition to blood has a beneficial effect on the blood filtration, has never been questioned. However, as is discussed above, the Board has not found evidence that D5 or D6 suggests maintaining the blood derived from the donor at a pH of 7.2 or less. The Board therefore considers that the information provided by D5 and D6 in combination still fails to give the skilled person any incentive to consider, without the benefit of hindsight, the possibility of lowering the blood pH to 7.2 or below. In other words, the Board holds that the appellants have at most shown that the skilled person could have arrived at the claimed solution of the problem but not that he would have done so with the view to solving the present technical problem.

D4 does not contain any more relevant information. This is not disputed by the appellants. The remaining documents cited during the opposition proceedings are even less relevant. In particular, all the documents concerning the storage of blood deal with the problem of long term handling of blood. This does not have a direct or obvious bearing on the short term process of blood filtration.

As a consequence, the Board has come to the conclusion that the subject-matter of claim 1 of the main request involves an inventive step. Claims 2 to 7 are dependent claims relating to specific embodiments of that subject-matter. The patent can therefore be maintained with these claims. From this, it follows that the auxiliary requests submitted by the respondent need not be considered.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Hue R. K. Spangenberg