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D E C I S I O N
of 1 December 2005

Case Number: T 0840/04 - 3.3.04

Application Number: 93912264.4

Publication Number: 0638127

IPC: C12Q 1/56

Language of the proceedings: EN

Title of invention:
Test article and method for performing blood coagulation assays

Patentee:
Beckman Coulter, Inc.

Opponent:
Roche Diagnostics GmbH

Headword:
Blood Coagulation/BECKMAN

Relevant legal provisions:
EPC Art. 54, 56, 83

Keyword:
"Main request - sufficiency of disclosure, novelty, inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0840/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 1 December 2005

Appellant: (Opponent)
Roche Diagnostics GmbH
Patentabteilung
Sandhoferstr. 116
68305 Mannheim (DE)

Representative:
Silber, Anton, Dr.

Respondent: (Proprietor of the patent)
Beckman Coulter, Inc.
4300 N. Harbor Boulevard
PO Box 3100
Fullerton, CA 92834-3100 (US)

Representative:
Baldock, Sharon Claire
BOULT WADE TENNANT
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT (GB)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 16 June 2004 rejecting the opposition filed against European patent No. 0638127 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: G. Alt
R. Moufang

Summary of Facts and Submissions

I. The appeal was lodged by the Opponent (Appellant) against the decision of the Opposition Division to reject the opposition against European patent No. 0 638 127 under Article 102(2) EPC.

II. The patent had been granted on the basis of claims 1 to 23. It had been opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC).

III. Independent claims 1 and 17 read:

"1. A test article comprising:

a single permeable membrane having an application face and an indicator face in lateral opposition, said membrane being substantially free from interference with a coagulation pathway;
a coagulation initiator impregnated within the membrane; and a substrate impregnated within the same membrane as the coagulation initiator, which substrate produces a detectable signal upon activation by a component of the coagulation pathway;
whereby whole blood may be applied to the application face of the membrane and a detectable signal produced on the indicator face as a result of production of the coagulation pathway component.

17. A method for determining coagulation capability of a patient, said method comprising:

applying a whole blood sample to an application face of a permeable membrane, wherein the membrane is substantially free from interference with a coagulation pathway and wherein a coagulation initiator and a substrate which produces a detectable signal upon activation by a component of the coagulation pathway are impregnated within the membrane; and
detecting the detectable signal upon an indicator face of the membrane, wherein the indicator face is laterally opposed to the application face and the detectable signal results from production of the coagulation pathway component initiated within the membrane by interaction of the coagulation initiator and the blood sample."

Dependent claims 2 to 16 referred to preferred embodiments of the test article of claim 1; claims 18 to 23 related to preferred embodiments of the method of claim 17.

IV. Oral proceedings were held on 1 December 2005.

The Appellant (Opponent) requested that the decision under appeal be set aside and that the European patent No. 0 638 127 be revoked.

The Respondent (Patent Proprietor) requested that the appeal be dismissed or, in the alternative, that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the claims of the auxiliary requests 1, 2, 6 or 8, all filed with the letter of 30 September 2005.

V. The present decision refers to the following documents:

(1) WO 89/10 788

(2) EP-A-0 182 373

(3) EP-A-0 245 802

(5) EP-A-0 345 781

VI. The submissions made by the Appellant at the oral proceedings with regard to Article 83 EPC may be summarised as follows:

The patent disclosed one single membrane only which was found to be suitable for the claimed test article. However, the claims generally referred to "a membrane". As the description did not sufficiently disclose how to find alternative materials, the requirements of Article 83 EPC were not met. The test criteria to find suitable membranes, indicated in paragraphs [0020] and [0021] of the patent, were of no help as they relied on relative terms and were unclear.

VII. The submissions made by the Appellant during the written procedure and at the oral proceedings with regard to Article 54 EPC and Article 56 EPC may be summarised as follows:

The subject-matter of claims 1 and 17 was not novel over the teaching in document (1), which disclosed all features of these claims (Article 54 EPC).

Document (3) represented the closest state of the art for the assessment of inventive step (Article 56 EPC). It disclosed a device which differed from the test article of present claim 1 only in so far as it did not allow the direct application of whole blood to the application face of the membrane, but required an additional fleece for separating erythrocytes from plasma, which then contacted the membrane. The skilled person when trying to solve the problem underlying the patent in suit, which was considered to be the provision of an alternative and simplified test article for performing blood coagulation assays, would turn to document (5). This document described test devices containing an asymmetric polysulfone membrane for determining the concentration of various analytes in blood. By replacing the membrane structure used in document (3) by the membrane disclosed in document (5) a skilled person would have arrived at the subject-matter of claims 1 to 23 in an obvious way.

VIII. The submissions made by the Respondent may be summarised as follows:

As the Appellant, during the written appeal procedure, had not argued on the ground of opposition of lack of sufficient disclosure, he should not have been allowed to do so at the oral proceedings. Nevertheless, the patent disclosed specific tests which allowed the selection of membranes having the properties which were required for their use in a test article according to claim 1. By carrying out these tests a skilled person, without undue burden, could have found alternatives to the membrane material disclosed in the patent.

Document (1) did not disclose all technically characterizing features of the test article of claim 1 and did not therefore anticipate the claimed subject-matter (Article 54 EPC).

Document (3), which represented the closest state of the art disclosed a multilayer device for carrying out blood coagulation assays. The problem underlying the patent in suit was to provide a simplified test article for home use. A skilled person when trying to solve this problem would not have considered the disclosure in document (5), which referred to a three layer device for determining the concentration of different analytes in blood and which did not mention blood coagulation assays. Even upon replacing the filamentous structure disclosed in document (3) by the membrane used as reagent matrix layer in document (5) one would not have arrived at the claimed subject-matter in an obvious way (Article 56 EPC).

Reasons for the decision

Sufficiency of disclosure - Article 83 EPC

1. The patent refers to a test article containing a permeable membrane and a method using it. According to its use for carrying out blood coagulation assays, and in the light of the problem underlying the patent, namely to provide an alternative and simplified test article, this membrane has to meet certain criteria, which are described in paragraphs [0019] to [0020] on page 4 of the description.

2. Paragraph [0021], starting on page 4, line 55, informs the skilled reader in points (A) to (G) how to proceed in order to select a membrane having the properties required to be used in a test article according to claim 1. A candidate membrane has to be tested with regard to the following criteria: Pore geometry and size distribution, hydrophilic behaviour, blood cell compatibility, ability to separate blood cells from plasma, coagulation neutrality, volume tolerance, optical properties (compatibility with observation wavelengths) and dimensional stability in the wet and dry state.

3. In paragraph [0022] the patent reports that several prior art membranes have failed one or more of these tests and discloses one membrane type that has been found to meet all criteria required. This is a commercially available asymmetric polysulfone membrane, designated by its producer BTS-25.

4. In detail, the Appellant criticized that the patent does not contain sufficient information enabling a skilled person to find alternative membranes which are substantially free from interference with a coagulation pathway as required in claims 1 and 17.

5. In order to find out if a candidate membrane meets this criterion the patent instructs the skilled reader to permeate the membrane with a reaction mixture, disclosed in the experimental part of the patent, drying it and reacting it with samples of whole blood or plasma. A coagulation neutral membrane must permit the production of clinically accurate results with both,

normal plasma and coagulation factor deficient plasma (see paragraph [0021] on page 5, lines 9 to 15).

Accordingly, the Board does not agree with the Appellant that the disclosure of the patent in suit is insufficient in this respect. In addition it is noted that a similar test for finding out if a membrane material is coagulation neutral is disclosed in the prior art (see document (3), page 3, second full paragraph).

6. The Board is convinced that the patent in suit, besides disclosing a specific suitable membrane, contains sufficient information to allow a skilled reader to select other, alternative membranes having the required properties, and thus meets the requirements of Article 83 EPC.

7. Considering the decision on this issue taken in point (6) above, the Board does not consider it as being necessary to decide on the formal aspect raised by the Respondent, namely whether or not the Appellant at the oral proceedings was entitled to present arguments with regard to Article 83 EPC.

Novelty - Article 54 EPC

8. Document (1), the only document the Appellant relied on when objecting lack of novelty, refers to coagulation assay systems which utilize paramagnetic particles. According to page 1, lines 10 to 14, coagulation assays are considered to include clot formation assays (as disclosed in the patent in suit), but also clot lysis assays and clotting parameter assays.

Clotting parameter assays are disclosed on page 33, line 9 to page 35, line 8 with reference to figures 11 and 12. It is stated that this embodiment of document (1) does not require the presence of magnetic particles. Examples of such assay are disclosed on pages 98 to 101 (examples 1 to 5) using polysulfone membranes impregnated (or coated) with various dried reagents. The following reagents are disclosed: plasmin, plasminogen, fibrin, tissue plasminogen activator (t-PA) and S-2251.

9. In order to anticipate the subject-mater of a patent claim a prior art document must disclose all features of the claim.

The test article according to claim 1 and used in the method of claim 17, requires that it contains a membrane impregnated, amongst others, with a coagulation initiator.

Coagulation initiators trigger the coagulation pathways (extrinsic/intrinsic) at the standard points that are commonly used for medical tests and are well known in the art as described in paragraph [0029] of the patent with reference to two standard text books.

10. None of the reagents impregnated within the membrane according to document (1) (pages 33 to 35 and examples 1 to 5) is a coagulation initiator. Fibrin is a plasma protein and the end-product of blood coagulation, S-2251 is a synthetic, chromogenic plasmin-substrate. Finally, t-PA which effects the activation of plasminogen to plasmin, the enzyme responsible for

lysis of blood-clots, is an initiator of the fibrinolytic system by which fibrin clots are lysed.

Accordingly, document 1 does not disclose a membrane impregnated with a coagulation initiator and fails to anticipate the subject-matter of claims 1 to 23. Thus, the claims meet the requirements of Article 54 EPC.

Inventive step - Article 56 EPC

11. In accordance with the problem and solution approach, the Boards of Appeal have developed in their case law certain criteria for identifying the closest prior art which provides the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be prior art relating to subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (cf Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

12. The Board in the present case considers document (3) to represent the closest state of the art.

This document discloses an analysis element for the determination of a coagulation parameter. The element consists of a carrier foil on which a glass fibre fleece is fixed which separates erythrocytes from plasma and transports the plasma to further membrane components fixed on the carrier. These components are an oxidising agent carrier, a reagent carrier and a covering foil. The reagent carrier is an open composite

structure, preferably a fabric, which is impregnated with a solution containing a film former, a buffer, a coagulation initiator and a substrate for a protease arising in the course of blood coagulation. The substrate is linked via oxidative coupling to an indicator which upon splitting by the protease gives a colour signal (page 5, last paragraph to page 7, third paragraph; figure 1).

13. In the light of the disclosure in the closest prior art, the problem to be solved by the patent in suit is seen in the provision of an alternative and simplified device for carrying out blood coagulation assays.

The Board is convinced that the problem has been solved by the test article according to claim 1. The article is characterized by comprising a single membrane, within which a coagulation initiator and a substrate producing a detectable signal upon activation by a component of the coagulation pathway are impregnated. The membrane is coagulation neutral and allows the application of whole blood to an application face which is laterally opposed to an indicator face where a detectable signal is produced as a result of the production of the coagulation pathway component.

14. In order to examine whether a skilled person would have arrived at this solution in an obvious way, the Board has first investigated whether the closest prior art document itself contains a suggestion to amend the analysis element described therein.

Document (3) disclosing a multilayer element, does not contain a hint that would encourage a skilled person to

simplify the disclosed device by reducing the number of its membrane layers. On the contrary, on page 5, first three paragraphs, it is suggested, in case of problems which could arise if one impregnates one membrane with several different compounds, to use additional membrane layers each being impregnated with one compound only.

15. The Appellant in order to convince the Board that the claimed subject-matter does not involve an inventive step, relied on document (5), which disclosed a defined volume test device for carrying out various analytical tests in liquid samples, for instance in blood. The device comprises three layers, an absorbent layer, a waterproof barrier layer and a reagent matrix layer. Said reagent matrix layer, which can be a single membrane or may be formed of a plurality of layers, preferably comprises an asymmetric polysulfone membrane wherein reagents for the respective analyte to be detected are impregnated (page 3, lines 10 to 12; page 4, lines 13 to 15; page 5, lines 24 to 34 and lines 47 to 55; page 6, lines 24 to 33).

The substances which can be measured by the claimed device in blood and other body fluids include "... glucose, galactose, pyruvic acid, amino acids, cholesterol, lactic acid, alcohol, urea, **etc."** (page 6, lines 29-31; emphasis added by the Board).

Document (5) does neither explicitly mention blood coagulation assays nor does it suggest that the disclosed defined volume test device is suitable for such assays.

16. Contrary to analytical tests for a single analyte like glucose, alcohol or cholesterol, coagulation testing relies upon a complex cascade of enzymatic reactions which take place even before the detectable analyte can be generated. These reactions are sensitive to many external agonists and antagonists that may affect the accuracy of blood coagulation assays. It is known that the coagulation cascade is very strongly influenced by surface forces and, in addition, that every plasma contains thrombocytes which are activated by solid surfaces and, in an activated state, influence the coagulation cascade and thereby falsify it (see document (2), page 1, third paragraph).

Thus, due to the high complexity of the coagulation system and the big number of possible sources of error, blood coagulation assays hold a special position in the field of analytical chemistry.

A skilled person reading document (5) and learning that the device disclosed therein may be used in assays for a long list of individual analytes, which list is terminated with terms like "etc." or "and other chemical assays", would not be motivated to use the device in an assay which is more complex than all examples disclosed in the document.

17. In addition, even if the skilled person would consider to use the device of document (5) in a coagulation assay as described in document (3), he/she would not directly arrive at the presently claimed subject-matter. Replacing the multilayer structure disclosed in document (3) (see point (12) above) by the three-layer structure disclosed in document (5) (see point (15)

above) would not result in the provision of a test article comprising a single membrane as defined in present claim 1. This would need further substantial adaptation of the device of document (5) which would require inventive activity and which can be regarded as being obvious with hindsight only.

18. Therefore, the Board comes to the conclusion that the subject-matter of claims 1 to 23 cannot be derived in an obvious way from the disclosure in the closest prior art, document (3), either if taken alone or in combination with document (5) or any other document on file.

The claims involve an inventive step and meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

Registrar: Chair:

C. Eickhoff M. Wieser