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Datasheet for the decision of 8 November 2023

Case Number: T 0196/21 - 3.3.08

Application Number: 15807510.1

Publication Number: 3155430

IPC: G01N33/558, G01N33/72

Language of the proceedings: EN

Title of invention:
Detection of hemolysis using a chromatographic detection pad

Applicant:
Siemens Healthcare Diagnostics Inc.

Headword:
Detection of hemolysis/SIEMENS HEALTHCARE DIAGNOSTICS

Relevant legal provisions:
EPC Art. 113(1), 56
EPC R. 103(1)(a)

Keyword:
Right to be heard - substantial procedural violation (no)
Inventive step - (no)

Decisions cited:
T 1816/15

Catchword:

Europäisches Patentamt
European Patent Office
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Beschwerdekammern

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Case Number: T 0196/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 8 November 2023

Appellant: (Applicant)	Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue Tarrytown, NY 10591 (US)
Representative:	Platen, Denise Plate Schweitzer Zounek Patentanwälte Rheingaustrasse 196 65203 Wiesbaden (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 30 September 2020 refusing European patent application No. 15807510.1 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	M. Montrone
	R. Winkelhofer

Summary of Facts and Submissions

I. The appeal of the applicant ("appellant") lies from the decision of an examining division to refuse the European patent application No. 15 807 510.1 which was filed as International patent application published as WO 2015/191450 ("patent application").

II. In the decision under appeal, the examining division held that the subject-matter of claim 1 of the main request and that of the auxiliary request lacked an inventive step (Article 56 EPC) in light of the teaching of document D1 combined with, *inter alia*, document D5.

III. With their statement of grounds of appeal, the appellant re-submitted the set of claims of the auxiliary request considered in the decision under appeal as their new main and sole request. Furthermore arguments in relation to an alleged substantial procedural violation were submitted as well as arguments in support of inventive step substantiated by new documentary evidence (document D7).

IV. In a communication pursuant to Article 15(1) RPBA, the appellant was informed of the board's preliminary opinion.

V. In reply, the appellant withdrew their request for oral proceedings and requested a decision according to the state of the file.

VI. Accordingly, the oral proceedings were canceled.

VII. Claim 1 of the main (sole) request reads:

"1. A chromatographic assay device for detecting the presence of free hemoglobin in a whole blood sample, the device comprising:

a chromatographic detection pad which defines a path for capillary fluid flow, the chromatographic detection pad having a pore size of between 8 and 13 microns, the pore size preventing agglutinated RBCs from flowing through the chromatographic detection pad the chromatographic detection pad comprising:

a sample application site on the chromatographic detection pad for application of a portion of the whole blood sample, the sample application site being adjacent to a first end of the chromatographic detection pad, wherein the sample application site contains at least one type of red blood cell (RBC) binding or agglutination material such that when the whole blood sample is applied to the chromatographic detection pad, the RBC binding or agglutination material agglutinates with any RBCs in the whole blood sample to produce agglutinated RBCs, and wherein the agglutinated RBCs have a size greater than the pore size of the chromatographic detection pad and thereby are prevented from flowing through the chromatographic detection pad;

a detection site on the chromatographic detection pad, the detection site spaced apart from the sample application site, the detection site being downstream of the sample application site, and wherein the free hemoglobin flows through the chromatographic detection pad from the sample

application site to the detection site and is detectable via a color change at the detection site, and the chromatographic detection pad being devoid of a compound located downstream of the application site that is reactive to the whole blood sample".

VIII. The following documents are referred to in this decision:

D1: WO 95/10044

D4: WO 2013/071301

D5: US 4,933,092

D6: US 5,725,774

D7: Li J. *et al.*, Sensors and Materials, 2015, Vol. 27, 549-561

IX. The appellant's written submissions, insofar as relevant to the present decision, may be summarised as follows:

Substantial procedural violation

The examining division committed a substantial procedural violation. The reasoning for finding lack of inventive step of the auxiliary request (now main and sole request) was based on criteria set out in the Guidelines under section G-VI.8 which were relevant for assessing novelty only (decision under appeal, point 17.2). Objections under lack of novelty against the subject-matter of the auxiliary request were, however, not raised by the examining division.

Inventive step

Document D1 represented the closest prior art. The chromatographic assay device as defined in claim 1 differed from the device in document D1 in that the chromatographic detection pad had a defined pore size and the sample application site contained at least one type of red blood cell (RBC) binding or agglutination material.
These features increased the sample flow rate through the assay device to achieve faster test results.
The objective technical problem to be solved resided therefore in the provision of a chromatographic assay device which prevented RBCs from flowing through the detection pad, while obtaining faster test results.
Since document D1 did not address this problem, let alone provide or point at the solution of the claimed chromatographic assay device, the subject-matter of claim 1 was inventive over the disclosure of document D1 alone. The same applied if the teaching of document D1 was combined with that of document D5.
Document D5 disclosed a device for separating plasma or serum from whole blood using a matrix which contained at least one RBC agglutinating agent. The matrix had pores with sizes ranging from 10 to 70 microns (µm).
Since however document D5 did not deal with hemolysis, i.e. free hemoglobin ("Hg") detection, the problem underlying the present invention was not addressed in this document. Accordingly, the skilled person would have disregarded document D5. Further reasons for the skilled person to disregard document D5 were that document D1 already disclosed a "*simple device*" which performed a qualitative assay at the patient's bedside "*in as quick a manner as possible*". Since the addition of a RBC agglutinating agent to membranes "*already*

capable of quickly separating plasma from red blood cells would be duplicative", no further advantages were provided to the device of document D1 (see statement of grounds of appeal, page 9, fourth paragraph). The use of document D5's RBC agglutinating agent in the membrane of document D1 could even have caused interferences as regards the speed and/or integrity of document D1's assay.

Even if the teaching of documents D1 and D5 were combined, the skilled person would not have arrived at the subject-matter of claim 1. Document D5 disclosed a membrane with pore sizes ranging from 10µm to 70µm through which most RBCs passed having a low agglutination degree. This was so because a membrane characterised by a pore size range contained pores of all sizes falling within this range. The number of these pores was however very different. Most of the membrane pores were of a medium range size while only a low number of pores had a size of the range limits (here 10µm or 70µm). Individual RBCs had a size of about 7µm, two agglutinated RBCs had thus a size of about 14µm. Since only a few 10µm pores were present on the membrane of document D5, most RBCs with a low agglutination degree passed through the membrane. Contrary thereto, the subject-matter of claim 1 retained all agglutinated RBCs, irrespective of their agglutination degree, because the maximum pore size was defined as "*13 microns*".

Document D7 disclosed that membranes with pore sizes falling within the claimed range were known to the skilled person. This document addressed the examining division's assertion in the decision under appeal (page 5, second paragraph) that it was questionable whether

membrane material with the claimed size properties existed.

X. The appellant requests:

- that the decision under appeal be set aside and to grant a patent on the basis of the main request;
- that the appeal fee be reimbursed due to a substantial procedural violation.

Reasons for the Decision

Substantial procedural violation

1. The appellant submitted in essence that the examining division committed a substantial procedural violation in the decision under appeal, because its reasoning for lack of inventive step was based on wrong legal criteria, i.e. those relevant for novelty.

2. This is not convincing.

A substantial procedural violation is an objective deficiency affecting the entire proceedings which prevents a full discussion and thorough assessment of the case and thus possibly leads to an incorrect decision (Case Law of the Boards of Appeal, 10th edition 2022 ("Case Law"), V.A.11.6; T 1816/15, Reasons 47.). Such a deficiency must be of a procedural nature and regularly implies that the appellant's right to be heard has been violated (Article 113(1) EPC).

2.1 This could, for example, be the case if the examining division had used an argument or a ground in the decision under appeal on which the appellant had not been heard, or that an essential fact/argument,

although raised by the appellant under inventive step, had not been considered. However, this has not even been argued by the appellant. Nor can the board identify any such ground and/or fact/argument in the decision under appeal.

2.2 Rather the appellant submitted that the examining division relied in their reasoning on wrong legal criteria for assessing the relevant facts. Thus, they did in fact not allege a substantial procedural violation, but an error in substance.

3. For that reason alone, there is no room for reimbursing the appeal fee (Rule 103(1)(a) EPC).

Inventive step

4. It is common ground that document D1 represents the closest prior art. The device disclosed therein (see abstract and page 9, last paragraph to page 10, last paragraph) is used for the same purpose as that underlying the subject-matter of claim 1, namely the detection of free hemoglobin ("Hb") in a whole blood sample. The dry separation material used for retarding the flow of red blood cells ("RBCs") relative to plasma or serum in document D1 is not characterised by a defined pore size. Instead document D1 discloses a composite structure of the material containing a blend of different types of fibers (see page 18, first to third paragraphs).

5. It is uncontested that the chromatographic assay device as defined in claim 1 differs from the device in document D1 in that:

- the chromatographic detection pad has a defined "*pore size of between 8 and 13 microns*", and

- the sample application site "*contains at least one type of red blood cell (RBC) binding or agglutination material*".

6. These two distinguishing features have the effect that the agglutinated RBCs are prevented "*from flowing through the chromatographic detection pad*" (see claim 1 and patent application, [0025]). No such prevention is mentioned in document D1. Instead, document D1 states that "*red blood cells are not transported readily along the material, and are thus retarded by the dry separation material, relative to the separated fraction*" (see page 18, lines 3 to 6, emphasis added). Thus the separation of RBCs and plasma/serum containing free Hb in document D1 results from a different flow rate of the two fractions within the chromatographic material, i.e. a faster plasma/serum fraction which contains free Hb versus a slower RBC fraction. Document D1 is silent about the flow rate of the plasma/serum Hb fraction. Nor are indications derivable from this document on how long a test run takes. Document D1 does not mention pores or pore sizes either.

7. The examining division held that the technical effects associated with the two distinguishing features of claim 1 mentioned above resided in the provision of a chromatographic assay device with "*a higher flow rate ultimately resulting in a faster test result*" (see decision under appeal, page 3, point 16 and patent application, [0026]). This view is shared by the appellant.

7.1 The board does not agree. The patent application is silent on any experimental data, let alone data that support a "*higher*" flow rate of the plasma fraction when using the claimed chromatographic assay device

compared to the device of document D1. Other data, for example supplementary comparative experiments, are not on file either.

7.2 The question thus arises if it is at least plausible that a faster separation is achieved across substantially the whole breadth of claim 1 in view of the patent application's teaching, taking the skilled person's common general knowledge into account.

7.3 The pore sizes of "*between 8 and 13 microns*" as specified in claim 1 are not particularly large. The patent application mentions itself the larger pore size of 40 microns (see [0025]), and that the average diameter of an RBC is "*approximately 7 microns*" (see [0023]), i.e. a size that lies only slightly below the lower limit of the pore size range of claim 1.

7.4 Document D4, for example, corroborates that the pore size is an essential parameter of a plasma's flow rate through a membrane. This document states in paragraph [0043] on page 10 that "*the rate of flow (Q) through a pore 102 scales with the fourth power of the pore 102 diameter (d), $Q \alpha d^4$, the smaller the diameter (d) of the pores 102 of the substrate 101, the less the volumetric flow rate of plasma through the substrate 101*" (emphasis added). In other words, the bigger the pore size, the higher is the plasma's flow rate through a membrane.

7.5 Furthermore, the appellant submitted that document D1 itself disclosed a qualitative method which quickly determined whether a biological sample contained hemolysed RBCs. This submission implies that the appellant is of the view that the device of document D1

generates fast test results. In other words, that the plasma flow rate through the device is likewise high.

7.6 In light of these considerations, it is not plausible that a pore size of at least 8 to 13 microns combined with at least one type of RBC agglutinating material as defined in claim 1 results in higher flow rates of plasma when compared to the device of document D1.

8. Accordingly, in line with established jurisprudence, a less ambitious technical problem has to be defined (see Case Law, I.D.4.4).

9. The objective technical problem to be solved thus resides in the provision of a chromatographic assay device for detecting free Hb based on an alternative RBC separation. The chromatographic assay device as defined in claim 1 solves this problem.

10. As regards obviousness, the board agrees with the examining division's finding that the subject-matter of claim 1 is obvious in light of the teaching of document D1 combined with that of document D5.

11. The skilled person, starting from the device of document D1 in view of the problem defined above, would turn to documents that describe alternative means for separating RBCs from whole blood samples.

11.1 Document D5 is directed to a device and a method for separating RBCs from plasma or serum in a whole blood sample. The device comprises a matrix which contains at least one RBC agglutinating agent (see abstract). Suitable matrices to be used have a pore size of "*from about 10 to about 70 microns. Such a pore size allows individual red blood cells to pass through the matrix,*

but retains agglutinated red blood cells within the matrix" (see column 3, lines 65 to 68, emphasis added).

11.2 Since the pore size range disclosed in document D5 overlaps with that of claim 1 and, moreover, an RBC agglutinating agent is used, the skilled person combining the teaching of document D1 with that of document D5 would automatically arrive at subject-matter falling within the subject-matter of claim 1.

12. The appellant submitted that since document D5 did not deal with hemolysis, the skilled person would not have turned to this document.

This is not convincing.

Document D1 already deals with the determination of free Hb, i.e. hemolysis. As set out above, the skilled person starting from document D1 in view of the technical problem defined above is in seek of alternative means for separating RBCs from plasma/ serum. Document D5 deals with this purpose and accordingly, the skilled person looking for alternative separation means would consider this document.

13. The appellant further submitted that document D1 disclosed a simple device which already provided a qualitative and quick Hb assay. The incorporation of an additional blood cell agglutinating agent as disclosed in document D5 into document D1's separation material was "*duplicative*" and might even have caused disadvantages.

13.1 This is likewise not convincing. As regards a potential redundancy of using document D5's RBC agglutinating agent in the membrane of document D1, the relevant

issue here is that this agent in conjunction with a membrane of a defined pore size range as disclosed in document D5 is an alternative separation means to the membrane disclosed in document D1. The issue of a potentially "*duplicative*" measure does therefore not pose.

13.2 Nor are indications derivable from any of the facts on file that the use of the RBC agglutinating agent in a membrane of a defined pore size range as disclosed in document D5 might negatively affect the integrity and/ or performance of the device. If this were the case, the subject-matter of claim 1 would suffer from the same disadvantages. Reasons that would deter the skilled person from combining the teaching of document D1 with that of document D5 are therefore not evident.

14. Lastly, the appellant submitted that the skilled person in using separation material with at least one agglutinating agent and a pore size ranging from 10µm to 70µm as disclosed in document D5 in combination with the device of claim 1 would still not arrive at the subject-matter claimed because RBCs with a low agglutination degree would pass through the membrane.

14.1 This is also not convincing.

The appellant's assertion is in clear contradiction to document D5's teaching which states that "*The matrix is characterized by a pore size such that individual blood cells will pass through it, but wherein agglutinated cells will be retained by the matrix. The devices are capable of performing rapid separations of serum or plasma from whole blood while retaining only minimal residual quantities of serum or plasma within the*

interstices of the porous material" (see column 3, lines 48 to 55).

14.2 Since, moreover, the average diameter/size of a single RBC is commonly known as "*approximately 7 microns*" or "*an average size of 5 µm*" (see patent application, [0023] and document D6, column 5, lines 50 to 52), it would be obvious for the skilled person to select a pore size of at least 10 µm as reported in document D5 to prevent agglutinated RBCs from passing through the separation material. Such a pore size falls within claim 1.

15. The subject-matter of claim 1 and, hence, the main request lacks an inventive step (Article 56 EPC).

16. In view of the board's conclusion on inventive step above, the disclosure of document D7 for assessing inventive step is irrelevant because the question of whether or not material with the required pore size was available at the relevant filing date of the patent application has no bearing on the outcome.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated