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D E C I S I O N
of 2 April 2001

Case Number: T 0108/97 - 3.3.4

Application Number: 88113756.6

Publication Number: 0306772

IPC: G01N 33/558

Language of the proceedings: EN

Title of invention:
Lateral flow chromatographic binding assay device

Patentee:
ABBOTT LABORATORIES

Opponents:
Roche Diagnostics GmbH
Dade Behring Marburg GmbH

Headword:
Assay device/ABBOTT LABORATORIES

Relevant legal provisions:
EPC Art. 123(2), 54, 56

Keyword:
"Added subject-matter (no)"
"Novelty (yes)"
"Inventive step (no)"

Decisions cited:
T 0268/89, T 0020/81

Catchword:
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Case Number: T 0108/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 2 April 2001

Appellant: (Proprietor of the patent)
ABBOTT LABORATORIES
One Abbott Park Road
Abbott Park
Illinois 60064-3500 (US)

Representative:
Modiano, Guido, Dr.-Ing., Dr. G. Staub
Modiano, Josif, Pisanty & Staub,
Baaderstrasse 3
D-80469 München (DE)

Respondents: (Opponent 01)
Roche Diagnostics GmbH
- Patentabteilung -
D-68298 Mannheim (DE)

Representative:
Dr. Jung, Dr. Silber
Roche Diagnostics GmbH
- Patentabteilung -
D-68298 Mannheim (DE)

(Opponent 02)
Dade Behring Marburg GmbH
Postfach 1149
D-35001 Marburg (DE)

Representative:
Dr. B. Auerbach
Dade Behring Marburg GmbH
Patente & Lizenzen
D-35001 Marburg (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 2 December 1996 revoking European patent No. 0 306 772 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey

Members: R. E. Gramaglia
V. Di Cerbo

Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No. 0 306 772 (application No. 88113756.6) filed on 24 August 1988 and claiming priority from US 95801 of 11 September 1987, which had been opposed by the respondents (opponents 01 and 02) on the grounds of lack of novelty and inventive step and insufficiency of disclosure. Independent claims 1 and 6 as granted read as follows:

"1. A test device for determining the presence or amount of an analyte substance in a sample by means of one or more specific binding reactions comprising:

a chromatographic medium having capillarity and the capacity for chromatographic solvent transport of one or more reactive sample components and non-immobilized reagents including a reaction site at which is present an immobilized reagent capable of binding a member from the group consisting of said analyte substance and a labelled specific binding material,

a sample application means located adjacent to said chromatographic medium and offset upstream from said reaction site, and

a liquid absorption means offset downstream from said reaction site.

6. A method for determining the presence or amount of an analyte substance in a sample which method utilizes:

a chromatographic medium having capillarity and the capacity for chromatographic solvent transport of one

or more non-immobilized reagents and reactive sample components including a reaction site at which is present an immobilized reagent capable of binding a member from the group consisting of said analyte substance and a labelled specific binding material,

sample application means located adjacent to said chromatographic material and offset upstream from said reaction site, and

a liquid absorption means offset downstream from said reaction site, said method comprising:

(a) applying a volume of said sample to said sample application means whereby said sample is transported along said chromatographic medium through said reaction site to said sample adsorption means,

(b) contacting said labelled specific binding material to said reaction site, and

(c) determining the presence or amount of labelled specific binding material immobilized at said reaction site as an indication of the presence or amount of the substance in the sample."

Claims 2 to 5 and 7 to 10 related to specific embodiments of the device of claim 1 or the method of claim 6, respectively.

II. The following documents are cited in the present decision:

(1) EP-A-0 186 799;

(3) EP-A-0 183 442;

(8) EP-A-0 306 336;

(9) EP-A-0 291 194.

III. Oral proceedings were held on 2 April 2001 during which the appellant submitted amended claims in the form of a new main request in replacement of all preceding requests. Claims 1 and 6 of the new request read as follows (the amendments over the granted claims are shown in bold):

"1. A test device for determining the presence or amount of an analyte substance in a sample by means of one or more specific binding reactions comprising **an upper and lower housing portion and comprising**:

a **one-piece** chromatographic medium having capillarity and the capacity for chromatographic solvent transport of one or more reactive sample components and non-immobilized reagents including a reaction site at which is present an immobilized reagent capable of binding a member from the group consisting of said analyte substance and a labelled specific binding material, and a first end upstream from the reaction site at which chromatographic solvent transport begins,

a sample **and reagent** application means **consisting of a well with a single opening for applying said sample and reagent** which is located **completely over and** adjacent to **and in fluid contact with** said **first end of the** chromatographic medium **and is** offset upstream from said reaction site, **and which is adapted to retain a volume**

of sample until it is transported along said chromatographic medium to said reaction site, said well being defined by the upper housing portion which defines walls completely surrounding said opening in an upright arrangement with respect to the chromatographic medium and

a liquid absorption means offset downstream from said reaction site.

6. A method for determining the presence or amount of an analyte substance in a sample which method utilizes a test device comprising **an upper and lower housing portion and comprising**:

a **one-piece** chromatographic medium having capillarity and the capacity for chromatographic solvent transport of one or more reactive sample components and non-immobilized reagents including a reaction site at which is present an immobilized reagent capable of binding a member from the group consisting of said analyte substance and a labelled specific binding material **and a first end upstream from the reaction site at which chromatographic solvent transport begins,**

a sample **and reagent** application means **consisting of a well with a single opening for applying said sample and reagent** which is located completely **over and** adjacent to **and in fluid contact with** said **first end of the** chromatographic medium **and is** offset upstream from said reaction site, **and which is adapted to retain a volume of sample until it is transported along said chromatographic medium to said reaction site, said well**

being defined by the upper housing portion which defines walls completely surrounding said feeding opening in an upright arrangement with respect to the chromatographic medium and

a liquid absorption means offset downstream from said reaction site,

said method comprising:

(a) applying a volume of said sample to said sample application means which allows said sample to be drawn out and transported along said chromatographic medium through said reaction site to said sample absorption means by capillarity action,

(b) contacting said labelled specific binding material to said reaction site, and

(c) determining the presence or amount of labelled specific binding material immobilized at said reaction site as an indication of the presence or amount of the substance in the sample."

Claims 2 to 5 and 7 to 10 were as granted.

IV. The submissions by the appellant can be summarized as follows:

Added subject-matter (Article 123(2) EPC)

- The feature "an upper and lower housing portion" found a basis in column 5, lines 38 to 41 of the "A1"- application as filed. The feature "one-

piece" was based on the previous wording "of integral length". It was clear from the drawings and the description as filed that the chromatographic medium was "one-piece". The Examples showed that a single strip was cut from a membrane. The wording "a single sample and reagent application means consisting of a well with a single opening was based on the "A1"-application as filed (column 3, lines 55 to 56 and Figures 1 to 3). The wording "a first end upstream from the reaction site at which chromatographic solvent transport begins" was based on column 5, lines 34 to 36 of the "A1"-application as filed.

Novelty (Article 54 EPC)

- The device of document (8) had two sample application means instead of one (see column 3, lines 28 to 32). The wording "a single sample and reagent application means consisting of a well with a single opening" in claims 1 and 6 was therefore a distinguishing feature.

- Document (9) related to a vertical flow device comprising a receptacle 202 (see Figures 7 and 8) located below the first end of the chromatographic medium and was not in an upright arrangement with respect to the chromatographic medium.

Inventive step (Article 56 EPC)

- The problem to be solved by the assay device of claim 1 vis-à-vis the closest prior art represented by the device of document (1) was the one stated in column 4, line 41 to column 5,

line 4 of the "A1"-application as filed, namely to provide a device with improved performance in terms of capture efficiency. High capture efficiency resulted from the so-called "lateral flow" effect, whereby the sample fluid flowed along and through the entire thickness of a thin strip of chromatographic medium and it was thus forced also through the capture zone with an increased capture efficiency.

- The improved capture efficiency rendered possible the use of the claimed device without the need of a prefilter in cases where the sample fluid had a heavy load of particulate matter (eg blood cells). It also avoided the need of impregnating the whole breadth of the chromatographic medium with the immobilized reagent, an expedient used in vertical flow assay devices for enhancing the extent to which the immobilized reagent can capture any analyte present in the migrating sample (see document (9) as an expert opinion, page 6, lines 11 to 14). All these advantages could not be achieved by using the device described in document (1). In fact "Übersicht II" on page 14 and page 4, line 20 ("saugfähiges Material") prescribed the presence of a prefilter.

- There was no suggestion in the documents of the prior art, dealing with solving a different problem, that the drawback of heavy particulate load could be solved by providing a device with high capture efficiency according to claim 1.

- The fact that the claimed device comprised a well which acted as a "volume metering device" was a

further inventive feature of the claimed device. The well ensured that all of the sample was transferred to the chromatographic material without loss or lateral leakage.

V. The submissions by the respondents can be summarized as follows:

Added subject-matter (Article 123(2) EPC)

- The features "one-piece" extended beyond the content of the application as filed.

- It could not be derived from the application as filed that the well retained a volume of sample until it was transported along the chromatographic medium.

Novelty

- The claimed device lacked novelty in view of conflicting European patent applications (8) and (9).

Inventive step (Article 56 EPC)

- The claimed device did not solve the problem of improving capture efficiency.

- There was no evidence in the patent in suit of improved performance in terms of capture efficiency in cases where the sample fluid had a heavy load of particulate matter.

- There was no evidence in the patent in suit

showing improved performance in terms of capture efficiency to the extent that the need of impregnating the whole breadth of the chromatographic medium with the immobilized reagent could be avoided.

- The provision of a device according to claim 1, differing from that of document (1) by the presence of a well was obvious in view of Figure 14 of document (3), showing a well. A well was equivalent to the "application pad" of document (1). If the problem to be solved according to the application as filed was the proviso of sufficiently sensitive devices, this problem was not solved by the addition of a well to the one-piece device of document (1).

VIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the request filed during the oral proceedings of 2 April 2001.

The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Article 123(2)(3) EPC

2. The expression "one-piece" finds a basis in Figures 1 to 3 and in Example 1 as filed. The drawings show that the chromatographic medium is "one-piece". Example 1

relates to a single strip cut from a membrane. The feature, according to which the well retains a volume of sample until it is transported by the chromatographic medium, is to be found in column 7, lines 43 to 50 of the "A1"-application as filed. The feature "an upper and lower housing portion" finds a basis in column 5, lines 38 to 41 of the "A1"-application as filed. The wording "a single sample and reagent application means consisting of a well with a single opening" is based on the "A1"-application as filed (column 3, lines 55 to 56, column 5, lines 51 to 52 and Figures 1 to 3). The wording "a first end upstream from the reaction site at which chromatographic solvent transport begins" is based on column 5, lines 42 to 44 of the "A1"-application as filed. The wording "said well being defined by the upper housing portion which defines walls completely surrounding said opening in an upright arrangement with respect to the chromatographic medium" can be derived from a combination of column 5, lines 42 to 44 and Figures 1 to 3 of the "A1"-application as filed. All the amendments are restrictive in nature, so that the claims satisfy the requirements of Article 123(2)(3) EPC.

Novelty

3. As regards document (8), the device described therein exhibits two application means (see column 3, lines 28 to 32). An embodiment relating to a single well is referred to in column 15, lines 37 to 8 of this document, however a "divider between the two openings" is also present, so that the expression in claims 1 and 6 "a sample and reagent application means consisting of a well with a single opening for applying said sample

and reagent" renders these claims novel vis-à-vis document (8).

Document (9) relates to a vertical flow device comprising a receptacle 202 (see Figures 7 and 8) which is parallel rather than in an upright arrangement (perpendicular) with respect to the chromatographic medium. As a consequence, the upper housing portion (if any) of the device of Figures 7 and 8 fails to define "walls completely surrounding said opening" as stated in claims 1 and 6 at issue.

In conclusion, the subject-matter of claims 1 and 6 and dependent claims 2 to 5 and 7 to 10 satisfies the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)
Closest prior art

4. The parties consider the assay device disclosed by document (1) as representing the closest prior art and the board agrees as well. "Übersicht I" on page 13 of this document shows a multi strip device comprising a sample application means, a series of chromatographic means, one of which is the reaction site ("Detektionszone"), and a liquid absorption means ("Saugzone"). According to page 4, lines 1 to 2 ("besteht aus einem oder auch aus mehreren") and page 6, lines 1 to 2 ("in Form von einem oder mehreren Streifen"), the device of document (1) may be a one-piece chromatographic medium. When compared with this one-piece device, the one of claim 1 differs therefrom by the further presence of a housing defining a well for applying the sample and reagents.

Problem to be solved

5. The appellant maintains that the problem solved by the subject-matter of claim 1 at issue vis-à-vis the one-piece device described in document (1) is to provide a device with improved performance in terms of capture efficiency (see paragraph IV supra). This advantageous technical effect, in the appellant's view, manifests itself as follows:

"The particulate matter problem"

(i) It avoids the need of a prefilter located at the sample application means in the case the sample fluid has a heavy load of particulate matter (eg whole blood).

"The vertical flow problem"

(ii) It avoids the need of impregnating the whole breadth of the chromatographic medium with the immobilized reagent, an expedient used in vertical flow assay devices for enhancing the extent to which the immobilized reagent can capture any analyte present in the migrating sample (see document (9) as an expert opinion, page 6, lines 11 to 14). The drawbacks encountered with vertical flow devices originate from the sample fluid flowing partly around the capture area.

6. As regards technical effect (i) above, the "A1"-application as filed indeed recites at the bottom of column 4 that "The devices are suitable for analysis of samples with heavy loads of particular matter without the necessity of a prefilter". In the board's view,

there is no evidence that technical effect (i) above ("The particulate matter problem") takes place at all. In fact, Examples 1 and 2 of the "A1"-application as filed relate to assays carried out on plasma as a sample (column 11, lines 6 and 48), ie a fluid which does not contain particulate material. Therefore, this experimental evidence does not relate to the improved sensitivity of the claimed diagnostic device in assays of samples with heavy particulate loads. Moreover, it has to be stressed that, according to the application as filed, the use of a prefilter is not excluded (see column 5, lines 4 to 8: "Nevertheless, prefilters, and particularly non-removable ones, may be used and fitted into sample application means where samples comprise especially heavy loads of particulate matter, for example, whole blood").

7. As for technical effect (ii) above, it has to be noted that any chromatographic assay device, be it a "lateral flow" device or a "vertical flow" one (as in document (3)), works thanks to capillarity (compare column 8, line 51 of the "A1"-application as filed: "having capillarity" with page 5, lines 6 to 7 of document (3): "the capillary action of the strip"). There is no evidence before the board that the flow properties of a migrating sample or solvent fluid in a chromatographic strip are different if the strip is used in horizontal compared to vertical position. The appellant has not convinced the board that eg, gravity is also an important factor affecting the flow properties. Moreover, the fact that the "A1"-application as filed exemplifies (see column 10, lines 56 to 58: "Devices generally similar to the device of Figure 1 through 3 were fashioned") only devices in which the whole breadth of the chromatographic medium is impregnated

with the immobilized reagent (see element 16 of Figures 1 to 3 in the light of column 6, line 10), does not assist the appellant.

Furthermore, it has to be noted that a technical advantage pointed out by a patent proprietor/applicant has to be derivable by the skilled person from a comparison of the application as filed with the prior art for it to contribute to the formulation of the problem solved (see e.g. decision T 268/89, OJ EPO 1994, 50). Yet in the present case, it is not possible to derive technical effect (ii) ("the vertical flow problem") even by taking into account the passage of document (9) (see point 5 (ii) supra) relied upon by the appellant, ie a document according to Article 54(3) EPC, which anyway does not belong to the prior art for the purpose of evaluating the inventive step.

8. The board is rather of the opinion that if the patent in suit discloses any improved performance in terms of capture efficiency, this is merely due to the presence of the absorption means. This view is supported by the passage in column 8, lines 6 to 16 of the "A1"-application as filed: "Without such absorption [means] chromatographic transport would cease and the efficiency advantage resulting from the lateral flow of sample through the reaction site would be lost". But this technical feature is already present in the device disclosed in document (1) (cf the "Saugzone" of "Übersicht" I and II). The board is thus not prepared to accept that the claimed device solves some capture efficiency problem that has not already been solved by the assay device of document (1). Also the appellant's proposition that all the advantages pointed out above cannot be achieved by using the device described in

document (1) must fail. In conclusion, being not supported by sufficient evidence, the advantages (i) and (ii) emphasized by the appellant cannot be taken into consideration in determining the underlying technical problem and hence in assessing the inventive step (decision T 20/81 (OJ EPO 1982, 217)).

9. During the proceedings before the opposition division, the appellant provided on 26 July 1994 comparative tests illustrating the superiority of the claimed "one-strip" device vis-à-vis the "multi strip" device disclosed in document (1). These tests showed that, while interface deposits occurred in the regions where two strips of chromatographic material overlapped in the device of document (1), no such deposits were present in the claimed device. However, in the board's judgement, the problem to be solved according to the application as filed (column 4, line 41 to column 5, line 4 of the "A1-application"), is to improve capture efficiency. The problem of interface deposits is not addressed at all. Without the above comparative tests provided by the appellant as later experimental evidence, the skilled person could not have become aware of it. Therefore, since this technical advantage pointed out by the appellant (absence of interface deposits) cannot be derived from a comparison of the application as filed with the prior art, it cannot contribute to the formulation of the problem solved by the claimed subject-matter (decision T 268/89, supra). It should also be noted that the appellant has withdrawn any reliance on these comparative tests during the oral proceedings before the board of appeal on 2 April 2001.

10. The appellant views the selection of a well among the

three possible "sample application means" listed in the description ("A1"-application, column 5, lines 23 to 25: "a well, an absorbent pad or a volumetric delivery device in contact with the chromatographic medium") as a further inventive feature of the claimed device. In the board's view, however, the well's possible contribution to the inventive step is not apparent, as the "A1"-application as filed does not emphasize this aspect and, moreover, no comparative tests showing the superiority of a device endowed with a well over a device without a well, are before the board. The appellant's argument, according to which the well behaves as a "volume metering device" which ensures that all the sample be transferred to the chromatographic material without loss or lateral leakage, is also not convincing, as the two remaining "sample application means" (absorbent pad or a volumetric delivery device) perform equally well. No lateral leakage would indeed occur if the skilled person opts for these solutions, provided he/she avoids applying too much sample. Moreover, as already emphasized under point 8 supra, the presence of the absorption means ensures that chromatographic transport does not cease and that all the sample migrates without loss to the reaction site.

11. In view of the foregoing, the objective technical problem solved by the claimed subject-matter vis-à-vis the closest prior art represented by the diagnostic device disclosed by document (1) has to be restated to meet a less ambitious objective, namely the provision of a further device, differing from the one piece device of document (1) by the further presence of a housing, the latter defining a well for applying the sample (see point 4 supra).

12. The question to be answered is whether or not it would have been obvious for the skilled person to arrive at something falling under the terms of claim 1. In the board's judgement, the prior art (document (3)) already discloses the ternary combination of the following elements: (i) strip of chromatographic/bibulous/capillary material, (ii) housing and (iii) housing defining a receptacle/cavity/well. An example of this combination is to be found not only in Figure 14, interpreted in the light of page 4, lines 29 to 30 and page 10, lines 25 to 26 ("The device comprises a housing and a strip"; "housing 22 contains an opening 52") of document (3), but also in an earlier U.S. patent cross-referenced in this document (see page 2, lines 19 to 24: "porous capillary material"; "covering material"; "defining an absorptive cavity of a preselected volume"). Bearing this in mind, the combination of features leading to the claimed device ((i) the one piece test strip of document (1); (ii) housing and (iii) housing defining a well) was obvious.

13. Since for the reasons given in this decision it was obvious for the skilled person to arrive at the claimed device, the appellant's request is not allowable under the terms of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey