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D E C I S I O N
of 12 March 2002

Case Number: T 1122/98 - 3.3.4

Application Number: 88301967.1

Publication Number: 0284232

IPC: G01N 33/558

Language of the proceedings: EN

Title of invention:

Solid phase assay

Patentee:

Becton, Dickinson and Company

Opponents:

Andrea von Preen
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Abbott Laboratories
Oy Medix Biochemica Ab
VEDALAB

Headword:

Assay device/BECTON

Relevant legal provisions:

EPC Art. 54, 56, 83

Keyword:

"Novelty (yes)"
"Inventive step (yes)"
"Sufficiency of disclosure (yes)"

Decisions cited:

T 0198/84, T 0305/85, T 0409/91

Catchword:

-



Case Number: T 1122/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 12 March 2002

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Decision under appeal: Interlocutory decision of the Opposition Division
of the European Patent Office posted 1 October
1998 concerning maintenance of European patent
No. 0 284 232 in amended form.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
V. Di Cerbo

Summary of Facts and Submissions

I. Opponents 02, 04 and 05 lodged an appeal against the interlocutory decision dated 1 October 1998 by which the European patent EP 0284 232 that had been opposed by six parties, one of which had later withdrawn the opposition, was maintained on the basis of claims 1 to 8.

Claim 1 read as follows:

"An assay device for determining the presence or absence of an analyte in a liquid sample comprising:

- a) a test strip having at least a first and second portion and being arranged on the strip in the same plane in a manner such that material can flow by capillary attraction from the first portion to the second portion;
- b) said first portion having a tracer movably supported therein wherein said tracer comprises a ligand, specific for the analyte when the device is configured for a sandwich assay and is the analyte or analogue thereof when the device is configured for a competitive assay, conjugated to a non-soluble particulate marker and being the site for addition of the sample;
- c) said second portion having immobilized therein a binder which is specific for the analyte when said device is configured for a sandwich assay and is specific for the analyte and ligand when said device is configured for a competitive assay; the binder being present in an amount such that tracer

bound in such portion is visible."

Claims 2 to 7 concerned particular embodiments of the device of claim 1, while claim 8 related to a method using it.

These claims differed from claims 1 to 8 as granted only for the presence of the expression "*by capillary attraction*" in item a) of claim 1 after "*material can flow*".

- II. All appellants filed a statement of grounds of appeal, appellants I and II (opponents 02 and 04, respectively) disputing both novelty and inventive step, and appellants III (opponents 05) disputing only inventive step. Appellants II and III alleged also lack of sufficient disclosure. Appellants II submitted further documental evidence; appellants III filed two later European patents and a technical report.
- III. The respondents (patentees) replied to the submissions by the appellants.
- IV. On 10 January 2002, the board sent a communication to the parties with an outline of the points to be discussed at oral proceedings.
- V. Oral proceedings took place on 12 March 2002. Opponents 01 and 03 (parties as of right under Article 107 EPC), although duly invited, did not attend them, opponents 03 having informed the board beforehand.
- VI. The following documents are referred to in the present decision:

(3) EP-A-0 186 799

(7) US-A-4 373 932

(10) EP-A-0 154 749

(12) WO-A-86/03839

(15) EP-A-0 212 599

VII. The arguments put forward by the appellants can be summarised as follows:

As regards novelty:

Appellants I submit that the assay device disclosed in document (3) has all the features of the claimed device, including the use of markers which are directly visible in the detection portion without the need of any further reaction (cf page 7, lines 1 to 10). Such markers include - although this is not explicitly mentioned - non-soluble particulate materials.

Appellants II maintain that the claimed device lacks novelty vis-à-vis document (15) which describes the same assay format (dip-stick or test strip) and makes explicit reference to mobile detectable groups. The latter include also "a polymer residue to which are attached internally quenched multiple fluoescers", which provides a visible result as it is unquenched when bound in the detection zone (cf page 18, lines 18 to 25). This type of detectable groups corresponds to those which are envisaged also by the patent in suit (cf page 4, line 20: "polymer nuclei coated with such a dye or pigment") with reference to document (7). The

indication in document (15) that the label reagent is solubilised (cf eg page 13, line 28) does not necessarily imply that it must be "dissolved" as it covers also the possibility of the label being simply taken up by the liquid fluid and mobilised toward the detection zone. In their view, it is clear from document (15) that the polymer particles used for marking (cf page 18) are different from those used for immobilising the binder (cf pages 34 to 37). They also submit that the claims at issue do not require the tracer to be "directly" or "immediately" or "itself" visible as the patent in suit refers also to embodiments in which "lysing the sac" is required to make the tracer visible when bound (cf page 4, lines 19 to 20). Thus, there is no real distinction between the device which is claimed and the device according to document (15).

As regards inventive step:

Essentially two lines of reasoning are put forward, namely:

- (i) that it was obvious for the skilled person to modify the two-part assay format of document (12) into the more convenient one-part format according to document (3) or (15); or
- (ii) that it was obvious for the skilled person to use in the assay format according to document (3) or (15) (dip-stick or test strip) non-soluble particulate markers as used in the devices with visual readout according to document (12) or (10).

Line of reasoning (i) is based on the following

considerations:

- Document (12) describes, particularly in Examples IX and X, solid-phase assay arrangements wherein a particulate tracer is mobilised and diffuses into a porous support to a sufficient distance to provide a directly visible result. Although the said specific examples relate to a two-part format, the document suggests on page 14, first paragraph also the strip format;
- Dip-stick or test strip assay devices were the general trend at the filing date of the patent in suit as they were of easier use also by non-technical personnel. Documents (3) and (15) were in this respect representative documents. These documents show either a layered structure or a planar structure of the device, the basic idea being to perform mixing of the reagents in a first sector and to have the mixed reagents flow to a separate sector where detection (also visual) takes place;
- It was obvious for the skilled person to change the two-part assay format described by document (12) into the one-part assay format of document (3) or (15). There were no prejudices of any kind against adopting such a solution, also in view of the fact that the mobility of particulate tracers in porous supports was shown in document (12). The practical advantages of adopting such an assay were all obvious to the skilled person.

Line (ii) of reasoning is based on the following considerations:

- Dip-stick or test strip assay devices in which a liquid sample is brought into contact with a specific functional sector(s) where it combines with a labelling agent and then flows by capillarity into a detection sector where a combination partner is immobilised were known in the art eg from documents (3) and (15). In such devices, a number of different labelling agents are usable (eg enzyme labelling), these being usually based on chromogenic systems or substrate systems producing - upon reaction - measurable fluorescence or chemiluminescence signals in the detection zone;
- The skilled person, while wanting to keep the advantage of such devices of being easy-to-use also for non-technical personnel, was faced with the problem of simplifying the visualisation step;
- Assay devices for **direct** visualisation of the results were known in the art. For example, documents (10) and (12) relied on the use of dye-type labels in a non-soluble particulate form (eg colloidal gold) which were shown to diffuse into adsorbent support membranes and provide an immediate visual result (cf pages 16 and 17 of document (10), and Example X in document (12));
- A number of different non-soluble particulate materials (eg colloidal gold, liposomes etc.) suitable for use in the latter devices were known (cf document (10), page 7 and document (7));
- There was an obvious incentive for the skilled

person to use non-soluble particulate markers known to provide direct visualisation of the results in dip-stick or test strip assay devices according to documents (3) and (15). The skilled person would not have had any hesitations in trying them as there were no doubts about the mobility of such tracers in porous materials, as shown in particular by document (12). In the latter it was shown that the tracer which was initially in a dry state in the swab (porous material) was mobilised by the urine sample and diffused well into the nitrocellulose membrane, with which the swab was contacted, giving a visible spot.

- Thus, the skilled person would have readily substituted the labelling detection systems of documents (3) or (15) with the known insoluble directly visible tracers expecting them to work without difficulties also in a dip-stick or test strip format.

As regards sufficiency of disclosure:

Appellants II and III submit that the disclosure of the only embodiment of liposomes moving in Sephadex does not provide a sufficient teaching for performing the invention over the whole area claimed (cf T 409/91 OJ EPO 1994, 653), **if** one maintains - as the respondents do - that a prejudice generally existed in the art against non-soluble particulate markers moving by capillary action in porous supports. In fact, apart from the said example, nothing in the description teaches how to arrange other solid supports so as to make a non-soluble particulate tracer mobile in the

sense of being able to be transported by capillarity once in the wetted state.

VIII. The respondents submit, as regards novelty, that neither document (3) nor document (15) disclose anywhere the use of non-soluble particulate markers. Nor do these documents disclose an assay device where the results are directly visible without a further step. Thus, none of them can affect novelty.

As for inventive step, they maintain that it was not obvious for the skilled person to combine the teachings relative to dip-stick or test strip assay devices (documents (3) and (15)) with those relative to visual read-out assays (documents (10) and (12)). Document (12) does not suggest using dip-stick in connection with particulate markers. The assay involving particulate material described in Examples IX and X thereof is based on a two-part format assay where a mechanical contact takes place between a swab with a premix and a limited area of spreading of the said premix on a support where a direct visualisation is possible.

The test device of document (10) is a spot test wherein a washing step is indispensable.

Both documents (3) and (15) rely on soluble labelling agents. Reference to particulate material is made only in relation to the immobilisation of the binder.

Thus, the skilled person would not have readily conceived from these two divergent approaches an assay arrangement such as that claimed in which a non-soluble particulate tracer is mobilised by capillarity to a

different sector where visualisation is made possible via the immobilised binder. Only with hindsight it is possible to derive the claimed invention from the quoted prior art.

- IX. The appellants request that the decision under appeal be set aside and that the patent be revoked.

The respondents request that the appeals be dismissed.

Reasons for the Decision

Novelty (Article 54 EPC)

1. One of the essential features of the claimed assay device is the presence in the first portion thereof of a movable tracer conjugated to a non-soluble particulate marker.
2. The appellants' view is that this feature characterises also the assay devices described in either document (3) or document (15), which are identical in respect of all other features. In their view, the said feature is included in the description of document (3) in the passage on page 7 which refers to the various known possibilities of labelling, and it is satisfied in document (15) when the labelled reagent referred to on page 18 is "a polymer residue to which are attached internally quenched multiple fluorescers".
3. It is observed that neither of the two documents explicitly refers to a non-soluble particulate marker. However, since in the examination as to novelty consideration has to be given not only to what is

explicitly disclosed by a given document but also to what is revealed as a whole in a technical teaching (cf T 198/84, OJ EPO 1985, 209 and T 305/85 of 11 June 1987), it has to be assessed whether from the whole contents of either document (3) or (15) the skilled person would have derived the feature in question. Of course, this approach does not involve considering well-known equivalents or alternative embodiments not disclosed in the document under consideration, which are a matter of obviousness.

4. In the board's judgement, in no way would the skilled person derive the use of a non-soluble particulate marker from the passage in document (3) which refers to the various known possibilities of labelling (cf page 7, lines 1 to 10). The emphasis in the disclosure as a whole is on the free movement of solutions or streams of liquids through the separate functional sectors. Enzyme labelling with substrate systems which produce fluorescence or chemiluminescence is indicated as the preferred form of labelling. As shown also by the example, these systems rely normally on the use of soluble components. The reference to fluorescence labelling measurements without the addition of a reagent being required (cf page 7, lines 8 to 10) constitutes no teaching of the use of non-soluble particulate markers. In the document, the use of dispersions of particles is mentioned only in relation to the fixed components of the device (cf page 9, lines 18 to 34). Thus, document (3) is not novelty-destroying as its technical teaching as a whole is not that of an assay device having all the features of the assay device at issue here.

5. Document (15) refers on page 18, lines 18 to 21 to "a

polymer residue to which are attached internally quenched multiple fluorescers" as a possible detectable group in the labelled reagent. It is not stated that this should be a non-soluble particulate polymer. Nor is there an indication of any kind which could imply a non-soluble particulate form, in particular a form of the polymer residue which could be seen as being identical to the polymer nuclei coated with a dye or pigment referred to in the patent in suit on page 4, line 20. As a matter of fact, document (15) indicates in the part of the description which precedes page 18 that the labelled agent is solubilised by the liquid test medium and migrates to the immobilised reagent zone where the detectable signal is provided (cf pages 12 to 15). This cannot be seen as a teaching of the use of non-soluble particulate markers that are transported by the capillary flow. Thus, also document (15) is not novelty-destroying as its technical teaching as a whole is not that of an assay device having all the features of the assay device at issue here.

Inventive step (Article 56 EPC)

6. As regards solid phase assays for the qualitative determination of an analyte in a liquid sample, the available prior art pursues essentially two different approaches:

- (i) Assay devices with visual readout wherein the liquid sample is applied to a given area with an immobilised binder where a directly visible result is provided via a particulate tracer. Documents (10) and (12) are representative of this art.

(ii) Assay devices of the type dip-stick or test strip wherein the liquid sample is applied in one area where it mixes with the labelling reagent and then moves by capillary force to a separate area with an immobilised binder where detection takes place. Documents (3) and (15) are representative of this art. In these devices soluble labelling reagents are used.

7. Both lines of reasoning developed by the appellants for denying an inventive step to the assay device at issue here (cf Section VII above) arrive essentially at the conclusion that it was obvious for the skilled person to combine the teachings relative to the two approaches when trying to simplify either of them.
8. Regardless of whether one or the other assay arrangement is taken as a starting point for the evaluation of the inventive step, the technical problem to be solved can be defined as finding an alternative easy-to-use assay format.
9. The relevant questions are what measures the skilled person, starting either from the approach (i) or from the approach (ii) referred to in point 6 above, would have considered adopting, and whether these would have led him or her to combine the different elements so as to obtain an assay device as claimed. This amounts essentially to the question whether it was obvious for the skilled person to use non-soluble particulate markers of the kind used in document (10) or (12) in an assay arrangement according to document (3) or (15) or, vice versa, whether it was obvious to change the assay arrangement according to document (10) or (12) into a dip-stick or test strip arrangement of the kind

described in document (3) or (15). As repeatedly emphasized in the case law of the boards of appeal, in answering such questions for assessing inventive step, it is important to avoid any ex-post-facto analysis, especially in cases - such as the present one - where the proposed solution looks *prima facie* quite simple.

10. As stated above, documents (10) and (12) are representative of the visual readout arrangement whereby immediate visualisation of the result takes place **at the site of application of the sample** on a support membrane:
- Document (10) uses non-soluble particulate markers of the same kind used in the patent in suit (eg a liposome including a dye) for a visual readout in a test area of a solid support where binder and analyte of the sample have interacted. This test arrangement requires a washing step to remove the unbound tracer;
 - Document (12) illustrates a solid phase diffusion assay performable in the kit form also by non-technical personnel (cf page 9, lines 11 to 12 and 17 to 18), whereby a sample containing an analyte to be tested is first mixed with a labelled binding substance, then applied to a region of an insoluble support (eg a nitrocellulose membrane) bearing immobilised adsorbent molecules and allowed to diffuse therein. The diffusion pattern is visualized and measured. In order to focus on the point of application of the sample, the document proposes placing a sheet of plastic or tape with a small hole on the support. The document refers to a number of labelling

substances (cf page 14, line 13 to page 15, line 23), including dye particles such as colloidal gold or silver which are said to allow direct visualisation of the results (cf passage bridging pages 14 and 15, and page 29, lines 14 to 17). The latter embodiment is exemplified in Examples IX to XIII. In Example X, in view of a pregnancy test, the following practical assay format is described: a swab containing lyophilised gold-labelled anti-human chorionic gonadotropin (HCG) monoclonal antibodies is wetted with a sample of urine suspected to contain HCG, and immediately brought into contact with a nitrocellulose membrane bearing immobilised polyclonal antibodies against HCG via the opening in the membrane cover and held in place for about 30 seconds. A red spot which is said to be obtained at concentrations of HCG higher than 50 mIU/ml, indicates a pregnancy. Lower concentrations are said to produce no visible spot.

11. The skilled person is always expected to seek, within the normal design procedures, modifications or simplifications of known devices for the sake of obtaining an easy-to-use product. When carrying out such activities, depending on the type of device, a number of different options are normally open, unless the prior art specifically directs the skilled person's attention to a particular problem. In the present case, the skilled person, starting from the visual readout devices of document (10) or (12), would have possibly tried to optimise the assay arrangement described therein so as to render it more user friendly, simple and reliable. His or her attention were not drawn to

any specific problem. The skilled person had thus a wide number of options open, as he or she could have intervened at a number of different levels, for example:

- (a) The choice of the materials, including eg the support and the tracer used for visualisation;
- (b) The focusing on the point of application of the sample;
- (c) The fixing of the binder on the support;
- (d) The ways for transferring a sample in order to ensure a reliable single point application and minimise losses of sample.
- (e) The form of the device (card, test, strip, dip-stick etc.)

12. In the board's judgement, although under options e) the skilled person had open - among various possibilities - also that of changing the format of the assay device, undertaking the step of separating the point of application of the sample from the actual point of visualisation of the result would have required a leap of imagination. This is because, in spite of the fact that dip-sticks or test strips with such an arrangement were known in the art (cf documents (3) and (15)), they relied on the use of freely movable labelling reagents (thus soluble) and their rheological conditions were quite different from those of visual readout devices. In the latter, although some diffusion of the tracer in the area of application was observed, the emphasis was on detection at the place of application (cf eg

Examples X to XII in document (12)). Under these circumstances, the skilled person would not have readily come to the idea of having the premix sample-labelling reagent move by capillary force from a first portion of the device to a second portion thereof where visualisation would take place. Only with hindsight can such a suggestion be derived from the practicalities of Example X of document (12), or from the reference in the same document to a test strip on page 14. In fact, although document (12) describes various ways of performing solid-phase diffusion assays and deals also with devices using soluble labels, nothing therein would have suggested including a non-soluble particulate tracer directly in a first portion of the device from which it would move by capillary attraction into a second portion of the same for detection.

13. As regards the other perspective, ie starting from approach (ii), the following considerations are made.

As stated under "novelty", both documents (3) and (15) are concerned with an assay format which requires the free mobility of the reagents in the supports, these latter being in the form of eg test strips or dip-stick etc. None of the two documents makes any direct or indirect reference to non-soluble particulate material being usable as a tracer. As matter of fact, any reference to particulate material is made only in relation to fixing components within the solid phase zone (cf document (3), page 9, last paragraph; document (15), page 34).

14. Here also, when considering various possibilities to optimise the known devices, the skilled person had different options open, among them possibly also that

of optimising the tracer in order to facilitate visualisation of the results. However, in the board's judgment, it would not have readily occurred to the skilled person changing from soluble labelling agents to the non-soluble particulate tracers used in known visual readout devices, because the mobility of the latter was not as good as that of the former. The manifestly more limited mobility of non-soluble particulate tracers was a property which made them suitable for use in devices where detection was at the site of application, such as those of documents (10) and (12) . Although a real prejudice against the possibility of mobilising them might not have existed, they were not ideal candidates for replacing the more mobile soluble labelling agents. The skilled person, based also on eg document (12), would have expected some diffusion of said tracers in porous membranes, well knowing that in the visual readout devices this was limited to the area of application of the sample. This, however, would not have prompted him or her to use this kind of tracers in devices where free mobility between two spatially distinct zones within solid supports was required, such as those of documents (3) and (15).

15. Thus, as already stated, the combination of the two elements required in the board's view a leap of imagination. This is indicative of an inventive step.

Sufficiency of disclosure (Article 83 EPC)

16. While it is true that only one example is provided in the description of the patent specification of the claimed assay device, it is also a fact that the appellants, who have the burden of proof, have not

provided any evidence that the claimed invention cannot be carried out in its more general outline (ie using other known materials) by a person skilled in the art.

17. The appellants' objection is essentially that, **if** an inventive step has to be recognised in the claimed invention based on the existence of a technical prejudice in the art against the possibility of mobilising non-soluble particulate markers, then the patent specification does not provide sufficient instructions how tracers and supports other than those of the specific example can be used in practice.

18. However, as stated above, inventive step is acknowledged by the board not on the basis of the existence of such a prejudice, but on the basis of the fact that the claimed assay device results from a non-obvious combination of elements which separately characterised two different approaches of the prior art. As there is no evidence on file that, once said combination is thought, more than ordinary skill is necessary to put the invention into practice over the whole range which is claimed, the board considers that the appellants' objection under Article 83 EPC is not justified.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar:

The Chairperson:

P. Cremona

U. Kinkeldey