(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 3 834 938 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
16.06.2021 Bulletin 2021/24

(51) Int Cl.:
B01L 3/00 *(2006.01)* ***G01N 33/543*** *(2006.01)*

(21) Application number: **19215013.4**

(22) Date of filing: **10.12.2019**

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME
KH MA MD TN

(71) Applicant: **TECAN TRADING AG**
8708 Männedorf (CH)

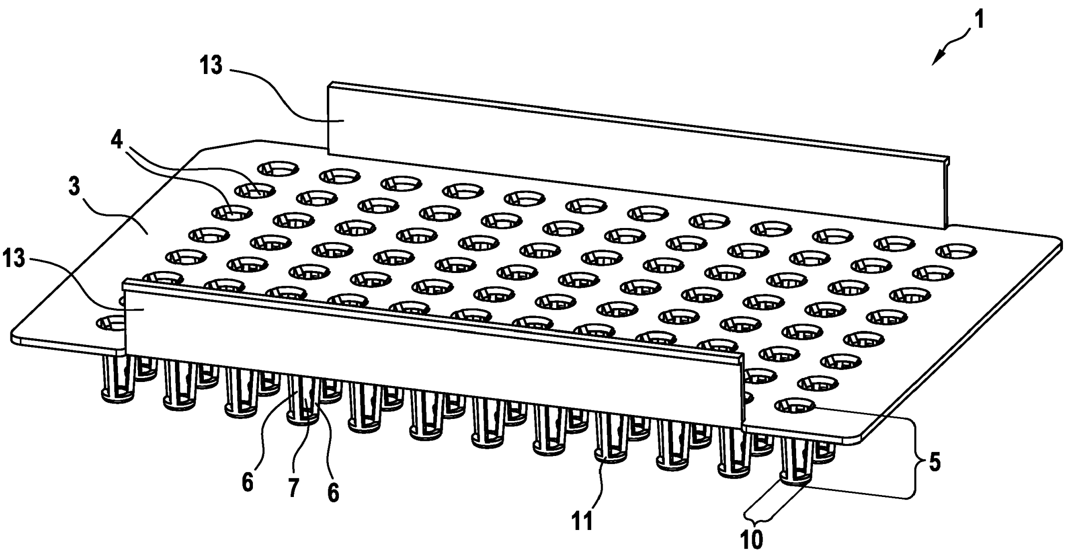
(72) Inventors:
- **ANGST-HELBLING, Marianne**
  8046 Zürich (CH)
- **MARTY, Roger**
  8610 Uster (CH)
- **SAGER, Adrian**
  8710 Männedorf (CH)
- **LANSING, Manfred**
  5020 Salzburg (AT)
- **HABENBACHER, Gerald**
  9065 Ebental (AT)

(74) Representative: **Troesch Scheidegger Werner AG**
Schwäntenmos 14
8126 Zumikon (CH)

(54) INSERT FOR AN ARRAY OF WELLS , APPLICATION METHOD AND USE

(57) According to the present invention, an insert (1) for an array (2) of wells (17) comprises an insert plate (3) with an array of recesses (4), wherein each of the recesses (4) includes a cone-shaped hollow recess part (5) devoid of a bottom which comprises at least two leg supports (6) with lateral gaps (7) in between, the leg supports (6) beginning at the edge (8) of the respective recess (4) and having lower ends (9), wherein the leg supports (6) lie on the surface of a mathematical cone of revolution. Moreover an application method for such an insert (1) in the processing of area-measured sample supports (16) in the wells (17) of an array (2) of wells (17) is proposed. A use of said insert (1) as a retainer or downholder for area-measured sample supports (16) in an array (2) of wells (17) is furthermore proposed.

Fig. 1



Printed by Jouve, 75001 PARIS (FR)

Description

FIELD OF THE INVENTION

[0001] The present invention relates to an insert for an array of wells and to an application method of the insert in analysis techniques and to a use of the insert.

BACKGROUND OF THE INVENTION AND PRIOR ART

[0002] In molecular biology, samples from plants or tissue samples from animals or samples of body fluids are collected for analysis in laboratories. Such samples can be collected in small containers or on absorbent filter paper. Absorbent filter paper is suitable if soft samples can be squashed or pressed out on it, so that squeezed juice is soaked into the paper. Or if the sample is a liquid such as blood or another body fluid, it may be dropped onto absorbent filter paper. Absorbent filter paper is also used in the field of clinical diagnostics (e.g. immune assays) or in the field of environmental monitoring.

[0003] The target of most analyses is the analysis of DNA (deoxyribonucleic acid) of living organisms for gaining genetic information. Other tests target antibodies or other proteins e.g. in newborn screening assays. Some analysis techniques use FTA® (Flinders Technology Associates) paper as sample cards. FTA® paper is a special absorbent cellulose-based filter paper that has been impregnated with a chemical formulation that lyses cells, captures and immobilizes nucleic acids in the paper matrix. The chemical substances moreover protect DNA molecules from degradation and preserve the paper from bacterial growth. The storage of an immobilized sample on FTA® paper is thus possible at room temperature over a period of several years.

[0004] For example a drop of blood is added to the FTA® paper and the bloodstain is allowed to dry. The cells are lysed upon contact with the paper and the DNA or other molecules of interest are bound in a stable form in the matrix of the paper. Later on, a small paper disc is punched out from the FTA® paper card bloodstain for processing and analysis in the laboratory. The usual procedure is to place the paper disc into a small tube or in a well of a multi-well microplate, for washing the paper disc with a wash fluid to wash away impurities and non-DNA material from the sample, the DNA being retained on the paper. After removing the supernatant washing solution and drying, the clean paper disc with the still bound DNA can then be used for amplification of a DNA segment by PCR (polymerase chain reaction). The amplified DNA is then used for DNA sequencing respectively for DNA profiling. For DNA testing, different samples on a plurality of individual paper discs are processed, preferably with robotized lab stations. For PCR amplification, the DNA can either remain attached to the washed paper discs, or it can be removed at first from the washed paper discs by elution respectively extraction.

[0005] For some applications, untreated absorbent filter paper is used. Cells are lysed just after elution of the sample from the absorbent filter paper. The lysate may be analysed by immune assay methods or by instrumental analysis (e.g. mass spectroscopy).

[0006] One of the bottlenecks in the process workflow of samples on absorbent filter paper is the paper disc washing, according to Stanislav Vitha, David W. Yoder: "High Throughput Processing of DNA Samples on FTA® Paper for PCR Analysis", 2005, (http://www.tamu.edu/mic). In one cited method, adding and removing the washing liquid in small tubes was carried out manually using a pipettor. Another cited method used a 96-well microplate modified by piercing a small hole in the bottom of each well so that the washing liquid can be pulled through and removed by centrifugation. Because the acceleration and deceleration of the centrifuge prolongs the washing process, the authors improved the procedure by using negative pressure (vacuum) instead of centrifugation to remove the washing liquid from the wells of the modified microplate. But this method was not suitable for robotic handling either, because after washing the paper discs had to be transferred by a manual operation from the pierced washing plate to a PCR plate.

[0007] That the upfront processing of DNA samples still creates a bottleneck, is also confirmed by A. Tereba, J. Krueger, R. Olson, P. Mandrekar and B. McLaren: "High-Throughput Processing of Samples on Solid Supports Using the Slicprep™ 96 Device", September 2005, Promega Corporation (www.promega.com). Due to the increasing cases of forensic DNA typing and the ever-expanding analyzing workload, automation of sample processing is desired. These authors prefer to remove DNA and cells by a lysis buffer from the solid support, wherein the solid support may be a punched-out disc from an FTA® paper blood card or a cotton swab with a buccal swab sample. Attempts for an automated removal of the DNA solution with robotic pipetting were not trouble-free because the solid supports were prone to clog the pipette tips when aspirating the solution. The authors of this article developed therefore a microplate device and method which allows an automated and failure-free extraction of DNA from solid supports, wherein the DNA solutions are removed by centrifugation. The pertaining device consists of a 96 deep well plate, a 96 spin basket with corresponding matrix which fits as an insert into the wells of the deep well plate, and a U-shaped collar for in between to raise the insert with the baskets after the lysis step into a spin position for centrifugation. First FTA® blood punches or cotton buccal swabs are placed in the individual baskets of the insert. Each individual basket of the insert has seven small holes in the bottom, so that during incubation with the lysis buffer and afterwards during centrifugation, the liquid solution from each basket can pass through the basket holes into the corresponding well of the deep well plate below. The extracted and collected fractions with DNA in the 96 deep well plate can then be further processed and analysed.

[0008] Similar inserts for microplates are also known from other prior art sources, wherein all individual recess parts of those inserts show a bottom with capillary openings or possess a membrane bottom with pores. Such a permeable bottom is designed for cultivating cell cultures on an upper level in the wells of the microplate in a certain distance from the bottom of the wells, and for performing for example assays with cells and chemical compounds. Following prior art documents with such a kind of cell culture inserts can be named: DE 20 2006 017 853 U1; US 2004/0091397 A1; WO 2011/127945 A1; US 8,163,537 B2; US 6,943,009 B2.

[0009] Another type of insert was disclosed in US 2007/0237683 A1. This insert has wells with an optically clear bottom and optically clear cylindrical walls. In order to prevent optical crosstalk in chemiluminescence assays, the insert is placed in a holding tray which is a thick plate with cylindrical vertical through holes and which is made of an opaque material.

SUMMARY OF THE INVENTION

[0010] It is the object of the present invention to propose an alternative insert for an array of wells. This alternative insert shall be applicable with area-measured sample supports for processing them in connection with pipettes.

[0011] This object is achieved by an insert for an array of wells with the features of claim 1.

[0012] The present invention also relates to an application method of such an insert in analysis techniques, and to a use of the insert.

[0013] Preferred embodiments of the insert and preferred variants of the application method and of the use arise from the respective dependent claims.

[0014] According to the present invention, an insert for an array of wells comprises an insert plate with an array of recesses, wherein each of the recesses includes a cone-shaped hollow recess part devoid of a bottom which comprises at least two leg supports with lateral gaps in between, the leg supports beginning at the edge of the respective recess and having lower ends, wherein the leg supports lie on the surface of a mathematical cone of revolution.

[0015] Unlike the known inserts from prior art, the recess parts of the insert of the present invention do not possess a bottom.

[0016] If the leg supports extend to the cone end, there lower ends end in a common point.

[0017] Preferably, the cone of the cone-shaped hollow recess parts is a truncated cone with truncation of the cone end. In such an embodiment, the leg supports might be separate legs with interspace between their lower ends.

[0018] However in a preferred embodiment of the insert with truncated cone, the leg supports being connected with each other at their lower ends.

[0019] In conformity with the basic feature "devoid of a bottom", the connection at the lower ends of the leg supports is not a continuous area, neither a plate nor a disc nor a slice. The connection may for example be bridges between nearby lower ends of the leg supports.

[0020] Preferably the leg supports being connected at their lower ends by a ring at the truncation. A ring being defined as a torus with a central opening.

[0021] In a preferred embodiment, the ring at the truncation has offsets at its lower side.

[0022] It is preferred for the insert according to the invention that each recess part comprises three or four leg supports.

[0023] In an embodiment of the insert according to the invention, the insert plate is provided with flanks for robotic handling.

[0024] In a preferred embodiment of the invention, the insert is of a one-piece design. In the case of a one-piece-design, the insert is preferably manufactured by injection moulding or 3D printing from a thermoplastic resin. Suitable thermoplastic resins can for example be selected from the group comprising polypropylene, polycarbonate, polyethylene terephthalate, cycloolefin copolymer, polystyrene, polyamides and polymethyl methacrylate.

[0025] In another embodiment of the insert according to the invention, the insert is not of a one-piece design. In this embodiment, the recess parts are designed as spring clips and are clicked into place at the edge of the recesses in the insert plate by spring clip leg supports. This embodiment requires the leg supports being connected with each other at their lower ends of the respective recess parts to be individual spring clips at first.

[0026] In the insert according to the invention, the array of recesses may be one-dimensional or two-dimensional. One-dimensional would mean arranged in one row. Two-dimensional would mean arranged within an area.

[0027] The array of recesses of the insert according to the invention may be smaller than or equal the array of wells. "Smaller than" would mean, that the insert would only cover a portion of the array of wells and not all the wells.

[0028] In a preferred embodiment of an insert in accordance with the invention, a two-dimensional array of recesses conforms to the inter-well spacing of a standard microplate, and the array of wells being a microplate.

[0029] The object of the invention is moreover achieved by an application method for an insert in accordance with the features of claim 1, wherein the method comprises:

- providing area-measured sample supports containing biological samples;
- placing or providing the area-measured sample supports in the wells of an array of wells;
- dispensing a liquid into the wells so that the area-measured sample supports are submerged;
- allowing the area-measured sample supports to be soaked in the liquid and an elution process of sample components to occur, yielding supernatant solutions

with eluted components;

- inserting an insert according to claim 1 into the wells of the array of wells, so that the area-measured sample supports are retained outside or under the recess parts of the insert;
- lowering pipette tips into the recess parts of the insert and aspirating the supernatant solutions;
- further processing of the area-measured sample supports and/or the aspirated eluates.

[0030] In the application method according to the invention, the area-measured sample supports are preferably punched out or cut out or cut off paper or fabric snippets or shreds or discs or area-measured pieces or cuts of electrophoresis gels.

[0031] Regarding electrophoresis gels, 2D gel electrophoresis is a method of separating molecules such as for example proteins. A spot of an electrophoresis gel can contain one or more proteins of note. By gel picking, said spots are removed from the gel, and the corresponding pieces or cuts of the electrophoresis gel are transferred into wells and eluted respectively extracted there.

[0032] In a preferred variant of the application method in accordance with the invention, the biological samples are body fluids, in particular dried blood spots, or samples containing proteins or other molecules of interest.

[0033] In the application method, the dispensed liquid is preferably a washing fluid or a buffer solution or a lysis buffer or an extraction liquid.

[0034] The invention relates also to a use of an insert in accordance with the features of claim 1 as a retainer or downholder for area-measured sample supports, preferably paper discs, in an array of wells, preferably in the wells of a microplate.

[0035] In a preferred use of such an insert, the paper discs are absorbent filter paper discs containing DNA or protein samples or other molecules of interest. Proteins also include antibodies. Other molecules of interest comprise for example RNA (ribonucleic acid) or metabolites. Especially preferred is the use of an insert according to the invention for processing FTA® paper discs containing DNA samples with pipettes. But also untreated absorbent filter paper may be used as for whole blood collection for newborn screening, e.g. Whatman® 903 and Whatman® 226 filter paper.

BRIEF DESCRIPTION OF THE FIGURES

[0036] The invention is explained in more detail by means of the enclosed figures. The figures illustrate exemplary embodiments, which do not limit the scope of the invention. It is shown in:

Fig. 1 a perspective view of an insert according to the invention;

Fig. 2 a perspective view as in Fig. 1, with the insert above a microplate;

Fig. 3 a perspective view as in Figs. 1 and 2, with the insert placed in the microplate;

Fig. 4A a perspective detail view of a single recess part in the insert plate, having a ring at the truncation;

Fig. 4B a perspective detail view of another single recess part in an insert plate, without a ring;

Fig. 5 a vertical cross-section of a single well of a microplate;

Fig. 6 a vertical cross-section of a single well of a microplate as in Fig. 5, with a paper disc placed on the bottom of the well;

Fig. 7 a vertical cross-section as in Fig. 6, with a single recess part of an insert according to the invention inserted into the well onto the paper disc;

Fig. 8 a vertical cross-section as in Fig. 7, with a pipette tip lowered into the recess part of the insert;

Fig. 9A a vertical cross-section of a single recess part in an insert plate, the recess part being here a spring clip clicked into place;

Fig. 9B as in Fig. 9A, but showing another variant of a recess part being a spring clip clicked into place;

Fig. 10 a perspective view of a section of an insert according to the invention, with offsets at the lower side of the ring at the cone truncation of the recess part;

Fig. 11 a perspective view as in Fig. 10 from below of an entire insert according to a preferred embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0037] Fig. 1 shows an insert 1 according to a preferred embodiment of the invention in a perspective view from oblique above. In this example, the shown insert 1 is designed to fit in a 96 well microplate. The insert 1 comprises an insert plate 3 with an array of 96 recesses 4, wherein each of the recesses 4 includes a cone-shaped hollow recess part 5 which comprises in the shown version three leg supports 6 with lateral gaps 7 in between. The leg supports 6 being connected with each other at their lower end by a ring 11 at the truncation 10 of the cone-shaped hollow recess part 5. The shown insert 1 possesses flanks 13 at the insert plate 3 in order to facilitate robotic handling with a gripper.

[0038] Fig. 2 shows the same perspective view of the insert 1 of Fig. 1, the insert 1 being here in a position above a microplate 2 with 96 wells 17. As shown in Fig. 2, the insert 1 is designed to fit with its array of recesses to the geometric pattern of the microplate 2.

[0039] Microplates usually have round circular wells 17, as shown in Fig. 2. In rare cases, microplates can have square-based wells. In the latter case it would be preferred for an insert according to the invention that each recess part 5 comprises four leg supports 6 oriented to the corners of the square-based wells. Moreover an embodiment without a ring or with straight connections at the lower ends of the leg supports would fit well in this case.

[0040] In the illustration of Fig. 3, in sequence of Fig. 2, the insert 1 is placed fitting in the microplate 2.

[0041] Fig. 4A shows a perspective detail view of a single recess part 5 in a recess 4 of the insert plate 3 of the insert 1 of Fig. 1. In this embodiment, the insert 1 is of a one-piece design. This means that the insert plate 3 and the recess parts 5 are integrally manufactured respectively integrally moulded of one material. Thus the three leg supports 6 begin at the edge 8 of the recess 4 as a continuation of the same material. There are lateral gaps 7 between the leg supports. At the lower end 9 of the leg supports 6, where the truncation 10 of the cone-shaped hollow recess part 5 is located, the leg supports 6 are connected by a ring 11 having a central opening.

[0042] Fig. 4B shows a perspective detail view of another single recess part 5 in an insert plate 3, without a ring at the lower ends 9 of the leg supports 6. In this embodiment the cone-shaped hollow recess part 5 is a truncated cone, but the leg supports 6 are separate legs with interspace between their lower ends 9 not being connected with each other.

[0043] The figures 5 to 8 illustrate schematically a representative process sequence in an application method for an insert 1 in accordance with the invention.

[0044] Fig. 5 shows a single well 17 of a microplate 2 in a vertical cross-section, the well 17 being still empty.

[0045] In Fig. 6, a paper disc 16 (as an example for an area-measured sample support in a schematic representation) is then placed on the bottom of the well 17. Afterwards a liquid can be dispensed into the well 17 so that the paper disc 16 is submerged and soaked.

[0046] Fig. 7 shows in further sequence of Fig. 6 a snap-shot with a single recess part of an insert according to the invention inserted into the well of microplate 2 onto the paper disc 16. By the ring 11 at the lower end of the leg supports 6, the paper disc 16 is retained under the recess part of the insert, so that the paper disc 16 does not float to the top. For this purpose, it is not a compulsory requirement that the paper disc 16 is clamped. The length of the recess part has just to be designed sufficient in relation to the depth of the well, so that the paper disc 16 is held down near the bottom of the well and cannot be aspirated into the inside of the recess 4 during the subsequent aspiration of the dispensed liquid. However the flow of a liquid from the outside to the inside of recess 4 is enabled by the lateral gaps between the leg supports 6 and preferably in addition by offsets 12 at the lower side of ring 11.

[0047] Fig. 8 shows in addition to Fig. 7 a pipette tip 18 which was subsequently lowered into the recess part of the insert for aspiration. Fig. 8 shows the pipette tip 18 at the so-called z-max position, the maximum possible lowering position in the insert. At this lowest point near the paper disc 16 but in a small distance of it, most of the supernatant solution can be aspirated. The supernatant solution consists of the previously dispensed liquid with eluted sample components from the paper disc 16. Due to the retaining or downholder function of the insert for the paper disc 16, an aspiration of the paper disc 16 or of another area-measured sample support is avoided, and thus the insert according to the invention prevents clogging of the pipette tip 18 during aspiration and enables a safe pipetting off of eluates out of the well.

[0048] The following figures 9A and 9B show two variants of a special embodiment of an insert in accordance with the invention, wherein the insert is not of a one-piece design. In fact this embodiment comprises separate recess parts being of a spring clip design which are clicked into place in the recess openings of an insert plate. The spring clip design requires that the leg supports of a recess part being connected with each other at their lower end in order to constitute a part with spring arms.

[0049] Fig. 9A shows a first possible variant of a recess part being a spring clips 14 clicked into place with the spring clip leg supports 15 in a recess opening of an insert plate 3. The spring clip leg supports 15 have a geometry at their upper beginning which allows to engage at the edge of the recess opening as a form lock fixing.

[0050] Fig. 9B shows a second possible variant with a spring clips recess part 14. Here the spring clip leg supports 15 are clicked into place with sideward spikes at their upper beginning which can engage into a groove at the inner side of the recess opening of an insert plate 3.

[0051] Fig. 10 shows a perspective view from oblique below of a section of an insert according to the invention. At the underside of an insert plate 3, there are arranged recess parts 5 with leg supports 6 and lateral gaps 7 between the leg supports 6. The leg supports 6 being connected with each other at their lower end 9 by a ring 11 at the cone truncation, wherein there are offsets 12 at the lower side of the ring 11.

[0052] Fig. 11 shows a perspective view from oblique below similar as in Fig. 10, but here of an entire insert 1 according to a preferred embodiment of the invention. Additional flanks 13 are arranged in this example at two corners of the insert plate 3 for precise positioning of the insert 1 in automatic handling.

[0053] At this point it should be noted that any combination of the features described and/or shown in the figures is part of the scope of the present invention as long as the combinations are not inconsistent. Also all variants of the application method according to the invention may be combined unless being inconsistent.

[0054] It is the merit of the present invention to provide an insert for a microplate and an application method of such an insert in microplates, which eliminate a bottleneck in the diagnostic laboratory workflow and enable effective analysis techniques in connection with punched-out paper discs in microplates, especially in processing punched-out FTA® paper discs containing DNA samples and in processing punched-out untreated absorbent filter paper discs containing dried blood spots for newborn screening based on immune assay techniques. The great advantage of the present invention is that the insert can be used with known pipetting robots, whereby aspiration instead of centrifugation can be applied, which allows an automated and high-throughput processing. Pipetting with the insert according to the invention as a downholder for paper discs in the wells of a microplate is fast and reliable, because the downholder insert prevents filter paper discs from floating and from clogging pipette tips during aspiration of supernatant solutions with extracts. And besides the downholder prevents that filter paper discs are sucked and would hang at the pipette tips and might then fall into another well of the microplate or into another receptacle on the laboratory bench, which would cause a cross-contamination. Finally it should be mentioned that the downholders are transportable with a robotic gripper and are stackable (with or without spacers) due to the cone-shaped hollow recess parts. The stackability is space-saving in the working area of a pipetting robot.

LIST OF REFERENCE NUMERALS

[0055] The same reference numerals in the figures indicate corresponding features, even if the description of the individual figures does not always refer to them explicitly.

1	insert
2	array of wells, e.g. a microplate
3	insert plate
4	recess, recesses
5	recess part, recess parts
6	leg supports
7	lateral gaps between leg supports 6
8	edge of recess 4
9	lower ends of the leg supports 6
10	truncation of the cone-shaped hollow recess parts 5
11	ring at the truncation 10
12	offsets at the lower side of the ring 11
13	flanks at the insert plate 3
14	spring clips (particular embodiment of recess parts 5)
15	spring clip leg supports
16	area-measured sample support(s), e.g. paper disc(s)
17	well or wells of an array 2 (e.g. of a microplate 2)
18	pipette tip, pipette tips

Claims

1. An insert (1) for an array (2) of wells (17), comprising an insert plate (3) with an array of recesses (4), **characterized in that** each of the recesses (4) includes a cone-shaped hollow recess part (5) devoid of a bottom which comprises at least two leg supports (6) with lateral gaps (7) in between, the leg supports (6) beginning at the edge (8) of the respective recess (4) and having lower ends (9), wherein the leg supports (6) lie on the surface of a mathematical cone of revolution.

2. The insert (1) according to claim 1, wherein the cone of the cone-shaped hollow recess parts (5) is a truncated cone with truncation (10) of the cone end.

3. The insert (1) according to claim 2, wherein the leg supports (6) being connected with each other at their lower ends (9).

4. The insert (1) according to claim 3, wherein the leg supports (6) being connected with each other at their lower ends (9) by a ring (11) at the truncation (10).

5. The insert (1) according to claim 4, wherein the ring (11) has offsets (12) at its lower side.

6. The insert (1) according to one of the preceding claims,
wherein each recess part (5) comprises three or four leg supports (6).

7. The insert (1) according to one of the preceding claims,
wherein the insert plate (3) is provided with flanks (13) for robotic handling.

8. The insert (1) according to one of claims 3 to 7, wherein the recess parts (5) are designed as spring clips (14) and are clicked into place at the edge (8) of the recesses (4) in the insert plate (3) by spring clip leg supports (15).

9. The insert (1) according to one of the preceding claims,
wherein the array of recesses (4) is one-dimensional or two-dimensional.

10. The insert (1) according to one of the preceding claims,
wherein the array of recesses (4) is smaller than or equals the array (2) of wells (17).

11. The insert (1) according to claim 9, wherein a two-

dimensional array of recesses (4) conforms to the inter-well spacing of a standard microplate, and the array (2) of wells (17) being a microplate (2).

12. An application method for an insert (1) in accordance with the features of claim 1, wherein the method comprises:

- providing area-measured sample supports (16) containing biological samples;
- placing or providing the area-measured sample supports (16) in the wells (17) of an array (2) of wells (17);
- dispensing a liquid into the wells (17) so that the area-measured sample supports (16) are submerged;
- allowing the area-measured sample supports (16) to be soaked in the liquid and an elution process of sample components to occur, yielding supernatant solutions with eluted components;
- inserting an insert (1) according to claim 1 into the wells (17) of the array (2) of wells (17), so that the area-measured sample supports (16) are retained outside or under the recess parts (5) of the insert (1);
- lowering pipette tips (18) into the recess parts (5) of the insert (1) and aspirating the supernatant solutions;
- further processing of the area-measured sample supports (16) and/or the aspirated eluates.

13. The application method according to claim 12, wherein the area-measured sample supports (16) are punched out or cut out or cut off paper or fabric snippets or shreds or discs or area-measured pieces or cuts of electrophoresis gels.

14. The application method according to claim 12 or 13, wherein the biological samples are body fluids, in particular dried blood spots, or samples containing proteins or other molecules of interest.

15. The application method according to one of claims 12 to 14,
wherein the dispensed liquid is a washing fluid or a buffer solution or a lysis buffer or an extraction liquid.

16. Use of an insert (1) in accordance with the features of claim 1 as a retainer or downholder for area-measured sample supports (16), preferably paper discs (16), in an array (2) of wells (17), preferably in the wells (17) of a microplate (2).

17. Use of an insert (1) according to claim 16, wherein the paper discs (16) are absorbent filter paper discs containing DNA or protein samples or other molecules of interest.

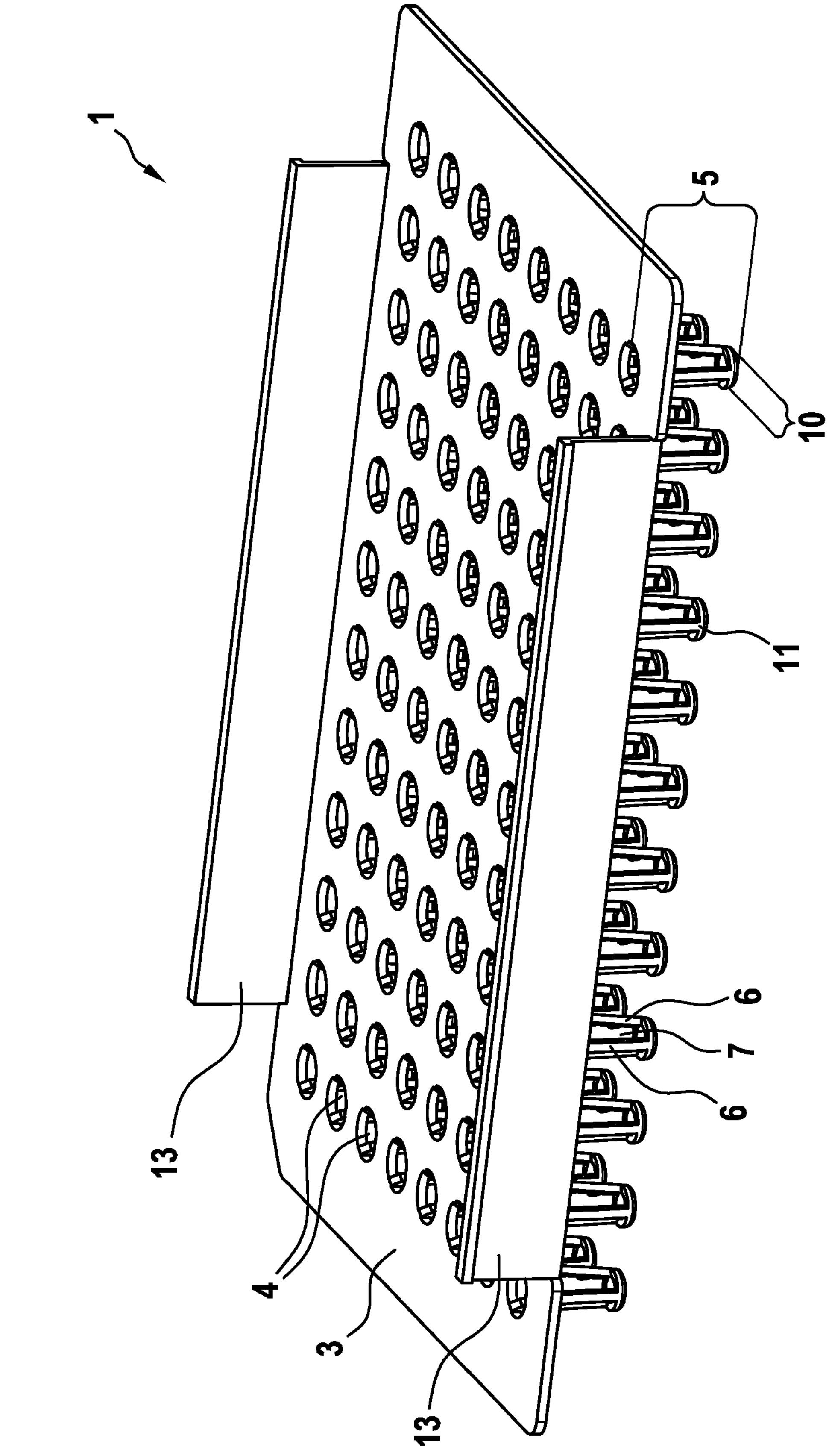


Fig. 1

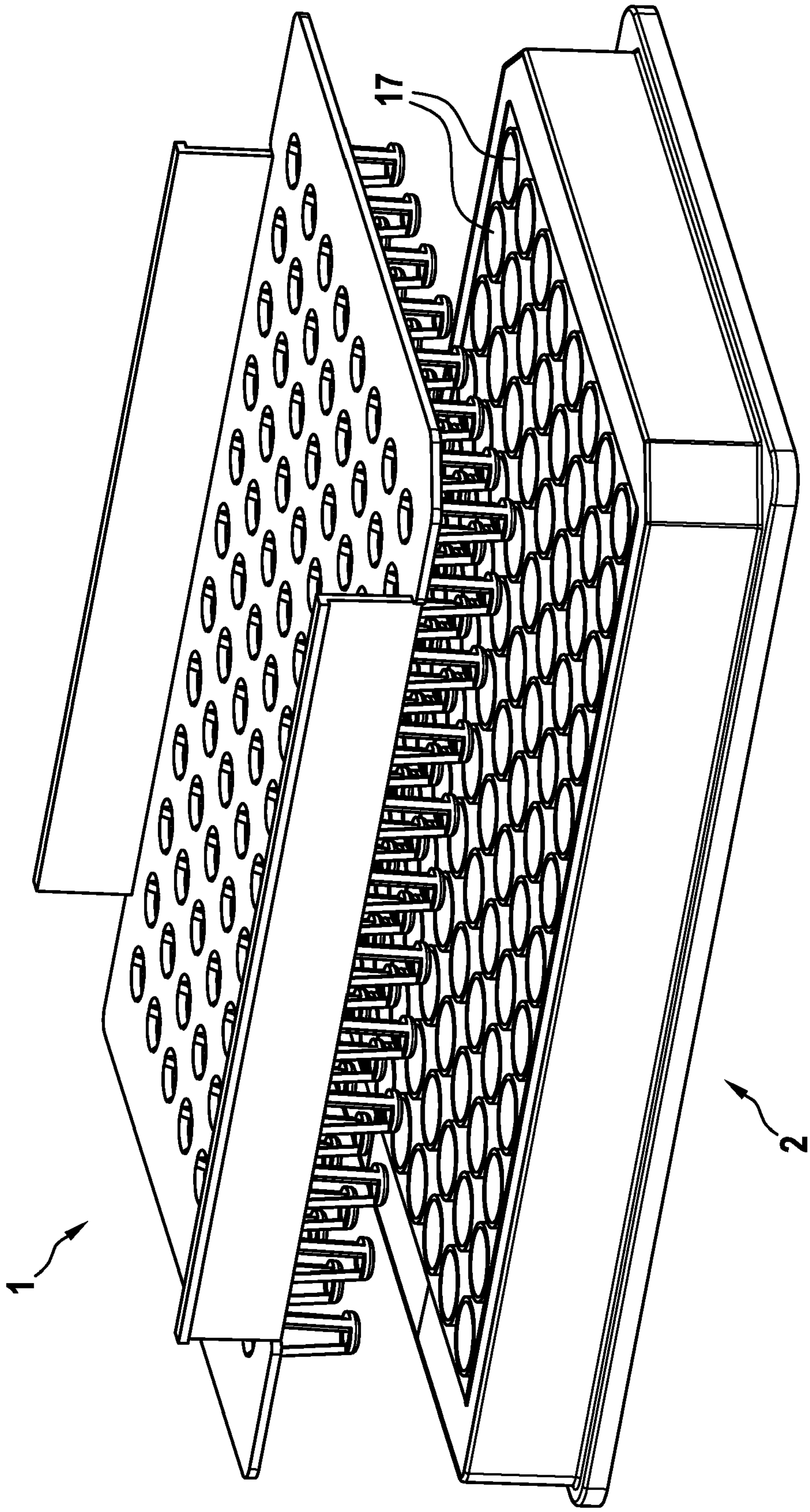


Fig. 2

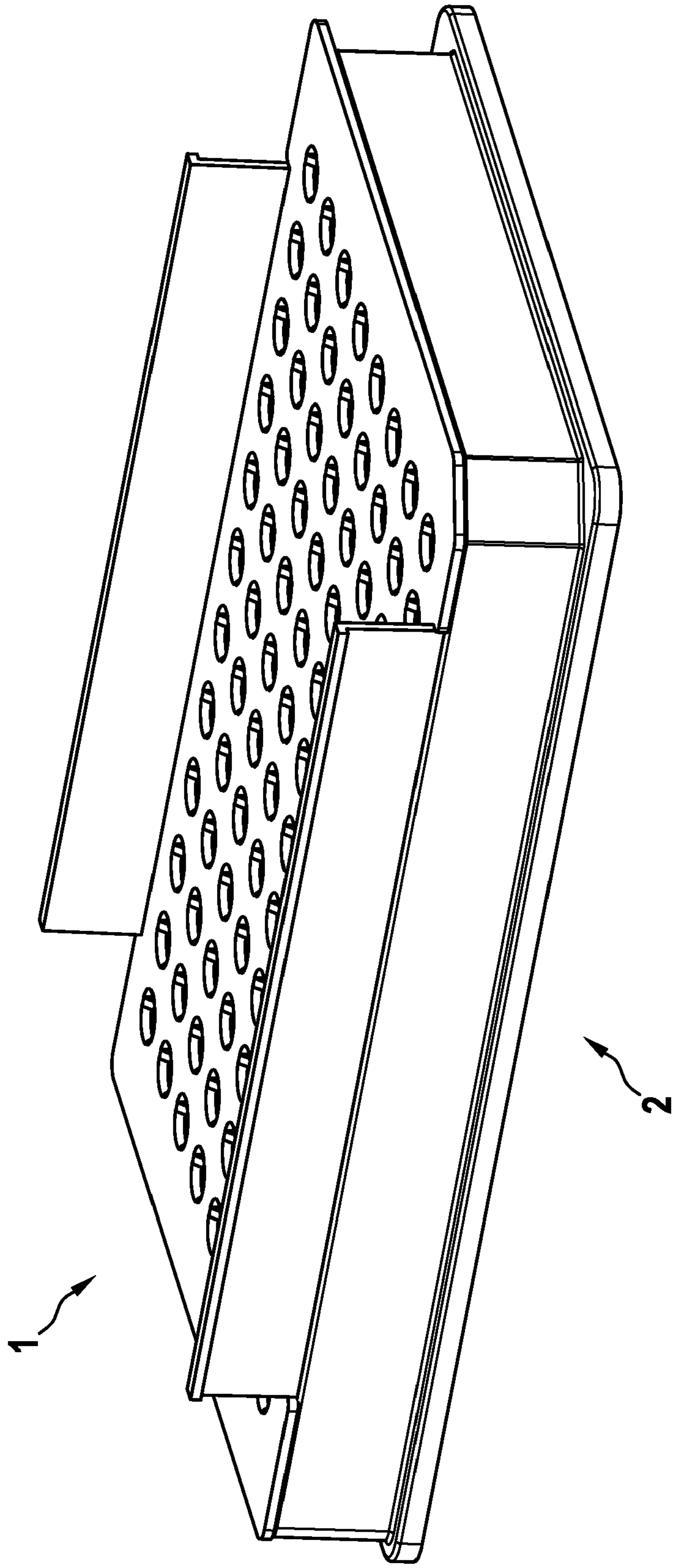


Fig. 3

Fig. 4A

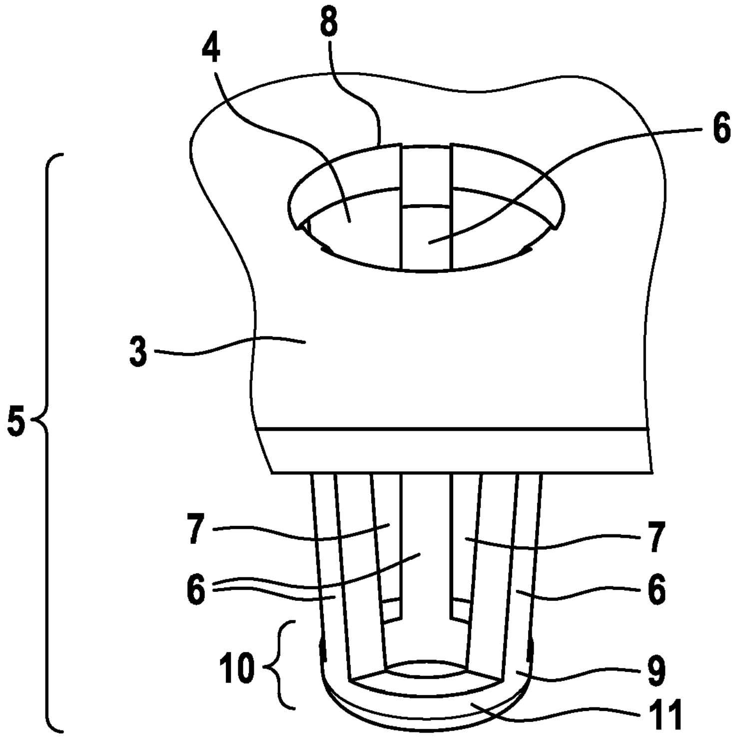


Fig. 4B

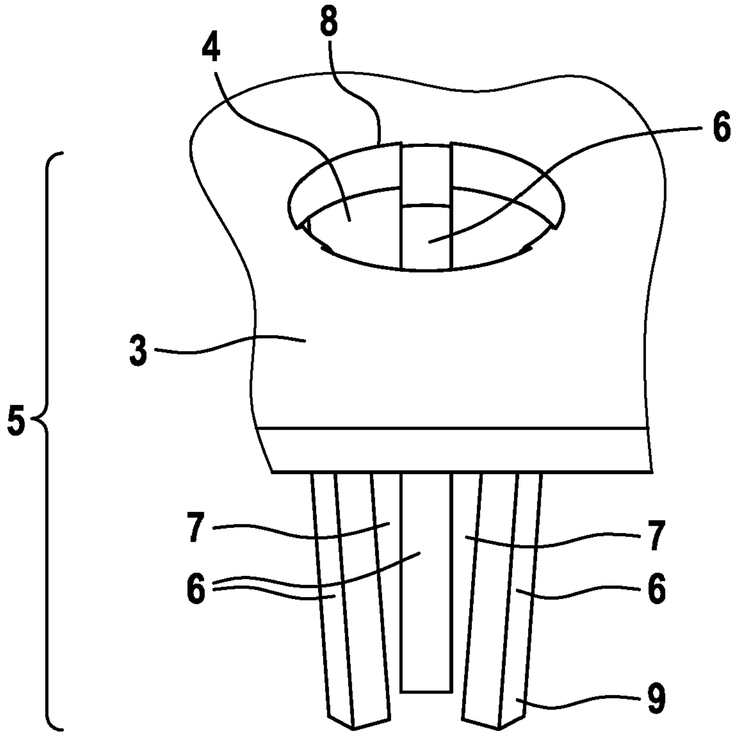


Fig. 5

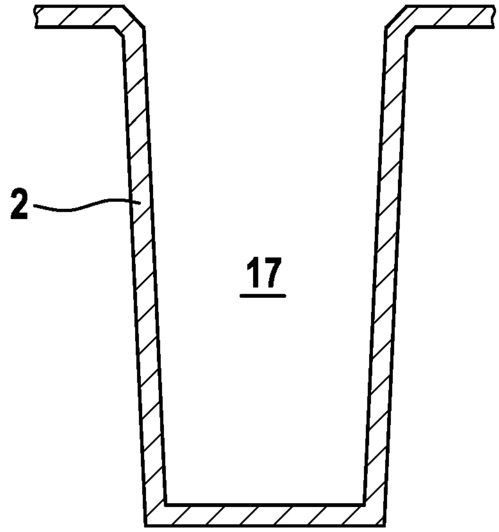


Fig. 6

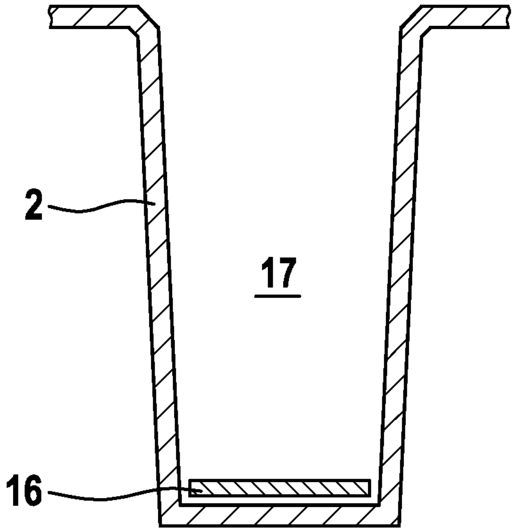


Fig. 7

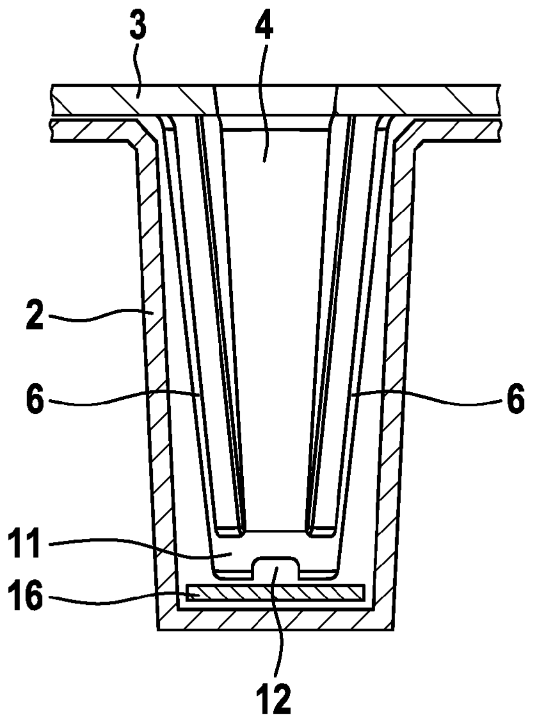


Fig. 8

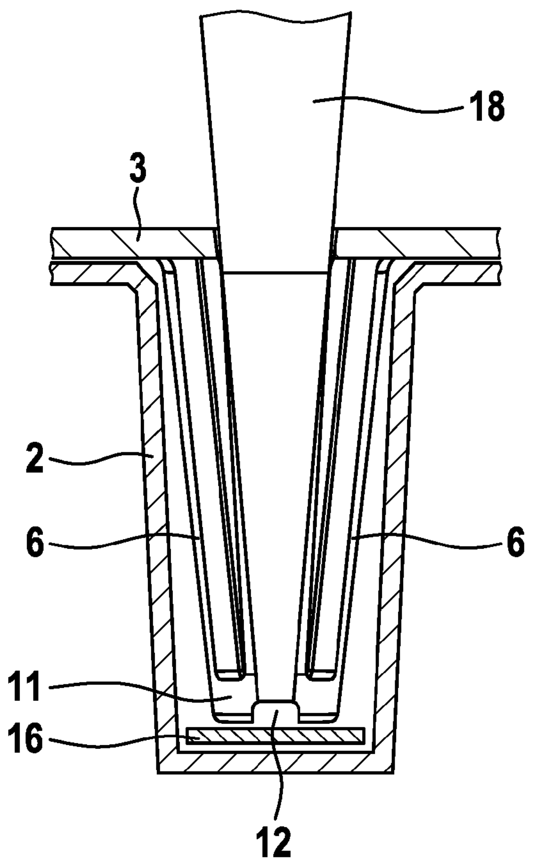


Fig. 9A

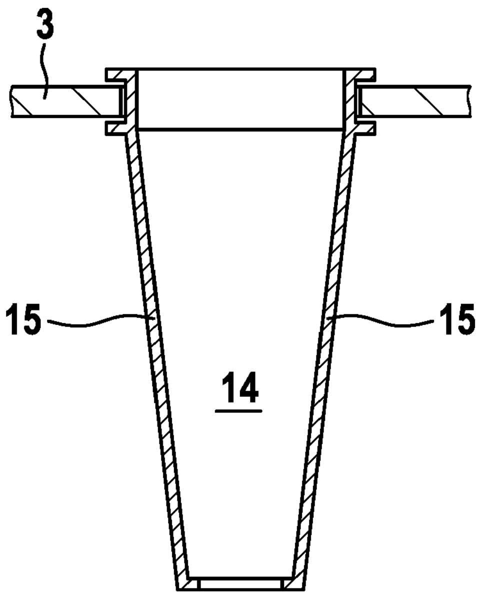


Fig. 9B

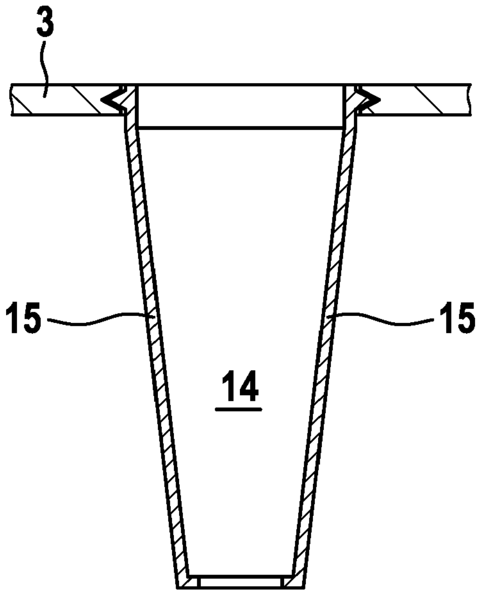


Fig. 10

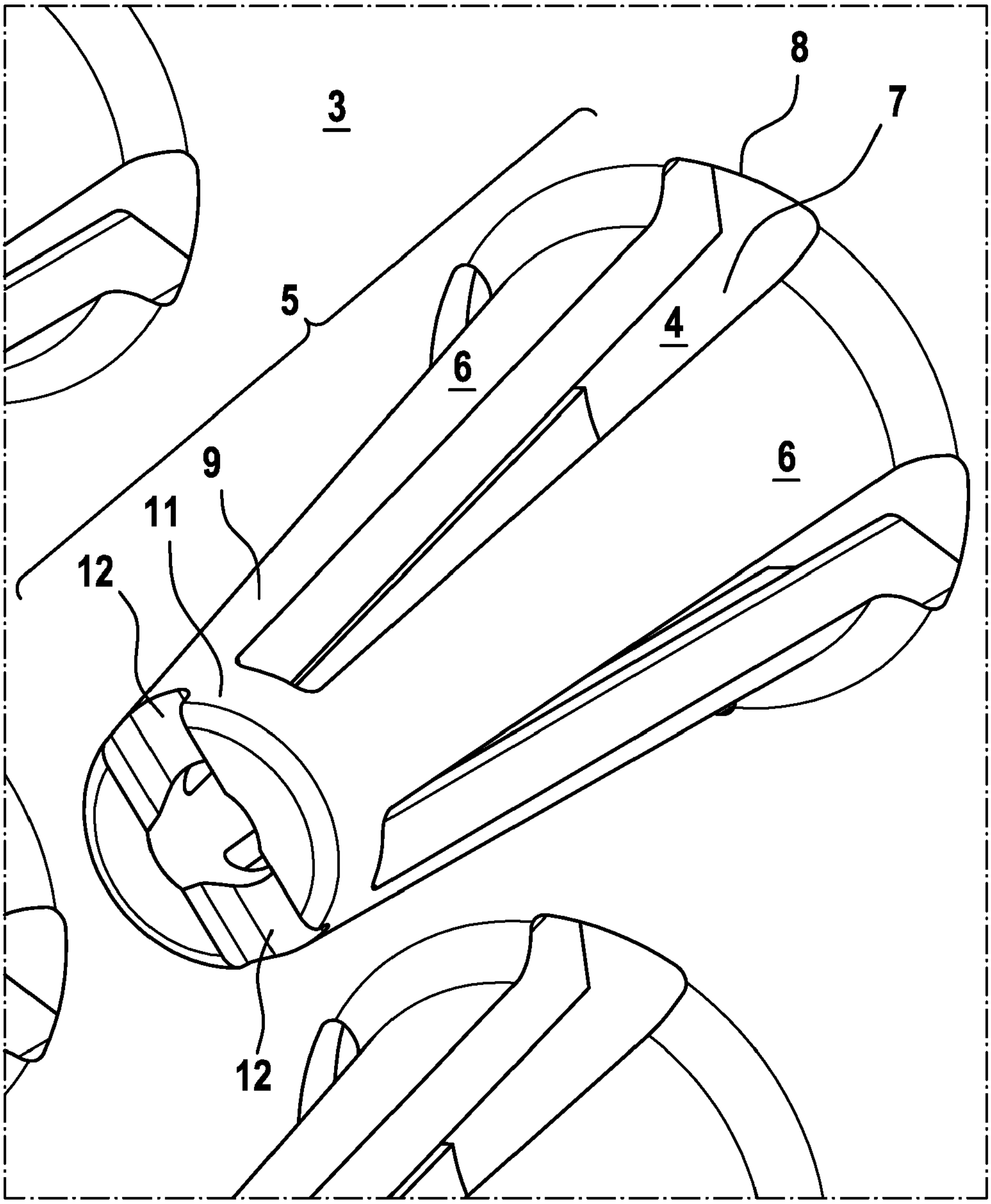
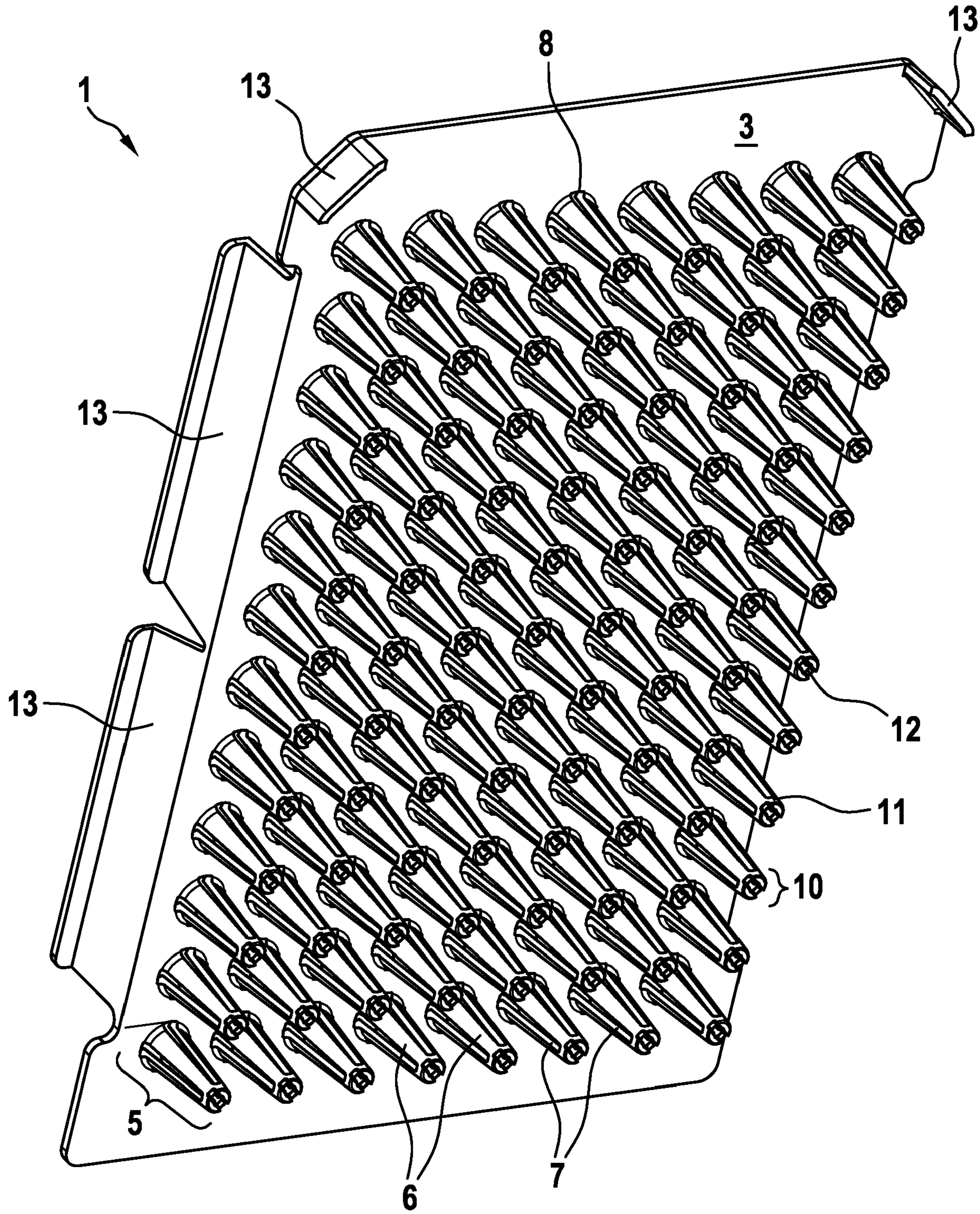


Fig. 11



Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 19 21 5013

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X Y	US 2013/260410 A1 (JOHANSEN ANNETTE HELLE [DK] ET AL) 3 October 2013 (2013-10-03) * paragraphs [0008], [0013], [0030], [0046], [0075] - [0080], [0240], [0252]; figures 5,16,18 *	1-7, 9-11,16 8,12-15, 17	INV. B01L3/00 G01N33/543
X	US 5 474 742 A (TUUMINEN TAMARA [FI]) 12 December 1995 (1995-12-12) * col.1 lines 55-67;paragraph bridging columns 2 and 4.; claims 1-5; figures 5-7 *	1-7,9-11	
X	WO 2014/018751 A1 (UNIV EMORY [US]; GEORGIA TECH RES INST [US]) 30 January 2014 (2014-01-30) * paragraphs [0035], [0038], [0041], [0051], [0052], [0066], [0069], [0080]; figures 1-5 *	1-7,9-11	
Y	WO 2019/089757 A1 (ILLUMINA INC [US]; ILLUMINA CAMBRIDGE LTD [GB]) 9 May 2019 (2019-05-09) * page 8, line 28 - page 9, line 20 * * page 20, line 28 - page 21, line 5 * * page 22, lines 25-28 * * page 23, line 1 - line 5; figures 1-7 *	12-15,17	TECHNICAL FIELDS SEARCHED (IPC) B01L G01N
Y	US 2017/225162 A1 (LIU DAVID M [US] ET AL) 10 August 2017 (2017-08-10) * paragraph [0042]; figure 13 *	8	
A	US 2010/190197 A1 (MARTIN GREGORY R [US] ET AL) 29 July 2010 (2010-07-29) * paragraph [0036]; figures 1A,2A-2E *	1-11	

The present search report has been drawn up for all claims

1

Place of search	Date of completion of the search	Examiner
The Hague	26 May 2020	Goodman, Marco

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 19 21 5013

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

26-05-2020

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2013260410 A1	03-10-2013	CA 2819084 A1	14-06-2012
		CN 103282481 A	04-09-2013
		EP 2649174 A1	16-10-2013
		US 2013260410 A1	03-10-2013
		WO 2012076636 A1	14-06-2012
US 5474742 A	12-12-1995	EP 0574243 A2	15-12-1993
		JP H08189927 A	23-07-1996
		US 5474742 A	12-12-1995
WO 2014018751 A1	30-01-2014	NONE	
WO 2019089757 A1	09-05-2019	CN 111094533 A	01-05-2020
		US 2020122147 A1	23-04-2020
		WO 2019089757 A1	09-05-2019
US 2017225162 A1	10-08-2017	DE 212008000018 U1	12-02-2009
		EP 2170514 A1	07-04-2010
		US 2009004064 A1	01-01-2009
		US 2011300037 A1	08-12-2011
		US 2017225162 A1	10-08-2017
		WO 2009005641 A1	08-01-2009
US 2010190197 A1	29-07-2010	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- DE 202006017853 U1 **[0008]**
- US 20040091397 A1 **[0008]**
- WO 2011127945 A1 **[0008]**
- US 8163537 B2 **[0008]**
- US 6943009 B2 **[0008]**
- US 20070237683 A1 **[0009]**

Non-patent literature cited in the description

- **STANISLAV VITHA ; DAVID W. YODER.** *High Throughput Processing of DNA Samples on FTA® Paper for PCR Analysis,* 2005, http://www.tamu.edu/mic **[0006]**
- **A. TEREBA ; J. KRUEGER ; R. OLSON ; P. MANDREKAR ; B. MCLAREN.** High-Throughput Processing of Samples on Solid Supports Using the Slicprep™ 96 Device. Promega Corporation, September 2005 **[0007]**