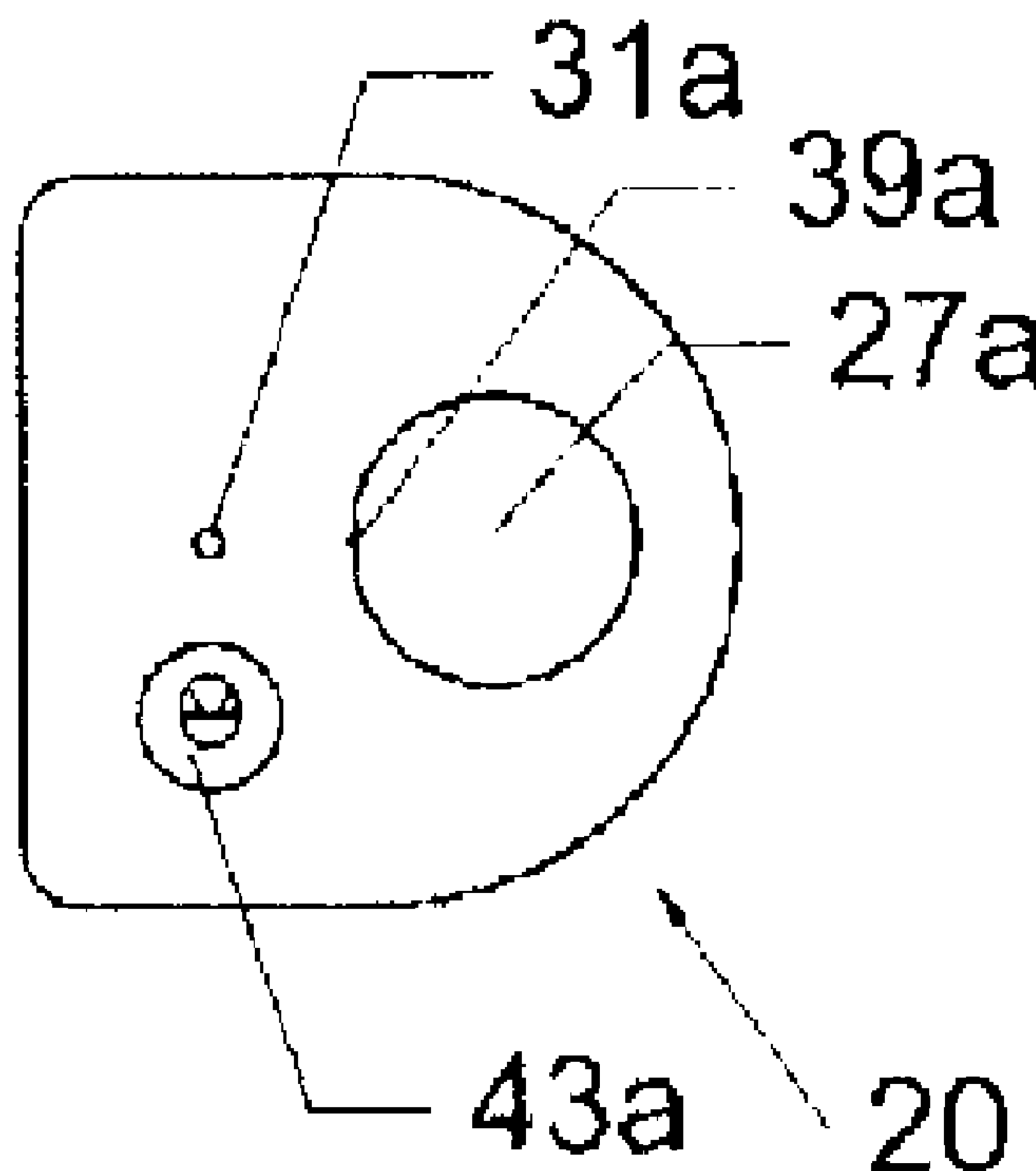




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(54) Title: AUTOMATED ULTRA-FILTRATION SYSTEM



(57) **Abrégé/Abstract:**

Many therapeutic drugs and hormones are highly protein bound, and a plasma or serum ultra-filtrate is sometimes required to measure the unbound biologically active drugs and hormones. The present invention provides an automated ultra-filtration system for automatically preparing plasma or serum ultra-filtrates, without the need for centrifugation or equilibrium dialysis. The regular assays that measure total drugs and hormones in plasma or serum will provide a measurement of the free drugs and hormones, when the plasma or serum ultra-filtrates are used. The present invention provides a system comprising a controller, an automated workstation incorporating disposable ultra-filtration apparatuses to prepare the plasma or serum ultra-filtrates, an analyzer calibrated to measure the total drugs and hormones, and a track for transporting the plasma or serum ultra-filtrates from the automated workstation to the analyzer.



ABSTRACT OF THE DISCLOSURE

Many therapeutic drugs and hormones are highly protein bound, and a plasma or serum ultra-filtrate is sometimes required to measure the unbound biologically active drugs and hormones. The present invention provides an automated ultra-filtration system for automatically preparing plasma or serum ultra-filtrates, without the need for centrifugation or equilibrium dialysis. The regular assays that measure total drugs and hormones in plasma or serum will provide a measurement of the free drugs and hormones, when the plasma or serum ultra-filtrates are used. The present invention provides a system comprising a controller, an automated workstation incorporating disposable ultra-filtration apparatuses to prepare the plasma or serum ultra-filtrates, an analyzer calibrated to measure the total drugs and hormones, and a track for transporting the plasma or serum ultra-filtrates from the automated workstation to the analyzer.

Title: Automated Ultra-filtration System**5 Related Applications**

[0001] This application is a PCT Patent Application, claiming the benefit of U.S. Provisional Patent Application No. 61/735,041, filed 9th December, 2012 entitled, "Disposable Ultra-filtration System".

Field Of The Invention

10 [0002] The invention relates to an automated ultra-filtration system for measuring at least one of a free therapeutic drug concentration and a free hormone concentration in a sample, the samples being either serum or plasma.

Background Of The Invention

15 [0003] Many medical diagnostic tests are performed in a medical laboratory, on serum and plasma. Serum is the yellow liquid obtained from whole blood after the blood is allowed to clot, and the clot is removed by centrifugation; plasma is the yellow liquid obtained from blood by centrifugation of blood mixed with an anticoagulant, e.g. heparin. Whole
20 blood comprises the formed elements (i.e., the cellular components and the cell-derived components), and plasma. Red blood cells are the most abundant formed elements in blood, and platelets are examples of cell-derived components.

 [0004] Measurement of the concentration of therapeutic drugs and
25 certain hormones are essential in patient management, and usually, the total concentration of the drugs and hormones are measured because with the exception of a few hormones, e.g. thyroid hormones, the tests or assays are designed to measure the total concentrations. Designing an assay to measure the concentration of the free drugs/hormones are more complex.
30 Only the free therapeutic drugs, ions and free hormones are available to cross vascular walls and biological membranes in order to produce biological activity, by attaching to specific and non-specific binding sites or receptors.

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Some examples of a therapeutic drug, an ion and a hormone are phenytoin, calcium and cortisol respectively.

[0005] Phenytoin, for example, is a therapeutic drug used to treat epilepsy. In the blood, about 90% of the phenytoin is bound to plasma
5 proteins. Only the portion of phenytoin that is unbound or "free" is pharmacologically or biologically active. A test for total phenytoin represents the sum of the bound and unbound phenytoin. Under normal conditions, the balance between bound and unbound phenytoin in the blood is relatively stable, so measuring the total phenytoin is appropriate for monitoring
10 therapeutic levels of phenytoin. However, in certain conditions and disease states, that balance can be upset, causing the percentage of free or active phenytoin to increase. Consequently, a patient may experience symptoms of phenytoin toxicity even though the total phenytoin concentration falls within a therapeutic range. In such cases, doctors may order serum or plasma free
15 phenytoin in order to more reliably monitor the patient's phenytoin levels, instead of serum or plasma total phenytoin.

[0006] One method used to measure free phenytoin in a patient's serum or plasma sample involves: 1) adding the patient's sample to the sample reservoir of an ultra-filtration device; 2) capping the sample reservoir;
20 3) placing the ultra-filtration device in a centrifuge and centrifuging for about 25 minutes; and 4) measuring total phenytoin in the ultra-filtrate of the serum or plasma.

[0007] By way of examples only, some embodiments of a filtration apparatus that can be used to extract plasma from whole blood can be found
25 in US Patents 7,816,124 and 7,807,450 awarded to the inventor. Subsequently, the inventor filed US Patent Application 13/549,443 entitled "Sample Filtration Apparatus", which describe other embodiments of filtration assemblies.

[0008] In the case of a serum or plasma sample, the filtrate (or more
30 appropriately, referred to as an ultra-filtrate since plasma is already considered to be a filtrate of whole blood) usually refers to the serum or

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plasma containing the smaller molecular weight substances like the free phenytoin, and the retentate usually refers to serum or plasma containing the higher molecular weight substances like the proteins that bind phenytoin. An example of such a protein is albumin, having a molecular weight of about 66
5 kilodaltons. In contrast, the molecular weight of phenytoin is about 0.25 kilodaltons. A person of ordinary skill in the art will appreciate that an ultra-filtrate is still a filtrate, and the term ultra-filtrate is used for clarity when the filtrate contains substances having low molecular weights relative to the molecular weight of large dissolved substances, for example large proteins
10 like immunoglobulins. Also, it seems appropriate to call the fraction of plasma having the smaller molecular weight substances a plasma ultra-filtrate, since the starting sample is plasma, which is already considered to be a filtrate of blood.

[0009] US Patent Application 13/549,443 filed by the inventor describes
15 cartridges for extracting plasma and serum ultra-filtrate, but the devices can only be operated manually. Moreover, some embodiments of these devices require at least one manually operable compression chamber. Moreover, in operation the sample ultra-filtration chamber is not vented to the atmosphere. There is a need for an ultra-filtration cartridge that can be used in an
20 automated laboratory system, where centrifugation is not required and manual handling of samples are minimal.

[0010] Laboratory automation is a strategy to develop, optimize and capitalize on technologies in the laboratory that enable new and improved processes for reducing laboratory process times. The most widely known
25 application of laboratory automation technology is laboratory robotics. More generally, the field of laboratory automation comprises many different automated laboratory analyzers, devices, software algorithms, and methodologies used to enable, expedite and increase the efficiency and effectiveness of providing test results.

30 **[0011]** The automated process of providing plasma and serum ultra-filtrates, for example, can be incorporated in laboratory automation, and the

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plasma and serum ultra-filtrates used to measure therapeutic drugs, ions and hormones, for example.

Summary Of The Invention

[0012] The present invention provides a disposable ultra-filtration
5 apparatus for automatic preparation of an ultra-filtrate from a sample, the
apparatus comprising a disposable ultra-filtration cartridge and a disposable
pipetting tip. The disposable ultra-filtration cartridge includes: a) a top end
having at least one opening providing an ultra-filtrate chamber vent and an
ultra-filtrate chamber opening; b) a bottom end for supporting the disposable
10 ultra-filtration cartridge in an upright position in cooperation with a cartridge
rack; c) a filtration chamber comprising (i) a membrane having a retentate
side, a filtrate side, and pores of a predetermined size, (ii) a sample inlet for
sealably engaging the disposable pipetting tip containing the sample, (iii) a
retentate outlet, (iv) an ultra-filtrate chamber defined substantially by the
15 filtrate side of the membrane, an ultra-filtrate chamber opening for the ultra-
filtrate to flow out of the ultra-filtrate chamber and the space therebetween,
and (v) an ultra-filtrate chamber vent for air to flow into the ultra-filtrate
chamber and the space therebetween when the ultra-filtrate flows out of the
ultra-filtrate chamber and the space therebetween; d) a dead-end channel
20 having an open end and a sealed end, wherein the open end is coincident
with the retentate outlet; e) an ultra-filtrate reservoir at the bottom end for
collecting the ultra-filtrate. The disposable pipetting tip includes a piston
movable in a first direction by applying a force to pressurize trapped air in the
dead-end channel. When the force is relaxed the piston is movable in a
25 second direction by the pressurized trapped air in the dead-end channel to
accommodate reverse flow of retentate to unplug the pores, the second
direction being opposite to the first direction.

[0013] The present invention also provides an automated workstation
for preparing ultra-filtrate in one or more disposable ultra-filtration apparatus,
30 the automated workstation operating in cooperation with a controller and
comprising: a) a base; b) one or more cartridge racks for holding one or more

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disposable ultra-filtration cartridges of the one or more disposable ultra-filtration apparatus, and cartridge rack positions on the base for positioning the one or more cartridge racks in predetermined locations; c) cartridge rack detectors for detecting the presence of a cartridge rack of the one or more
5 cartridge racks on the base at the predetermined locations, the cartridge rack detectors having an output element for signaling the presence of the cartridge rack to the controller; d) one or more sample tube racks for holding one or more sample tubes, and sample tube rack positions on the base for positioning the one or more sample tube racks in predetermined locations; e)
10 sample tube rack detectors for detecting the presence of a sample tube rack of the one or more sample tube racks on the base at the predetermined locations, the sample tube rack detectors having an output element for signaling the presence of the sample tube rack to the controller; f) one or more pipetting tip racks for holding one or more disposable pipetting tips of
15 the one or more disposable ultra-filtration apparatus, and pipetting tip rack positions on the base for positioning the one or more pipetting tip racks in predetermined locations; g) pipetting tip rack detectors for detecting the presence of a pipetting tip rack of the one or more pipetting tip racks on the base at the predetermined locations, the pipetting tip rack detectors having an
20 output element for signaling the presence of the pipetting tip rack to the controller; h) a pipetting tool for releasably engaging the one or more disposable pipetting tips; i) a movable arm, supported from the base, the movable arm supporting the pipetting tool; and j) a waste container for receiving the one or more disposable pipetting tips released by the pipetting
25 tool. The pipetting tool is configured to apply a force to move a piston of the one or more disposable pipetting tips in a first direction.

[0014] The present invention also provides a system for measuring at least one of a free therapeutic drug concentration and a free hormone concentration in one or more samples, the samples being either serum or
30 plasma, the system comprising: a) an analyzer calibrated to measure at least one of a total therapeutic drug concentration and a total hormone concentration; b) a controller comprising memory storage and a data input

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element for inputting processing instructions for the one or more samples, the processing instructions being stored in the memory storage; c) an automated workstation operating in cooperation with the controller, the automated workstation being capable of preparing one or more ultra-filtrates in one or more disposable ultra-filtration cartridges of one or more disposable ultra-filtration apparatus, the automated workstation having a transport system for accepting the one or more samples and releasing the one or more ultra-filtrates in ultra-filtrate reservoirs of the one or more disposable ultra-filtration cartridges, the automated workstation also having a pipetting tool for releasably engaging one or more disposable pipetting tips of the one or more disposable ultra-filtration apparatuses; and d) a track for transporting the one or more ultra-filtrates from the automated workstation to the analyzer. The analyzer is used to measure the at least one of a free therapeutic drug concentration and a free hormone concentration in the one or more ultra-filtrates the one or more disposable ultra-filtration cartridges of the one or more disposable ultra-filtration apparatuses prepared by the automated workstation. The pipetting tool is configured to apply a force to move a piston of the one or more disposable pipetting tips of the one or more disposable ultra-filtration apparatuses in a first direction.

20 **[0015]** Some embodiments of the system further comprise an indicia reader for tracking the one or more sample tubes and the one or more disposable ultra-filtration cartridges. The indicia comprises one of a one-dimensional barcode, a two-dimensional barcode, and a radio frequency identification tag attached to the one or more sample tubes and the one or more disposable ultra-filtration cartridges.

[0016] Other aspects and features of the present invention will become apparent, to those ordinarily skilled in the art, upon review of the following description of the specific embodiments of the invention.

Brief Description Of The Drawings

[0017] For a better understanding of the present invention, and to show more clearly how it may be carried into effect, reference will now be made, by way of example, to the accompanying drawings, which illustrate aspects of
5 embodiments of the present invention and in which:

[0018] Figure 1A is a schematic drawing showing details of a top view of an ultra-filtration cartridge 20 used for preparing an ultra-filtrate according to a first embodiment of the ultra-filtration cartridge;

[0019] Figure 1B is a right side view of the cartridge 20 shown in Figure
10 1A;

[0020] Figure 1C is a first cross-sectional view through the cartridge 20 shown in Figure 1B along line C-C;

[0021] Figure 1D is a front view of the cartridge 20 shown in Figure 1A;

[0022] Figure 1E is a second cross-sectional view through the cartridge
15 20 shown in Figure 1D along line E-E;

[0023] Figure 1F is a third cross-sectional view through the cartridge 20 shown in Figure 1D along line F-F;

[0024] Figure 1G is a perspective view of the apparatus 20 shown in Figure 1A;

20 [0025] Figure 2A is schematic drawing showing details of a top view of a hollow fiber filtration membrane assembly 60a shown in Figures 1C and 1F;

[0026] Figure 2B is a right side view of the hollow fiber filtration membrane assembly 60a shown in Figures 1C and 1F;

[0027] Figure 2C is a front view of hollow fiber filtration membrane
25 assembly 60a shown in Figure 2A;

[0028] Figure 2D is a perspective view of the hollow fiber filtration membrane assembly 60a shown in Figure 2A

[0029] Figure 2E is a cross-sectional view through the hollow fiber filtration membrane assembly 60a shown in Figure 2C along line E-E;

[0030] Figure 2F is a detailed view of detail F shown in Figure 2E showing a schematic representation of the membrane 67a;

5 **[0031]** Figure 3A is a schematic drawing showing details of a top view of an assembly comprising an ultra-filtration cartridge 40 according to a second embodiment of the ultra-filtration cartridge, sealably engaged with a pipetting tip 70, used for preparing an ultra-filtrate;

10 **[0032]** Figure 3B is a front view of the assembly comprising the cartridge 40 and the pipetting tip 70 shown in Figure 3A;

[0033] Figure 3C is a first cross-sectional view through the assembly comprising the cartridge 40 and the pipetting tip 70 shown in Figure 3B along line C-C;

15 **[0034]** Figure 3D is a second cross-sectional view through the assembly comprising the cartridge 40 and the pipetting tip 70 shown in Figure 3B along line D-D;

[0035] Figure 3E is a perspective view of the pipetting piston 87 shown in cross-section in Figure 3D;

[0036] Figure 3F is a perspective view of the pipetting tip 70 alone;

20 **[0037]** Figure 3G is a perspective view of the upper portion 30 of the cartridge 40 shown Figure 3A, Figure 3B and Figure 3D;

[0038] Figure 3H is a perspective view of the lower portion 10 of the cartridge 40 shown Figure 3A, Figure 3B and Figure 3D;

25 **[0039]** Figure 4A is a schematic drawing showing details of a top view of the ultra-filtration cartridge 40 used for preparing an ultra-filtrate according to the second embodiment of the ultra-filtration cartridge, comprising the upper section 30 shown in two parts 30' and 30'', and the lower section 10, with section 30'' at the top;

[0040] Figure 4B is a front view of the cartridge 40 shown in Figure 4A;

- [0041] Figure 4C is a top view of cartridge 40 shown in Figure 4A, with parts 30" and lower section 10 hidden;
- [0042] Figure 4D is a front view of the cartridge 40 shown in Figure 4C;
- [0043] Figure 4E is a top view of cartridge 40 shown in Figure 4A, with
5 parts 30", lower section 10 and filtration membrane assembly 60b hidden;
- [0044] Figure 4F is a front view of the cartridge 40 shown in Figure 4E;
- [0045] Figure 4G is a schematic drawing showing details of a top view of an ultra-filtration cartridge 40 used for preparing an ultra-filtrate according to a second embodiment of the ultra-filtration cartridge, comprising the upper
10 section 30 shown in two parts 30' and 30", and the lower section 10, with section 30' at the top;
- [0046] Figure 4H is a front view of the cartridge 40 shown in Figure 4G;
- [0047] Figure 4J is a top view of cartridge 40 shown in Figure 4G, with parts 30' and lower section 10 hidden;
- 15 [0048] Figure 4K is a front view of the cartridge 40 shown in Figure 4J;
- [0049] Figure 4L is a top view of cartridge 40 shown in Figure 4G, with parts 30', lower section 10 and filtration membrane assembly 60b hidden;
- [0050] Figure 4M is a front view of the cartridge 40 shown in Figure 4L;
- [0051] Figure 5A is a schematic drawing showing details of a front view
20 of the filtration membrane assembly 60b shown in Figure 4D and Figure 4K;
- [0052] Figure 5B is a top view of the filtration membrane assembly 60b shown in Figure 5A;
- [0053] Figure 5C is a bottom view of the filtration membrane assembly 60b shown in Figure 5A;
- 25 [0054] Figure 5D is a first perspective view of the filtration membrane assembly 60b shown in Figure 5A;
- [0055] Figure 5E is a second perspective view of the filtration membrane assembly 60b shown in Figure 5A;

- [0056] Figure 5F is a third perspective view of the filtration membrane assembly 60b shown in Figure 5A;
- [0057] Figure 5G is a fourth perspective view of the filtration membrane assembly 60b shown in Figure 5A;
- 5 [0058] Figure 5H is a cross-sectional view of the filtration membrane assembly 60b shown in Figure 5A along line H-H;
- [0059] Figure 5J is a detailed view of detail J shown in Figure 5H showing a schematic representation of the membrane 67b;
- [0060] Figure 6A is a schematic drawing showing details of a top view
10 of an assembly comprising an ultra-filtration cartridge 50 according to a third embodiment of the ultra-filtration cartridge, engaged with a pipetting tip 70, used for preparing an ultra-filtrate;
- [0061] Figure 6B is a right side view of the assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6A;
- 15 [0062] Figure 6C is a first cross-sectional view through the assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6B along line C-C;
- [0063] Figure 6D is a perspective view of the cartridge 50 shown Figure 6B and Figure 6F;
- 20 [0064] Figure 6E is a perspective view of the pipetting tip 70 shown Figure 6B and Figure 6F;
- [0065] Figure 6F is a front view of the assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6A;
- [0066] Figure 6G is a second cross-sectional view through the
25 assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6F along line G-G;
- [0067] Figure 6H is a third cross-sectional view through the assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6F along line H-H;

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[0068] Figure 6J is an enlarged of the cross-sectional view shown in Figure 6H;

[0069] Figure 7A is a schematic drawing showing details of a top view of an ultra-filtration cartridge 50 used for preparing an ultra-filtrate according to a third embodiment of the ultra-filtration cartridge, shown in three parts 50', 50" and 50"', with the part 50''' at the bottom;

[0070] Figure 7B is a front view of the cartridge 50 shown in Figure 7A;

[0071] Figure 7C is a top view of cartridge 50 shown in Figure 7A, with front part 50''' hidden;

10 [0072] Figure 7D is a front view of the cartridge 50 shown in Figure 7C;

[0073] Figure 7E is a top view of cartridge 50 shown in Figure 7A, with the front part 50''' and the middle part 50'' hidden;

[0074] Figure 7F is a front view of the cartridge 50 shown in Figure 7E;

[0075] Figure 7G is a top view of the cartridge 50 shown in Figure 7A, with the front part 50''', the middle part 50'' and the and filtration membrane assembly 60c hidden;

[0076] Figure 7H is a front view of the cartridge 50 shown in Figure 7G;

[0077] Figure 7J is a schematic drawing showing details of a top view of an ultra-filtration cartridge 50 used for preparing an ultra-filtrate according to a third embodiment of the ultra-filtration cartridge, shown in three parts 50', 50" and 50''', with the part 50' at the bottom;

[0078] Figure 7K is a front view of the cartridge 50 shown in Figure 7J;

[0079] Figure 7L is a top view of cartridge 50 shown in Figure 7J, with back part 50' hidden;

25 [0080] Figure 7M is a front view of the cartridge 50 shown in Figure 7L;

[0081] Figure 7N is a top view of cartridge 50 shown in Figure 7J, with the back part 50' and the filtration membrane assembly 60c hidden;

[0082] Figure 7P is a front view of the cartridge 50 shown in Figure 7N;

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[0083] Figure 7R is a top view of the cartridge 50 shown in Figure 7A, with the back part 50', the filtration membrane assembly 60c and the middle part 50'' hidden;

[0084] Figure 7S is a front view of the cartridge 50 shown in Figure 7R;

5 **[0085]** Figure 7T is a cross-sectional view through the cartridge 50 shown in Figure 7K along line T-T;

[0086] Figure 8A is a schematic drawing showing details of a front view of the filtration membrane assembly 60c shown in Figure 6F and Figure 6M;

10 **[0087]** Figure 8B is a top view of the filtration membrane assembly 60c shown in Figure 8A;

[0088] Figure 8C is a bottom view of the filtration membrane assembly 60c shown in Figure 8A;

[0089] Figure 8D is a first perspective view of the filtration membrane assembly 60c shown in Figure 8A;

15 **[0090]** Figure 8E is a second perspective view of the filtration membrane assembly 60c shown in Figure 8A;

[0091] Figure 8F is a third perspective view of the filtration membrane assembly 60c shown in Figure 8A;

20 **[0092]** Figure 8G is a fourth perspective view of the filtration membrane assembly 60c shown in Figure 8A;

[0093] Figure 8H is a cross-sectional view of the filtration membrane assembly 60c shown in Figure 8A along line H-H;

[0094] Figure 8J is a detailed view of detail J shown in Figure 8H showing a schematic representation of the membrane 67c;

25 **[0095]** Figure 9A is a schematic drawing showing details of a top view of another embodiment 60d of a filtration membrane assembly;

[0096] Figure 9B is a back view of the filtration membrane assembly 60d shown in Figure 9A;

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- [0097] Figure 9C is a front view of the filtration membrane assembly 60d shown in Figure 9A;
- [0098] Figure 9D is a right side view of the filtration membrane assembly 60d shown in Figure 9A;
- 5 [0099] Figure 9E is a first perspective view of the filtration membrane assembly 60d shown in Figure 9A;
- [00100] Figure 9F is a second perspective view of the filtration membrane assembly 60d shown in Figure 9A;
- [00101] Figure 9G is a third perspective view of the filtration membrane
10 assembly 60d shown in Figure 9A;
- [00102] Figure 9H is a fourth perspective view of the filtration membrane assembly 60d shown in Figure 9A;
- [00103] Figure 9J is a cross-sectional view of the filtration membrane assembly 60d shown in Figure 9C along line J-J;
- 15 [00104] Figure 9K is a detailed view of detail K shown in Figure 9J showing a schematic representation of the membrane 67d;
- [00105] Figure 10A is a schematic drawing showing details of a top view of another embodiment 60e of a filtration membrane assembly;
- [00106] Figure 10B is a back view of the filtration membrane assembly
20 60e shown in Figure 9A;
- [00107] Figure 10C is a front view of the filtration membrane assembly 60e shown in Figure 10A;
- [00108] Figure 10D is a right side view of the filtration membrane assembly 60e shown in Figure 10A;
- 25 [00109] Figure 10E is a first perspective view of the filtration membrane assembly 60e shown in Figure 10A;
- [00110] Figure 10F is a second perspective view of the filtration membrane assembly 60e shown in Figure 10A;

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[00111] Figure 10G is a third perspective view of the filtration membrane assembly 60e shown in Figure 10A;

[00112] Figure 10H is a fourth perspective view of the filtration membrane assembly 60e shown in Figure 10A;

5 **[00113]** Figure 10J is a first cross-sectional view of the filtration membrane assembly 60e shown in Figure 10B along line J-J;

[00114] Figure 10K is a second cross-sectional view of the filtration membrane assembly 60e shown in Figure 10C along line K-K;

10 **[00115]** Figure 11A is a schematic drawing showing details of a top view of a workstation 100 for automatically preparing sample ultra-filtrate from a sample;

[00116] Figure 11B is a top view of the workstation 100 shown in Figure 11A;

15 **[00117]** Figure 11C is a detailed view of detail C shown in Figure 11B showing details of ultra-filtration cartridges in an ultra-filtration cartridge rack, and ultra-filtration cartridge reservoir containing sample ultra-filtrate, in an analyzer sector for presenting sample ultra-filtrate to the analyzer;

[00118] Figure 11D is a first perspective view of the workstation 100 shown in Figure 11A;

20 **[00119]** Figure 11E is a second perspective view of the workstation 100 shown in Figure 11A;

25 **[00120]** Figure 12A is a schematic drawing showing details of a top view of an ultra-filtration system 800 for automatically preparing serum or plasma ultra-filtrate from a sample and presenting the ultra-filtrate to an analyzer for measuring free therapeutic drugs and hormones in serum or plasma;

[00121] Figure 12B is a top view of the system 800 shown in Figure 12A;

[00122] Figure 12C is perspective view of the system 800 shown in Figure 12A; and

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[00123] Figure 12D is a detailed view of detail D shown in Figure 12C showing details of ultra-filtration cartridges in an ultra-filtration cartridge rack, ultra-filtration cartridge reservoir containing sample ultra-filtrate, in an analyzer sector for presenting sample ultra-filtrate to the analyzer, and ultra-filtration
 5 cartridge reservoir containing sample ultra-filtrate in an analyzer sector, on a transport track used to present the sample ultra-filtrate to the analyzer.

Detailed Description of Preferred Embodiments

[00124] The reference numerals used in describing the preferred
 10 embodiments of the invention are provided in Table 1.

Table 1

Reference Numerals	Description of Structural Features
10	A body of an ultra-filtration cartridge reservoir according to the second embodiment of an ultra-filtration cartridge
20	A first embodiment of an ultra-filtration cartridge
27	An opening for allowing access to ultra-filtrate reservoir
30	A body comprising a filtration chamber of an ultra-filtration cartridge according to the second embodiment of an ultra-filtration cartridge
31	A vent fluidly connected to the filtrate side of the membrane
33	Retentate side of membrane and adjacent space
35	Filtrate side of membrane and adjacent space, the adjacent space being a portion of an ultra-filtrate chamber (An ultra-filtration chamber is not shown as a specific structure, but refers substantially to space defined by the filtrate side of the membrane, the ultra-filtrate chamber outlet 39, and the space therebetween)
37	A channel fluidly connecting filtrate side of membrane and

Reference Numerals	Description of Structural Features
	adjacent space, with ultra-filtrate chamber outlet
39	An ultra-filtrate chamber outlet
40	A second embodiment of an ultra-filtration cartridge
41	A bottom cavity of an ultra-filtrate reservoir of an ultra-filtration cartridge
43	An opening for allowing pipetting tip to access inlet of the filtration chamber
45	A cavity occupied by a pipetting tip when the pipetting tip is engaged with ultra-filtration cartridge
47	A filtration chamber inlet for sealably engaging pipetting tip
48	An extension of the filtration inlet, fluidly connected to the filtration chamber
49	A filtration chamber outlet, coincident with the open end of a dead-end channel 51
50	A third embodiment of an ultra-filtration cartridge
51	A dead-end channel of an ultra-filtration cartridge
53	A sealed end of a dead-end channel 51 of an ultra-filtration cartridge
60	A filtration membrane assembly
61	A first flange in membrane assembly
62	A filtration membrane assembly supporting structure
63	A second flange in membrane assembly
65	A hollow fiber filtration membrane
67	A filtration membrane (Wall of a hollow fiber filter when the filtration membrane is in the form of a hollow fiber filter)
69	A cavity usually occupied by a filtration membrane assembly
70	A pipetting tip
73	A pipetting tip housing
77	A pipetting tip housing recess

Reference Numerals	Description of Structural Features
79	A pipetting tip piston flange
81	A pipetting tip housing gripping end
83	A pipetting tip housing piston flange stop (inclined interior wall of pipetting tip housing)
85	A pipetting tip dispensing end
87	A pipetting tip piston
89	A pipetting tip piston gripping stem
91	A pipetting tip piston flange upper face
93	A pipetting tip piston flange lower face
95	A pipetting tip piston sealing O-ring
100	A workstation for automatically preparing sample ultra-filtrate from the sample
110	Pipetting tool for releasably holding a pipetting tip
112	A pipetting tool carriage for supporting and cooperating with pipetting tool
114	A pipetting tool carriage movable arm for supporting and moving pipetting tool carriage
116	A pipetting tool carriage movable arm carriage
120	A pipetting tip rack
122	A pipetting tip
130	A gripping tool for gripping for example, a sample tube or an ultra-filtration cartridge, to enable transportation thereof
132	A gripping tool carriage for supporting and cooperating with gripping tool
134	A gripping tool carriage movable arm for supporting and moving gripping tool carriage
136	A gripping tool carriage movable arm
138	A track for facilitating movement of pipetting tool carriage movable arm carriage and gripping tool carriage movable arm

Reference Numerals	Description of Structural Features
140	An ultra-filtration cartridge rack
142	An ultra-filtration cartridge (one similar to the third embodiment of an ultra-filtration cartridge 50 is shown)
144	A projected member in the ultra-filtration cartridge rack, for enabling proper orientation of ultra-filtration cartridge when it is located in the ultra-filtration rack for processing a sample
150	A sample tube rack
152	A sample tube
160	A waste container for receiving ejected used pipetting tip
170	A controller
172	A controller data input element and display touch screen
180	An analyzer sector for presenting sample ultra-filtrate to the analyzer
190	An ultra-filtration cartridge reservoir containing sample ultra-filtrate (The third embodiment of an ultra-filtration cartridge is shown as this example, wherein the reservoir is an integral part of the ultra-filtration cartridge.)
200	An automated workstation base
202	An automated workstation supporting frame
	A pipetting tip rack site for housing pipetting tips contained in pipetting tip racks
204	A sample delivery site on the workstation for receiving samples in sample tubes contained in sample tube racks
206	An ultra-filtration cartridge rack site for on the workstation for housing ultra-filtration cartridges contained in ultra-filtration cartridge racks
208	An analyzer sector site on the workstation for housing analyzer sectors

Reference Numerals	Description of Structural Features
300	An analyzer, for example, an immunoanalyzer for performing immunoassays
400	A transport track for transporting a single ultra-filtration cartridge reservoir containing sample ultra-filtrate or a plurality of ultra-filtration cartridge reservoirs containing sample ultra-filtrates in analyzer sectors
500	A workstation table for aligning the workstation with the analyzer on a horizontal plane
800	An ultra-filtration system for measuring free therapeutic drugs and free hormones in serum or plasma

[00125] The same reference numerals are used to represent similar structural features in different embodiments. In some cases, letters are added to the end of the numerals to indicate different embodiments. For example, the indicia 60 is used to represent a filtration membrane assembly, but in the first embodiment (20), second embodiment (40), and third embodiment (50), the indicia 60a, 60b, and 60c are used to refer to the filtration membrane assembly in the respective embodiments.

[00126] The present invention describes several embodiments of disposable ultra-filtration cartridges for automatic preparation of sample ultra-filtrates. The sample used with the present invention is one of serum or plasma. However, the sample can be any biological sample as well as a non-biological sample. The ultra-filtration cartridge can be used in a stand-alone automated workstation operating in cooperation with a controller, or can be used in an automated workstation that is integrated into an automated laboratory, operating in cooperation with a more centralized controller.

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[00127] To the best knowledge of the inventor, there is no known automated workstation or system that includes ultra-filtration cartridges for preparing sample ultra-filtrates automatically, without the use of a centrifuge. Moreover, there is no known automated system for measuring free fractions
5 (i.e., not bound to substantially larger molecules like proteins, for example albumin) of a therapeutic drug or a hormone, using the assays designed to measure total drug or total hormone concentration in plasma or serum.

[00128] Disposable ultra-filtration cartridges are described, followed by an automated workstation, and finally a system that expands beyond the
10 workstation is described. Some embodiments of the ultra-filtration cartridges are described as seamless units and some are described as comprising parts that can be easily manufactured by for example, plastic molding or 3-D printing; the parts are then assembled together using for example, double-sided sticky gasket, application of glue to the faces or ultrasonic welding. By
15 illustrating some of the embodiments of cartridges in parts, ideas are provide regarding manufacturing the cartridges, and the parts provide views of internal structures, without having to view cross-sections.

[00129] An element of the disposable ultra-filtration cartridges is a filtration membrane assembly. Several embodiments of filtration membrane
20 assembly are illustrated, for example filtration membrane assemblies 60a illustrated in Figures 2A-2F, 60b illustrated in Figures 5A-5J, 60c illustrated in Figures 8A-8J, 60d illustrated in Figures 9A-9K, and 60e illustrated in Figures 10A-10K. For a more general description of a membrane, the side of the membrane in contact with retentate is referred to as the retentate side, and
25 the side of the membrane in contact with the filtrate is referred to as the filtrate side. When the sample is plasma, the retentate will initially be plasma, which progressively becomes more concentrated plasma; the filtrate will be a plasma ultra-filtrate. A person of ordinary skill in the art will appreciate that the membrane could take on any shape, provided that the membrane allows
30 sample ultra-filtrate to travel from the retentate side to the filtrate side, and a barrier is maintained between the retentate side and the filtrate side. The

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pore size of the membrane depends on the size of molecules that are required to pass through the filtration membrane.

[00130] Another element of the present invention is a filtration chamber. A person of ordinary skill in the art will appreciate that a filtration chamber
5 does not point to any isolated structure in the embodiments of the invention, but refers to a general structure that comprises a filtration membrane assembly, a sample inlet fluidly connected to the retentate side of the membrane, and a retentate outlet for outflow of the fraction of sample that does not penetrate the membrane, and an outlet for the fraction of sample
10 that penetrates the membrane. The space occupied by the filtration chamber is illustrated as cavity 69a in Figure 1E. Flow across a surface of the membrane effectively reduces sample viscosity, and unplugs the membrane pores.

[00131] Referring collectively to Figures 1A-1G, shown are different
15 views of an ultra-filtration cartridge 20 according to a first embodiment of an ultra-filtration cartridge. Cartridge 20 represents a disposable ultra-filtration cartridge for automatic preparation of sample ultra-filtrate. The cartridge has a top end shown in Figure 1A, and a bottom end for supporting the cartridge in an upright position in cooperation with a cartridge rack. The cartridge can
20 be provided in individual holders or racks for holding more than one cartridge. The bottom end is shown in Figure 1D as the part towards the bottom of the page, and in Figure 1B as the part towards the right side of the page. At the top end is shown an opening 27a for allowing access to an ultra-filtrate reservoir 41a, a vent 31a for enabling the ultra-filtrate to flow into the ultra-
25 filtrate reservoir 41a, and an opening 43 for allowing a pipetting tip to access sample inlet 47a of a filtration chamber. Also shown in Figure 1A is an ultra-filtrate chamber outlet 39a, shown clearly in Figure 1C. A right side view, a top view and a perspective view of ultra-filtration cartridge 20 are shown in Figures 1B, 1D, and 1G respectively. The bottom of the cartridge is intended
30 to fit in a cartridge rack or analyzer sector, so that the opening 27a to the ultra-filtrate reservoir 41a is substantially concentric with the annular shape of

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the bottom of the cartridge, in order for an analyzer sampling probe to have unobstructive access to the ultra-filtrate.

[00132] A cross-sectional view of the cartridge 20 shown in Figure 1B through line C-C is shown as Figure 1C. Shown are a filtration membrane assembly 60a, portion of the an ultra-filtrate chamber shown as 35a, the ultra-filtrate chamber outlet 39a, and a vent 31a fluidly connected to the ultra-filtrate chamber, and a channel 37a fluidly connecting filtrate side of membrane and adjacent space 35a with the ultra-filtrate chamber outlet 39a. The ultra-filtrate chamber is not shown as a specific structure, but refers substantially to space defined by the filtrate side of the membrane, the ultra-filtrate chamber outlet 39a, and the space therebetween. Also shown is a cross-sectional view of a dead-end channel 51a (see Figure 1E).

[00133] Cross-sectional views of the cartridge 20 shown in Figure 1D through lines E-E and F-F are shown as Figures 1E and 1F respectively. A cavity 69a is shown in Figure 1E, which is usually occupied by the membrane assembly 60a, and is therefore a substantial representation the space occupied by the filtration chamber. Details of the filtration membrane assembly 60a are shown collectively in Figures 2A-2F. The filtration membrane assembly 60a comprises hollow fibers 65a, and perforated flanges 61a and 63a. The flanges 61a and 63a provide support for the individual hollow fibers 65a, and the annular surface of the flanges provide seals when the assembly 60a is installed in the cavity 69a. The outside portions of the fibers 65a are also sealed at the flanges, in order to provide fluid-tight separation between ultra-filtrate and retentate. Sealing can be accomplished by, for example, a resin or glue, without obstructing the lumens of the fibers. A cross-section of the membrane 67a, which is the wall of the hollow fiber, is shown as F in Figure 2E, and details of F is shown in Figure 2F, showing the filtrate side 35a, and the retentate side 33a of the membrane 67a. In other embodiments as illustrated in Figure 9K for example, the filtrate side is 33d and the retentate side is 35d.

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[00134] Referring to Figure 1E, shown is a dead-end channel 51a having an open end 49a and a sealed end 53a. The open end 49a of the dead-end channel 51a is coincident with the filtration chamber outlet. Also shown is a cavity 45a occupied by a pipetting tip when the pipetting tip is engaged with ultra-filtration cartridge. Details of a pipetting tip 70 are shown in Figures 3B, 3D, and 3F, in association with a second embodiment 40 of an ultra-filtration cartridge. In operation the sample inlet 47a is sealably engaged with the dispensing end 85 of a disposable pipetting tip 70 containing sample.

[00135] Referring to Figures 3B, 3D, 3E, and 3F, shown are details of the pipetting tip 70. The pipetting tip 70 comprises a pipetting tip housing 73, a pipetting tip housing recess 77, a pipetting tip piston flange 79, a pipetting tip housing gripping end 81, a pipetting tip housing piston flange stop (inclined interior wall of pipetting tip housing) 83, a pipetting tip dispensing end 85, a pipetting tip piston 87, a pipetting tip piston gripping stem 89, a pipetting tip piston flange upper face 91, a pipetting tip piston flange lower face 93, and a pipetting tip piston sealing O-ring 95 at a piston sealing end (or any other means for moving the piston 87 inside the piston tip housing 73 in a fluid-tight manner). This type of positive displacement pipetting system is known, for example, US Pat. No. 4,474,071 teaches a manually operable positive displacement pipette.

[00136] Still referring to Figures 3B, 3D, 3E, and 3F, the pipetting tip 70 operates in cooperation with a pipetting tool 110 shown in a workstation 100 illustrated in Figure 11E. Details are not shown, but the pipetting tool 110 comprises resilient fingers that open radially by movement against the force exerted by a spring, whereby the resilient fingers can grab the pipetting tip piston gripping stem 89 up to and not beyond the pipetting tip piston flange upper face 91. An outer sleeve of the pipetting tool surrounding the resilient fingers frictionally engages the pipetting tip recess 77, enabling the pipetting tool 110 to move the pipetting piston 87 inside the pipetting tip housing 73 in a fluid-tight manner. By pushing the piston flange lower face 93 against the pipetting tip housing piston flange stop (inclined interior wall of pipetting tip

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housing) 83, and both the pipetting tip housing 73 and the pipetting tip piston 87 can be ejected into a waste container, as directed by a controller 170 that works in cooperating with the pipetting tool 110 (see workstation 100 shown in Figures 11D and 11E).

5 **[00137]** Referring to Figure 1E, the pipetting tip 70 containing sample is inserted through the opening 43a into the cavity 45a, and sealably engages the filtration chamber inlet 47a. Force is applied to the piston 87, simultaneously forcing sample into the filtration chamber and compressing the air in the dead-end channel 51. After relaxing the force on the piston 87 to a
10 predetermined level, the compressed air in the dead-end channel 51 reverses the flow of retentate. By repeating this piston force-release cycle, a forward and backward flow of sample across the surface of the membrane 67a is created, and trans-membrane pressure is created as well, causing ultra-filtrate to accumulate on the filtrate side of the membrane 35a. The vent 31a
15 facilitates flow of ultra-filtrate into the bottom cavity of an ultra-filtrate reservoir 41a. The forward and backward flow of retentate across the membrane is a means for continuously washing the retentate side of the membrane and unplugging the membrane pores. The amount of ultra-filtrate that accumulates in the reservoir 41a is proportional to the number of piston force-
20 release cycles.

[00138] Referring collectively to Figures 3A-3H and Figures 4A-4M, shown is a second embodiment of a disposable ultra-filtration cartridge 40 for automatic preparation of sample ultra-filtrate. Cartridge 40 is similar to cartridge 20 and accordingly, elements common to both cartridges share
25 common reference numerals, but the letter "b" appended at the end of reference numerals to indicate a different embodiment; the letter "a" is used for cartridge 20. The pipetting tip 70 was previously described when cartridge 20 was described. A first difference between cartridge 40 and cartridge 20 are that the filtration membrane assembly 60b shown in Figures 4D and 4K
30 are very different, and details of the filtration membrane assembly 60b are shown collectively in Figures 5A-5J. A second difference is that the opening

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43b for allowing pipetting tip 70 to access the inlet 47b of the filtration chamber is substantially concentric with the circular shape of the cartridge along a horizontal plane. The implication is that in operation, the cartridge 40 does not have to be in any particular orientation (with respect to the X-Z and Y-Z planes) in the ultra-filtration cartridge rack 140 shown in Figure 11E and Figure 12D in the workstation 100 shown collectively in Figures 11A-11E, which shows a cartridge 142. Cartridge 142 is very similar to cartridge 20, in that the opening 43a is offset from the central vertical axis, and therefore the cartridges 142 have to be aligned with the programmed positions of the pipetting tool 110. In other words, opening 43a and 27a shown in Figures 1A and 1G are not aligned with each other. In contrast, opening 43b (see Figure 3G) and opening 27b (see Figure 3H) are substantially concentric.

[00139] Still referring collectively to Figures 3A-3H, and Figures 4A-4M, a third difference between cartridge 20 and 40 is that cartridge 40 comprises an upper section 30 frictionally engaged with a lower section 10. The upper section 30 comprises the filtration chamber, and the lower section is the ultra-filtrate reservoir with bottom cavity 41b. After processing a sample, upper section 30 is automatically removed with a gripping tool as for example, a gripping tool 130 shown in the workstation 100 (see Figures 11A & 11D). The remaining ultra-filtrate reservoir 10 containing ultra-filtrate is presented to an analyzer, like for example, analyzer 300 shown in Figures 12A-12C. As mentioned previously, some cartridges are shown in pieces, so that the individual pieces can be manufactured and then assembled. The upper section 30 of cartridge 40 is shown as pieces 30' and 30''. The lengths of the upper section 30 and lower section 10 are sufficient to allow removal of section 30 and allow presentation of an ultra-filtrate in section 10 to an analyzer.

[00140] Referring collectively to Figures 4A-4M, various pieces of the cartridge are hidden sequentially in order to reveal underneath the hidden sections of the cartridge, without having to view cross-sections. Figure 4A shows a schematic drawing showing details of a top view of the ultra-filtration

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cartridge 40 used for preparing an ultra-filtrate according to the second embodiment of the ultra-filtration cartridge, comprising the upper section 30 shown in two parts 30' and 30'', and the lower section 10, with section 30'' at the top. Figure 4B shows a front view of the cartridge 40 shown in Figure 4A. Figure 4C shows a top view of cartridge 40 shown in Figure 4A, with parts 30'' and lower section 10 hidden. Figure 4D shows a front view of the cartridge 40 shown in Figure 4C. Figure 4E shows a top view of cartridge 40 shown in Figure 4A, with parts 30'', lower section 10 and filtration membrane assembly 60b hidden. Figure 4F shows a front view of the cartridge 40 shown in Figure 4E. Figure 4G shows a schematic drawing showing details of a top view of an ultra-filtration cartridge 40 used for preparing an ultra-filtrate according to a second embodiment of the ultra-filtration cartridge, comprising the upper section 30 shown in two parts 30' and 30'', and the lower section 10, with section 30' at the top. Figure 4H shows a front view of the cartridge 40 shown in Figure 4G. Figure 4J shows a top view of cartridge 40 shown in Figure 4G, with parts 30' and lower section 10 hidden. Figure 4K shows a front view of the cartridge 40 shown in Figure 4J. Figure 4L shows a top view of cartridge 40 shown in Figure 4G, with parts 30', lower section 10 and filtration membrane assembly 60b hidden. Figure 4M shows a front view of the cartridge 40 shown in Figure 4L. Details of the filtration membrane assembly 60b are shown collectively in Figures 5B-5J.

[00141] Referring collectively to Figures 5B-5J, the views of the filtration membrane assembly 60b are described. Figure 5A shows a schematic drawing showing details of a front view of the filtration membrane assembly 60b shown in Figure 4D and Figure 4K. Figure 5B shows a top view of the filtration membrane assembly 60b shown in Figure 5A. Figure 5C shows a bottom view of the filtration membrane assembly 60b shown in Figure 5A. Figure 5D shows a first perspective view of the filtration membrane assembly 60b shown in Figure 5A. Figure 5E shows a second perspective view of the filtration membrane assembly 60b shown in Figure 5A. Figure 5F shows a third perspective view of the filtration membrane assembly 60b shown in Figure 5A. Figure 5G shows a fourth perspective view of the filtration

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membrane assembly 60b shown in Figure 5A. Figure 5H shows a cross-sectional view of the filtration membrane assembly 60b shown in Figure 5A along line H-H. Figure 5J shows a detailed view of detail J shown in Figure 5H showing a schematic representation of the membrane 67b.

5 **[00142]** Referring collectively to Figures 6A-3J, and Figures 7A-7T shown is a third embodiment of a disposable ultra-filtration cartridge 50 for automatic preparation of sample ultra-filtrate. Cartridge 50 is similar to cartridge 20 and accordingly, elements common to both cartridges share common reference numerals, but letter "c" appended at the end of reference
10 numerals to indicate a different embodiment; the letter "a" is used for cartridge 20 and the letter "b" is used for cartridge 40. The pipetting tip 70 was previously described when cartridge 20 was described. A first difference between cartridge 50 and cartridge 20 are that the filtration membrane assembly 60c shown in Figures 7F and 7M are very different, and details of
15 the filtration membrane assembly 60c are shown collectively in Figures 8A-8J. The second difference is regarding the dead-end channel 51a shown in Figure 1E, which is depicted as a groove in the body of the cartridge 20. The dead-end channel 51c in cartridge 50 is depicted as a piece of tubing with a closed end 53c and the open end 49c inserted into the filtration chamber
20 outlet 49c. As mentioned previously, the open end and the outlet are coincidental, hence the same indicia 49c. A piece of tubing performs the same function as a groove described previously for cartridge 20, and are both within the scope of the invention.

[00143] The disposable ultra-filtration cartridge 50 is depicted in three
25 major pieces: 50', 50'', and 50'''. Figure 6A shows a schematic drawing showing details of a top view of an assembly comprising an ultra-filtration cartridge 50 according to a third embodiment of the ultra-filtration cartridge, engaged with a pipetting tip 70, used for preparing an ultra-filtrate. Figure 6B shows a right side view of the assembly comprising the cartridge 50 and the
30 pipetting tip 70 shown in Figure 6A. Figure 6C shows a first cross-sectional view through the assembly comprising the cartridge 50 and the pipetting tip 70

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shown in Figure 6B along line C-C. Figure 6D shows a perspective view of the cartridge 50 shown Figure 6B and Figure 6F. Figure 6E shows a perspective view of the pipetting tip 70 shown Figure 6B and Figure 6F. Figure 6F shows a front view of the assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6A. Figure 6G shows a second cross-sectional view through the assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6F along line G-G. Figure 6H shows a third cross-sectional view through the assembly comprising the cartridge 50 and the pipetting tip 70 shown in Figure 6F along line H-H. Figure 6J shows an enlarged of the cross-sectional view shown in Figure 6H.

[00144] Figure 7A shows a schematic drawing showing details of a top view of an ultra-filtration cartridge 50 used for preparing an ultra-filtrate according to a third embodiment of the ultra-filtration cartridge, shown in three parts 50', 50'' and 50''', with the part 50''' at the bottom. Figure 7B shows a front view of the cartridge 50 shown in Figure 7A. Figure 7C shows a top view of cartridge 50 shown in Figure 7A, with front part 50''' hidden. Figure 7D shows a front view of the cartridge 50 shown in Figure 7C. Figure 7E shows a top view of cartridge 50 shown in Figure 7A, with the front part 50''' and the middle part 50'' hidden. Figure 7F shows a front view of the cartridge 50 shown in Figure 7E. Figure 7G shows a top view of the cartridge 50 shown in Figure 7A, with the front part 50''', the middle part 50'' and the filtration membrane assembly 60c hidden. Figure 7H shows a front view of the cartridge 50 shown in Figure 7G. Figure 7J shows a schematic drawing showing details of a top view of an ultra-filtration cartridge 50 used for preparing an ultra-filtrate according to a third embodiment of the ultra-filtration cartridge, shown in three parts 50', 50'' and 50''', with the part 50' at the bottom. Figure 7K shows a front view of the cartridge 50 shown in Figure 7J. Figure 7L is a top view of cartridge 50 shown in Figure 7J, with back part 50' hidden. Figure 7M shows a front view of the cartridge 50 shown in Figure 7L. Figure 7N shows a top view of cartridge 50 shown in Figure 7J, with the back part 50' and the filtration membrane assembly 60c hidden. Figure 7P shows a front view of the cartridge 50 shown in Figure 7N. Figure 7R shows a top

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view of the cartridge 50 shown in Figure 7A, with the back part 50', the filtration membrane assembly 60c and the middle part 50'' hidden. Figure 7S shows a front view of the cartridge 50 shown in Figure 7R. Figure 7T is a cross-sectional view through the cartridge 50 shown in Figure 7K along line T-T.

[00145] Regarding filtration membrane assembly 60c, Figure 8A shows a schematic drawing showing details of a front view of the filtration membrane assembly 60c shown in Figure 6F and Figure 6M. Figure 8B shows a top view of the filtration membrane assembly 60c shown in Figure 8A. Figure 8C shows a bottom view of the filtration membrane assembly 60c shown in Figure 8A. Figure 8D shows a first perspective view of the filtration membrane assembly 60c shown in Figure 8A. Figure 8E shows a second perspective view of the filtration membrane assembly 60c shown in Figure 8A. Figure 8F shows a third perspective view of the filtration membrane assembly 60c shown in Figure 8A. Figure 8G shows a fourth perspective view of the filtration membrane assembly 60c shown in Figure 8A. Figure 8H shows a cross-sectional view of the filtration membrane assembly 60c shown in Figure 8A along line H-H. Figure 8J shows a detailed view of detail J shown in Figure 8H showing a schematic representation of the membrane 67c.

[00146] The filtration membrane assemblies 60a, 60b, and 60c for cartridges 20, 40, and 50 respectively comprise hollow fiber filtration membranes, wherein the outside represents the retentate side and the inside (lumen of the hollow fibers) represents the filtrate side. A person of reasonable skill in the art will appreciate that other membrane configurations can be used, and two other examples of membrane configurations are provided and referenced as 60d and 60e.

[00147] Filtration membrane assembly 60d also comprises hollow fiber filtration membranes, but the inside represents the retentate side and the outside represents the filtrate side. Figure 9A shows a schematic drawing showing details of a top view of another embodiment 60d of a filtration membrane assembly. Figure 9B shows a back view of the filtration membrane

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assembly 60d shown in Figure 9A. Figure 9C shows a front view of the filtration membrane assembly 60d shown in Figure 9A. Figure 9D shows a right side view of the filtration membrane assembly 60d shown in Figure 9A. Figure 9E shows a first perspective view of the filtration membrane assembly 60d shown in Figure 9A. Figure 9F shows a second perspective view of the filtration membrane assembly 60d shown in Figure 9A. Figure 9G shows a third perspective view of the filtration membrane assembly 60d shown in Figure 9A. Figure 9H shows a fourth perspective view of the filtration membrane assembly 60d shown in Figure 9A. Figure 9J shows a cross-sectional view of the filtration membrane assembly 60d shown in Figure 9C along line J-J. Figure 9K shows a detailed view of detail K shown in Figure 9J showing a schematic representation of the membrane 67d.

[00148] Filtration membrane assembly 60e comprises a curved sheet of membrane. Figure 10A shows a schematic drawing showing details of a top view of another embodiment 60e of a filtration membrane assembly. Figure 10B shows a back view of the filtration membrane assembly 60e shown in Figure 9A. Figure 10C shows a front view of the filtration membrane assembly 60e shown in Figure 10A. Figure 10D shows a right side view of the filtration membrane assembly 60e shown in Figure 10A. Figure 10E shows a first perspective view of the filtration membrane assembly 60e shown in Figure 10A. Figure 10F shows a second perspective view of the filtration membrane assembly 60e shown in Figure 10A. Figure 10G shows a third perspective view of the filtration membrane assembly 60e shown in Figure 10A. Figure 10H shows a fourth perspective view of the filtration membrane assembly 60e shown in Figure 10A. Figure 10J shows a first cross-sectional view of the filtration membrane assembly 60e shown in Figure 10B along line J-J. Figure 10K shows a second cross-sectional view of the filtration membrane assembly 60e shown in Figure 10C along line K-K. Other embodiments comprise one or more layers of flat membranes, and fluted membranes.

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[00149] Referring collectively to Figures 11A-11E, shown is an automated workstation 100 for automatically preparing sample ultra-filtrates in disposable ultra-filtration cartridges. Although any disposable ultra-filtration cartridge similar to the ones described previously can be used, and therefore
5 labeled 142, the cartridge 142 is very similar to the third embodiment ultra-filtration cartridge 50, illustrated collectively in Figures 6A-6J and Figures 7A-7T. Figure 11A shows a schematic drawing showing details of a top view of a workstation 100 for automatically preparing sample ultra-filtrate from a sample. Figure 11B shows a top view of the workstation 100 shown in Figure
10 11A. Figure 11C shows a detailed view of detail C shown in Figure 11B showing details of ultra-filtration cartridges in an ultra-filtration cartridge rack, and ultra-filtration cartridge reservoir containing sample ultra-filtrate, in an analyzer sector for presenting sample ultra-filtrate to the analyzer. Figure 11D shows a first perspective view of the workstation 100 shown in Figure 11A.
15 Figure 11E shows a second perspective view of the workstation 100 shown in Figure 11A.

[00150] The embodiment of a workstation 100 shown collectively in Figures 11A-11E has several features, but the features required in a workstation depend on for example, if the workstation used as a stand-alone
20 machine, and if the workstation is integrated in an automated laboratory. Moreover, there are features that are not shown that are present in some embodiments. As examples which should not be considered limiting in anyway, some of these features are: a) cartridge rack detectors for detecting the presence of a cartridge rack on the base at the predetermined locations;
25 b) cartridge rack detectors output element for signaling the presence of a cartridge rack to the controller; c) sample tube rack detectors for detecting the presence of a sample tube rack on the base at the predetermined locations;
d) sample tube rack detectors output element for signaling the presence of a sample tube rack to the controller; e) pipetting tip rack detectors for detecting
30 the presence of a pipetting tip racks on the base at the predetermined locations; f) pipetting tip rack detectors output element for signaling the presence of a pipetting tip rack to the controller; g) rack position detectors; h)

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pins disposed on the base for enabling the different types of racks to be placed in the correct rack positions; i) sensors mounted slightly below the surface of the base in predetermined positions, which can be activated by providing the racks with magnets strong enough to activate the sensors; j) optical interrupters where a rack interrupts a light path; k) indicia reader for tracking the sample tubes, sample tube racks, ultra-filtration cartridges, ultra-filtration cartridge racks, ultra-filtration cartridge reservoirs containing sample ultra-filtrate, analyzer sectors for presenting sample ultra-filtrates to an analyzer, pipetting tip racks. Some examples of indicia, which should not be considered limiting in any way, include one-dimensional barcodes, a two-dimensional barcodes, and radio frequency identification tag attached to the sample tubes and the ultra-filtration cartridges. Many of these features are described in the prior art, for example US Patent No. 7,141,213.

[00151] Still referring collectively to Figures 11A-11E, shown in embodiment 100 of a workstation are a pipetting tool 110 for releasably holding a pipetting tip, a pipetting tool carriage 112 for supporting and cooperating with pipetting tool 110, a pipetting tool carriage movable arm 114 for supporting and moving pipetting tool carriage, a pipetting tip rack 120 for storing pipetting tips 70, a pipetting tool carriage movable arm carriage 116. On the left side of the workstation 100 is shown a gripping tool 130 for gripping for example, a sample tube or an ultra-filtration cartridge, to enable transportation thereof. Also shown are a gripping tool carriage 132 for supporting and cooperating with gripping tool, a gripping tool carriage movable arm 134 for supporting and moving gripping tool carriage, a gripping tool carriage movable arm 136, a track for facilitating movement of pipetting tool carriage movable arm carriage 116 and the gripping tool carriage movable arm 136 (shown as 138), an ultra-filtration cartridge rack 140, an ultra-filtration cartridge 142, a projected member 144 in the ultra-filtration cartridge rack, for enabling proper orientation of ultra-filtration cartridge with respect to X-Z and Y-Z planes, when the cartridge is located in the ultra-filtration rack for processing a sample. Also shown are, a sample tube rack 150, sample tube 152, a waste container 160 for receiving ejected used

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pipetting tip, a controller 170 for controlling the workstation, a controller data input element and display touch screen 172, a sample delivery site on the workstation for receiving samples in sample tubes contained in sample tube racks (204), an ultra-filtration cartridge rack site for on the workstation for
5 housing ultra-filtration cartridges contained in ultra-filtration cartridge racks (206), and an analyzer sector site on the workstation for housing analyzer sectors (208).

[00152] Referring collectively to Figures 12A-12D, Figure 12A shows a schematic drawing showing details of a top view of an ultra-filtration system
10 800 for automatically preparing serum or plasma ultra-filtrate from a sample and presenting the ultra-filtrate to an analyzer for measuring free therapeutic drugs and hormones in serum or plasma. Figure 12B shows a top view of the system 800 shown in Figure 12A. Figure 12C shows perspective view of the system 800 shown in Figure 12A. Figure 12D shows a detailed view of detail
15 D shown in Figure 12C showing details of ultra-filtration cartridges 142 in an ultra-filtration cartridge rack 140, ultra-filtration cartridge reservoir containing sample ultra-filtrate 190 in an analyzer sector 180 for presenting sample ultra-filtrate to the analyzer, and ultra-filtration cartridge reservoir 190 containing sample ultra-filtrate in an analyzer sector 180 on a transport track 400 used to
20 present the sample ultra-filtrate to the analyzer 300.

[00153] Referring to Figure 12D and Figure 11C, shown is a projected member 144 in the ultra-filtration cartridge rack 140, for enabling proper orientation of ultra-filtration cartridge with respect to X-Z and a Y-Z axes, when the cartridge is located in the ultra-filtration cartridge rack for processing
25 a sample. This feature is not required with the second embodiment 40 of an ultra-filtration cartridge, which has a single opening at the top, having a center approximately concentric with the bottom of the cartridge. Therefore there is no concern that the pipetting tip will crash on the cartridge 40. However the concern with respect to the third embodiment of the cartridge 50, as shown in
30 Figure 12D, is addressed by, for example which should be considered limiting in any way, the projected members 144 between each holding position in the

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rack 140. In embodiments 20 and 50, the openings 27a and 27c respectively used by the analyzer probe for accessing sample ultra-filtrate, are approximately concentric with the bottom of the respective cartridge. Therefore when the ultra-filtrate is presented to an analyzer in ultra-filtrate
5 reservoirs in any of the embodiment described, no orientation of the cartridge ultra-filtrate reservoirs with respect to X-Z or Y-Z planes is required.

[00154] The scope of the claims should not be limited by the preferred embodiments and examples, but should be given the broadest interpretation consistent with the description as a whole.

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References cited:

1. US Patent No. 7,816,124
2. US Patent No. 7,807,450
- 5 3. US Patent Application No.13/549,443
4. US Patent No. 4,474,071
5. US Patent No. 7,141,213.

CLAIMS:

1. A system for measuring at least one of a free therapeutic drug concentration and a free hormone concentration in one or more samples, the samples being either serum or plasma, the system
5 comprising:
 - an analyzer calibrated to measure at least one of a total therapeutic drug concentration and a total hormone concentration;
 - a controller comprising memory storage and a data input element for inputting processing instructions for the one or more samples,
10 the processing instructions being stored in the memory storage;
 - an automated workstation operating in cooperation with the controller, the automated workstation being capable of preparing one or more ultra-filtrates in one or more disposable ultra-filtration cartridges, the automated workstation having a transport system for
15 accepting the one or more samples and releasing the one or more ultra-filtrates in ultra-filtrate reservoirs of the one or more disposable ultra-filtration cartridges, the automated workstation also having a pipetting tool for releasably engaging one or more disposable pipetting tips;
 - 20 a track for transporting the one or more disposable ultra-filtration cartridges from the automated workstation to the analyzer;
- whereby
- the analyzer is used to measure the at least one of the free therapeutic drug concentration and the free hormone concentration in the one or more ultra-
25 filtrates in the one or more disposable ultra-filtration cartridges prepared by the automated workstation; and

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the pipetting tool is configured to apply a force to move a piston of the one or more disposable pipetting tips in a first direction.

2. The system according to claim 1, further comprising an indicia reader for tracking one or more sample tubes, and the one or more disposable
5 ultra-filtration cartridges, wherein an indicia comprises one of a one-dimensional barcode, a two-dimensional barcode, and a radio frequency identification tag attached to the one or more sample tubes and the one or more disposable ultra-filtration cartridges.
3. The system according to claim 1, the system further comprising one or
10 more disposable ultra-filtration apparatuses, wherein each of the one or more disposable ultra-filtration apparatuses comprises a disposable ultra-filtration cartridge and a disposable pipetting tip,

each disposable ultra-filtration cartridge of the one or more disposable ultra-filtration apparatuses including

- 15 a top end having a top face, the top face comprising at least one opening including a first opening providing an ultra-filtrate chamber vent;
- a bottom end for supporting the disposable ultra-filtration cartridge in an upright position in cooperation with a cartridge
20 rack;
- a filtration chamber comprising (i) a membrane having a retentate side, a filtrate side, and pores of a predetermined pore size, (ii) a sample inlet for sealably engaging the disposable pipetting tip containing a sample of the one or more samples,
25 (iii) a retentate outlet, (iv) an ultra-filtrate chamber having an interior space defined substantially by the filtrate side of the membrane and an ultra-filtrate outlet for the ultra-filtrate to flow out of the ultra-filtrate chamber, and (v) the ultra-filtrate chamber

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vent for air to flow into the ultra-filtrate chamber when the ultra-filtrate flows out of the ultra-filtrate outlet;

a dead-end channel having an open end and a sealed end, wherein the open end is coincident with the retentate outlet; and

5 an ultra-filtrate reservoir at the bottom end for collecting the ultra-filtrate when the ultra-filtrate flows out of the ultra-filtrate outlet;

wherein

each disposable pipetting tip of the one or more disposable ultra-filtration
10 apparatuses includes a piston movable in the first direction by applying a force to pressurize trapped air in the dead-end channel;

such that when the force is relaxed the piston is movable in a second direction by the pressurized trapped air in the dead-end channel, the second direction being opposite to the first direction.

15 4. The system according to claim 1, wherein the automated workstation further comprises:

a base;

one or more cartridge racks for holding the one or more disposable ultra-filtration cartridges, and cartridge rack positions on the base
20 for positioning the one or more cartridge racks in predetermined locations;

cartridge rack detectors for detecting the presence of a cartridge rack of the one or more cartridge racks on the base at the predetermined locations, the cartridge rack detectors having an
25 output element for signaling the presence of the cartridge rack to the controller;

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one or more sample tube racks for holding one or more sample tubes, and sample tube rack positions on the base for positioning the one or more sample tube racks in predetermined locations;

5 sample tube rack detectors for detecting the presence of a sample tube rack of the one or more sample tube racks on the base at the predetermined locations, the sample tube rack detectors having an output element for signaling the presence of the sample tube rack to the controller;

10 one or more pipetting tip racks for holding the one or more disposable pipetting tips, and pipetting tip rack positions on the base for positioning the one or more pipetting tip racks in predetermined locations;

15 pipetting tip rack detectors for detecting the presence of a pipetting tip rack of the one or more pipetting tip racks on the base at the predetermined locations, the pipetting tip rack detectors having an output element for signaling the presence of the pipetting tip rack to the controller;

a movable arm, supported from the base, the movable arm supporting the pipetting tool; and

20 a waste container for receiving the one or more disposable pipetting tips released by the pipetting tool.

5. The system according to claim 1, wherein the pipetting tool is further configured to relax the force applied to the piston of the one or more disposable pipetting tips, and is further configured to accommodate
25 movement of the piston of the one or more disposable pipetting tips in a second direction, the second direction being opposite to the first direction.

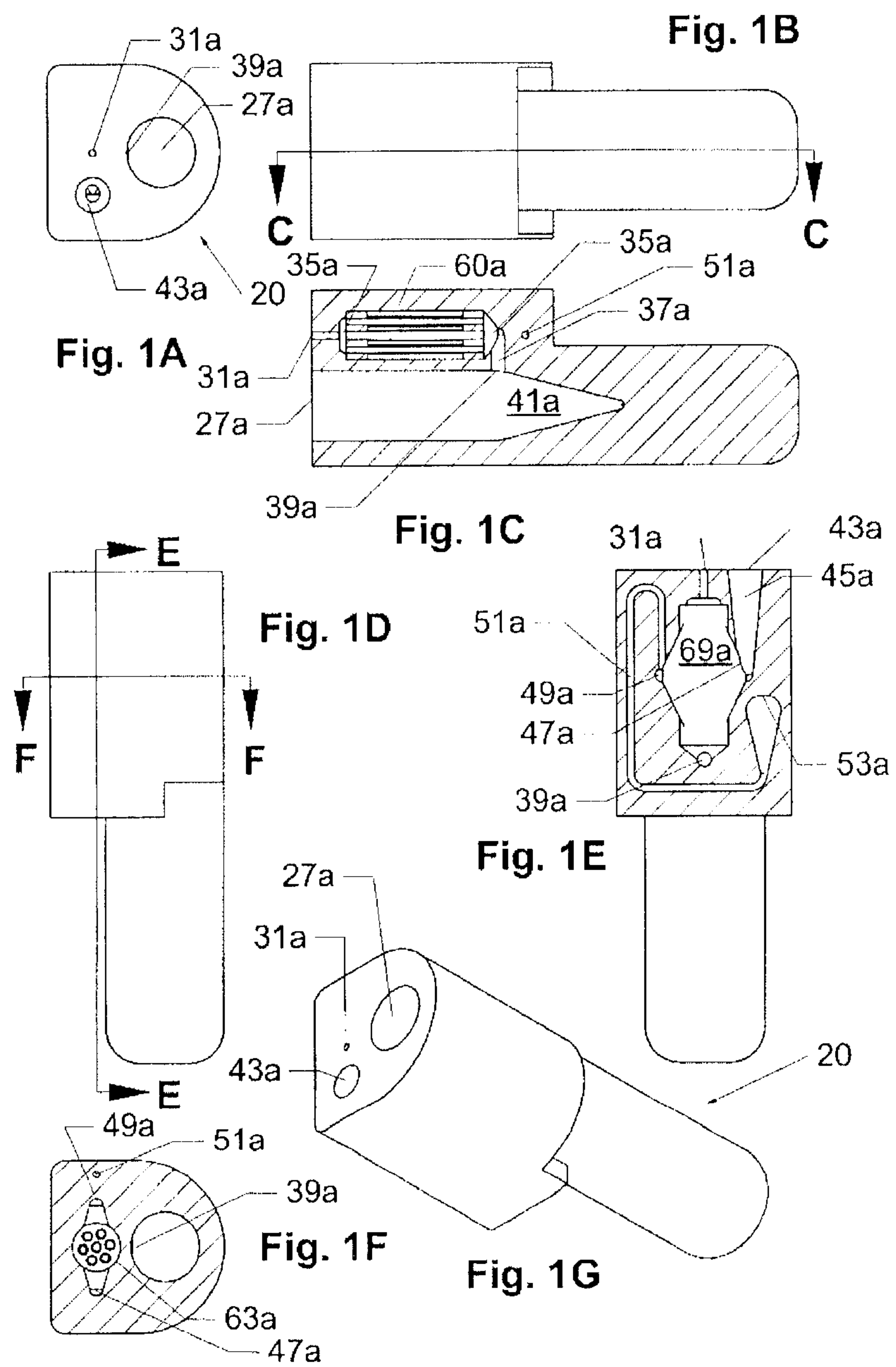
-40-

6. The system according to claim 1, wherein the pipetting tool is configured to:
- 5 repeatedly move the piston of the one or more disposable pipetting tips in the first direction to pressurize trapped air in the one or more disposable ultra-filtration cartridges; and
- provide depressurization of the trapped air in the one or more disposable ultra-filtration cartridges between consecutive movements of the piston of the one or more disposable pipetting tips.
- 10 7. The system according to claim 6, wherein the pipetting tool is configured to provide the depressurization of the trapped air in a dead-end channel of the one or more disposable ultra-filtration cartridges between consecutive movements of the piston of the one or more disposable pipetting tips by accommodating movement of the piston in a second
- 15 direction, the second direction being opposite to the first direction.
8. The system according to claim 1, wherein the automated workstation is configured to provide the one or more ultra-filtrates in the one or more disposable ultra-filtration cartridges such that the one or more ultra-filtrates comprise only substances having a molecular weight of less
- 20 than 30 kilodaltons.
9. The system according to claim 1, wherein the system further comprises an analyzer sector configured to hold the one or more disposable ultra-filtration cartridges containing the one or more ultra-filtrates prepared by the automated workstation for analysis by the analyzer.
- 25 10. The system according to claim 1, wherein the analyzer comprises an analyzer probe configured to access ultra-filtrate in each of the one or more disposable ultra-filtration cartridges.

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11. The system according to claim 4, wherein the controller further comprises a data input element for receiving signals from the cartridge rack detectors signaling the presence of a cartridge rack of the one or more cartridge racks.
- 5 12. The system according to claim 4, wherein the controller further comprises a data input element for receiving signals from the sample tube rack detectors signaling the presence of a sample tube rack of the one or more sample tube racks.
- 10 13. The system according to claim 4, wherein the controller further comprises a data input element for receiving signals from the pipetting tip rack detectors signaling the presence of a pipetting tip rack of the one or more pipetting tip racks.
14. The system according to claim 1, wherein the controller is configured to operate the pipetting tool.
- 15 15. The system according to claim 14, wherein the memory storage of the controller stores instructions for operating the pipetting tool to position the pipetting tool in predetermined positions.

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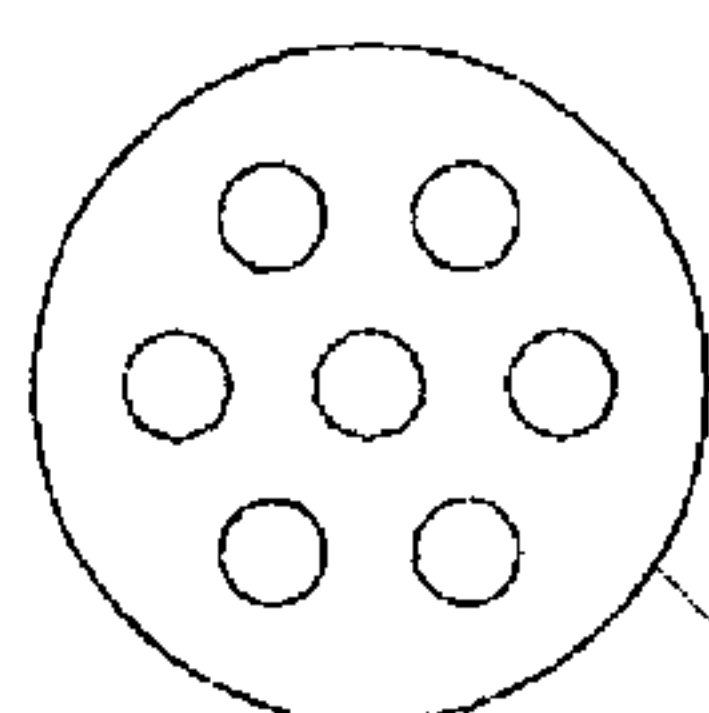


Fig. 2A

61a

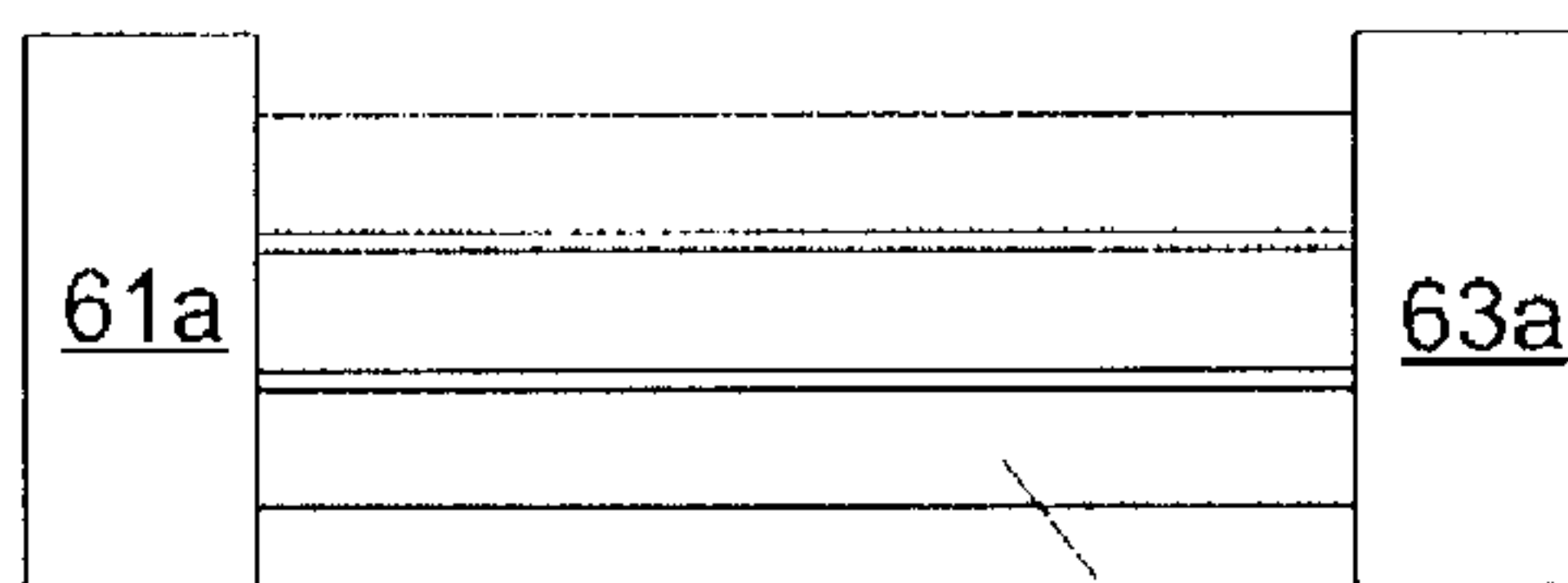


Fig. 2B

65a

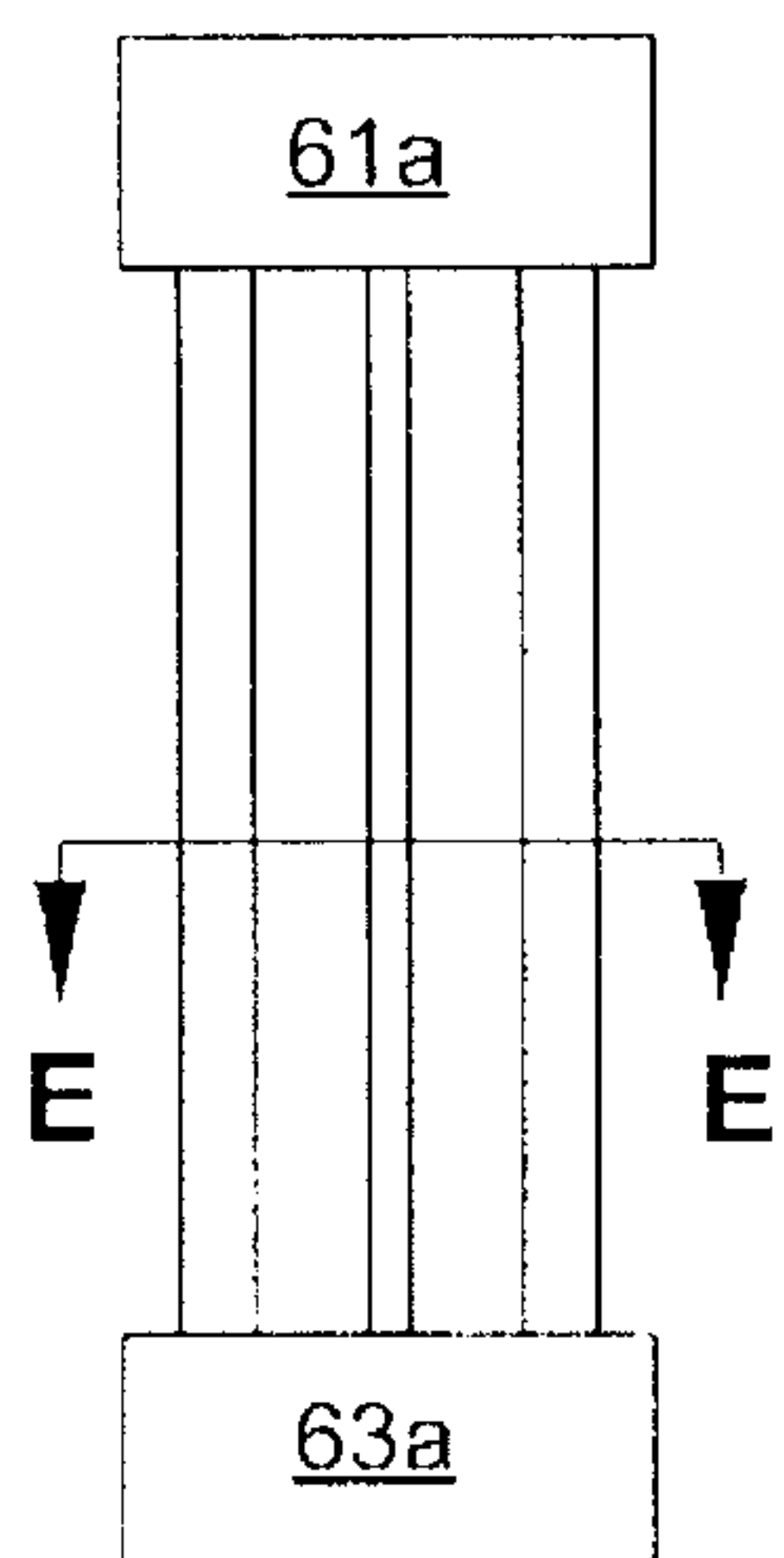


Fig. 2C

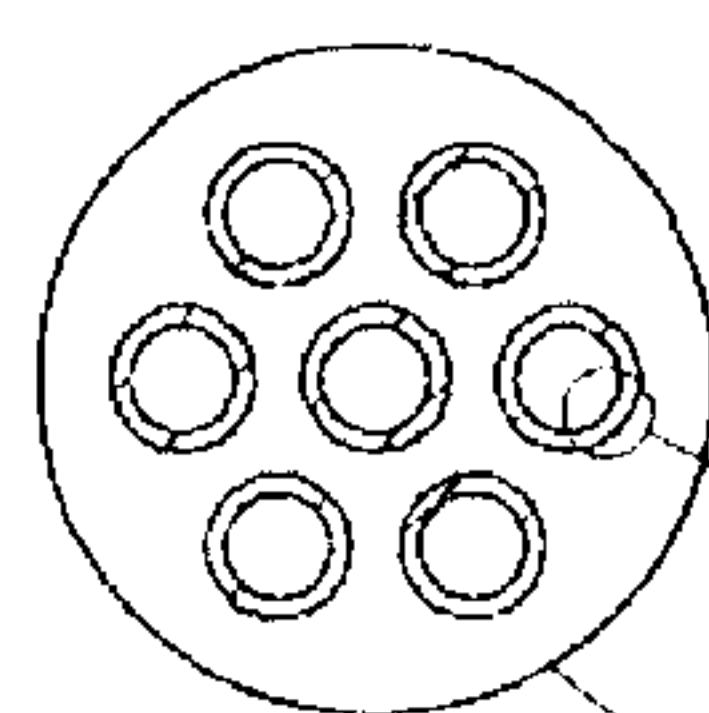


Fig. 2E

63a

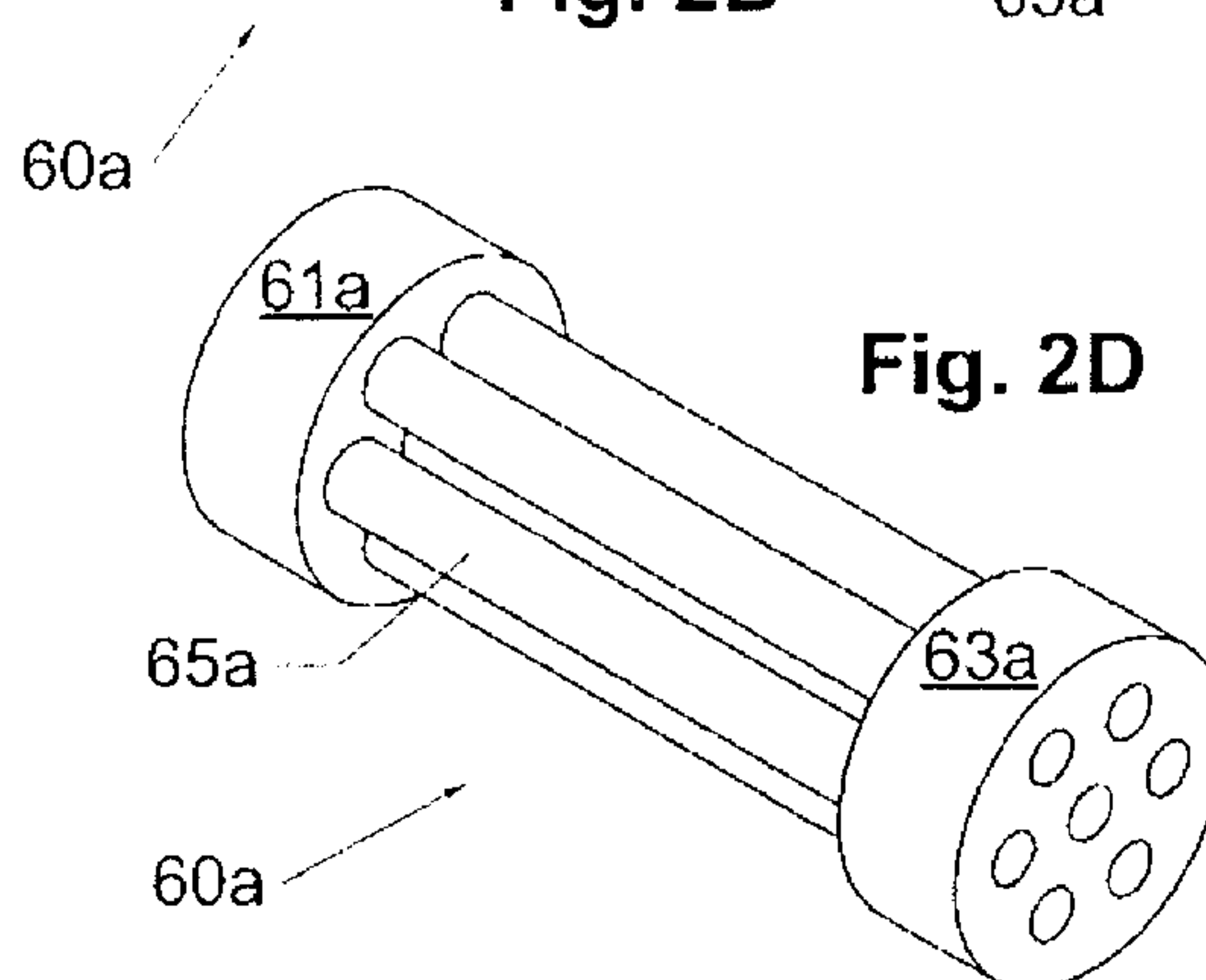
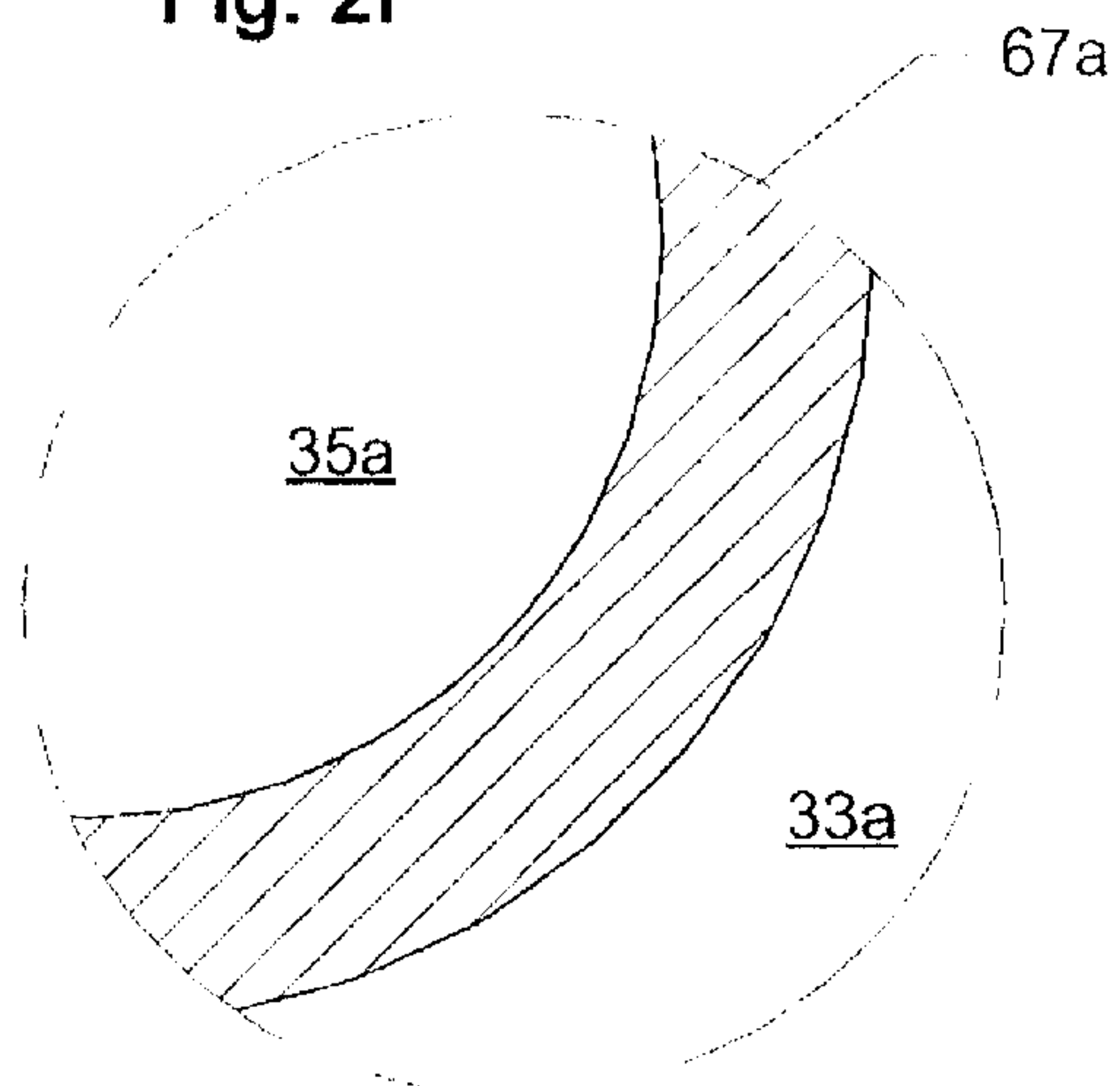
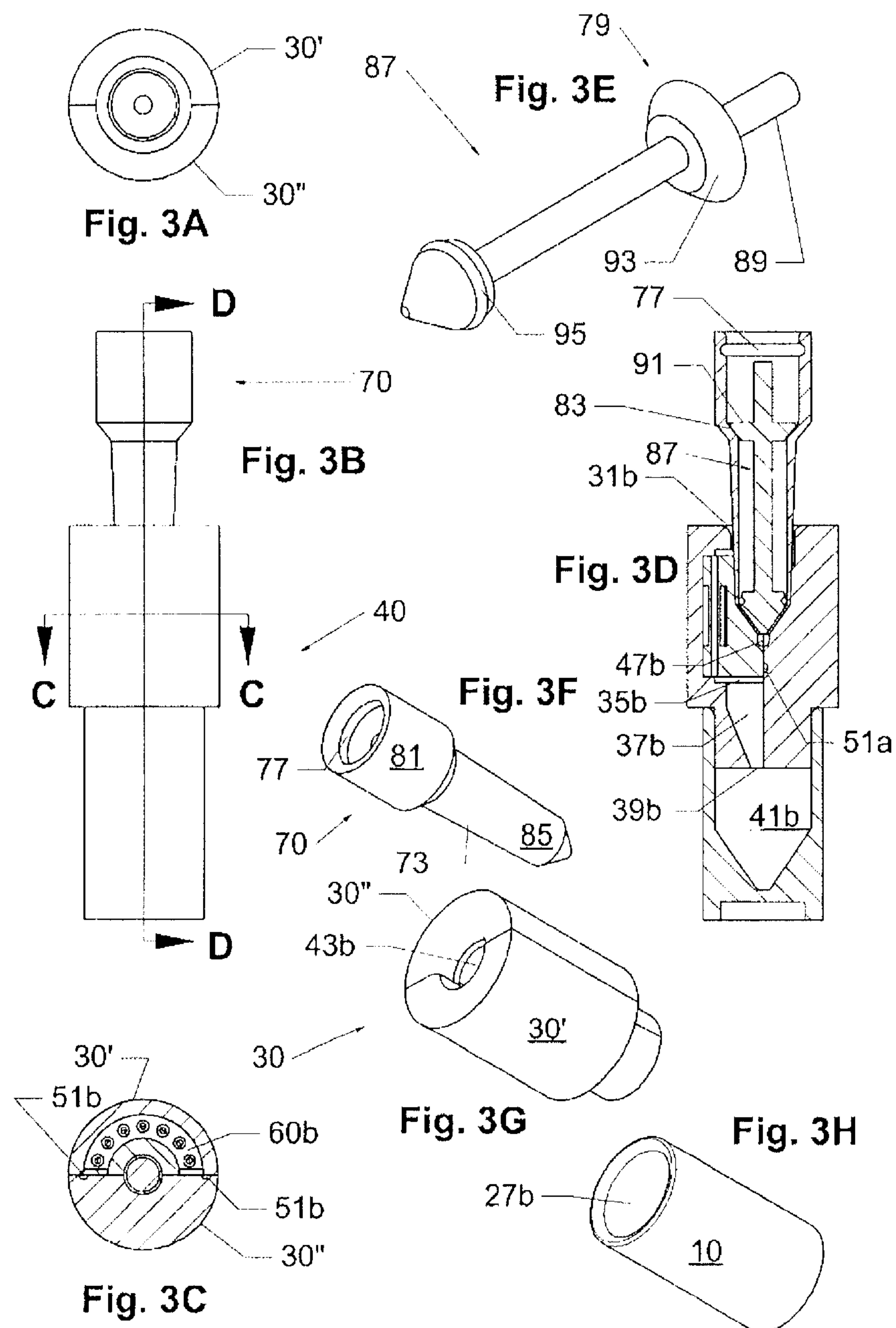


Fig. 2D

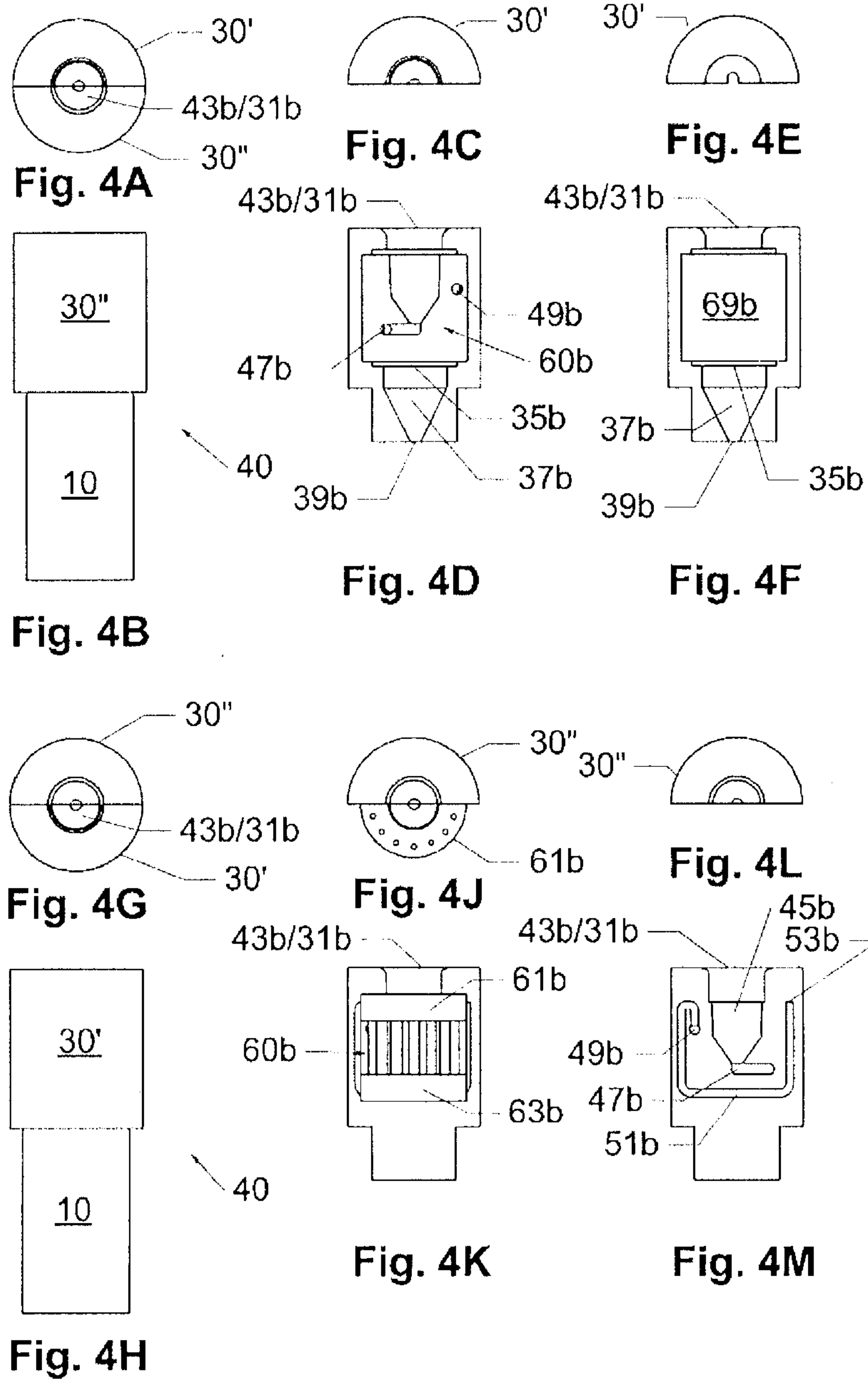
Fig. 2F



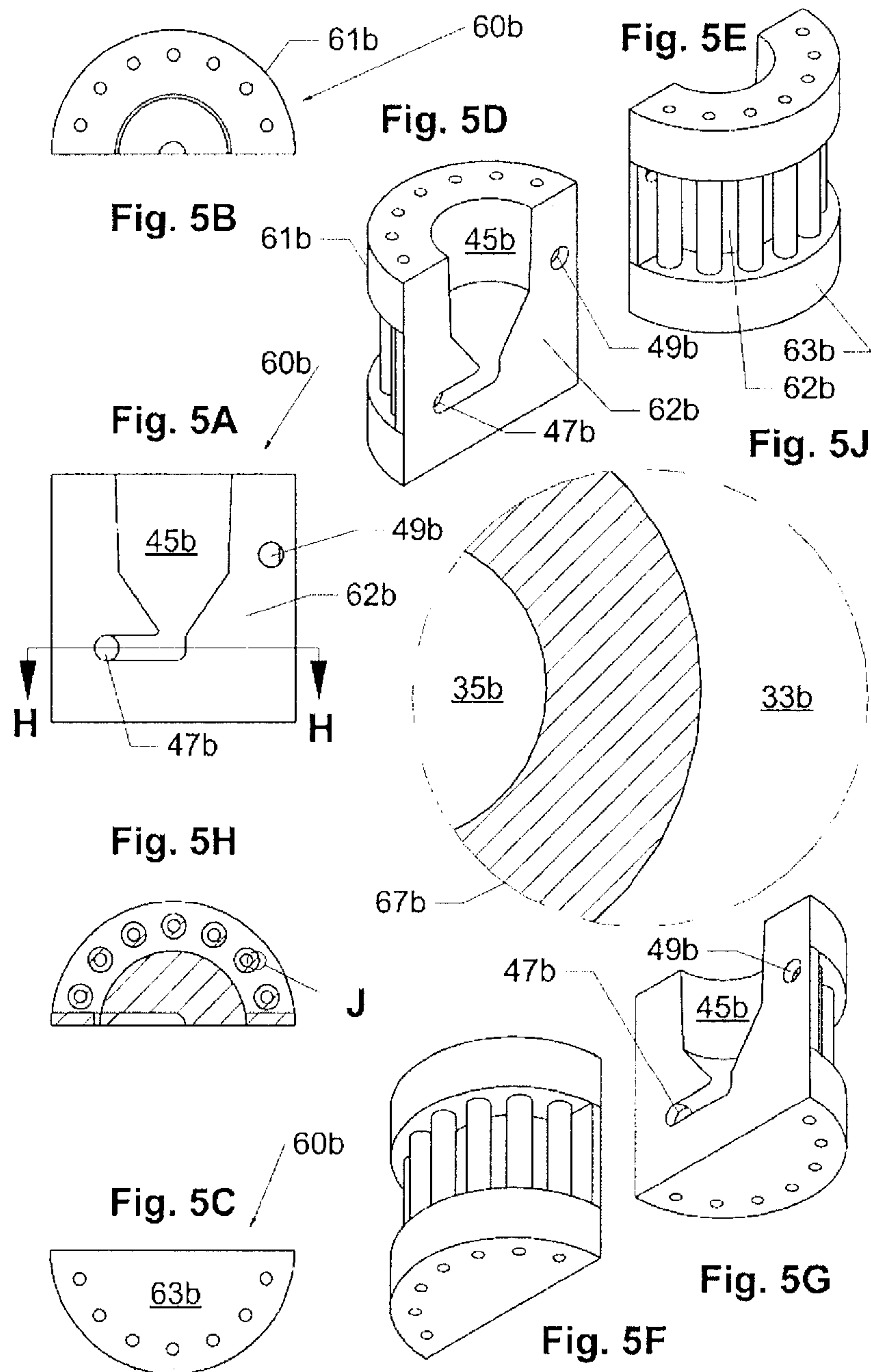
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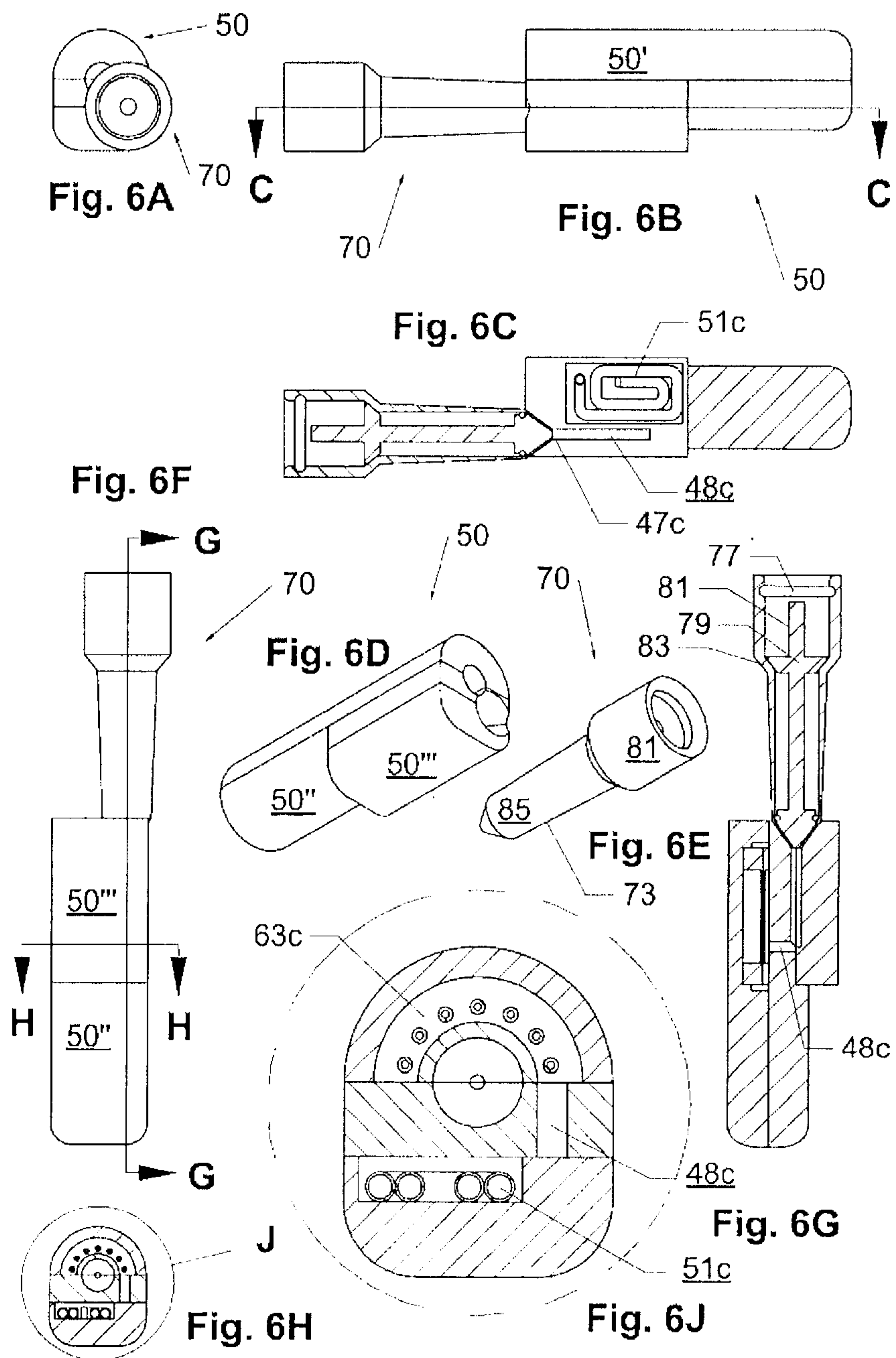
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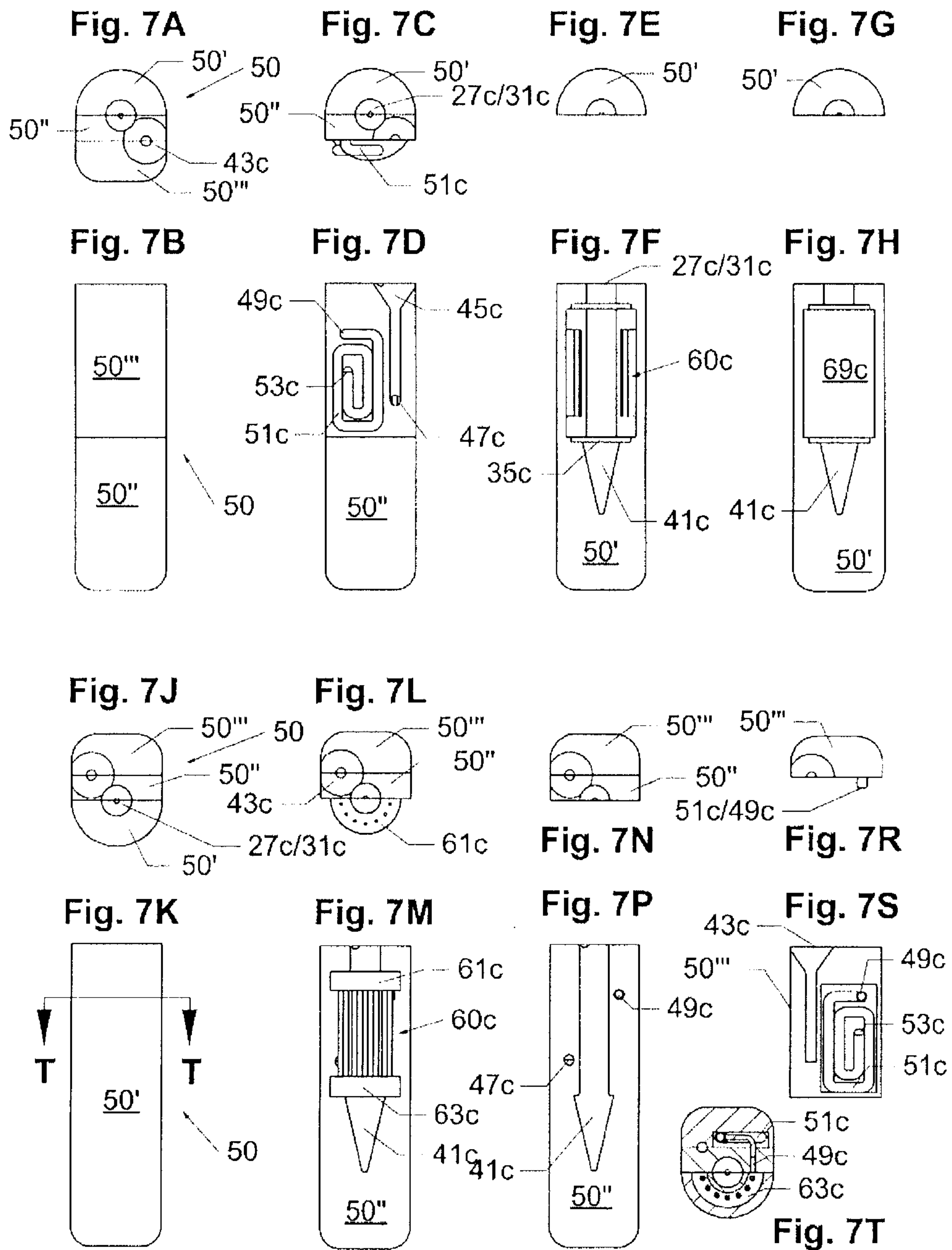
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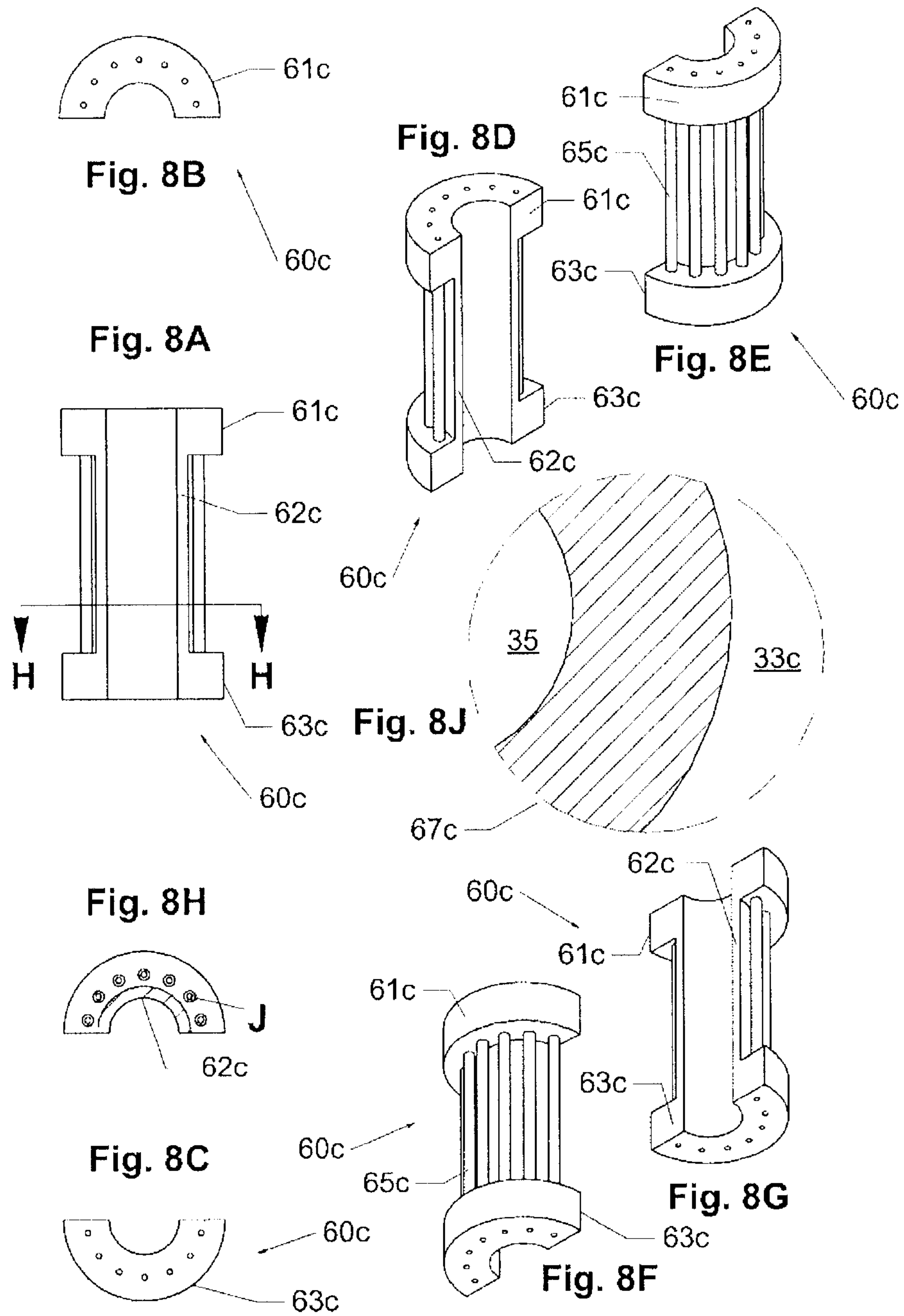
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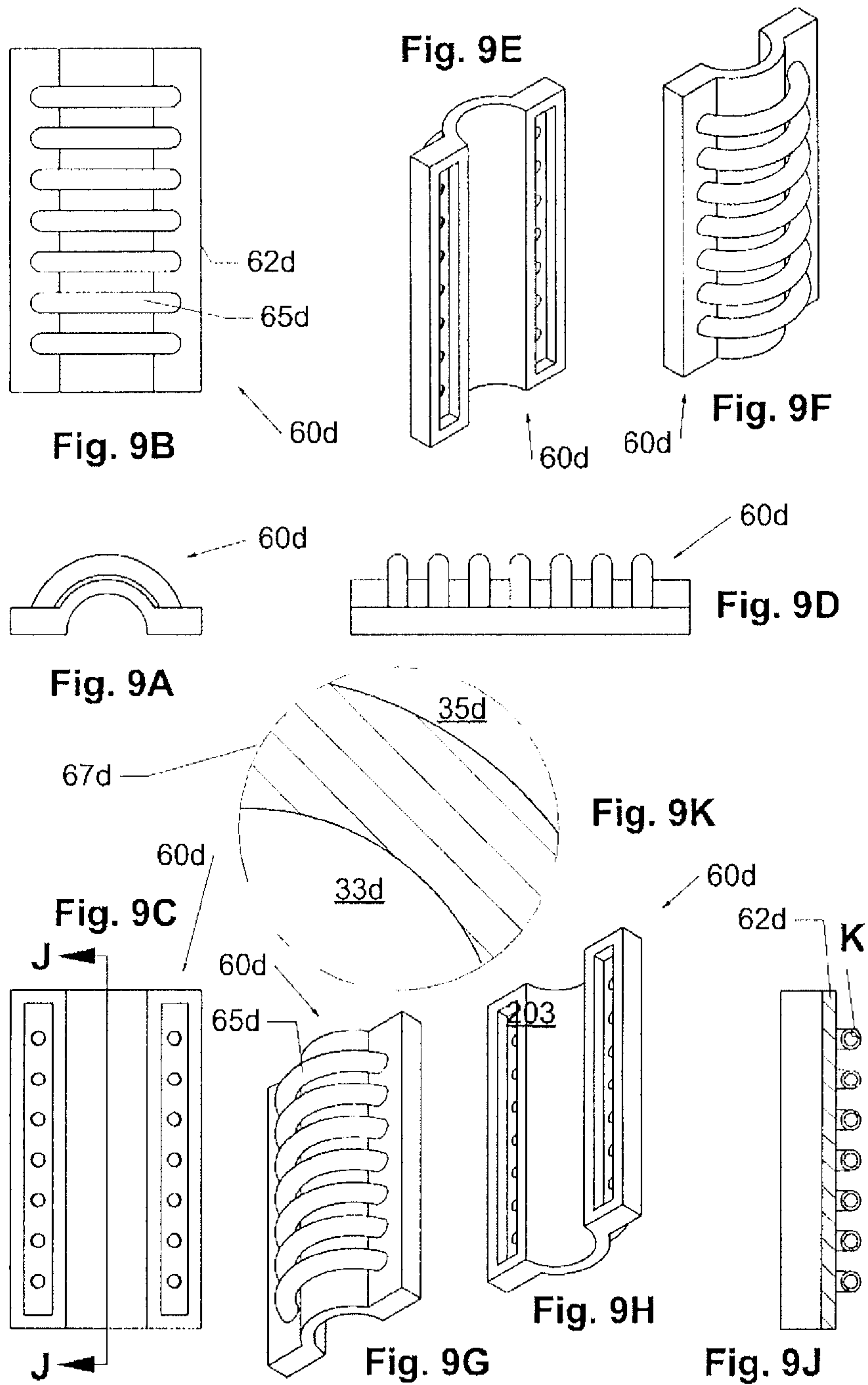
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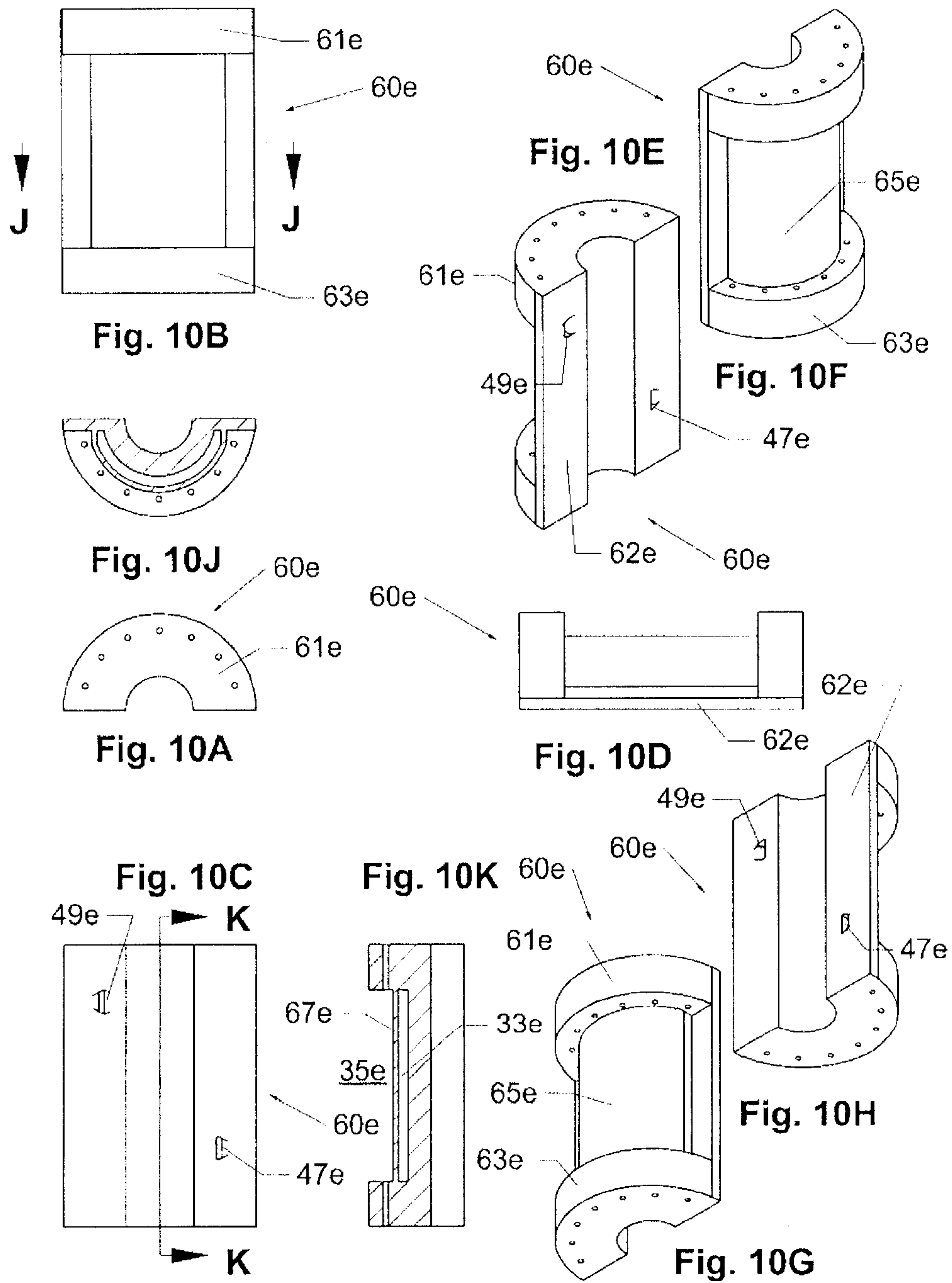
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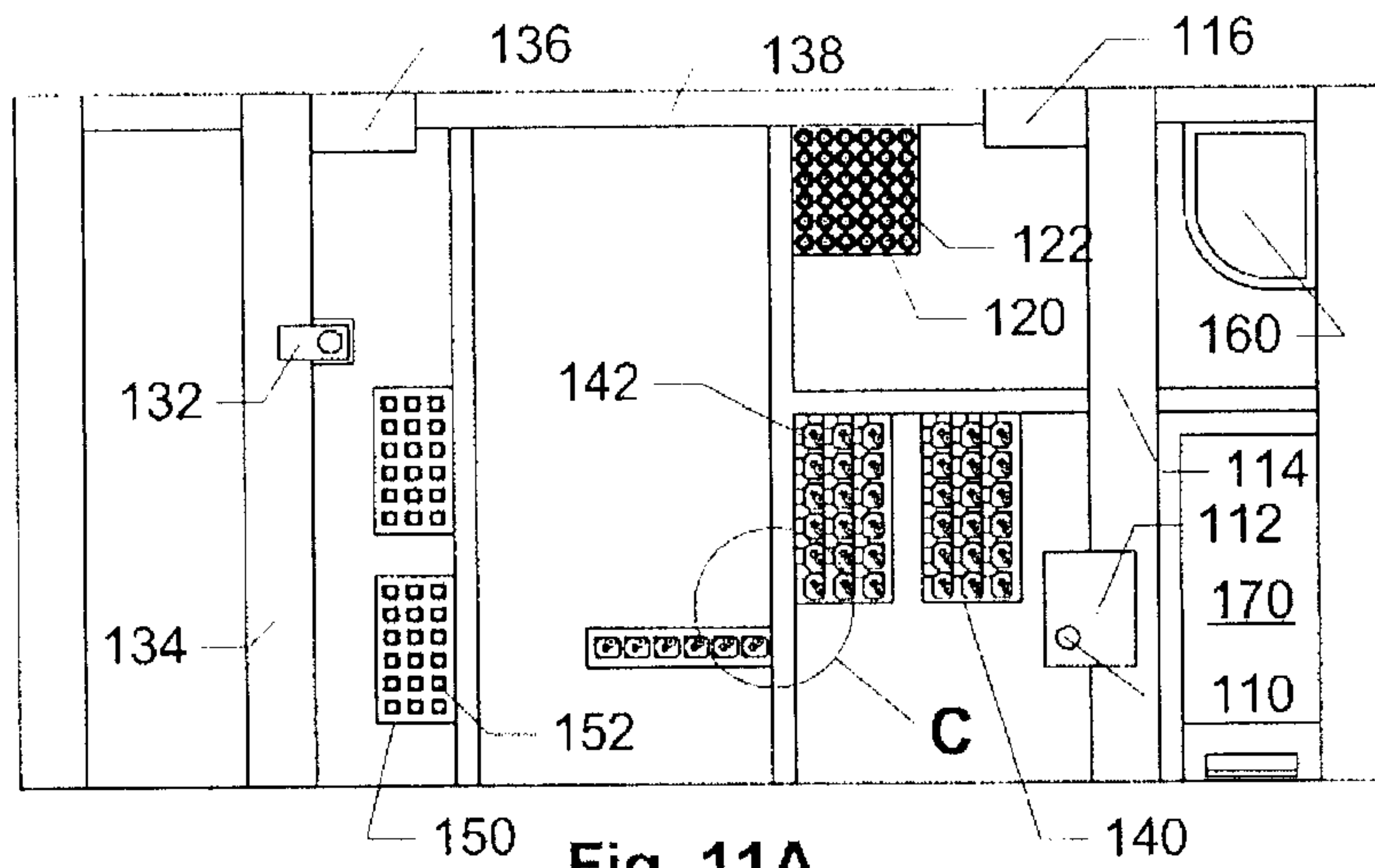


Fig. 11A

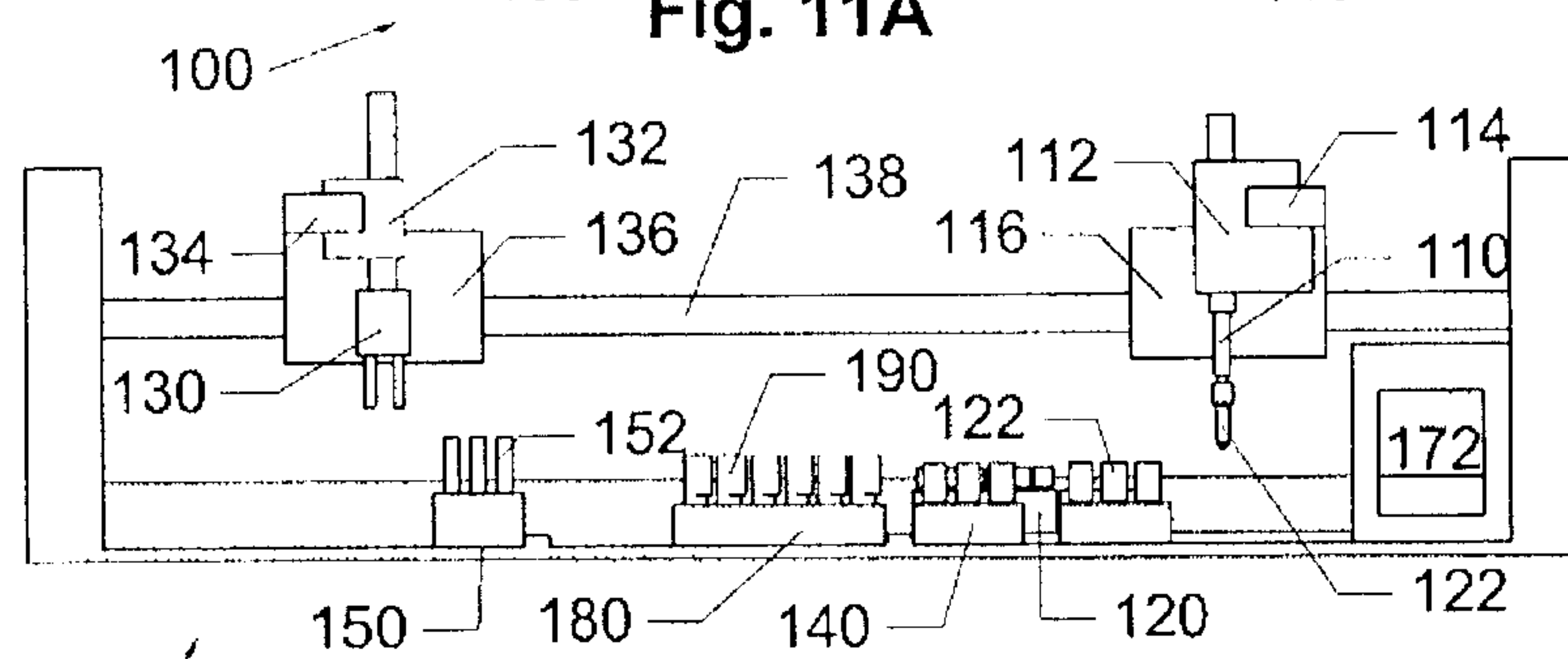


Fig. 11B

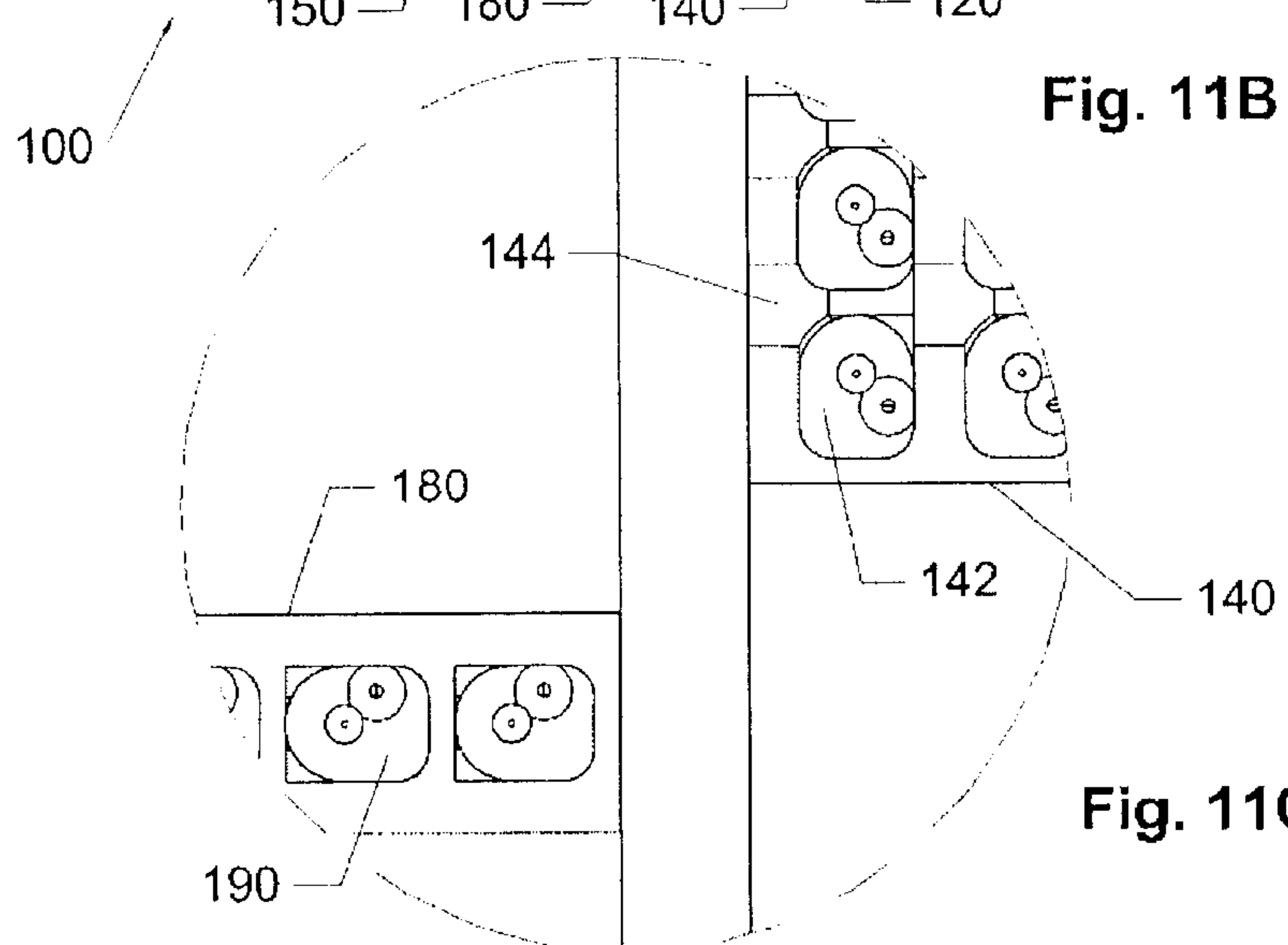
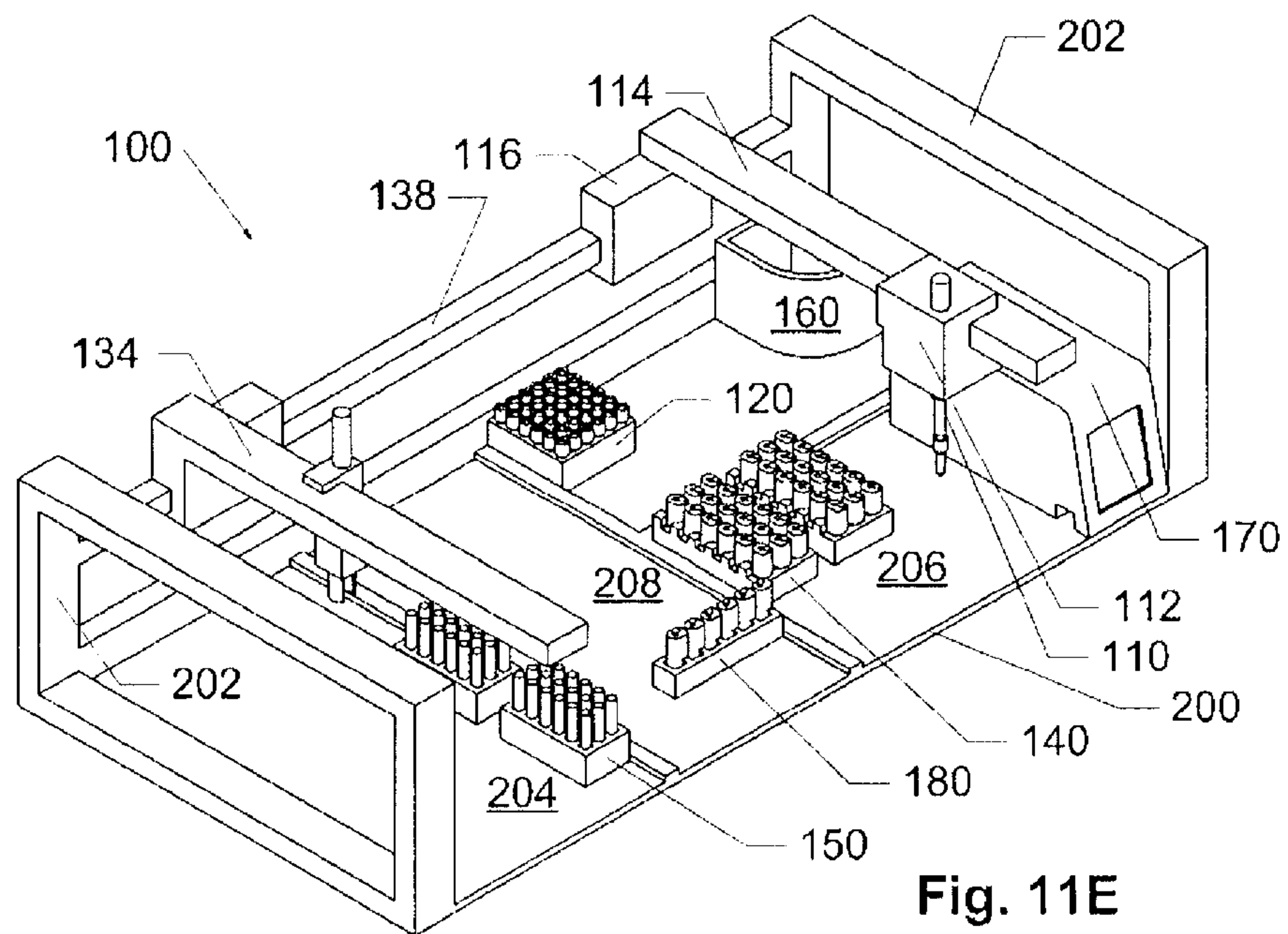
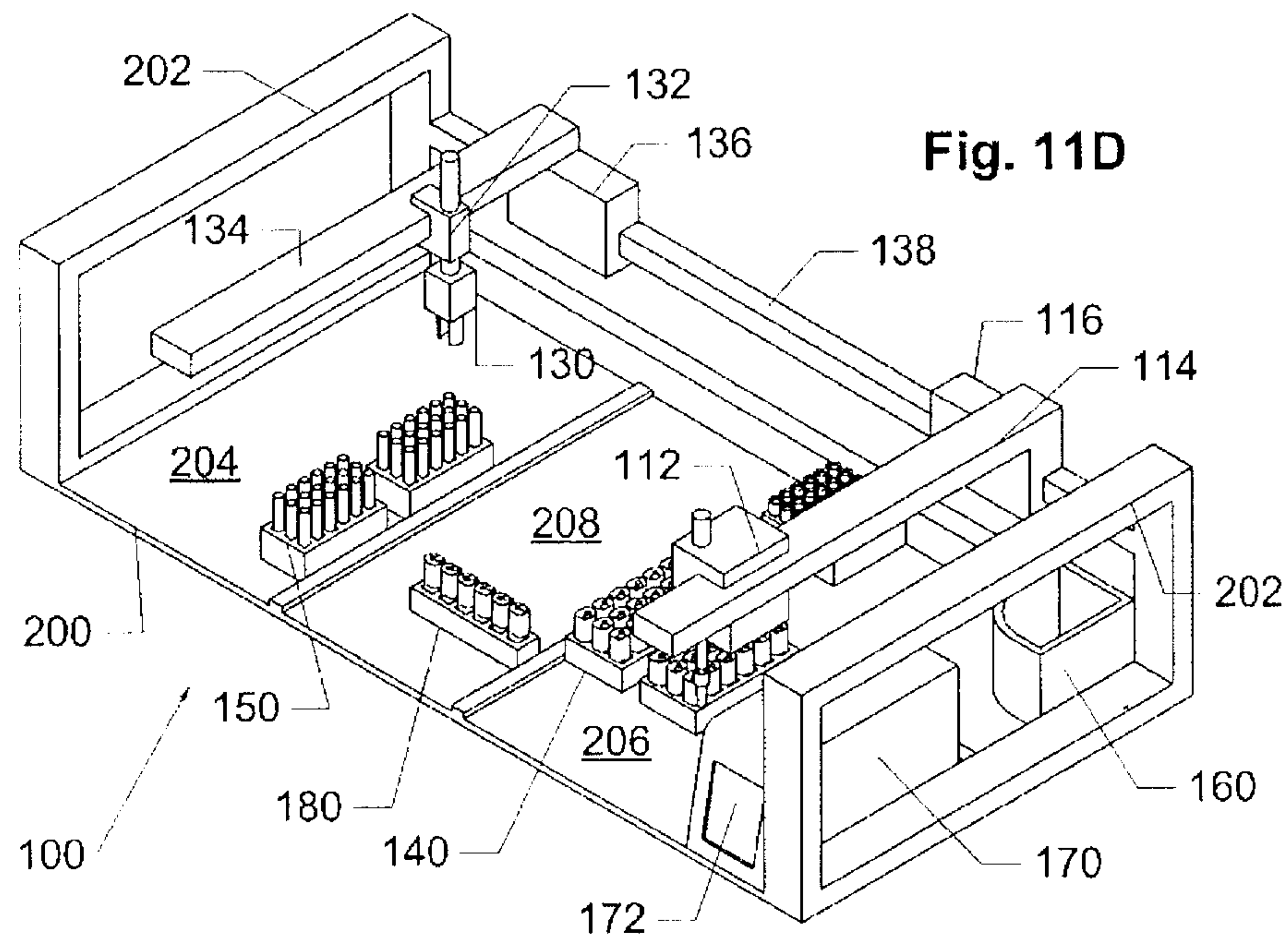
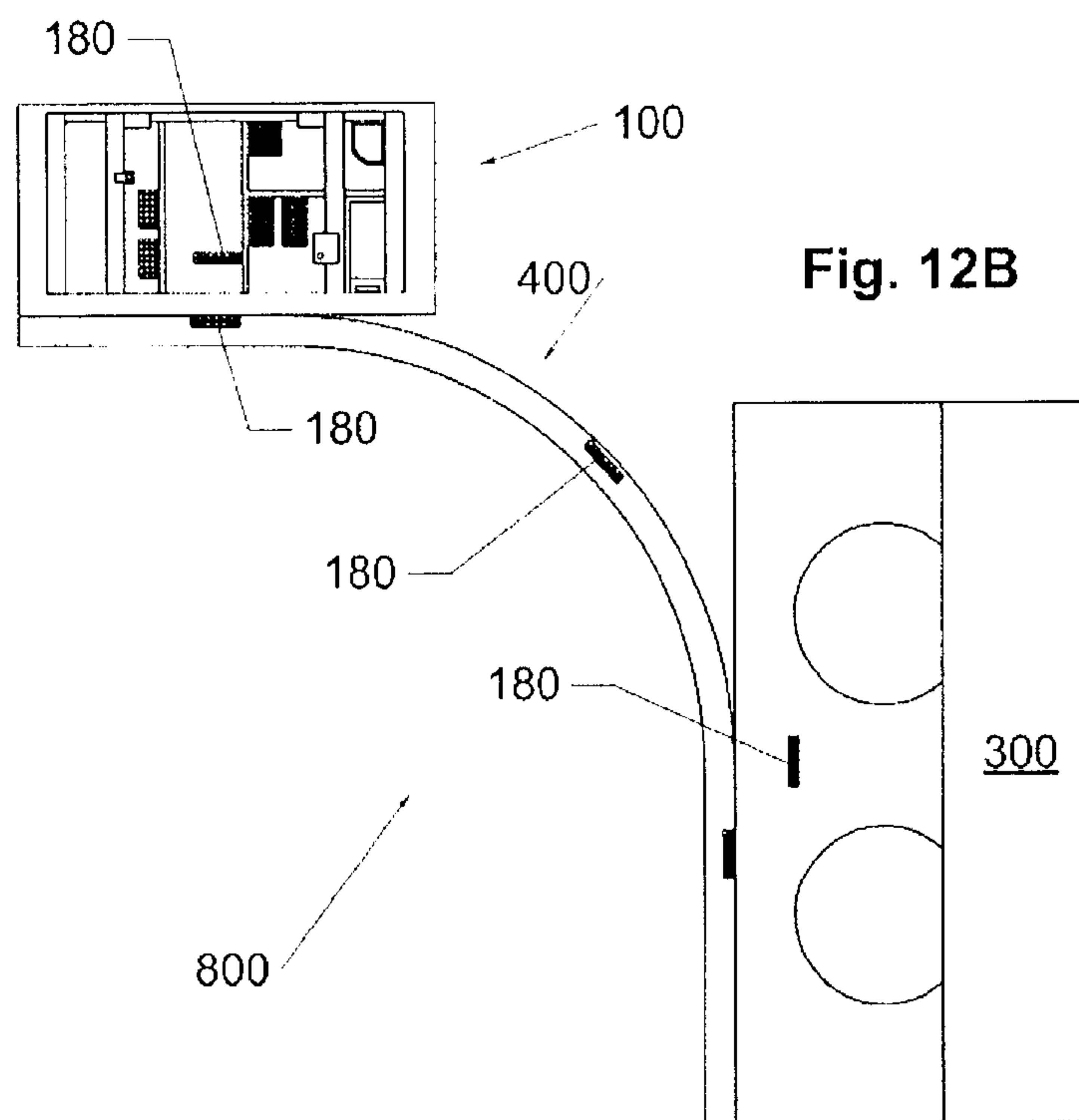
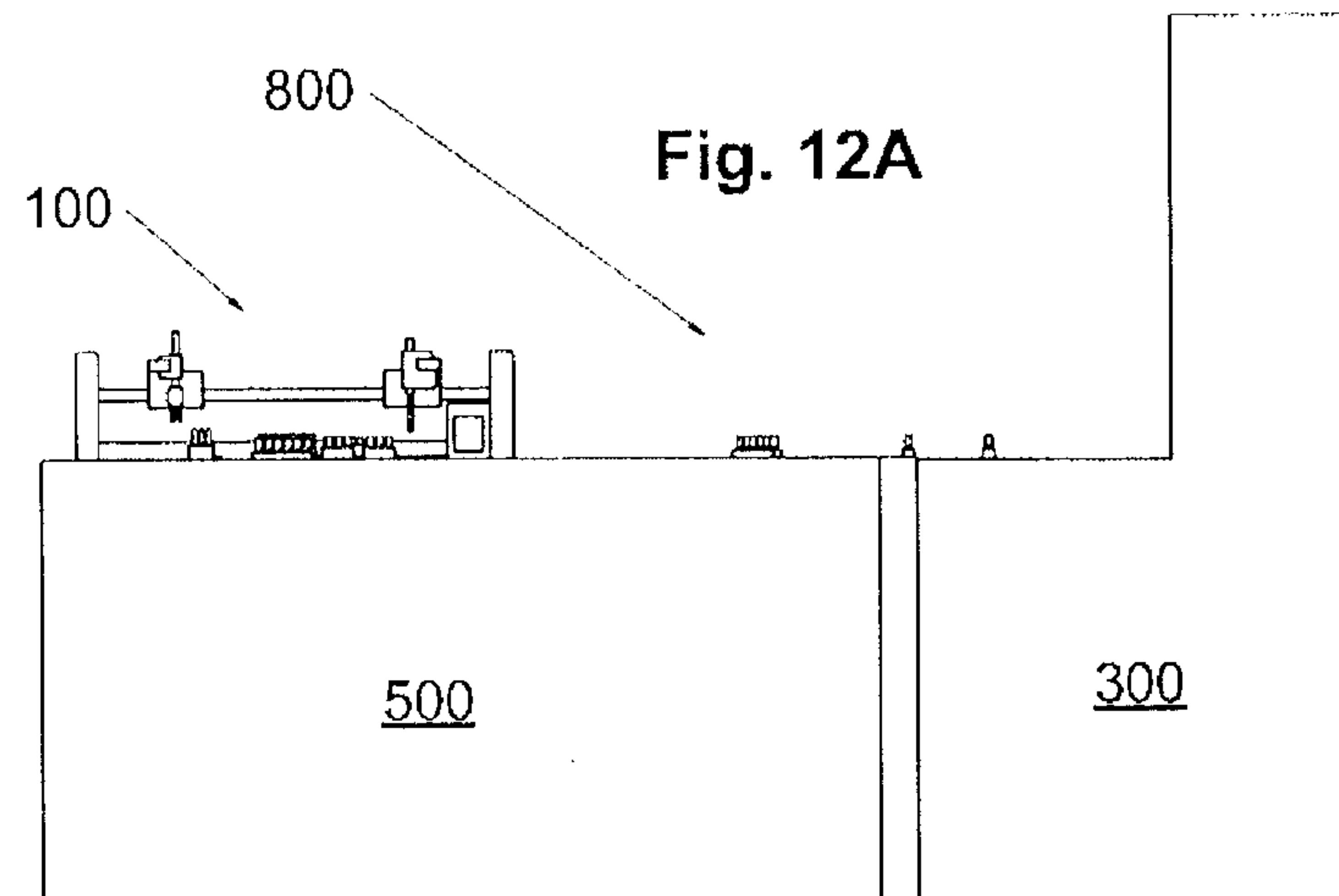


Fig. 11C

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