(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 July 2014 (03.07.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/100859 A1

(51) **International Patent Classification**:
G01N 30/14 (2006.01) ***G01N 1/10*** (2006.01)
G01N 30/50 (2006.01) ***B01D 11/04*** (2006.01)

(21) **International Application Number**:
PCT/AU2013/001526

(22) **International Filing Date**:
24 December 2013 (24.12.2013)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
2012905688 31 December 2012 (31.12.2012) AU
2013900284 30 January 2013 (30.01.2013) AU
2013904489 20 November 2013 (20.11.2013) AU

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

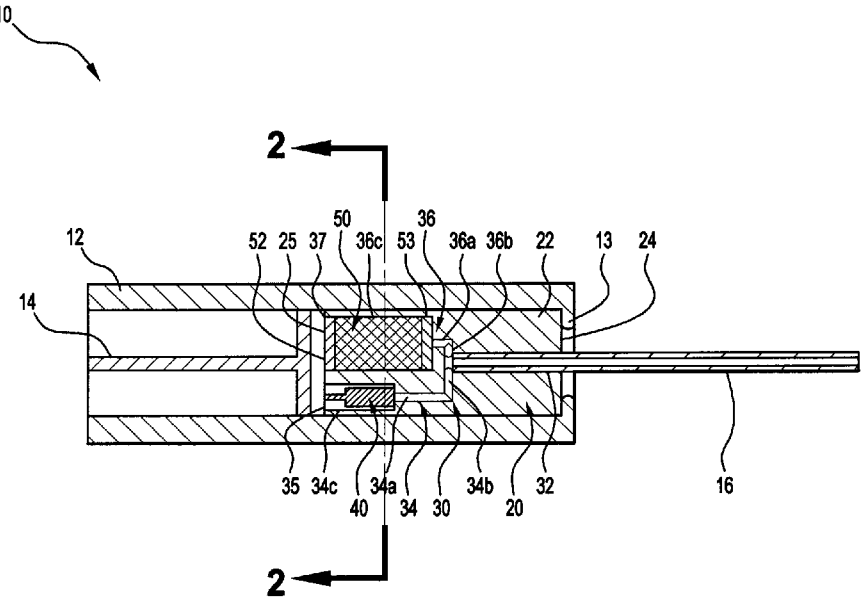
Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: FLOW CONTROL APPARATUS FOR SAMPLE FLUIDS



(57) **Abstract**: Flow control apparatus for facilitating treatment of a fluid containing a sample for analysis, includes: a body (22) having spaced ends (24, 25) and defining a fluid flow passage arrangement (30) that extends between the ends. The fluid flow passage arrangement includes two flow paths (34, 36) that are configured in parallel, merge within said body at least once, and respectively contain a one-way check valve (40) and a medium (50) selected to treat or modify sample-containing fluid flowing therethrough.

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Flow Control Apparatus for sample fluids

Field of the invention

This invention relates generally to the preparation of samples for analysis, and more particularly provides a flow control apparatus for facilitating treatment of a fluid containing a sample for analysis. The apparatus incorporates a one-way check valve and is especially useful in conjunction with a syringe and pipette.

Background of the invention

In analytical chemistry there are a range of sophisticated techniques available such as chromatography, mass spectrometry and other spectroscopy techniques but rarely can the sample be introduced directly into the instrument. Some modification of the sample is usually required, for example removal of interfering matrix, elimination of components that will interfere in the analysis, concentration of the sample, or switching the matrix or solution in which the sample components of interest are dissolved.

There are a variety of techniques involved in sample preparation but amongst the most common are filtering, targeted pre-separation to simplify the sample, concentration of the sample and changing the matrix. It has been reported that 40% of all analytical sample preparation requires Solid Phase Extraction (SPE) and 60% of all analytical sample preparation requires sample filtering during the procedure.

Syringes are used in many areas of laboratories including sample preparation for instrumental analysis. Fundamentally a syringe fulfils a triple role as a pump for displacing fluids, as a metering device for accurately determining the precise volume dispensed and the rate it is dispensed, and as a transport device. Syringes are used manually by hand or motor driven for automated operation.

Manual filtering generally involves aspirating the sample into the syringe, removing the syringe needle, fitting a filter membrane to the front of the syringe, dispensing the fluid through the filter, removing the filter and fitting a needle to the syringe for the next sample. Often this process leads to spillage and occupational health and safety issues

related to repetitive strain injury. The process is slow when performed manually but is also not an efficient process to automate.

Syringe filters typically have high dead volume resulting in the need for considerable prefiltered sample to obtain the required quantity of filtered sample.

While there is a strong need for increased focus on laboratory automation or simplification of sample preparation processes using conventional syringe filters these processes are not easily amendable to automation.

Solid Phase Extraction (SPE) is based on partitioning molecules between a solid stationary phase and liquid mobile phase (e.g. liquid chromatography). The technique of SPE is most commonly practised by loading the sample on the top of the solid stationary phase bed and the flow through the bed is either driven by gravity or vacuum assisted, which means the pressure differential across the bed is limited to atmospheric pressure. Pressure differential limitation means large particle size separation media (usually 35-50micron) must be used. Smaller particle sizes are not practical using normal SPE techniques as the fluid flow is too restricted for both drawing fluids through the bed and dispensing the fluids. Smaller particle seizes for the media would offer significant advantages in terms of increased absorption capacity of the media (From larger surface area per volume), improved extraction efficiencies, and the possibility for more selective separation of compounds from either other on the bed in the same way that smaller particle size gives greater compound separation efficiency on a liquid chromatography column.

Conventional SPE cartridges require a relatively large amount of solvent to elute the compounds from the SPE bed. Typically evaporation of this excess extraction solvent is then required as an additional part of the process.

The cartridges also do not lend the process to simple automation due to method process, connectability and manual manipulation issues during operation.

Elevated pressure driven SPE has been practised by using gas pressure above the SPE bed.

A further development of SPE for sample preparation was Micro Extraction by Packed Sorbent (MEPS) (described for example in US patent publication US2004/0241874) which is a syringe-based design. The stationary phase bed is packed into the barrel of a syringe. The syringe is then used to draw a defined volume of sample through the bed with bed and solvent conditions chosen to trap targeted compounds on the bed. Targeted compounds are then eluted off the bed by aspirating a suitable solvent through the bed. The targeted compounds are thereby desorbed into the solvent and thereby carried into the barrel of the syringe. The solution containing the targeted compounds is then dispensed from the barrel, back through the bed and into a vial for analysis, or directly into an analytical instrument.

The MEPS technique had large advantages over conventional SPE including ease of automation and reduced volumes of elution solvent containing the targeted compounds, which gives greater concentration of the eluted compounds for analysis. The disadvantage remains of having to use large particle size separation media because the sample must be aspirated through the media using suction from the syringe. Also, when the elution solvent is drawn through the MEPS bed, the sample compounds are spread evenly through the elution volume from the syringe barrel, meaning the concentration factor of the sample in the eluted solvent is not as high as could be achieved.

The sample needs to be drawn through the bed where targeted compounds are trapped and non-trapped material is dispensed to waste back through the bed. The compounds are released from the bed when an elution solvent is aspirated through the sorbent bed bringing the elution solvent containing the targeted compounds into the barrel of the syringe. This solution is then dispensed through the bed out through the needle. It is significant that the compounds of interest are spread evenly through the dispensed volume so they are somewhat diluted over the entire elution volume rather than primarily in a concentrated band, which would give greater detection sensitivity.

The discussion thus far has focused on sample preparation techniques that employ syringes, but much of the discussion applies equally to the use of pipette tips, including disposable pipette tips.

It is an object of the invention to at least in part address or alleviate one or more of the difficulties mentioned above.

Reference to any prior art or background information in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art or background information forms part of the common general knowledge in Australia or any other jurisdiction; or that this prior art or background information could reasonably be expected to be ascertained, understood and regarded as relevant by a person skilled in the art.

Summary of the invention

The invention entails a concept of providing a one-way check valve and a treatment medium in parallel passages at the front part of a syringe or pipette.

The invention provides, in one aspect, flow control apparatus for facilitating treatment of a fluid containing a sample for analysis, comprising:

a body having spaced ends, which body defines therein a fluid flow passage arrangement extending between said ends;

wherein the fluid flow passage arrangement includes two flow paths that are configured in parallel, merge within said body at least once, and respectively contain a one-way check valve and a medium selected to treat or modify sample-containing fluid flowing therethrough.

In another aspect, the invention provides a syringe assembly for facilitating treatment of a fluid containing a sample for analysis, comprising:

a syringe barrel and a complementary plunger;

a fluid flow passage arrangement in communication with a chamber defined by the barrel and the plunger;

wherein the fluid flow passage arrangement includes two flow paths that are configured in parallel, and respectively contain a one-way check valve and a medium selected to treat or modify sample-containing fluid flowing therethrough.

In an embodiment, the one-way check valve is arranged to substantially prevent flow along the flow path containing the valve to the merge with the other flow path.

In an embodiment, the flow paths open separately from one of said ends of said body from spaced ports.

Preferably, the one-way valve is a plug seal valve.

The plug seal valve may include an integral plug seal having respective axially adjacent portions of relatively larger and smaller cross-section, the latter defining a peripheral sealing surface that engages a complementary female surface, and the former defining a shoulder that biases the valve closed under pressure of the fluid.

In an embodiment, the medium has ends spaced along its respective passages and frits or sorbent terminations are provided at one of both of said ends.

In one application, the medium is a sorbent bed selected to trap target compounds from said fluid as it passes through the sorbent bed, for subsequent recovery from the bed by an elution solvent. The sorbent bed may be, for example, a solid stationary phase bed, for practising Solid Phase Extraction (SPE) or Micro Extraction by Packed Solvent (MEPS) of said target compounds.

More generally, the medium is selected from the group comprising filtering media, monoliths and immobilised biologically active materials.

In an embodiment, the flow control apparatus is mounted within a barrel of a syringe, wherein the merged passages form a single duct communicable with a needle of the syringe, and the flow paths open separately into the interior chamber of the barrel.

Alternatively, the flow control apparatus can be provided as a separate unit attachable on the front of a syringe.

In a further aspect the invention provides a one-way plug seal valve having a valve seat and a valve plug, where the valve plug comprises respective axially adjacent portions of relatively larger and smaller cross-section, the latter defining a peripheral sealing surface that engages the valve seat and the former defining a shoulder that biases the valve closed under pressure of the fluid.

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

Brief description of the drawings

The invention will now be further described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 is an axial cross-section of a flow control apparatus according to an embodiment of the invention, in the form of a check valve cartridge fitted in the end of a syringe barrel;

Figure 2 is a cross-section on the line 2-2 in Figure 1;

Figure 3 is a three-dimensional view of the valve plug of the plug seal check valve in the embodiment of Figures 1 and 2;

Figure 4 is a partially sectioned alternative embodiment in which the check valve cartridge is a separate attachable unit for mounting on the front of a syringe;

Figure 5 is a further alternative embodiment with a different configuration of passages within the body of the check valve cartridge;

Figure 6 depicts the four operational states (A to D) of the check valve cartridge of Figures 1 and 2 during the operation of a syringe for an SPE application;

Figure 7 is a graph illustrating the elution profile and carryover for a target compound in an SPE application, the graph also showing, for comparison purposes, a standard elution profile and carryover in a MEPS application.

Figure 8 is an axial cross-sectional view of a pipette tip incorporating a flow control apparatus similar to the embodiment of Figure 1; and

Figure 9 is an axial cross-sectional view of a further embodiment in which the one-way valve is a ball valve.

Description of embodiments of the invention

The syringe assembly 10 illustrated in Figures 1 and 2 includes a tubular syringe barrel 12 of annular cross-section, a reciprocable plunger 14, and a forwardly projecting hollow syringe needle 16. The front end of barrel 12 has a return lip 13 that locates a flow control apparatus in the form of a check valve cartridge 20. Cartridge 20 may be a press fit in the end of the barrel or otherwise secured in position, eg with adhesive.

Cartridge 20 comprises a generally cylindrical body 22 of a suitable inert material having spaced ends comprising end-faces 24,25. The body 22 is moulded or machined to define therein a fluid flow passage arrangement 30 extending between end-faces 24,25.

Passage arrangement 30 includes an axially extending bore 32 in body 22of uniform diameter dimensioned to receive, in a press fit, syringe needle 16. This bore 32 opens at end-face 24, which abuts the return lip 13 of the front of syringe barrel 12. Passage arrangement 30 is completed by a pair of flow paths 34,36 in body 22 that are configured in parallel, merge within body 22 into the inner end of bore 32, and open separately at end-face 25 at respective ports 35,37. Flow paths 34,36 thereby

communicate the interior of syringe needle 16 with the interior of syringe barrel 12 in a parallel flow arrangement.

Each flow path 34, 36 comprises a first duct portion 34a,36a extending parallel to the axis 11 of the syringe barrel and needle, a second duct portion 34b,36b extending radially to link portion 34a,36a to bore 32, and an enlarged chamber portion 34c,36c that respectively contains a one-way check valve 40 and a medium 50 selected to treat or modify fluid flowing through the medium.

In this embodiment, one-way check valve 40 is a plug seal valve including a valve plug 42 as shown in Figure 3. Valve plug 42 is an integral moulding in a suitable rubber and consists of a first portion 44 of larger cross-section and a second portion 46 of smaller cross-section. In this case, plug portions 44,46 are solid coaxial cylinders. Larger plug portion 44 defines a cylindrical surface for seating and sealing the valve onto a cone sealing seat 45 at the junction between the chamber portion 36c and the axially parallel duct portion 36b of flow path 36. Smaller diameter portion 46 of the valve plug 42 provides a tail that defines a shoulder 47 by which the plug is biased closed onto the cone seat by fluid pressure.

It has been found that there are optimum dimensions for the diameter and length of the two cylindrical portions of the valve plug to obtain optimum operation. The larger diameter portion 44 effects pressure differential for sealing and aspiration back pressure. Its length ensures that the plug remains parallel in the valve during operation. The relative diameter of the smaller portion 46 determines 'spring force' and its length will effect the normally closed position of the valve. The valve must allow opening (flow) at low differential pressures to ensure that sample is not drawn into the sorbent bed during aspiration. Conversely the valve ideally allows sealing during dispensing at very low flowrates (low differential pressure) to enable a wide range of applications

Adopting a and c as the respective diameters of the smaller and larger portions 44,46,b as the overall length of the plug and d as the length of the larger diameter portion, the ratio c/a is conveniently in the range 2 to 4 while the ratio b/d is conveniently in the

range 1.25 to 2.5. One example of an effective set of dimensions is c = 1mm, a = 0.4mm, b = 4mm and d = 2.5mm.

A suitable material for the plug 42 is a silicone rubber. Rubber hardness and constitution should be chosen to combine low flow rate sealing with chemical inertness so as not to interfere with, contaminate or absorb compounds from the sample fluid. A suitable material is a 40 duran hardness fluorosiloxane chosen for softness and chemical resistance.

The check valve depicted in Figures 1 to 3 has been found to perform reliably in flow rates ranging from 20 µL /min to 5mL/min. Operation of the valve and flow paths were checked using dye solutions under a microscope. The plug seal valve also showed acceptable opening pressure, resulting in minimal back flow into the sorbent bed 50. The valve reliably closed immediately on liquid dispensing to ensure that substantially no sample was lost.

Medium 50 is typically a media bed that may comprise or contain but is not limited to SPE packing materials, SPE disks, sorbents, filtering media, monoliths and immobilised biologically active materials. Medium 50 is retained in chamber portion 36c of flow path 36 between frits or sorbent terminations 52,53, one of which is flush with the end face 25 of the valve cartridge body.

It will be appreciated that check valve cartridge 20 can alternatively be provided as a separate self-contained unit 120 that can be attached on the front of a syringe, as illustrated in Figure 4. In this arrangement, cartridge body 122 has a two-part body and is fitted within an outer housing 160 which is press fitted or screw threaded onto a syringe end fitting 162. Bore 132 can receive the syringe needle 116 as before, while housing 160 and fitting 162 include an axially located duct arrangement communicating flow paths 134, 136 with the interior of the syringe barrel. Additional radial grooves are provided in the end face 125 of body 122 to provide fluid communication between this duct arrangement and the flow paths 134, 136.

It will also be understood that the parallel flow paths, one-way check valve and treatment medium can be incorporated into a single piece plastic moulded, machined or 3D printed syringe barrel.

Figure 5 illustrates a further embodiment in which body 220 is a single piece and flow path 234 is co-axially aligned with bore 232.

The particular operational advantage of the illustrated embodiment is that when the syringe plunger is retracted to aspirate fluid into the syringe through needle 16, the reduced pressure in the syringe opens valve 40, 140, 240, and there is then sufficient restriction to flow through the media bed 50 to substantially prevent any flow through the bed when the valve is open. On the other hand, once the fluid has been drawn into the syringe and the plunger of the syringe is depressed, the check valve defaults to its closed position, assisted by the pressure generated in the syringe barrel by the back pressure due to restriction of flow through the media bed. With the valve closed, the dispensed fluid will flow only through the bed to exit through the needle of the syringe.

A typical operational flow sequence will now be described, with reference to Figures 6A to 6D, for an application where the media bed is an SPE medium chosen to trap targeted compounds from a sample liquid onto the bed. Drawback of the syringe plunger 14 opens the valve 40 and aspirates sample liquid into the barrel chamber 15 via flow path 34. The liquid does not pass through the medium or bed 50 (Figure 6A). When the plunger 14 is depressed to close the valve, the sample is directed out through the sorbent bed 50, trapping targeted compounds on the bed (Figure 6B). After brief contact with rinse fluid in the syringe needle, the syringe assembly is then moved to access an elution solvent. Here drawback of the syringe plunger 14 again opens the valve 40 and allows elution solvent to enter the barrel without traversing the sorbent bed (Figure 6C). Finally, the plunger 14 is depressed to close the valve and solvent is directed through the sorbent bed 50, eluting the trapped compounds as it passes (Figure 6D).

It will be appreciated that fraction collection and multiple solvent elution operations are also feasible.

Because the aspiration steps draw fluid through the check valve path and only the dispensing steps force fluid through the medium path, the reason for a minimum particle size restriction in media beds is removed. This permits the use of smaller particle sized media, for example down to as little as 1 micron diameter. The advantage of smaller media particle size is much higher compound capacity before saturation/breakthrough occurs and a much narrower band of eluted compound. The result is a nearly true chromatographic separation. The higher sample concentration in the elution band gives much greater sensitivity for analytical analysis.

These outcomes are illustrated in the graph of Figure 7, which depicts an experimental SPE elution profile and SPE carryover for the embodiment of Figures 1 and 2 in comparison to the standard MEPS solution profile and MEPS carryover.

With the increased capacity and single directional flow of the sample through the bed the targeted compounds are focused in a narrow band at the top of the bed and when they are eluted with the elution solvent, the sample components can come off in a very narrow band or in a small volume. This small elution volume means the concentration of the targeted sample compounds can be very high, in fact higher than conventional SPE and even MEPS. This eliminates the need to concentrate the sample ready for analysis as is always necessary in conventional SPE.

For example, it has been demonstrated that 10ml of sample can be processed down to 10 microlitres of eluent containing the targeted compounds. This is a concentration factor of 1000 : 1 and can be achieved in minutes.

The flow characteristics of the device are such that there is minimal dead volume and good Gaussian elution profiles of the sample compounds can be achieved from the SPE cartridge.

The cleaning of a syringe, particularly in an automated system, is limited to filing and dispensing solvent multiple times. Conventionally, with each cycle of filling and dispensing, materials in the syringe flow path are diluted. With this check valve design, there is a one direction flow at all times through the areas of the syringe where

contamination can occur, so the process is a purge of the syringe which is far more efficient cleaning process than repeated dilutions.

While originally designed for SPE applications, the ability to use small particle sorbent materials enables the check valve cartridge to be used as a pseudo liquid chromatography column where partition separation can be altered for various SPE media.

Combined with an automated system, the configuration of the invention can be programmed to elute and collect defined partition bands for concentration or targeted pre-analytical separation.

Often a liquid chromatography system is used as the sample preparation step for mass spectrometry involving specialised high pressure solvent delivery systems and valving systems. There are some sample analysis types where a syringe with a check valve cartridge as illustrated with SPE media can perform the same function as the sophisticated LC system.

Figure 8 illustrates a further embodiment generally similar to that of Figures 1 and 2, but with a ball valve 440 as the one-way check valve. Other possible forms of the check valve include, without limitation, flap valves, duck bill valves, and umbrella valves.

Figure 9 illustrates how the inventive concept is readily extendable to a disposal pipette 510 tip. Such tips can have a variety of volumes, materials and shapes, and can subsequently be used on a standard or modified pipettor. Again, after the fluid has been drawn into the barrel side 512 of the tip, the pipettor is depressed, the check valve 540 defaults to the closed position assisted by the pressure generated in the syringe component by the back pressure due to restriction of flow through the media bed 550. With the valve closed, the dispensed liquid from the pipettor tip can only flow through the media bed 550 and exit through the tip outlet 500.

CLAIMS

1. Flow control apparatus for facilitating treatment of a fluid containing a sample for analysis, comprising:

a body having spaced ends, which body defines therein a fluid flow passage arrangement extending between said ends;

wherein the fluid flow passage arrangement includes two flow paths that are configured in parallel, merge within said body at least once, and respectively contain a one-way check valve and a medium selected to treat or modify sample-containing fluid flowing therethrough.

2. Flow control apparatus according to claim 1 wherein said one-way check valve is arranged to substantially prevent flow along the flow path containing the valve to the merge with the other flow path.

3. Flow control apparatus according to claim 1 or 2 wherein said flow paths open separately from one of said ends of said body at spaced ports.

4. Flow control apparatus according to any one of claims 1 to 3, wherein said one-way check valve is a plug seal valve.

5. Flow control apparatus according to claim 4, wherein said plug seal valve includes an integral seal plug having respective axially adjacent portions of relatively larger and smaller cross-section, the latter defining a peripheral sealing surface that engages a complementary female surface, and the former defining a shoulder that biases the valve closed under pressure of the fluid.

6. Flow control apparatus according to claim 5, wherein the portions of relatively larger and smaller cross-section are generally cylindrical and:

(i) the ratio of the diameter of the portion of larger cross-section to the diameter of the portion of smaller cross-section is in the range 2 to 4, and

(ii) the ratio of the combined length of both portions to the length of the portion of smaller cross-section is in the range 1.25 to 2.5.

7. Flow control apparatus according to claim 5 or 6 where said seal plug is silicone rubber.

8. Flow control apparatus according to any one of claims 1 to 3, wherein said one-way check valve is a ball valve.

9. Flow control apparatus according to any one of claims 1 to 8 wherein said medium has ends spaced along its respective passage and frits or sorbent terminations are provided at one of both of said ends of the medium.

10. Flow control apparatus according to any one of claims 1 to 9 wherein said medium is a sorbent bed selected to trap targeted compounds from said fluid as it passes through the sorbent bed, for subsequent recovery from the bed by an elution solvent.

11. Flow control apparatus according to claim 10 wherein the sorbent bed is a solid stationary phase bed, for practising Solid Phase Extraction (SPE) or Micro Extraction by Packed Solvent (MEPS) of the targeted compounds.

12. Flow control apparatus according to any one of claims 1 to 11 wherein said medium is selected from the group comprising filtering media, monoliths and immobilised biologically active materials.

13. Flow control apparatus according to any one of claims 1 to 12 mounted within a barrel of a syringe, wherein said merged passages form a single duct communicable with a needle for the syringe, and said flow paths open separately into the interior chamber of said barrel.

14. Flow control apparatus according to any one of claims 1 to 12 provided as a separate unit attachable on the front of a syringe.

15. A syringe assembly for facilitating treatment of a fluid containing a sample for analysis, comprising:

a syringe barrel and a complementary plunger;

a fluid flow passage arrangement in communication with a chamber defined by the barrel and the plunger;

wherein the fluid flow passage arrangement includes two flow paths that are configured in parallel, and respectively contain a one-way check valve and a medium selected to treat or modify sample-containing fluid flowing therethrough.

16. A syringe assembly according to claim 15 wherein said one-way check valve is arranged to substantially prevent flow along the flow path containing the valve.

17. A syringe assembly according to claim 15 or 16 wherein said flow paths open separately into said chamber.

18. A syringe assembly according to any one of claims 15 to 17, wherein said one-way valve is a plug seal valve.

19. A syringe assembly according to claim 18, wherein said plug seal valve includes an integral seal plug having respective axially adjacent portions of relatively larger and smaller cross-section, the latter defining a peripheral sealing surface that engages a complementary female surface, and the former defining a shoulder that biases the check valve closed under pressure of the fluid.

20. A syringe assembly according to claim 19, wherein the portions of relatively larger and smaller cross-section are generally cylindrical and:

(i) the ratio of the diameter of the portion of larger cross-section to the diameter of the portion of smaller cross-section is in the range 2 to 4, and

(ii) the ratio of the combined length of both portions to the length of the portion of smaller cross-section is in the range 1.25 to 2.5.

21. A syringe assembly according to claim 19 or 20 where said seal plug is silicone rubber.

22. A syringe assembly according to any one of claims 15 to 17, wherein said one-way valve is a ball valve.

23. A syringe assembly according to any one of claims 15 to 22 wherein said medium has ends spaced along its respective passage and frits or sorbent terminations are provided at one of both of said ends of the medium.

24. A syringe assembly according to any one of claims 15 to 23 wherein said medium is a sorbent bed selected to trap targeted compounds from said fluid as it passes through the sorbent bed, for subsequent recovery from the bed by an elution solvent.

25. A syringe assembly according to claim 24 wherein the sorbent bed is a solid stationary phase bed, for practising Solid Phase Extraction (SPE) or Micro Extraction by Packed Solvent (MEPS) of targeted compounds.

26. A syringe assembly according to any one of claims 15 to 25 wherein said medium is selected from the group comprising filtering media, monoliths and immobilised biologically active materials.

27. A one-way plug seal valve having a valve seat and a valve plug, where the valve plug comprises respective axially adjacent portions of relatively larger and smaller cross-section, the latter defining a peripheral sealing surface that engages the valve seat and the former defining a shoulder that biases the valve closed under pressure of the fluid.

28. A one-way plug seal valve according to claim 27 wherein the portions of relatively larger and smaller cross-section are generally cylindrical and:

(i) the ratio of the diameter of the portion of larger cross-section to the diameter of the portion of smaller cross-section is in the range 2 to 4, and

(ii) the ratio of the combined length of both portions to the length of the portion of smaller cross-section is in the range 1.25 to 2.5.

29. A one-way plug seal valve according to claim 27 or 28 where said seat plug is silicone rubber.

30. A one-way plug seal valve according to claim 27, 28 or 29, wherein said valve seat is conical.

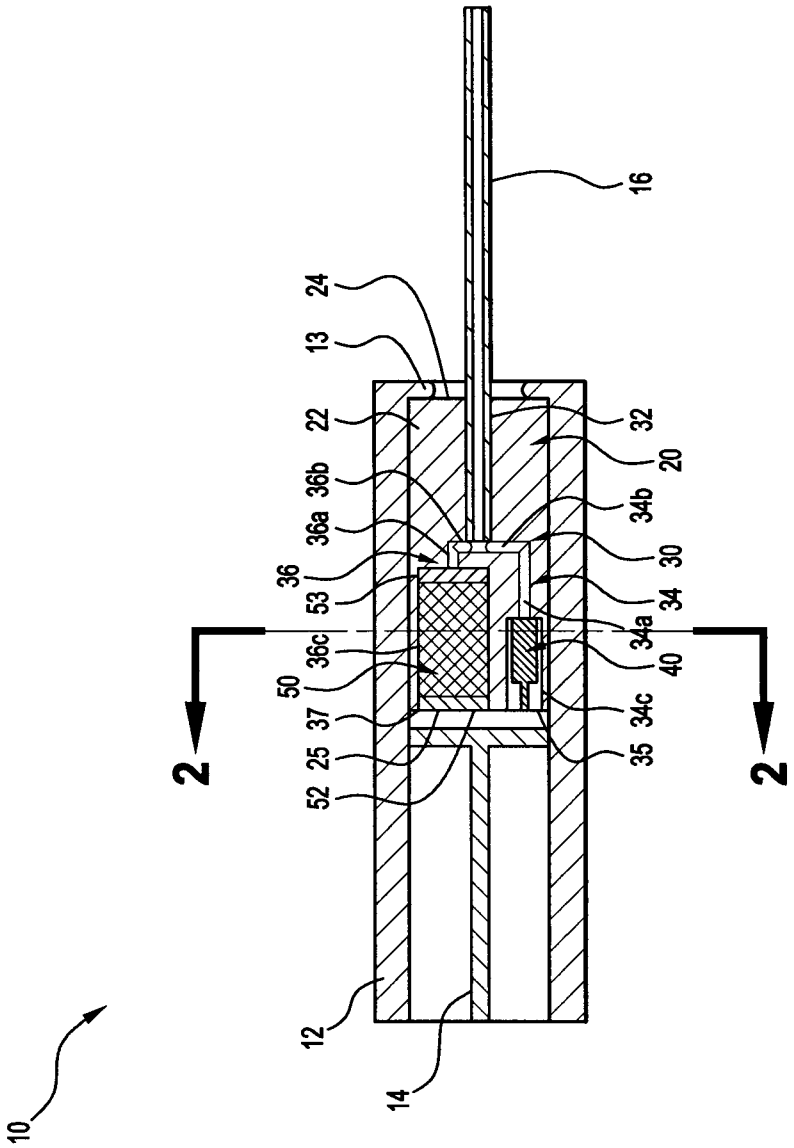
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FIG. 1

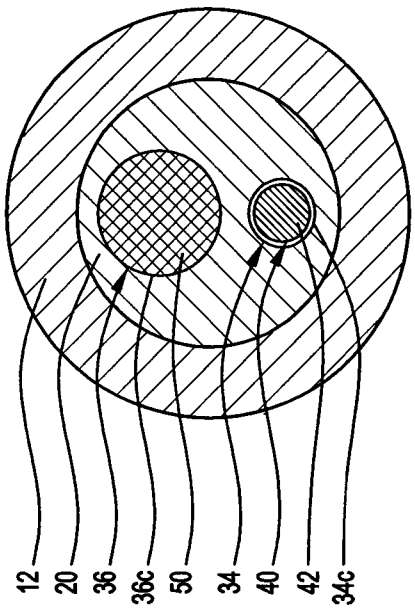

FIG. 2

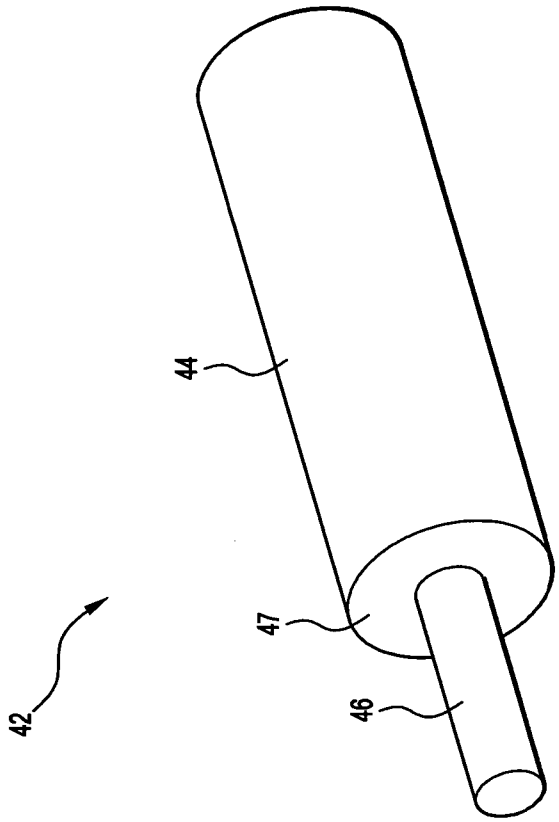

FIG. 3

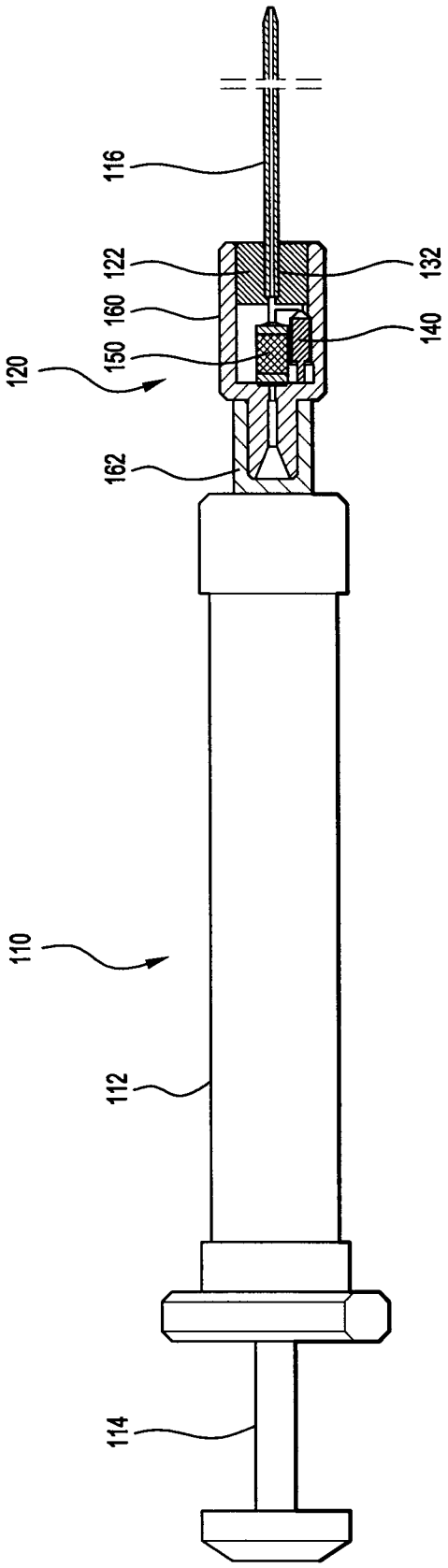

FIG. 4

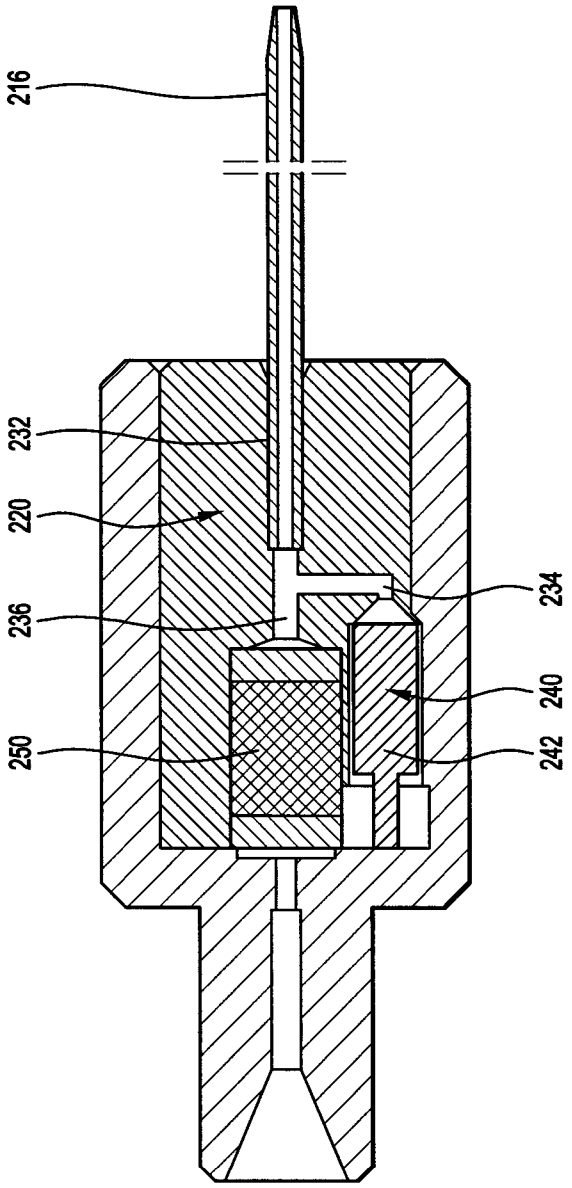

FIG. 5

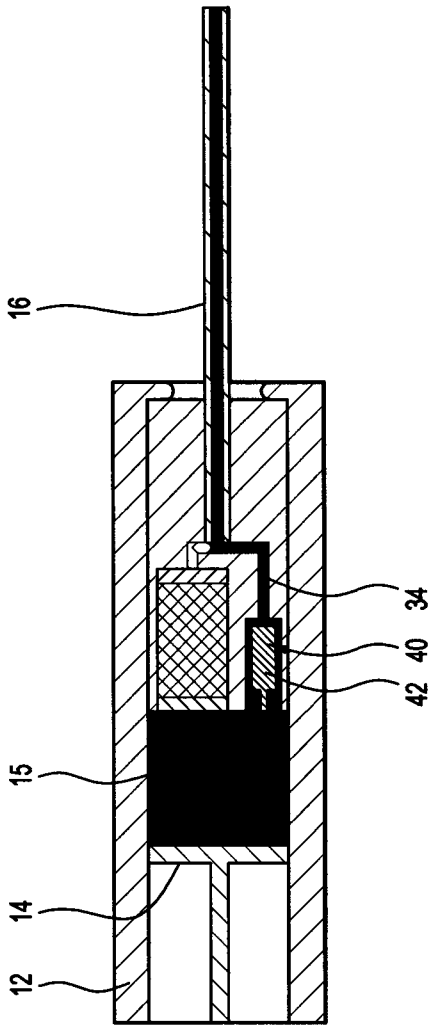

FIG. 6A

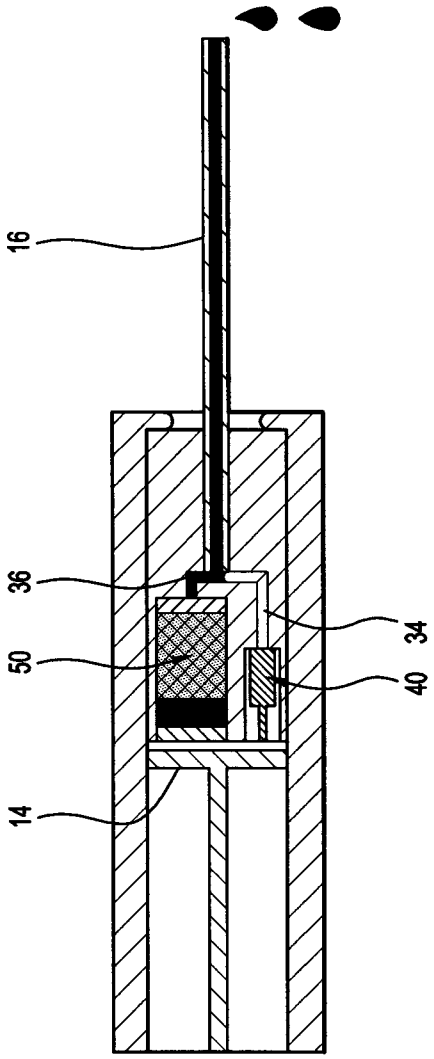

FIG. 6B

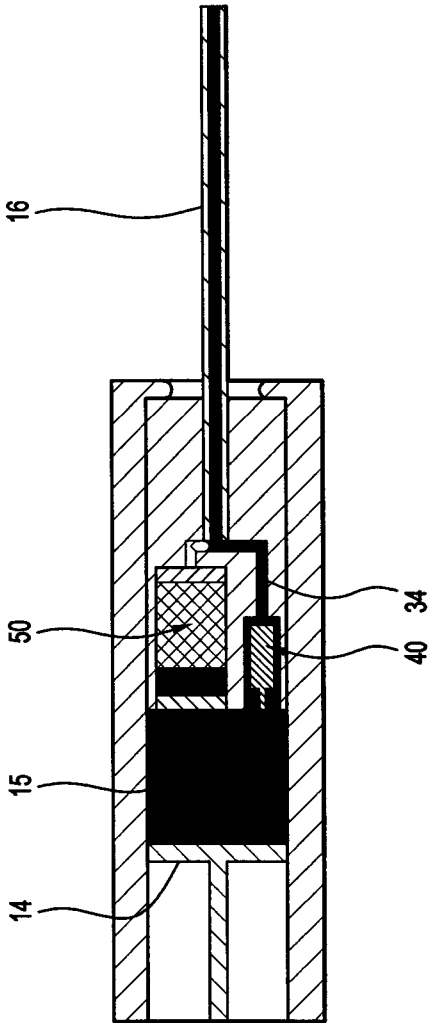

FIG. 6C

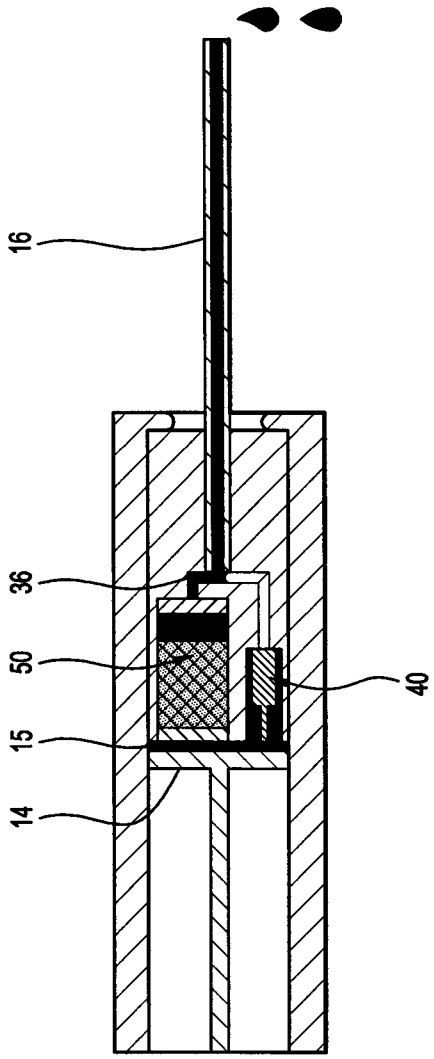

FIG. 6D

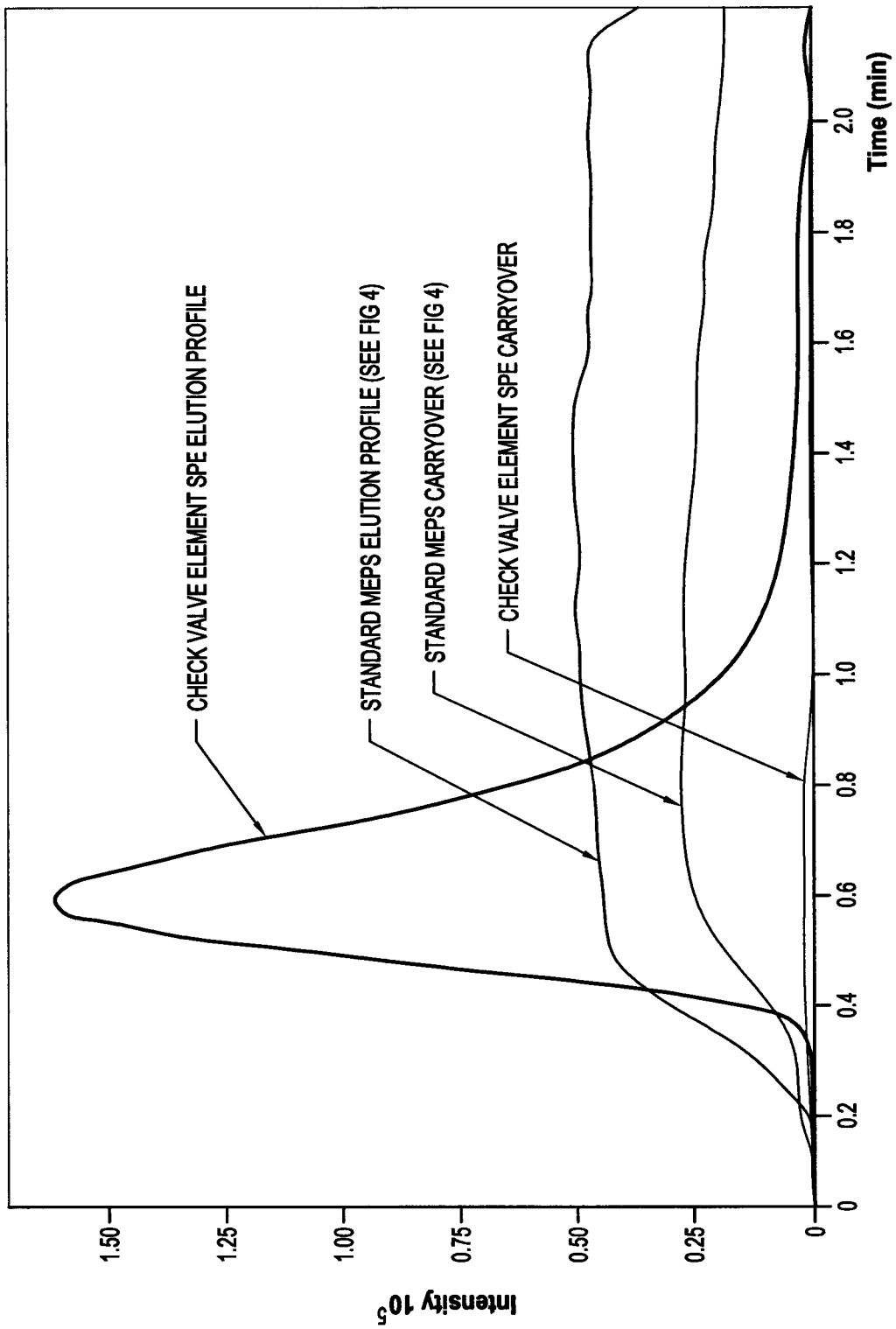
CHECK VALVE ELEMENT SPE ELUTION PROFILE
STANDARD MEPS ELUTION PROFILE (SEE FIG 4)
STANDARD MEPS CARRYOVER (SEE FIG 4)
CHECK VALVE ELEMENT SPE CARRYOVER
Intensity 10^5
1.50
1.25
1.00
0.75
0.50
0.25
0
0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
Time (min)

FIG. 7

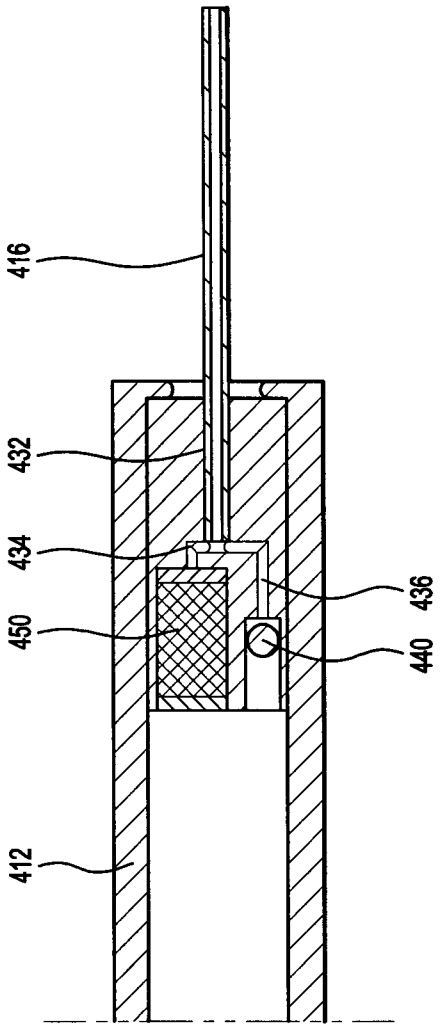

FIG. 8

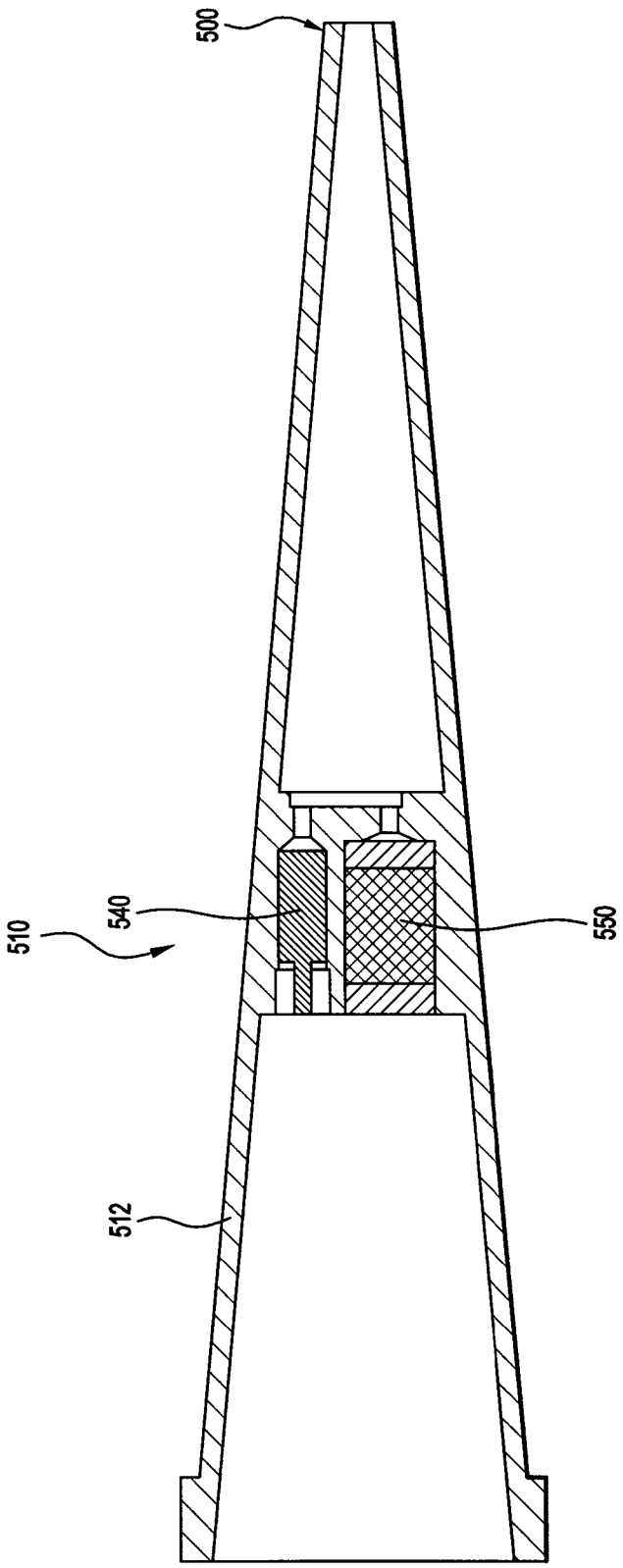

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2013/001526

A. CLASSIFICATION OF SUBJECT MATTER

G01N 30/14 (2006.01) G01N 30/50 (2006.01) G01N 1/10 (2006.01) B01D 11/04 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases: GOOGLE PATENTS, GOOGLE SCHOLAR, ESPACENET, EPODOC, WPI, English fulltext cluster (TXTUS5, TXTUS4, TXTUS3, TXTUS2, TXTUS1, TXTUS0, TXTEP1, TXTGB1, TXTWO1, TXTAU1, TXTCA1, TXTSG1)

Keywords: Analytical, Spectroscopy, Chromatography, Syringe, Inject, Needle, Flow Path, Passages, Fluid, Parallel, Valve, Preparation, Treatment, Elution, Sorbent Bed, Filter, Solid Phase Extraction, Micro extraction by packed solvent and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2014	28 February 2014
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au Facsimile No.: +61 2 6283 7999	ISAAC TAN AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832814

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2013/001526

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1 - 14, 15 - 26

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	**PCT/AU2013/001526**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5770029 A (NELSON et al.) 23 June 1998 Abstract, Figure 1, Columns 4 - 6 & 9 - 10	1 - 26
A	US 6613525 B2 (NELSON et al.) 02 September 2003 Whole Document	1 - 26
A	WO 2012/158315 A1 (PURADYN FILTER TECHNOLOGIES, INC.) 22 November 2012 Whole Document	1 - 26
A	WO 1998/039099 A1 (ARGONAUT TECHNOLOGIES, INC.) 11 September 1998 Whole Document	1 - 26
A	WO 2005/121963 A2 (IQUUM, INC.) 22 December 2005 Whole Document	1 - 26

INTERNATIONAL SEARCH REPORT	International application No. PCT/AU2013/001526

Supplemental Box

Continuation of: **Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1 - 14 & 15 - 26 are directed to a flow control apparatus/syringe assembly for facilitating the treatment of a fluid containing a sample for analysis wherein the features of a fluid flow passage arrangement including two flow paths that are configured in parallel, and respectively contain a one-way check valve and a medium selected to treat or modify sample-containing fluid flowing therethrough is specific to this group of claims.

- Claims 27 - 30 are directed towards a one-way plug seal valve having a value seat and a valve plug, where the valve plug comprises respective axially adjacent portions of relatively larger and smaller cross-section, the latter defining a peripheral sealing surface that engages the valve seat and the former defining a shoulder that biases the valve closed under pressure of the fluid is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention. In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed invention is the reference to valves (one-way check valve or one-way plug seal valve). However it is considered that this feature is generic. Therefore this common feature cannot be a special technical feature. Hence there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently
not satisfied a priori.

It is considered that search and examination for the second invention will require more than negligible additional search and examination effort over that for the first invention, and therefore an additional search fee is warranted.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/001526**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 5770029 A	23 Jun 1998	AU 715268 B2	20 Jan 2000
		AU 744264 B2	21 Feb 2002
		AU 758140 B2	13 Mar 2003
		AU 2436497 A	29 Oct 1997
		AU 2488799 A	23 Aug 1999
		AU 3968097 A	20 Feb 1998
		AU 4431597 A	14 Apr 1998
		AU 7101698 A	30 Oct 1998
		AU 7467591 A	18 Sep 1991
		CA 2075969 A1	29 Aug 1991
		CA 2249886 A1	16 Oct 1997
		CA 2261869 A1	05 Feb 1998
		CA 2266105 A1	26 Mar 1998
		CA 2285938 A1	15 Oct 1998
		CA 2320362 A1	12 Aug 1999
		EP 0521911 A1	13 Jan 1993
		EP 0927352 A2	07 Jul 1999
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		EP 1007953 B1	06 Dec 2006
		EP 1015878 A1	05 Jul 2000
		EP 1015878 B1	09 Jun 2010
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		EP 1053298 B1	25 Sep 2013
		JP H05504628 A	15 Jul 1993
		JP 2601595 B2	16 Apr 1997
		JP H08327597 A	13 Dec 1996
		JP 3103031 B2	23 Oct 2000
		JP 2000515978 A	28 Nov 2000
		JP 3989964 B2	10 Oct 2007
		JP 2000508763 A	11 Jul 2000
		JP 2001500971 A	23 Jan 2001
		JP 2001519907 A	23 Oct 2001
		JP 2002502597 A	29 Jan 2002
		US 5126022 A	30 Jun 1992
		US 5750015 A	12 May 1998

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/001526**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		US 5770029 A	23 Jun 1998
		US 5858188 A	12 Jan 1999
		US 5935401 A	10 Aug 1999
		US 6007690 A	28 Dec 1999
		US 6054034 A	25 Apr 2000
		US 6056860 A	02 May 2000
		US 6074827 A	13 Jun 2000
		US 6093296 A	25 Jul 2000
		US 6176962 B1	23 Jan 2001
		US 6306272 B1	23 Oct 2001
		US 6344326 B1	05 Feb 2002
		US 6413400 B1	02 Jul 2002
		US 2002119482 A1	29 Aug 2002
		US 6613525 B2	02 Sep 2003
		US 6808609 B1	26 Oct 2004
		US 2002056640 A1	16 May 2002
		US 6964735 B2	15 Nov 2005
		US 2002053399 A1	09 May 2002
		US 2003224436 A1	04 Dec 2003
		WO 9112904 A1	05 Sep 1991
		WO 9738300 A1	16 Oct 1997
		WO 9804909 A1	05 Feb 1998
		WO 9812530 A2	26 Mar 1998
		WO 9845693 A1	15 Oct 1998
		WO 9940174 A1	12 Aug 1999

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/001526**

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		AU 7467591 A	18 Sep 1991
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		EP 0990147 A1	05 Apr 2000
		EP 1007953 A1	14 Jun 2000
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		EP 1053298 B1	25 Sep 2013
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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/001526**

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		US 5770029 A	23 Jun 1998
		US 5858188 A	12 Jan 1999
		US 5935401 A	10 Aug 1999
		US 6007690 A	28 Dec 1999
		US 6054034 A	25 Apr 2000
		US 6056860 A	02 May 2000
		US 6074827 A	13 Jun 2000
		US 6093296 A	25 Jul 2000
		US 6176962 B1	23 Jan 2001
		US 6306272 B1	23 Oct 2001
		US 6344326 B1	05 Feb 2002
		US 6413400 B1	02 Jul 2002
		US 2002119482 A1	29 Aug 2002
		US 6613525 B2	02 Sep 2003
		US 6808609 B1	26 Oct 2004
		US 2002056640 A1	16 May 2002
		US 6964735 B2	15 Nov 2005
		US 2002053399 A1	09 May 2002
		US 2003224436 A1	04 Dec 2003
		WO 9112904 A1	05 Sep 1991
		WO 9738300 A1	16 Oct 1997
		WO 9804909 A1	05 Feb 1998
		WO 9812530 A2	26 Mar 1998
		WO 9845693 A1	15 Oct 1998
		WO 9940174 A1	12 Aug 1999

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/001526**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2012/158315 A1	22 Nov 2012	CN 103534448 A	22 Jan 2014
		US 2012292236 A1	22 Nov 2012
		WO 2012158315 A1	22 Nov 2012
WO 1998/039099 A1	11 Sep 1998	EP 0971791 A1	19 Jan 2000
		JP 2002503141 A	29 Jan 2002
		US 6126904 A	03 Oct 2000
		WO 9839099 A1	11 Sep 1998
WO 2005/121963 A2	22 Dec 2005	AU 2005253151 B2	19 Aug 2010
		CA 2569601 A1	06 Dec 2006
		CN 101432698 A	13 May 2009
		CN 101432698 B	06 Jun 2012
		EP 1771786 A2	11 Apr 2007
		JP 2008505346 A	21 Feb 2008
		US 2007292858 A1	20 Dec 2007
		US 7785535 B2	31 Aug 2010
		US 2010323919 A1	23 Dec 2010
		US 8414845 B2	09 Apr 2013
		WO 2005121963 A2	22 Dec 2005

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.