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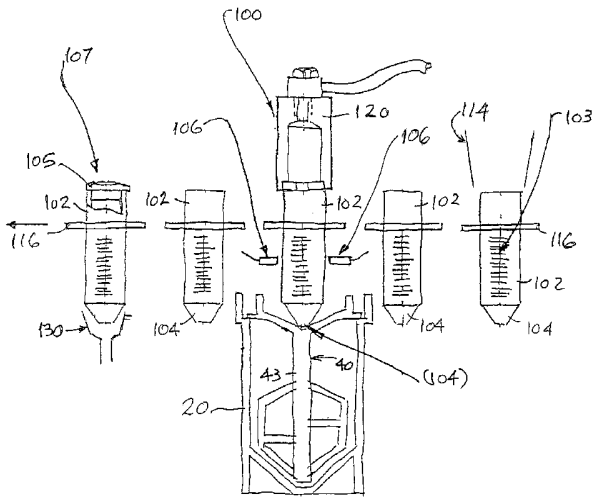

(57) Abstract: Apparatus and method for processing specimens, e.g., biological specimens, to extract samples for both liquid (i.e., extracellular) and slide-based (i.e., intracellular) testing. Both types of samples can be obtained from a single fluid specimen. A fluid sampling station removes fluid from a specimen container and places it in a sample receptacle. A specimen acquisition station removes fluid from the container, separates particulate matter (e.g., cells) from the removed fluid, and forms a sample layer of particulate matter, which is transferred to a slide. The two sampling operations can be carried out in any order. The fluid sample receptacle may have a special one-way valve arrangement. The apparatus can be automated so as to process multiple fluid specimens in their respective containers. The machine according to this invention is a "platform instrument" that can produce all required liquid samples and slide-based samples for essentially all cytopathology tests.

WO 03/054552 A2

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AUTOMATED SYSTEM AND METHOD FOR PROCESSING SPECIMENS TO EXTRACT SAMPLES FOR BOTH LIQUID-BASED AND SLIDE-BASED TESTING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of commonly owned U.S. provisional application Nos. 60/330,092, filed October 19, 2001, 60/372,080, filed April 15, 2002, and 60/373,658, filed April 19, 2002, all of which are incorporated herein by reference. This application also is related to the commonly owned non-provisional application filed concurrently herewith, entitled "Automated System and Method for Processing Multiple Liquid-Based Specimens" and naming Norman J. Pressman and William J. Mayer as inventors, which is also incorporated herein by reference.

TECHNICAL FIELD

The invention relates to processing fluid specimens, e.g., biological fluid specimens, to extract samples for testing.

BACKGROUND

In the medical community it is commonly hypothesized and accepted that patient outcomes are improved by early disease detection, diagnosis, and therapeutic monitoring and intervention. Scientific advances in cell biology, cytogenetics, and molecular pathology are leading to new screening and diagnostic methods with increased sensitivity and specificity. These improved means for early detection and diagnosis, as well as these improved means for therapeutic monitoring, are being implemented, for example, in reference laboratories, medical clinics, and hospital-based clinical testing laboratories.

Many classes of diseases are either cell-based (e.g., (a) cancers such as lung, colorectal, bladder, prostate, cervical and breast cancer, and (b) neurological and muscular degenerative diseases such as Alzheimer's and Parkinson's diseases) or based upon the cellular environment and products within the patient or host organism (e.g., (a) immune diseases such as HIV/AIDS and autoimmune diseases, and (b) other infectious diseases such as sexually transmitted diseases (STDs) of the gynecological tract caused by viral, bacterial, fungal, parasitic or other infectious agents). Advanced screening and diagnostic methods are often based on the detection of molecules, molecular events, or foreign organisms both within (i.e., intracellular) and external to (i.e., extracellular) suspicious, atypical, infected, and/or cancer cells.

Specimens from patients are collected when patients undergo screening, diagnostic or therapeutic monitoring examinations. Examples of screening examinations during which such specimens are collected include examinations for lung cancer as evidenced by sputum analyses, colorectal cancer, cervical cancer as evidenced by PAP smears and pelvic gynecological examinations, bladder cancer as evidenced by voided urine analyses, and skin cancer examinations. These specimens need to be processed before expert medical professionals and analytical instruments (e.g., cytotechnologists, pathologists, hematologists, blood chemistry analyzers, flow cytometers, spectrometers) can evaluate, interpret and classify/diagnose samples from these specimens. Specimen processing may involve many diverse steps including, but not limited to specimen collection, cell dispersal, disaggregation of mucous, fixation, aliquoting, homogenization, cell-deposition, staining, cellular molecular labeling, and glass microscope-slide coverslipping techniques.

The outcome or byproducts of specimen processing protocols are patient samples that are ready for subsequent human or machine assessment. Typically, two types of cytopathology samples are prepared depending upon whether the clinical material will be subjected to intracellular or extracellular analyses. Samples prepared for intracellular cytopathology analyses are either microscope slide-based (for expert human review or machine assessment) or liquid-based for assessment by flow cytometers, PCR analyzers and/or other analytical instruments. Samples prepared for extracellular cytopathology analyses are predominantly liquid samples collected or subsequently placed into test tubes, vials or other sample containers for biomedical liquid samples.

Slide-based preparations can be produced by several techniques, such as conventional cervical-vaginal Papanicolaou (PAP) smears or by improved means such as LBP (liquid-based preparation) technologies that result in thin-layer or monolayers of cells deposited onto glass microscope slides for improved visualization and/or machine analysis. The MonoGen MONOPREP™ LBP instrument, which is disclosed in the aforementioned provisional application No. 60/372,080 and in the aforementioned non-provisional application filed concurrently herewith, is an example of such a slide and sample preparation device. These types of sample preparations (i.e., LBP slides) are used for intracellular analyses with numerous testing methods such as the direct visualization employed by conventional PAP tests performed by expert cytotechnologists and pathologists, and peripheral blood leukocyte differential whole blood counts performed by hematologists. Other intracellular analyses include molecular diagnostic tests that

determine the presence, absence, overexpression or underexpression of proteins (e.g., immunocytochemistry techniques) or other molecules found within cells or organelles (e.g., nuclear, nucleolar, mitochondrial, cytoplasmic) including the detection of cytogenetic molecular changes in DNA structure (e.g., sequencing) and content (e.g., *in situ* hybridization techniques).

Liquid samples are often produced for machine analyses of extracellular content. These samples include test tubes of heparinized blood for blood chemistry tests (e.g., SGOT, NA, K, CA, Alkaline Phosphatase, PSA, BUN/creatinine ratio, hemoglobin, hematocrit, blood gluocose, and HDL and LDL cholesterol content). Technologies used for extracellular analyses from liquid samples include, but are not limited to, PCR (i.e., Polymerase Chain Reaction), NASBA (Nucleic Acid Strand-Based Amplification), microarray genetyping, hybrid capture, direct hybridization, sequencing, spectrometers, liquid chromatography, fluorescent antibody detection, antigen detection, immunochemistry, enzyme chemistry, DNA analysis, nuclear probe detection, viral and RNA quantification, flow microfluorometric cytometers, and cell sorters. Tests on these liquid samples include, but are not limited to tests for chlamydia, cytomegalovirus (CMV) including detection of CMV antigens by EIA, trachomatis detection by direct and amplified probes, hepatitis (B and C) core IgG and IgM and surface antibodies and antigens, pneumonia including by direct probe techniques, HIV-1 detection by detection and quanitification by direct and amplified probes, and mycobacteria turberculosis DNA and RNA quantitation and detection *via* direct and amplified probes.

Some tests (e.g., detection of presence of non-host infectious organisms) can be based upon either intracellular assays (e.g., slide-based samples) or extracellular assays (e.g., liquid samples). Examples include tests for the detection of STDs including gonorrhea, trachomatis, and chlamydia (GTC).

Machines already exist to take specimens collected at the point-of-care (POC) site and produce LBP microscope slide-based samples (e.g., the MonoGen MONOPREP™ LBP system referenced above, and the Cytyc THINPREP® 2000 and 3000 LBP machines). Other machines already exist to take POC specimens and produce liquid samples (e.g., blood chemistry analyzers from Olympus America, Inc.) and perform a variety of extracellular tests. No single instrument exists that can produce samples from clinical cytology specimens that are suitable for both types of analyses.

SUMMARY DISCLOSURE OF THE INVENTION

The invention is a system and method for processing specimens to extract samples for both liquid (i.e., extracellular) and slide-based (i.e., intracellular) testing. It is an improvement on the LBP device, system and method disclosed in the aforementioned provisional application No. 60/372,080 and in the aforementioned non-provisional application filed concurrently herewith; and, like that LBP device and system, is compatible with post-processing machines, and can be interfaced with other devices as well as a central hospital or laboratory information system.

The machine according to this invention is a "platform instrument" that can produce all required liquid samples and slide-based samples for essentially all cytopathology tests, whether performed by visual examination by expert humans or analytical instruments, and/or whether performed based upon cytomorphological, cytogenetic, molecular diagnostic, microbiological, virological or other technologies and techniques. This is accomplished in a safe, fast, automated and efficient manner. The integration of the need for both types of samples from a single specimen minimizes the risk of introducing clerical errors associated with mislabeling and mishandling of patient specimens, samples, and associated data. This integration also minimizes the risk of producing disparate results from a variety of types of assays that are each based upon non-representative samples from the specimens of a single patient.

One aspect of the invention relates to a method and apparatus for obtaining different types of samples from a fluid specimen in a container. The container is supported in the apparatus, and the specimen is placed in fluid communication with a fluid sampling station of the apparatus, which removes fluid from the container and places in a sample receptacle. The specimen is also placed in fluid communication with a specimen acquisition station of the apparatus, which removes fluid from the container, separates particulate matter from the removed fluid, and forms a sample layer of particulate matter. The two sampling operations can be carried out in any order.

The method and apparatus may be automated for processing multiple specimens in respective containers. For example, the specimen containers may be transported seriatim along a processing path, and may first be subjected to an optional preprocessing operation. Here, too, the two sampling operations can be carried out in any order. Sample receptacles used to collect fluid samples can be fed to the fluid sampling station automatically along a path that intersects the container processing path. Movement of containers and receptacles along their respective paths can be synchronized. The sample

layer formed at the specimen acquisition station may be transferred to a slide. As used herein, the term "slide" encompasses glass microscope slides as well as any other substrate on which a sample may be placed for subsequent testing or analysis.

Another aspect of the invention relates to a receptacle for collecting a fluid sample, e.g., for use at the fluid sampling station. The receptacle has a hollow body for receiving and holding fluid. A one-way valve is carried by the body and has a fluid flow passage between the exterior and the interior of the body. The valve is pressure-actuated to permit fluid flow into the body interior when the exterior pressure exceeds the interior pressure, and prevents outflow of fluid from the body under the influence of any other relative pressure conditions. There is also a vent in the body remote from the valve.

The valve has an inlet portion opening to the exterior of the body, and an outlet portion opening to the body interior. The flow passage extends between the inlet portion and the outlet portion. At least a portion of the flow passage is resiliently biased to a closed position when the interior and exterior pressures are substantially equal, and is expandable to allow fluid flow into the body in response to a positive pressure differential across the valve from the inlet portion to the outlet portion. The valve preferably is made of resilient material, e.g., an elastomer, and preferably is configured so that it can be coupled directly to the fluid source to be sampled.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Preferred embodiments of the disclosed apparatus and method, including the best mode for carrying out the invention, are described in detail below, purely by way of example, with reference to the accompanying drawing figures, in which:

Fig. 1a is a top plan view of the LBP device disclosed in the aforementioned provisional application No. 60/372,080 and in the aforementioned non-provisional application filed concurrently herewith, showing a modification according to this invention;

Fig. 1b is a schematic diagram of the operating sequence of the LBP device, adapted in accordance with this invention;

Fig. 2 is a schematic illustration of the fluid sampling draw station according to this invention;

Fig. 3 is a schematic detail view of the fluid sampling draw station of Fig. 2;

Fig. 4 is a schematic detail plan view showing how the fluid sampling draw station of this invention interfaces with the LBP device; and

Fig. 5 is a schematic view showing sample fluid extraction for testing.

DETAILED DESCRIPTION OF BEST MODE

Fig. 1a shows the overall arrangement of the aforementioned LBP device, which transports multiple specimen containers sequentially through various processing stations and produces fixed specimens on slides, each slide being bar-coded and linked through a data management system (DMS) to the vial and the patient from which it came. In the preferred arrangement, each container has a special internal processing assembly detachably coupled to its cover, and is transported through the LBP device on a computer-controlled transport (conveyor) 240, in its own receptacle 246. (In the example shown the conveyor has thirty receptacles.) The containers and the receptacles are keyed so that the containers proceed along the processing path in the proper orientation, and cannot rotate independently of their respective receptacles.

The containers first pass a bar code reader 230 (at a data acquisition station), where the vial bar code is read, and then proceed stepwise through the following processing stations of the LBP device: an uncapping station 400 including a cap disposal operation; a preprocessing station 500; a filter loading station 600; a specimen acquisition and filter disposal station 700; and a re-capping station 800. These six stations are structured for parallel processing, meaning that all of these stations can operate simultaneously on different specimens in their respective containers, and independently of the other. The conveyor will not advance until all of these operating stations have completed their respective tasks.

The preprocessing station is the location at which preprocessing operations, such as specimen dispersal within its container, are performed prior to the container and its specimen moving on for further handling. The preprocessing station typically performs a dispersal operation. In the preferred embodiment, the dispersal operation is performed by a mechanical mixer, which rotates at a fixed speed and for a fixed duration within the specimen container. In this example, the mixer serves to disperse large particulates and microscopic particulates, such as human cells, within the liquid-based specimen by homogenizing the specimen. Alternatively, the specimen may contain subcellular sized objects such as molecules in crystalline or other conformational forms. In that case, a chemical agent may be introduced to the specimen at the preprocessing station to, for example, dissolve certain crystalline structures and allow the molecules to be dispersed throughout the liquid-based specimen through chemical diffusion processes without the need for mechanical agitation. Such a chemical preprocessing station introduces its dispersing agent through the preprocessing head.

There is also an integrated system 900 that includes additional bar code readers, slide cassettes, handling mechanisms for slide cassettes and individual slides, and a slide presentation station 702 at which the specimen acquisition station transfers a representative sample from a specimen to a fresh microscope slide. An optional auto loading mechanism 300 automatically loads and unloads specimen vials onto and from the transport mechanism. All stations and mechanisms are computer-controlled. Fig. 1b shows the operating sequence of the LBP device. This is the top-level table from which the operating software is structured.

In the preferred embodiment of the LBP device disclosed in the aforementioned applications, the vial uncapping station 400 has a rotary gripper that unscrews the cover from the vial, and discards it into a biosafety disposable waste handling bag. Before doing so, however, the uncapping head presses on the center of the cover to detach the internal processing assembly from the cover. The preprocessing (mixing) station 500 has an expanding collet that grips the processing assembly, lifts it slightly and moves (e.g., spins) it in accordance with a specimen-specific stirring protocol (speed and duration). The filter loading station 600 dispenses a specimen-specific filter type into a particulate matter separation chamber (manifold) at the top of the processing assembly. The specimen acquisition station 700 has a suction head that seals to the filter at the top of the processing assembly and first moves the processing assembly slowly to re-suspend particulate matter in the liquid-based specimen. Then the suction head draws a vacuum on the filter to aspirate the liquid-based specimen from the vial and past the filter, leaving a thin layer of cells on the bottom surface of the filter. Thereafter the thin layer specimen is transferred to a fresh slide, and the container moves to the re-capping station, where a foil-type seal is applied.

In accordance with a preferred embodiment of the present invention, the LBP device shown in Fig. 1a also is equipped with a fluid sampling draw station 100, which is adapted to engage the processing assembly (stirrer) present in any of the specimen containers processed by the LBP device. As illustrated in this figure, the fluid sampling draw station 100 is located just after (downstream of) the mixing station 500 of the LBP device. However, the fluid sampling draw station instead could be located downstream of the specimen acquisition station 700.

Referring to Figs. 2 and 3, sample receptacles in the form of special molded plastic test tubes 102 are used to collect specimen fluid at the fluid sampling draw station 100, to be processed by other preprocessing devices, or external PCR or other test protocols,

devices, or systems. Test tube 102 preferably is transparent to a sensor, and is designed to collect about 5 ml of specimen fluid, although smaller or larger test tubes or other types of sample receptacles could be employed. Each test tube 102 preferably is laser-etched with a unique machine-readable bar code number 103. The test tubes themselves and/or their closure caps 105 may be color-coded to distinguish specimen types (e.g., blood, urine, sputum, gastrointestinal, cervical, prostate). Specimen types may also be distinguished by employing receptacles (test tubes) of different size or height.

Test tube 102 is fitted with a thermoplastic elastomer one-way valve 104, e.g., a flap valve, on one end. The resilient nature of the valve material normally keeps the small flow passage therein squeezed tightly shut without the potential of sample leakage. This valve has an exposed frontal surface 112, the purpose of which is to act as a gasket when it is coupled to the element from which it is to draw fluid. In the preferred arrangement, that element is the suction tube 43 of the processing assembly (stirrer) 40 already in the specimen container 20, which is on the conveyor of the LBP device. The exposed tip of the valve, adjacent the inlet port 108, preferably is tapered so as to enter and positively seal against the upper end of the stirrer suction tube 43. The normally closed very small flow passage through outlet port 110 is formed in a tapered tip that is exposed to the test tube interior. The opposite end of the test tube is open, but can be sealed after filling by a cap 105 (e.g., sealed with an elastomer stopper).

One-way valve 104 is actuated by elevating the pressure on its inlet port 108 relative to the pressure on its outlet port 110. In this embodiment, a vacuum applied to the open end of the test tube also is applied to outlet port 110 of the valve, causing fluid to be drawn through the normally closed valve flow passage therein in only one direction – inwardly. Alternatively, pressurization of specimen container 20 would force fluid through stirrer tube 43 and one-way valve 104, into test tube 102.

After filling and capping, neither a positive pressure within test tube 102 nor rough handling of the test tube can force fluid back out through one-way valve 104. This eliminates a source of potential biohazard and cross-sample contamination. However, the resilient material of valve 104 can be coaxed mechanically to allow outflow of fluid. Fig. 5 shows one example of how a sample of the collected fluid can be extracted from a test tube 102. A syringe 103 may be used to access fluid through the one-way valve 104. The action of the one-way valve allows a blunt-faced cannula to enter the test tube 102 without damaging the self-sealing characteristics of the valve. Either a hand-held syringe or a

mechanically actuated cannula (connected to a vacuum source) can be used for this purpose.

In operation, as part of the LBP device, the fluid sampling draw station 100 moves the test tube 102 downwardly to force-couple the one-way valve 104 to the stirrer 40 in a specimen container 20 presented to the station. A vacuum cap 120 fitted with a gasket is coupled to the distal (uncapped) end of the test tube to draw fluid up through the hollow stirrer tube 43 and through the one-way valve 104. The vacuum cap 120 is connected to the LBP system vacuum source and is controlled by a solenoid valve. The same pneumatic actuator (not shown) that forces the one-way valve 104 into engagement with the stirrer 40 also presses the vacuum cap 120 against the test tube to make the vacuum seal. A conventional fluid-level control system includes liquid-level sensors 106 that monitor the aspiration process and signal operation cut-off to a controller when the proper level is reached. A bar code reader 109 (see Fig. 4) reads the bar code on the test tube, links the test tube bar code number to the bar code number of the specimen container (e.g., vial), and the acquired data is entered into the data management system (DMS). Thereafter, a cap 105 is applied to the distal end of the test tube at a capping station 107.

Actuation of the fluid sampling draw station 100 preferably is governed by the particular processing protocol for each specimen. Accordingly, there may be specimen containers 20 from which no fluid sample is drawn, in which case the fluid sampling draw station will remain idle while such a container dwells there. It is also possible for the fluid sampling draw station to draw a variable fluid volume, again dependent on the particular processing protocol for each specimen. To accomplish that, a plurality of vertically spaced fluid level sensors 106 would monitor the changing level of fluid in the test tube 102, and liquid draw would be terminated when the specified fluid volume is acquired.

Fig. 4 shows details of how the fluid sampling draw station 100 interfaces with the LBP device. In one embodiment, empty test tubes 102 are loaded in a vibratory bin feeder 114, which orients the test tubes valve-end-down and dispenses them via a gravity-operated track into a transport feed mechanism, such as a bandolier carrier or ribbon feeder 116. This transport mechanism indexes the test tubes laterally of the container transport conveyor 240 of the LBP device (top to bottom as seen in Fig. 4, left to right as seen in Fig. 2). This may be accomplished, e.g., by means of a walking beam escapement operated by two air cylinders (not shown). One cylinder delivers linear motion, while the other supplies the engage/disengage function. The bandolier carrier 116 also allows the.

vertical motion of a test tube required to clamp the valve tip seal 112 to the stirrer tube 43 during aspiration.

Test tube capping takes place at a capping station 107, as mentioned above. Here, a molded elastomer stopper 105 is escapement-fed from a supply bowl (not shown) and pressed into the open top of the test tube to form a seal. For this operation, stoppers 105 are supplied to the unit in pre-loaded tubes and escaped from the tube into a pressing chamber (not shown), where an air-operated actuator forces the stopper onto the test tube neck. An air blow/vacuum system 130 cleans any residual fluid from the tip of the one-way valve 104. Filled test tubes are then ejected from the carrier 116 at an ejection station, where they are delivered to a collection bin 118.

It is to be understood that the invention is not limited in its application to the details of construction and the arrangement of components and methods of the preferred embodiments described above and illustrated in the drawing figures. Variations will be apparent to those skilled in the art without departing from the scope of the invention, which is defined by the appended claims. As one example, the one-way valve could be made of any suitable resilient material, or could be made of a harder material that is coated or otherwise joined to a resilient material in those areas that require flexibility for sealing. As another example, sample receptacles (e.g., test tubes) may be fed to (and removed from) the fluid sampling draw station using any suitable mechanism(s), such as direct feed by a vibratory bowl feeder, or individual placement and removal by a pick-and-place mechanism.

Further, it should be noted that the invention in its broadest aspects does not require specimen premixing, or any type of specimen preprocessing. Nor does it require the use of specimen vials that come prepackaged with the special internal processing assembly 40 shown in Fig. 2 and disclosed in the aforementioned provisional application No. 60/372,080 and the aforementioned non-provisional application filed concurrently herewith. Nor does it require a conveyor to feed specimens to the operating stations/heads automatically. And it does not require use of the specific type of specimen acquisition/slide-making station 700 disclosed in those applications and described above. Thus, for example, other commercially available LBP processes and machines, such as the Cytyc THINPREP® 2000 and 3000 LBP devices, could be used to make the slide-based samples in accordance with this novel method for processing fluid specimens to obtain both liquid samples and slide-based samples. In such embodiments, the specimen

container, microscope slide, filter, and liquid sample receptacle can be placed manually into the device by a machine operator.

INDUSTRIAL APPLICABILITY

The above disclosure presents a safe, effective, accurate, precise, reproducible, inexpensive, efficient, fast and convenient system and method for handling and processing liquid-based specimens, e.g., cellular specimens, to obtain both liquid samples and slide-based samples for subsequent testing and/or analysis.

CLAIMS

1. An automated method for individually processing multiple fluid specimens of in respective containers, the method comprising:

transporting the containers seriatim along a processing path to present them to a preprocessing head, and subsequently to other processing heads comprising a fluid sampling draw head and a specimen acquisition head, in either order,

the preprocessing head adapted to perform a preprocessing operation on the specimen in each container presented to it,

the fluid sampling draw head adapted to remove preprocessed fluid from any container presented to it and place the removed fluid sample in a respective sample receptacle,

the specimen acquisition head adapted to aspirate preprocessed fluid from any container presented to it, pass the aspirated fluid through a filter so as to collect a particulate matter sample on the surface of the filter, and press the filter against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide;

actuating the preprocessing head in response to presentation of a container thereto so as to carry out the preprocessing operation independently;

actuating the fluid sampling draw head in response to presentation of a container thereto so as to carry out the fluid removal operation independently; and

actuating the specimen acquisition head in response to presentation of a container thereto so as to carry out the aspirating/sample transfer-to-slide operation independently.

2. An automated method according to claim 1, comprising transporting sample receptacles seriatim to the fluid sampling draw head along a receptacle path that intersects the processing path.

3. An automated method according to claim 2, comprising transporting sample receptacles with fluid samples therein seriatim from the fluid sampling draw head along a receptacle path that intersects the processing path.

4. An automated method according to claim 3, wherein the transport of sample receptacles to and from the fluid sampling draw head is synchronized with the transport of containers along the processing path.

5. An automated method according to claim 1, wherein each container has therein a processing assembly with an aspiration tube, and the fluid sampling draw head removes fluid from the container through the aspiration tube.

6. An automated method according to claim 5, wherein the processing assembly has an upper particulate matter separation chamber adapted to receive a filter, and the aspiration tube depends from and communicates with the separation chamber.

7. An automated method according to claim 5 or claim 6, wherein each sample receptacle has an inlet, the fluid sampling draw head places the inlet of a sample receptacle into sealing engagement with the processing assembly aspiration tube, and fluid is drawn directly into the sample receptacle.

8. An automated method according to claim 7, wherein the inlet of the sample receptacle comprises a one-way valve that allows fluid flow into but not out of the sample receptacle, the fluid sampling draw head places the one-way valve into sealing engagement with the processing assembly aspiration tube, and fluid is drawn directly into the sample receptacle through the one-way valve.

9. An automated method according to claim 8, wherein the fluid sampling draw head moves the sample receptacle downwardly to engage the one-way valve with the processing assembly aspiration tube before fluid is drawn into the sample receptacle, and upwardly to disengage the one-way valve from the aspiration tube after fluid draw.

10. An automated method according to claim 9, comprising transporting sample receptacles seriatim to the fluid sampling draw head along a receptacle path that intersects the processing path.

11. An automated method according to claim 10, comprising transporting sample receptacles with fluid samples therein seriatim from the fluid sampling draw head along a receptacle path that intersects the processing path.

12. An automated method according to claim 11, wherein the transport of sample receptacles to and from the fluid sampling draw head is synchronized with the transport of containers along the processing path.

13. An automated method according to claim 12, wherein the fluid sampling draw head draws a predetermined quantity of fluid into the sample receptacle.

14. An automated method according to claim 1, wherein the fluid sampling draw head draws a predetermined quantity of fluid into the sample receptacle.

15. An automated apparatus for individually processing multiple fluid specimens of in respective containers, the apparatus comprising:

a container transport for supporting and advancing containers seriatim along a processing path;

a preprocessing head along the processing path adapted to perform a preprocessing operation on the specimen in each container presented thereto by the container transport;

a fluid sampling draw head along the processing path downstream of the preprocessing head adapted to remove preprocessed fluid from the containers and place the removed fluid samples in respective sample receptacles;

a specimen acquisition head along the processing path downstream of the preprocessing head adapted to aspirate preprocessed fluid from the container presented thereto by the container transport and pass the fluid through a filter so as to collect a particulate matter sample on the surface of the filter, and press the filter against a respective slide positioned in proximity to processing path to transfer the particulate matter sample to the slide; and

a controller governing operation of the preprocessing head, operation of the fluid sampling draw head, operation of the specimen acquisition head and movement of the container transport, the controller responding to presentation of a container to the preprocessing head to cause the preprocessing head independently to preprocess the specimen in the container presented thereto, the controller responding to presentation of a container to the fluid sampling draw head to cause the fluid sampling draw head independently to remove preprocessed fluid therefrom, and the controller responding to presentation of a container to the specimen acquisition head to cause the specimen

acquisition head independently to aspirate preprocessed fluid therefrom and transfer the particulate matter sample from the filter to the slide.

16. An automated apparatus according to claim 15, comprising a receptacle transport that transports sample receptacles seriatim to the fluid sampling draw head along a receptacle path that intersects the processing path.

17. An automated apparatus according to claim 16, wherein the receptacle transport transports sample receptacles with fluid samples therein seriatim from the fluid sampling draw head along a receptacle path that intersects the processing path.

18. An automated apparatus according to claim 17, wherein the receptacle transport transports sample receptacles to the fluid sampling draw head on one side of the processing path, and transports sample receptacles with fluid samples therein away from the fluid sampling draw head on the other side of the processing path.

19. An automated apparatus according to claim 18, wherein the receptacle transport and the container transport are synchronized.

20. An automated apparatus according to claim 15, wherein each container has therein a processing assembly with an aspiration tube, and the fluid sampling draw head is adapted to draw fluid from the container through the aspiration tube.

21. An automated apparatus according to claim 20, wherein the processing assembly has an upper particulate matter separation chamber adapted to receive a filter, and the aspiration tube depends from and communicates with the separation chamber.

22. An automated apparatus according to claim 20 or claim 21, wherein each sample receptacle has an inlet, and the fluid sampling draw head has an actuator that moves a sample receptacle toward the container to place the inlet of the sample receptacle into sealing engagement with the processing assembly aspiration tube, whereby fluid is drawn directly into the sample receptacle.

23. An automated apparatus according to claim 22, wherein the inlet of the sample receptacle comprises a one-way valve that allows fluid flow into but not out of the sample receptacle, and the actuator of the fluid sampling draw head moves the sample receptacle to place the one-way valve into sealing engagement with the processing assembly aspiration tube, whereby fluid is drawn directly into the sample receptacle through the one-way valve.

24. An automated apparatus according to claim 23, wherein the actuator of the fluid sampling draw head moves the sample receptacle downwardly to engage the one-way valve with the processing assembly aspiration tube before fluid is drawn into the sample receptacle, and upwardly to disengage the one-way valve from the aspiration tube after fluid draw.

25. An automated apparatus according to claim 24, comprising a receptacle transport that transports sample receptacles seriatim to the fluid sampling draw head along a receptacle path that intersects the processing path.

26. An automated apparatus according to claim 25, wherein the receptacle transport transports sample receptacles with fluid samples therein seriatim from the fluid sampling draw head along a receptacle path that intersects the processing path.

27. An automated apparatus according to claim 26, wherein the receptacle transport transports sample receptacles to the fluid sampling draw head on one side of the processing path, and transports sample receptacles with fluid samples therein away from the fluid sampling draw head on the other side of the processing path.

28. An automated apparatus according to claim 27, wherein the receptacle transport and the container transport are synchronized.

29. An automated apparatus according to claim 28, wherein the fluid sampling draw head draws a predetermined quantity of fluid into the sample receptacle.

30. An automated apparatus according to claim 15, wherein the fluid sampling draw head draws a predetermined quantity of fluid into the sample receptacle.

31. An automated apparatus according to claim 15, wherein each sample receptacle comprises a test tube having an open end and a one-way valve at the other end that allows fluid flow into but not out of the test tube, and the fluid sampling draw head comprises a vacuum fitting adapted to releasably engage the open end of a test tube and apply suction thereto.

32. An automated apparatus according to claim 31, wherein each container has therein a processing assembly with an aspiration tube, and the fluid sampling draw head comprises an actuator that moves the test tube to place the one-way valve into sealing engagement with the processing assembly aspiration tube, whereby fluid is drawn directly into the test tube through the one-way valve.

33. An automated method for individually processing multiple fluid specimens in respective containers, the method comprising:

transporting the containers seriatim along a processing path to present them to a fluid sampling station and a specimen acquisition station, in either order;

the fluid sampling station adapted to remove fluid from any container presented to it and place the removed fluid sample in a sample receptacle,

the specimen acquisition station adapted to remove fluid from any container presented to it, separate particulate matter from the removed fluid and form a sample layer of particulate matter;

actuating the fluid sampling station in response to presentation of a container thereto so as to carry out the fluid removal operation independently; and

actuating the specimen acquisition station in response to presentation of a container thereto so as to carry out the fluid removal, particulate matter separation and sample formation operation independently.

34. An automated method according to claim 33, comprising transporting sample receptacles seriatim to and from the fluid sampling station along a receptacle path.

35. An automated method according to claim 34, wherein the transport of sample receptacles to and from the fluid sampling station is synchronized with the transport of containers along the processing path.

36. An automated method according to claim 35, wherein the receptacle path is that intersects the processing path.

37. An automated method according to claim 36, wherein the specimen acquisition station is adapted to collect a layer of particulate matter on a surface of a filter, and press the filter against a slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

38. An automated method according to claim 33, wherein the specimen acquisition station is adapted to collect a layer of particulate matter on a surface of a filter, and press the filter against a slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

39. An automated apparatus for individually processing multiple fluid specimens in respective containers, the apparatus comprising:

a container transport for supporting and advancing containers seriatim along a processing path;

a fluid sampling head along the processing path adapted to remove fluid from any container presented to it and place the removed fluid sample in a sample receptacle;

a specimen acquisition head along the processing path adapted to remove fluid from any container presented to it, separate particulate matter from the removed fluid, and form a sample layer of particulate matter; and

a controller governing operation of the fluid sampling head, operation of the specimen acquisition head and movement of the container transport, the controller responding to presentation of a container to the fluid sampling head to cause the fluid sampling head independently to remove fluid therefrom, and the controller responding to presentation of a container to the specimen acquisition head to cause the specimen acquisition head independently to remove fluid therefrom, separate particulate matter from the removed fluid, and form a sample layer of particulate matter.

40. An automated apparatus according to claim 39, comprising a receptacle transport that transports sample receptacles seriatim to and from the fluid sampling station along a receptacle path.

41. An automated apparatus according to claim 40, wherein the receptacle transport and the container transport are synchronized.

42. An automated apparatus according to claim 41, wherein the receptacle path is that intersects the processing path.

43. An automated apparatus according to claim 42, wherein the specimen acquisition station is adapted to collect a layer of particulate matter on a surface of a filter, and press the filter against a slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

44. A receptacle for collecting a fluid sample, comprising:

a hollow body for receiving and holding fluid;

a one-way valve carried by the body and having a fluid flow passage between the exterior and the interior of the body, the valve being pressure-actuated to permit fluid flow into the body interior when the exterior pressure exceeds the interior pressure, and preventing outflow of fluid from the body under the influence of any other relative pressure conditions; and

a vent in the body remote from the valve.

45. A receptacle according to claim 44, wherein the valve comprises an inlet portion opening to the exterior of the body, and an outlet portion opening to the body interior, the flow passage extending between the inlet portion and the outlet portion, at least a portion of the flow passage being resiliently biased to a closed position when the interior and exterior pressures are substantially equal, and expandable to allow fluid flow into the body in response to a positive pressure differential across the valve from the inlet portion to the outlet portion.

46. A receptacle according to claim 45, wherein the portion of the flow passage in the outlet portion tapers toward the resiliently biased portion.

47. A receptacle according to claim 46, wherein the outlet portion has a tapered tip that is exposed to the body interior, and the resiliently biased portion of the flow passage extends through the tapered tip.

48. A receptacle according to any one of claims 45-47, wherein the portion of the valve in which the resilient flow passage is formed is made of resilient material.

49. A receptacle according to claim 48, wherein said resilient material is an elastomer.

50. A receptacle according to claim 48, wherein the entire valve is made of resilient material, the inlet portion adapted to form a seal with the source of the fluid to be collected.

51. A receptacle according to claim 50, wherein said resilient material is an elastomer.

52. A receptacle according to any one of claims 45-47, wherein the inlet portion is made of a resilient material adapted to form a seal with the source of the fluid to be collected.

53. A receptacle according to claim 52, wherein said resilient material is an elastomer.

54. A receptacle according to any one of claims 44-47, wherein the vent comprises a port through which gases leave the body interior as the body fills with fluid.

55. A receptacle according to claim 54, wherein the body is generally tubular with the valve at one end of the tube and the vent comprising the open other end of the tube.

56. A receptacle according to claim 55, wherein the vent is adapted to be sealed with a closure after the fluid sample is obtained.

57. An apparatus for obtaining different types of samples from a fluid specimen in a container, comprising:

a support for the container;

a fluid sampling head adapted to remove fluid from the container and place the removed fluid in a sample receptacle; and

a specimen acquisition head adapted to remove fluid from the container, separate particulate matter from the removed fluid, and form a sample layer of particulate matter.

58. An apparatus according to claim 57, wherein the receptacle has an inlet, and the fluid sampling head is adapted to aspirate fluid from the container and through the inlet directly into the receptacle by applying suction to the receptacle.

59. An apparatus according to claim 58, wherein the specimen acquisition head is adapted to aspirate fluid from the container and through a filter to collect the sample layer on the filter.

60. An apparatus according to claim 59, wherein the specimen acquisition head is adapted to transfer the sample layer of particulate material to a slide.

61. A method for obtaining different types of samples from a fluid specimen in a container using a single apparatus, comprising:

supporting the container in the apparatus;

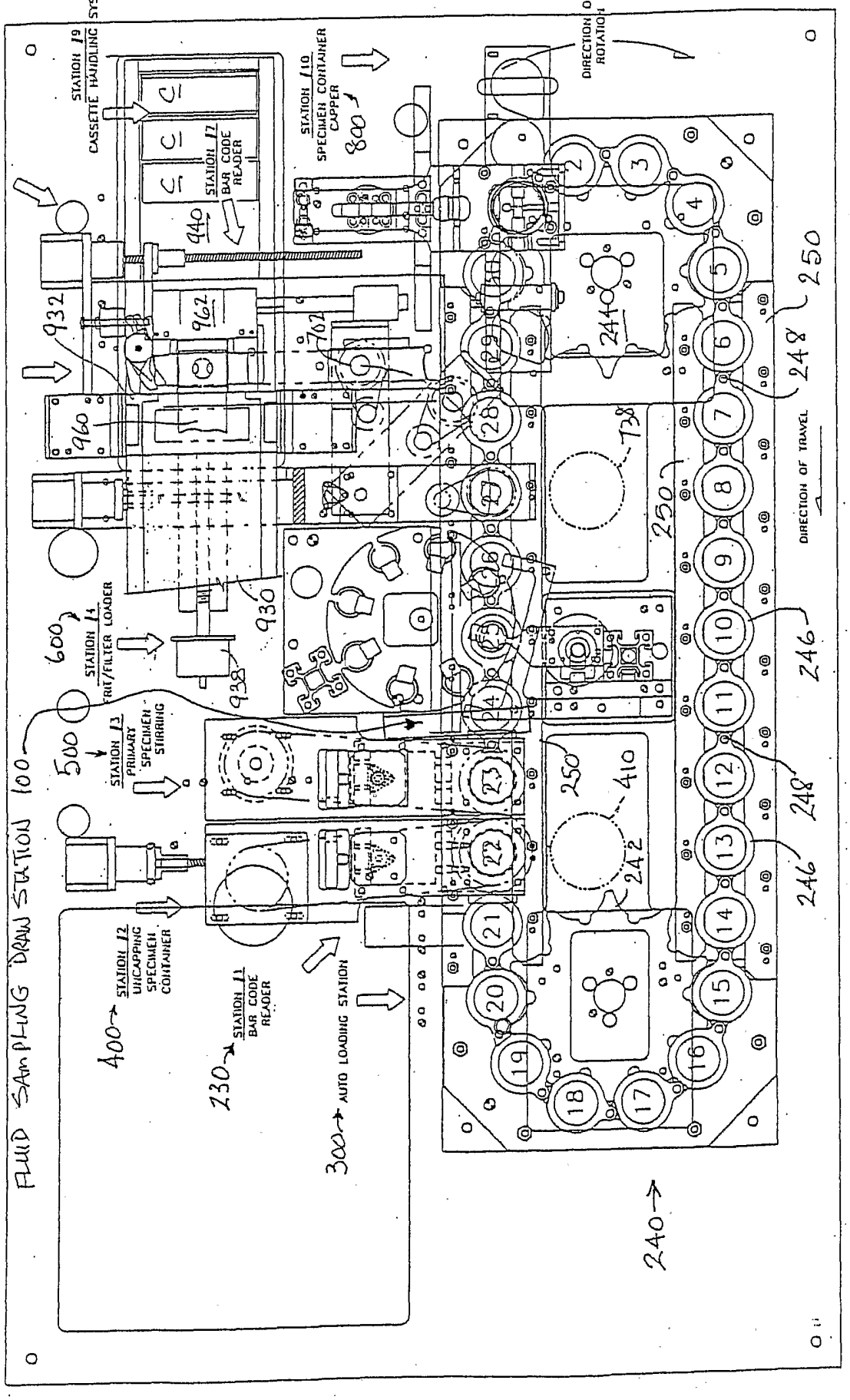
placing the specimen in fluid communication with a fluid sampling station of the apparatus, whereby fluid is removed from the container and placed in a sample receptacle; and

placing the specimen in fluid communication with a specimen acquisition station of the apparatus, whereby fluid is removed from the container, particulate matter is separated from the removed fluid, and a sample layer of particulate matter is formed.

62. A method according to claim 61, wherein the apparatus places the sample layer of particulate matter on a slide.

63. A method according to claim 60, claim 61 or claim 62, wherein the specimen is a biological specimen.

FIG. 1a


FLUID SAMPLING DRAW STATION 100
STATION 15 SPECIMEN ACQUISITION
STATION 16 SLIDE PRESENTATION
STATION 18 SLIDE HANDLING, UNLOAD & RELOAD
STATION 19 CASSETTE HANDLING SYSTEMS
STATION 17 BAR CODE READER
STATION 110 SPECIMEN CONTAINER CAPPER
STATION 14 FIX/FILTER LOADER
STATION 13 PRIMARY SPECIMEN STIRRING
STATION 12 UNCAPPING SPECIMEN CONTAINER
STATION 11 BAR CODE READER
AUTO LOADING STATION
DIRECTION OF ROTATION
DIRECTION OF TRAVEL
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932
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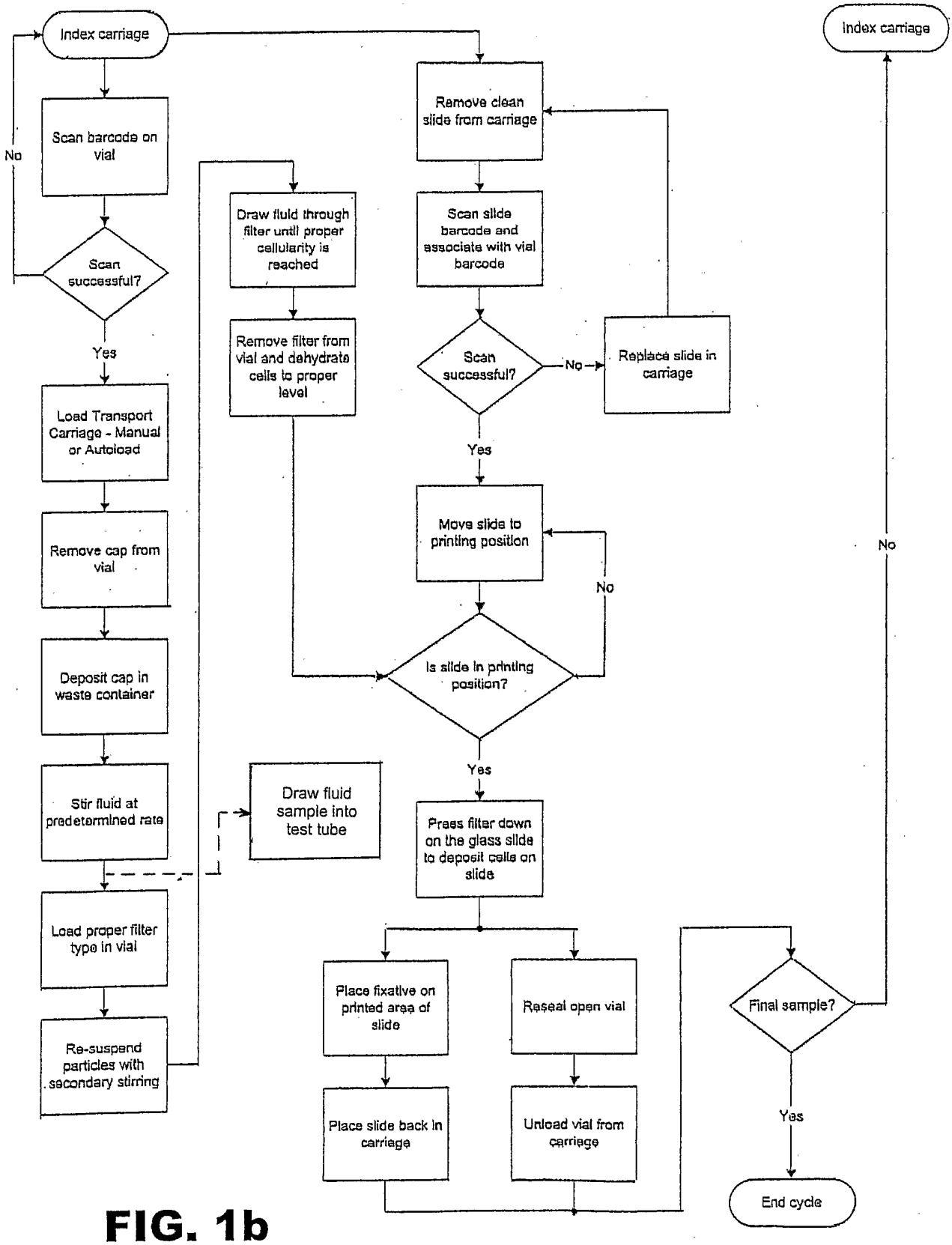
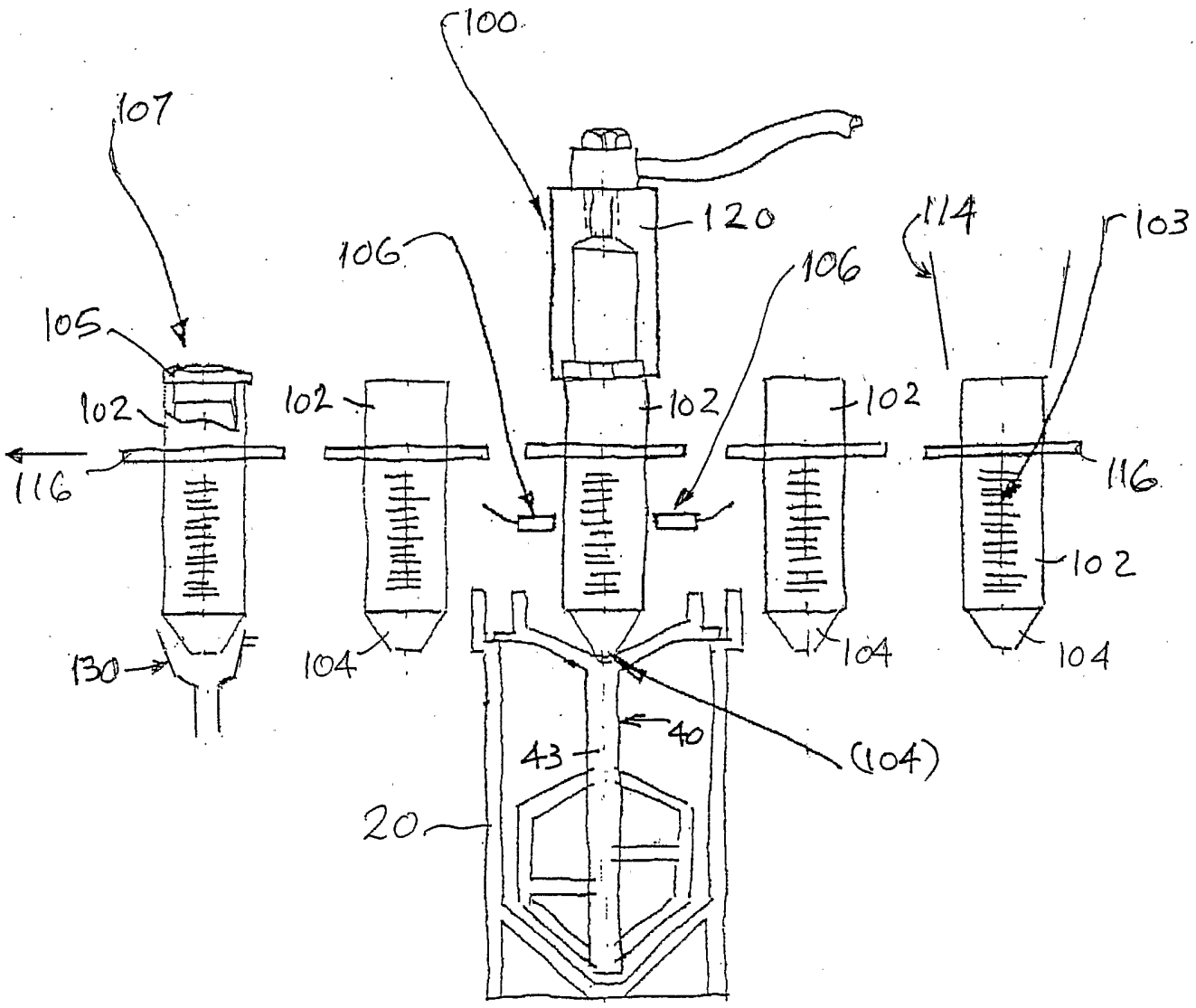

Index carriage
Scan barcode on vial
No
Scan successful?
Yes
Load Transport Carriage - Manual or Autoload
Remove cap from vial
Deposit cap in waste container
Stir fluid at predetermined rate
Load proper filter type in vial
Re-suspend particles with secondary stirring
Draw fluid through filter until proper cellularity is reached
Remove filter from vial and dehydrate cells to proper level
Draw fluid sample into test tube
Remove clean slide from carriage
Scan slide barcode and associate with vial barcode
Scan successful?
No
Replace slide in carriage
Yes
Move slide to printing position
No
Is slide in printing position?
Yes
Press filter down on the glass slide to deposit cells on slide
Place fixative on printed area of slide
Place slide back in carriage
Reseal open vial
Unload vial from carriage
Final sample?
No
Yes
End cycle
Index carriage

FIG. 1b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(104)
20

FIG. 2

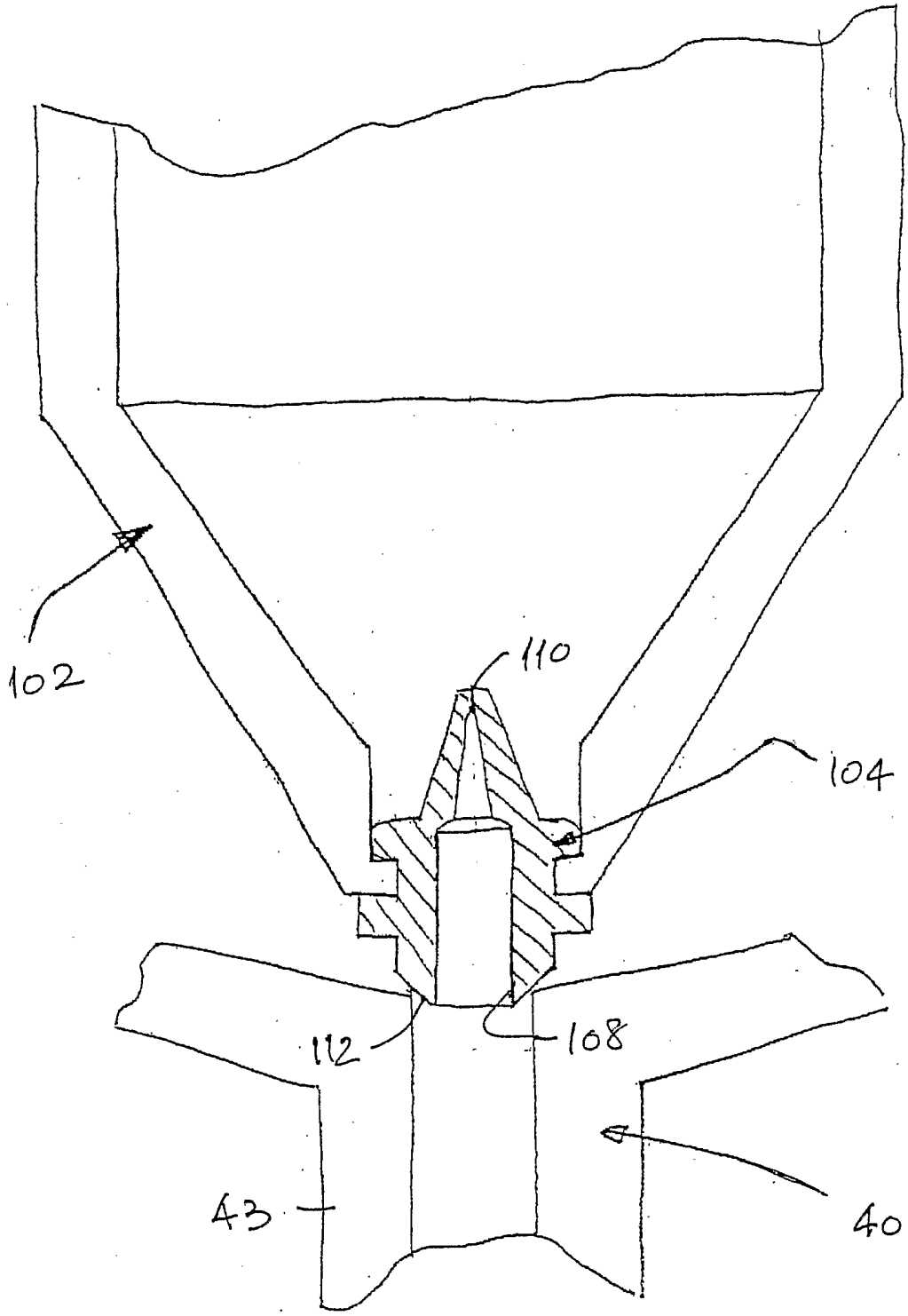

FIG. 3

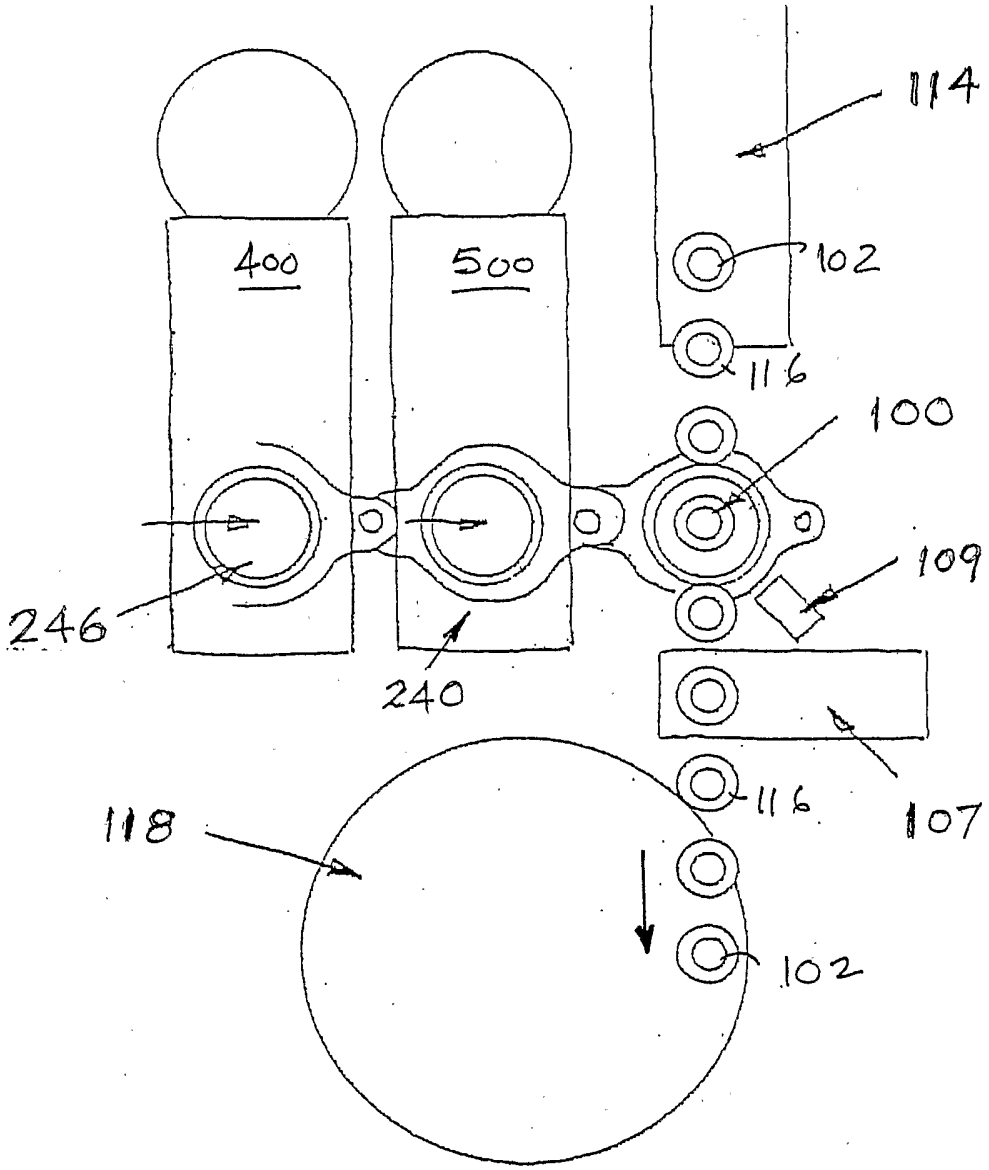

FIG. 4

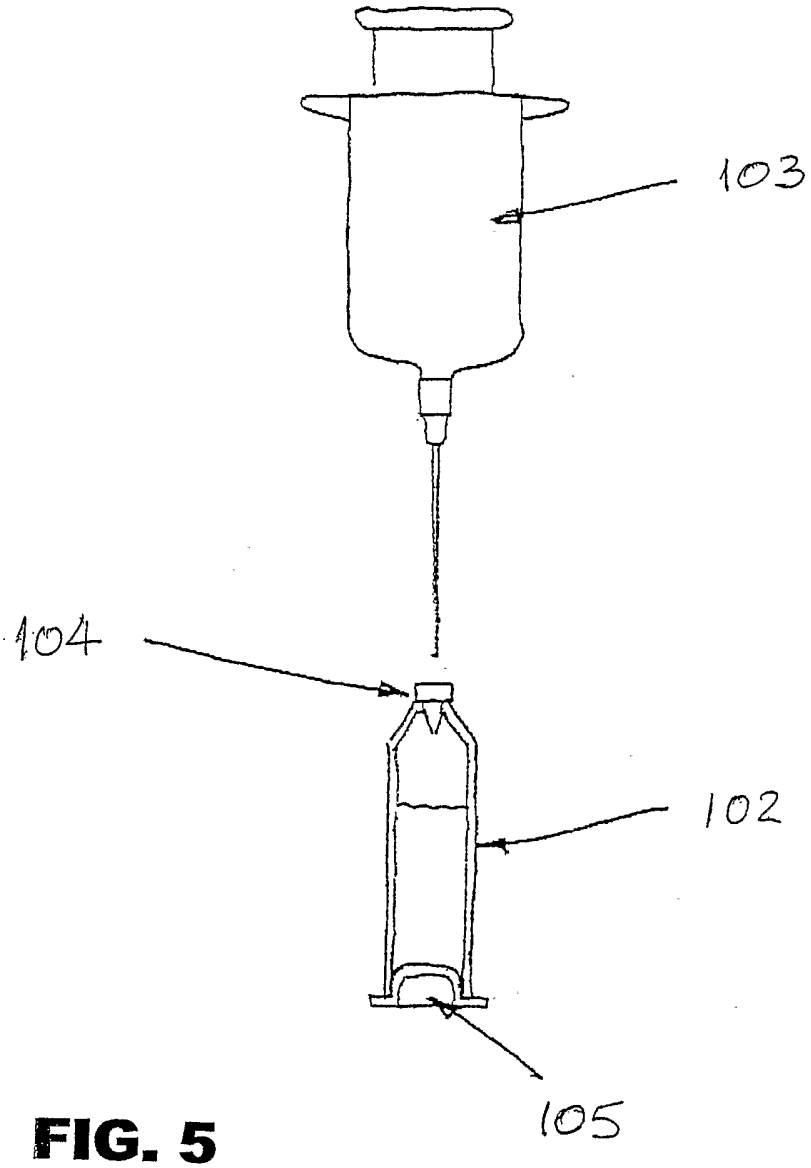

FIG. 5