

"INTEGRAL REAGENT DISPENSER"

The present invention relates to the field of reagent dispenser devices and packages, particularly those suitable for repeated introduction of reagents into automated analytical systems.

5 Reagents are supplied to most analytical systems from separate reagent reservoirs by feed tubing. In many of these systems, the reagents are introduced into a fluid stream in a continuous flow conduit or into a reaction cuvette. The reservoirs are refilled from supply containers in which the reagent is shipped
10 and stored. Some types of reagent storage containers use fragile or breakable capsules or ampoules to hold lyophilized or otherwise dried reagent in combination with a reconstituting fluid. This lyophilized form provides the advantage of long-term stability and shelf life in stored reagent.

15 Some systems have used discrete reaction packages which include reagent sufficient for a single reaction. Sample is introduced and reacts with the reagent therein. Often, the portion of the package in which the reaction occurs is used in the system as an optical cuvette. This type of reaction vessel test
20 pack is disclosed in U. S. Patent No. Re. 29,725; U. S. Patent No. 3,986,834; and U. S. Patent No. 3,036,894. Certain of these devices provide for filtering capacity whereby reagent and/or sample are filtered prior to their introduction into a reaction chamber. This is disclosed for example in U.S.
25 Patent No. 3,437,452.

None of these provides an integral package combining a stable storage/shipment container, reconstituting vessel, reagent reservoir and dispenser which delivers liquid reagent for repeated aspiration of reaction aliquots.

5 One of the most advanced types of analytical systems is a continuous flow system using conduits whose inner walls are coated with an immiscible liquid, such as the system described in Smythe et al, U. S. Patent No. 3,479,141, which discloses a transport system for auto-
10 matic analysis apparatus in which a series of aqueous liquid samples are processed as a flowing fluid stream with substantially no contamination between segments. A fluoropolymer conduit and intersample carrier segments of silicone are used. This patent teaches that the silicone encapsulates the aqueous liquid seg-
15 ments, substantially completely eliminating the intermixing of successive liquid segments. Reagents are separately introduced on a continuous basis, e.g. in conventional fashion as described with respect to previous continuous flow systems.

In Smythe et al, U. S. Patent No. 4,253,846,
20 selective injection of reagent into a moving stream of sample segments is provided to such a continuous flow system and allows for an increase in the efficiency and throughput of sample processing. Using injectors such as poppet valves, the reagent is introduced by piercing the immiscible liquid layer encapsulating the selected sample segments.
25 The immiscible liquid layer reforms after injection to maintain sample integrity and prevent carryover. Air and sample are alternately aspirated via a probe which periodically dips into a sample cup. The immiscible liquid is said to be introduced to the inlet

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end of the probe by an applicator (not shown) and aspirated along with air between successive sample immersions. The immiscible liquid can be a fluorocarbon and both the conduit wall and the poppet valve tip can be a fluorinated polymer. This patent does
5 not further address the actual mechanism of immiscible liquid introduction and clearly indicates that it is separate from the "on-line" introduction of reagent.

Diebler et al, U. S. Patent No. 4,121,466,
disclose a metering apparatus useful
10 to either dispense or aspirate sample. The surface of the aspirating probe is coated with an immiscible liquid film which, in the preferred embodiment, is flowed continuously down the peripheral probe surface at a rate substantially equal to the aspiration rate, so as to be eventually aspirated into the probe inlet. During immersion, excess immiscible liquid on the peri-
15 pheral probe surface floats onto the surface of the liquid being aspirated but a small film remains on the probe surface. Also, during aspiration, a thin film of immiscible liquid continuously wets the interior probe surface. As the probe is withdrawn, the flow of immiscible liquid is commenced so as to be aspirated
20 along the probe immediately upon withdrawal thereof from the liquid. Segments of the immiscible liquid and aspirated liquid are therefore successively passed along the probe system.

Smythe, U. S. Patent No. 4,259,291,
refers to the continuous flow systems described
25 in the above Smythe et al and Diebler et al patents and addresses the need for more precise and uniform application of protective immiscible liquid coatings. An applicator directly surrounds

the probe and layers a thin uniform film of immiscible liquid on the outer surface thereof. The applicator is moved relative to the probe to coat its outer surface. An aspirating mechanism connected to the probe alternately aspirates controlled volumes of air and aqueous sample therethrough. Immiscible liquid is said to be drawn into the probe along with the air segment so aspirated. Thus, alternating sample and air segments encased within the immiscible liquid are passed along the probe to a rotary valve which transfers each aspirated aqueous sample in turn from the probe to a conduit for dispensing to an analytical system. As described herein, a pool of wiped immiscible liquid forms about the probe due to the interplay of surface forces of the liquid in combination with the wetting forces of the immiscible liquid with the respect to the probe surface. When the sample cup is withdrawn from the probe, this pool forms a small globule of immiscible liquid over the inlet of the probe, inasmuch as it preferentially wets the probe material to the substantial exclusion of the aqueous sample. This patent teaches that the globule of immiscible liquid is aspirated into the probe inlet along with an air segment. Reagent is introduced "downstream" in a manner which is not further described.

Each of the above patents has provided an advance of one sort or another in the elimination of successive sample intermixing and carryover. This end has been widely recognized as a major consideration in the improvement of continuous flow systems. The combined references provide a significant background literature on the technology available to prevent interaction of segments in continuous flow analysis systems.

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Nonetheless, none of these has provided an integral reagent dispenser which is adapted to control the introduction of precise volumes of immiscible liquids to analyzer systems of the continuous flow type. Continuous flow systems using conduits whose inner walls are coated with an immiscible liquid have not been previously available, and thus have not heretofore presented a need such as that addressed by the present invention.

A new concept in controlled fluid handling has been developed for use in a new generation of clinical chemistry analysis systems. These are continuous flow systems using conduits whose inner walls are coated with a probe accessed immiscible liquid. Controlled introduction of sufficient amounts of this immiscible liquid is critical for the proper operation of the system. This having now been recognized and the need addressed, the present invention provides an integral reagent dispenser which presents a liquid reagent and positions a lens of immiscible liquid for introduction into the system. The integral dispenser of this invention properly positions that immiscible liquid which replenishes the coating on the conduits of these continuous flow systems.

The integral reagent dispenser disclosed comprises a reagent dispenser component provided with a reagent dispenser well having an opening adapted to present a liquid reagent for withdrawal therethrough and means for positioning a lens of immiscible liquid between the surface of such reagent when contained in said well and the opening thereof. For example, the dispenser can have suitable dimensions and an inner surface, usually hydrophilic, which combine with the wetting characteristics of the reagent to form a concave reagent meniscus suitably reliable to position a drop of immiscible liquid thereon. In this embodiment, the dispenser well inner diameter is at most about that of the diameter of the lens plus twice the radius of the meniscus curvature, usually less than about 0.25 inch (6.4mm). So long as the well.

inner surface is fully wet by the reagent liquid, e.g. is hydrophilic in the preferred embodiment, the meniscus curvature is controlled by the surface tension of the particular reagent liquid in use. The drop of immiscible liquid forms a discrete lens (so-called because of its shape) due to the balance of interfacial tensions of the three fluids (reagent, immiscible liquid and air) at those points of three-phase contact which constitute the periphery of the lens. The lens so formed is centrally located by the concave shape of the meniscus. Preferably, the reagent dispenser further includes an integrally associated source of liquid reagent. The source of liquid reagent is, for example, a reagent reservoir having flexible side walls and a plurality of breakable capsules which are broken by external pressure on said side walls to reconstitute the contents thereof into a liquid reagent.

In a particularly preferred embodiment, the integral reagent dispenser of the invention comprises (a) a reagent dispenser assembly having a dispenser housing and, therein, first and second reagent dispenser components, each provided with a dispenser well having a hydrophilic inner surface and an inner diameter of less than about 0.25 inch (6.4mm) and (b) a reagent reservoir assembly having a reservoir housing and, therein, a first reservoir component containing at least one reagent of a composition effective to detectably react with a sample and associated with said first reagent dispenser to supply said at least one reagent thereto as a liquid; and a second reservoir component containing the remaining reagents of said composition and associated with said second reagent dispenser to supply said remaining reagent thereto as a liquid. In one example of this embodiment, each reservoir

component includes a breakable capsule containing reagent, as described, in a lyophilized powder form as well as a breakable capsule containing a reconstituting liquid therefor.

This example of the preferred embodiment confers numerous
5 advantages, including the long-term storage of unmixed ingredients and inherently secure packaging for shipping incorporated with a vessel for reconstitution, mixing and dispensing having a configuration adapted to present immiscible fluid and a plurality
of related reagents for aspiration through an analyzer probe
10 and to prevent contents spillage during rotation on an analyzer turntable. Further, the dispenser is integrally formed so as to prevent the risks of contamination and error inherent in manual reagent preparation and package refilling.

In order that the invention may be more fully understood,
15 various embodiments thereof will now be described, by way of example only, with reference to the accompanying drawings, wherein:

Fig. 1 is an isometric view of a preferred embodiment of the integral reagent dispenser in accordance with the invention;

Fig. 2 is a cross-sectional view of the same embodiment of the integral reagent dispenser depicted in Fig. 1, shown here
5 as prepared for use;

Fig. 3 is an enlarged partial view of the dispenser well of Fig. 2;

Fig. 4 is a top view of the integral reagent dispenser of Fig. 2;

10 Fig. 5 is an isometric view of another preferred embodiment of the integral reagent dispenser of the invention;

Fig. 6 is a cross-sectional view of the same embodiment of the integral reagent dispenser depicted in Fig. 5, shown here as prepared for use;

15 Fig. 7 is a top view of the integral reagent dispenser of Fig. 6;

Fig. 8 is an enlarged partial view of another embodiment of the integral reagent dispenser of the invention which includes an immiscible liquid lens yoke;

20 Fig. 9 is a cross-sectional view of the integral reagent dispenser of Fig. 8; and

Fig. 10 is a top view of the integral reagent dispenser of Fig. 8.

Although specific terms are used in the following description for clarity, they refer only to the particular embodiment(s) selected for illustration, and are not intended to limit the scope of the invention.

5 The reagent package of the present invention is particularly suitable for use in association with either batch type or continuous flow analyzers which aspirate sample(s), reagent(s) and immiscible liquid(s) through a probe assembly. Sample fluids on which tests are performed include biological, physiological,
10 industrial, environmental and other types of liquids. Of particular interest are biological liquids such as whole blood, serum, plasma, urine, cerebrospinal fluid, broth and other culture media and supernatants as well as fractions of any of them. Each package holds at least some of the individual reagents of a conventional reagent composition known for the analysis of the/above-
15 described samples, in amounts sufficient for testing of a plurality of samples. The preferred immiscible liquid is one which preferentially wets the inner and outer probe surfaces and the inner wall surfaces of the conduits in the system to the substantial
20 exclusion of all other fluids in the system and is usually a fluorocarbon.

Referring now to Fig. 1, a two-reagent reservoir/dispenser package I, as shown, contains separated portions of a complete reagent composition necessary for the analysis of a sample.

25 Two-reagent reservoir/dispenser package I includes a reagent reservoir assembly 10 having a reservoir housing 12 and a reagent supply component for each of the two reagents to be dispensed.

Reservoir housing 12 includes integral flexible side walls 14 which are continuous with back wall 16, front wall 18 and top 20. Reservoir housing 12 is fixed to base 22 by conventional adhesive or bonding techniques to form an enclosure. Base 22
5 is provided with an inclined floor 24 to maximize availability of reagent contents, shard fins 26 to insure against occlusion of openings in the package, support ribs 28 which provide desired structural rigidity at selected portions of housing 12 and insulation chamber 29, within housing 12, which separates reagent supply
10 components 30 and 40.

Reagent R_1 supply component 30 comprises component wall 31, reagent R_1 capsule 32, which is filled with lyophilized reagent R_1 powder, reconstituting liquid capsule 34 which is filled with reconstituting liquid 35 and a supply trough 36. Reagent
15 R_2 supply component 40 is substantially identical to the above-described reagent supply component but for its position. As such, it comprises an enclosed component wall 41, reagent R_2 capsule 42 which contains lyophilized reagent R_2 powder, reconstituting liquid capsule 44 which contains reconstituting liquid
20 45, and supply trough 46. After appropriate package preparation, as described in detail below, supply component troughs 36 and 46 each deliver reconstituted liquid reagent to different components of a reagent dispenser assembly.

Still referring to Fig. 1, reagent dispenser assembly 50
25 includes a dispenser housing 52 and a dispenser component for each of the two reagents to be dispensed. Dispenser housing 52 includes housing wall 54, which forms an enclosure with top 56 and base 58. Base 58 is provided with a stepped floor 60, the step height of which is commensurate with the height of filter

25 cups 78 and 88. Divider 64 separates the reagent dispenser components provided for each of the two reconstituted liquid reagents.

Reagent R_1 dispenser component 70 comprises a supply port 71, trough wall 72, vent hole 73, filter 74 and dispenser well 575, the interior of which is defined by dispenser well wall 76 having hydrophilic inner surface 77. As shown in later drawings, reagent R_1 which flows through supply port 71 is confined by trough wall 72 and thereby directed into the side of filter 74. From filter 74, it enters the interior of dispenser well 75, 10 through the bottom, to present a standing volume of reagent R_1 liquid.

Reagent R_2 dispenser component 80 is substantially identical to the above-described reagent dispenser component but for its position and operates in the same manner. As such, it comprises 15 a supply port 81, trough wall 82, vent hole 83, filter 84 and dispenser well 85, the interior of which is defined by dispenser well wall 86 having hydrophilic inner surface 87.

Dispenser wells 75 and 85 each has suitable dimensions which cooperate with the hydrophilic inner surfaces 77 and 87, respectively, 20 and the wetting characteristics of the liquid therein to form reliably a concave reagent meniscus suitable to position a drop of immiscible liquid thereon as is more fully described with reference to later drawings.

Fig. 2 shows a cross-section of two-reagent package I as 25 prepared for use. To prepare dispenser package I for positioning of an immiscible liquid lens and liquid aspiration, it is tilted to rest on back wall 16, flexible side walls 14 are forced inwardly by external pressure, applied manually or by a suitably designed apparatus, to break capsules 32, 34, 42 and 44 and dispenser package I is gently rocked to reconstitute and mix each 30

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of the lyophilized reagent powders with its respective reconstituting liquid. After mixing, the dispenser package I is righted to the position shown in the drawing and can thereafter be positioned on a turntable, conveyor table or other transport means for use in an automated analysis system. Such a system can be, for example, the continuous flow system which is the subject of and more fully described in our European patent application entitled, "SINGLE CHANNEL CONTINUOUS FLOW SYSTEM" filed on even date herewith. The metering apparatus and method used during aspiration can be those which are the subject of and more fully described in our European patent application no. 83306274.8 entitled, "CONTINUOUS FLOW METERING APPARATUS".

Reconstituted reagent R_1 and R_2 liquids are made ready for aspiration, along with immiscible liquid, in identical manner. As such, the following description will refer to reagent R_1 liquid as exemplary. Reconstituted reagent R_1 liquid flows into R_1 dispenser component 70 to at least partially fill dispenser well 75. The continuous body of fluid between R_1 supply component 30 and R_1 dispenser component 70 reaches an equilibrium level, which is achieved by flow of reagent into dispenser component 70 until supply port 71 is occluded by the level of reagent liquid. Thus, an initial reservoir fluid level 92 and an initial dispenser well fluid level 94 are achieved for the continuous body of reconstituted reagent R_1 liquid. A concave reagent meniscus 97 is formed at the surface of reagent R_1 because of the hydrophilic inner surface 77 of dispenser well 75. A drop of immiscible liquid is dispensed onto this reagent surface, forming an immiscible liquid lens 100 which is centrally positioned thereon by

the curvature of the meniscus. The drop of immiscible liquid can be dispensed manually, such as by pipette, or automatically such as from an immiscible liquid dispenser component of an automated analysis system. The tip of a probe P (shown in phantom), which is a component of the analysis system and preferably made of a solid fluoropolymer sequentially intersects immiscible liquid lens 100 and reconstituted reagent R_1 liquid. Both segments of liquid are aspirated into the analysis system. Probe P can be provided with an immiscible liquid dispenser (not shown) having an applicator shroud, which dispenses immiscible liquid onto the outer surface thereof. the immiscible liquid introduced into probe P from lens 100 is replaced by the immiscible liquid flowing down the outer surface of probe P. The volume of immiscible liquid lens 100 is thereby kept substantially constant.

By repetition of the aspirating operation, a certain amount of reagent in dispensing well 75 is used up. As this occurs, the dispenser well fluid level 94 is lowered. When the level falls enough partially to expose supply port 71 to air, air flows into supply component 30 to replace that volume of reagent which is permitted to flow out into dispensing well 75. Vent hole 73 allows introduction of replacement air to supply component 30. Thus, the reagent level in dispensing well 75 remains within a narrow range until the supply of reagent R_1 is nearly depleted. Upon depletion, the unit is discarded.

Fig. 3 is an enlarged partial view of that section of dispenser well 75 where the hydrophilic surface 77 of dispenser well wall 76 is in contact with the interface between reconstituted reagent R_1 liquid and air to form concave reagent meniscus.

96. Dispenser well 75 has an inner diameter D which is at most about equal to the diameter d of immiscible liquid lens 100 plus twice the radius r of the curvature of reagent meniscus 96.

In an example of this embodiment, well inner diameter D is 0.25 inches (6.4mm), diameter d of lens 100 is 0.10 inches (2.5mm) and the radius r of concave reagent meniscus 96 is 0.08 inches (2.0mm).

Fig. 4 shows a top view of the two-reagent package I of Fig. 2. Reservoir housing 12 is shown to include reagent R_1 supply component 30 and reagent R_2 supply component 40 in which reconstituted reagent R_1 and reagent R_2 liquids are standing for supply to R_1 dispenser component 70 and R_2 dispenser component 80, respectively. Reagent R_1 and reagent R_2 liquids in dispenser components 70 and 80 are shown with an immiscible liquid lens 100 centrally positioned on the surface of each.

Fig. 5 shows another preferred embodiment of the invention, a one-reagent dispenser II which includes a reagent reservoir assembly 110 having a reservoir housing 112 which encloses a supply component 130 for the single reagent to be dispensed. Reservoir housing 112 includes integral flexible side walls 114 which are continuous with back wall 116, front wall 118 and top 120. Reservoir housing 112 is fixed to base 122 by conventional adhesive or bonding techniques to form an enclosure. Base 122 provides the interior of the enclosure with an inclined floor 124 to maximize availability of reagent contents, shard fins 126 to insure against occlusion of openings in the package and support ribs 128 which provide desired structural rigidity at selected portions of housing 112.

Reagent R_1 supply component 130 comprises component wall 131, reagent R_1 capsule 132, which is filled with lyophilized

reagent R_1 powder, reconstituting liquid capsule 134 which is filled with reconstituting liquid 135 and a supply trough 136. After appropriate package preparation, as described with reference to the previous embodiment, supply component trough 136 delivers
5 reconstituted liquid reagent to a reagent dispenser assembly.

Still referring to Fig. 5, reagent dispenser assembly 150 includes a dispenser housing 152 and a dispenser component for the reagent to be dispensed. Dispenser housing 152 includes housing wall 154, which forms an enclosure with top 156 and base 158. Base 158 is provided with a stepped floor 160, the step
10 height of which is commensurate with the height of filter cup 178.

Reagent R_1 dispenser component 170 comprises a supply port 171, trough wall 172, vent hole 173, filter 174 and dispenser well 175, the interior of which is defined by dispenser well
15 wall 176 having hydrophilic inner surface 177. As shown in later drawings, reagent R_1 , which flows through supply port 171, is confined by trough wall 172 and thereby directed into the side of filter 174. From filter 174, it enters the interior of dispenser well 175, through the bottom, to present a standing volume
20 of reagent R_1 liquid.

Fig. 6 shows a cross-section of the one-reagent package II, which has been prepared for use in the same way as the previously described embodiment. Reconstituted reagent R_1 liquid flows into R_1 dispenser component 170 to at least partially fill dispenser well 175. The continuous body of liquid between R_1
25 supply component 130 and R_1 dispenser component 170 reaches an equilibrium level, based on the same principal as in the previously described embodiment. Thus, a reservoir fluid level 192

and a dispenser well fluid level 194 are achieved for the continuous body of reconstituted reagent R_1 liquid. A concave reagent meniscus 198 is formed at the surface of the reagent R_1 liquid because of the hydrophilic inner surface 177 of dispenser well 175. A drop of immiscible liquid is dispensed onto this reagent surface, in the same manner as described for the previous embodiment forming an immiscible liquid lens 200, which is centrally positioned thereon by the curvature of the meniscus. The drop of immiscible liquid can be dispensed manually, such as by pipet, or automatically, such as from an immiscible liquid dispenser component of an automated analysis system. The tip of a probe P (shown in phantom), which is a component of the analysis system and preferably made of a solid fluoropolymer, sequentially intersects immiscible liquid lens 200 and reconstituted reagent R_1 liquid. Both segments of liquid are aspirated into the analysis systems. The volume of immiscible liquid lens 200 is maintained as described with reference to the previous embodiment.

By repetition of the aspirating operation, a certain amount of reagent in dispensing well 175 is used up. As this occurs, dispenser well fluid level 194 is also lowered. When this level falls enough to partially expose supply port 171 to air, air flows into supply component 130 to replace that volume of reagent which is permitted to flow out into dispensing well 175. Vent hole 173 allows introduction of air to supply component 130. Thus, the reagent level in the dispensing well remains within a range until the reagent supply is nearly depleted. Upon depletion, the unit is discarded.

Fig. 7 shows a top view of the two-reagent package II of Fig. 5. Reservoir housing 112 is shown to include reagent R_1

supply component 130 in which reagent R_1 liquid is standing for supply to R_1 dispenser component 170. The top surface of reconstituted reagent R_1 liquid are shown with immiscible liquid lens 200 centrally positioned on the surface.

5 Fig. 8 shows an enlarged partial view of another embodiment, integral reagent dispenser III, of the invention, which includes a reagent dispenser assembly 250 having a dispenser housing 252, a reagent dispenser component 270, holding a volume of reconstituted reagent R_1 liquid and an immiscible liquid lens
10 yoke 290. Dispenser package III is prepared for positioning of an immiscible liquid lens and use in the same way as described for the previous embodiments. Lens yoke 290 includes a lens loop 292 which has a hydrophobic fluoropolymer inner surface and is, preferably, centrally positioned in dispenser well 275
15 of dispenser component 270 by support arms 294. Preferably, lens yoke 290 is integrally formed or molded of a material which is nonreactive with and floats on the reagent surface. Lens loop 292 is usually circular and has an inner diameter which is usually less than about 0.10 inches (2.5mm). Notably, the liquid
20 reagent need not have a concave meniscus in this embodiment. Support arms 294 contact, but are not fixed to, dispenser well 275 in this embodiment. Immiscible fluid lens yoke 290 floats on the surface of reconstituted reagent R_1 liquid and thus vertically travels with it as the reagent level is lowered by repetition of the aspiration operation. Because support arms 294 can be of any desired number and each individually, of any desired length, a dispenser well is optional in this embodiment. For example, the support arms can extend directly from the inner surface of the dispenser housing, which can have any of a variety

of different shapes. As shown in phantom, lens loop 292 can have downwardly extended walls to form an enclosure, lens cylinder 293, which maintains the position of immiscible liquid lens 300, as the reagent level is lowered, in examples where
5 support arms 294 are fixed to dispenser well 275. Dispenser assembly 250 can be associated with any of a variety of reagent reservoir assemblies, particularly including those illustrated by and described with reference to earlier drawings. A filter or screen (not shown) can be positioned at the point of reagent
10 liquid entry into dispenser component 270 when a dispenser well is not required or provided.

Fig. 9 shows a cross-section of the enlarged partial view of the single reagent package III of Fig. 8, as prepared for use and having an immiscible liquid lens 300 on the surface of
15 the reagent. Support arms 294 extend transversely from lens loop 292 to the inner surface of dispenser well 275 at a level determined by that of reagent R_1 liquid. Notably, the surface of reagent R_1 does not form, and is not required to form, a curved meniscus.

20 Fig. 10 shows a top view of the reagent package III of Fig. 8. The top surface of reagent R_1 is shown with immiscible liquid lens 300 centrally positioned on the surface. Notably, the rotational position of each of support arms 294 has changed, illustrating that they are not fixed to the inner surface of dispenser
25 well 275.

Although the invention has been described with particularity, numerous changes in the details, combinations and arrangement of elements may be resorted to without departing from the scope of the invention.



CLAIMS

1. A unitary integral reagent container comprising means defining a reagent well having a first opening for withdrawal of liquid reagent from said well therethrough and a second opening for introduction of liquid reagent
5 into said well; means for establishing a standing level of reagent in said reagent well; means for maintaining a lens of immiscible liquid on the surface of such reagent and within a defined area of such surface when such reagent is contained in said reagent well; means defining
10 a reagent reservoir integral with said reagent well for containing a supply of reagent liquid; and means for repeatedly releasing a controlled amount of reagent liquid from said reagent reservoir through an opening between said reagent reservoir and reagent well and for introducing
15 the controlled amount of reagent so-released into said reagent well through said second opening thereof.
2. An integral reagent container according to claim 1, wherein said lens maintaining means comprises means for
20 centrally positioning said lens on the reagent liquid surface.
3. An integral reagent container according to claim 1 or 2, wherein said lens maintaining means comprises a
25 reagent well hydrophilic inner surface providing a well inner diameter which is at most about that of the diameter of the lens plus twice the radius of curvature of a meniscus produced by interaction of the reagent in the reagent well with the hydrophilic inner surface of the
30 reagent well.



4. A container according to claim 3 wherein said dispenser well inner diameter is less than about 0.25 inch (6.4 mm).
- 5 5. An integral reagent container according to claim 1, wherein the lens maintaining means comprises a lens yoke having lens enclosure means and means for positioning said enclosure means.
- 10 6. An integral reagent container according to claim 5 wherein said reagent well is cylindrical.
7. An integral reagent container according to claim 5 or 6, wherein said lens enclosure means is
15 cylindrical.
8. An integral reagent container according to any one of claims 5 to 7, wherein said positioning means comprises at least one support arm extending from said
20 lens enclosure means to said reagent well.
9. An integral reagent container according to any one of claims 5 to 8, wherein said lens enclosure means is of a solid fluoropolymer.
- 25 10. An integral reagent container according to any one of the preceeding claims, which further comprises means for passing reagent from said reagent reservoir to said means defining a reagent well through a supply port.
- 30 11. An integral reagent container according to any one of the preceding claims, wherein said means for establishing a standing reagent level comprises means for maintaining a substantially constant level of reagent
35 liquid in said reagent well.

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12. An integral reagent container according to any one of the preceding claims, which comprises means for passing air from said means defining a reagent well to said reagent reservoir.

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13. An integral reagent container according to claim 12, which includes a vent hole in said means defining a reagent well to introduce air thereinto for replacement of air passing therefrom to said reagent reservoir.

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14. An integral reagent container according to any one of the preceding claims, wherein said reagent reservoir comprises a breakable capsule containing a reagent.

15 15.

An integral reagent container according to claim 14, wherein said reagent is dried and said reagent reservoir further comprises a breakable capsule containing a reconstituting liquid.

20 16.

An integral reagent container according to any one of the preceding claims which further comprises a filter positioned along the reagent flow path between said reagent reservoir and said reagent well.

25 17.

An integral reagent container according to claim 16, wherein said filter is positioned at a reagent entrance to said reagent well.

18.

30 one of the preceding claims, wherein the reagent reservoir is of a size to contain sufficient reagent to maintain the dispenser well reagent level within a range during repeated withdrawal of reagent therefrom.



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19. A unitary integral reagent container comprising a plurality of reagent containers each according to any one of the preceding claims, wherein the reagent reservoir of each container cooperates with a selected reagent well.

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20. A unitary integral reagent container according to claim 19, in which a first reagent reservoir contains at least one reagent of a composition effective to detectably react with a sample and a second reagent reservoir 10 contains the remaining reagents of said composition.

21. An integral reagent container substantially as herein described with reference to Figures 1 to 4, or 5 to 7, or 8 to 10 of the accompanying drawings.
