United States Patent

Coleman

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[54] REAGENT SOLUTION PREPARATION

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[52] **U.S. Cl.** **23/309,** 23/267, 23/272.7, 23/311

[51] **Int. Cl.** **B01f 1/00,** B01d 11/02

[58] **Field of Search** 23/267, 271, 272.6, 272.7, 23/272.8, 309, 311, 312

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Assistant Examiner—S. J. Emery
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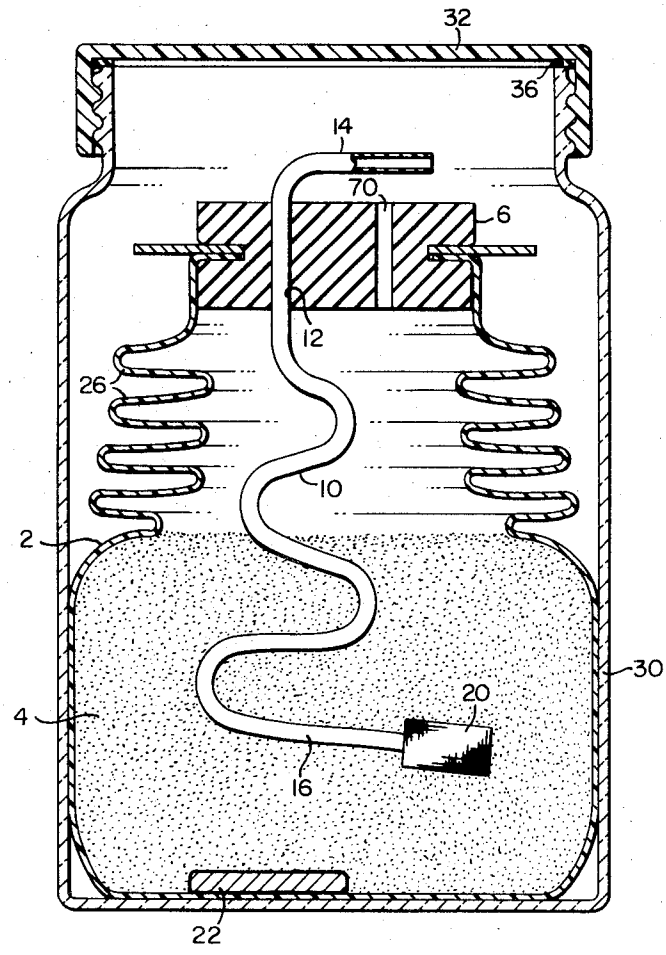
[57] **ABSTRACT**

A method of preparing sterile chemical reagent solutions including providing a sterile expandable mixing container with a quantity of reagent concentrate material, positioning said mixing container on or within a support structure, introducing a predetermined quantity of mixing fluid into the mixing container, mixing the concentrate material and fluid to establish a uniform homogeneous reagent solution and subsequently filtering the solution to remove particulate material. Mixing may be effected by an inertly covered magnetic stirring element positioned within the container.

A sterile container assembly for chemical reagent concentrates including an expandable inner container having a chemical reagent concentrate therein, closure means having a passageway therethrough secured to the mouth of said inner container, a tubular reagent discharge conduit having one portion extending into the closure passageway and one end disposed within the container. Filter means secured to said conduit and an outer container protectively surrounding said inner container. Sterile sealing means on at least one of said inner and outer containers to prevent communication between the surrounding air and the interior of the inner container.

7 Claims, 8 Drawing Figures



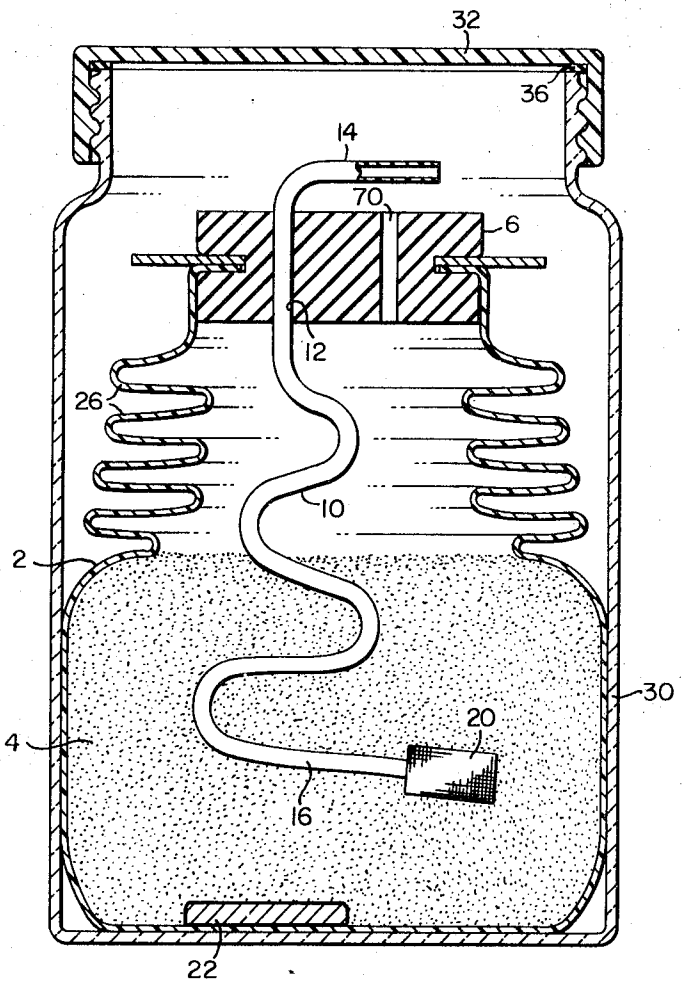

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FIG. 1.

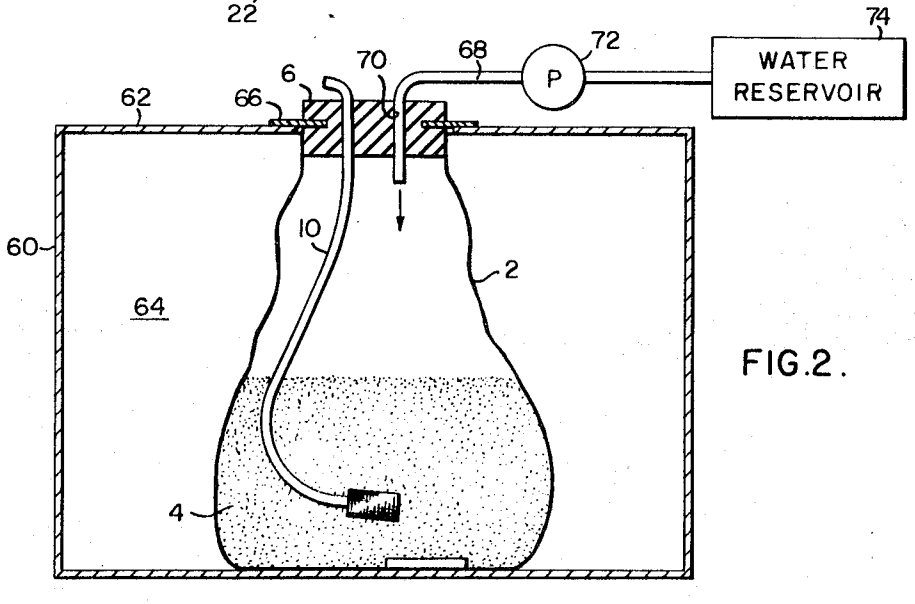
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FIG. 2.

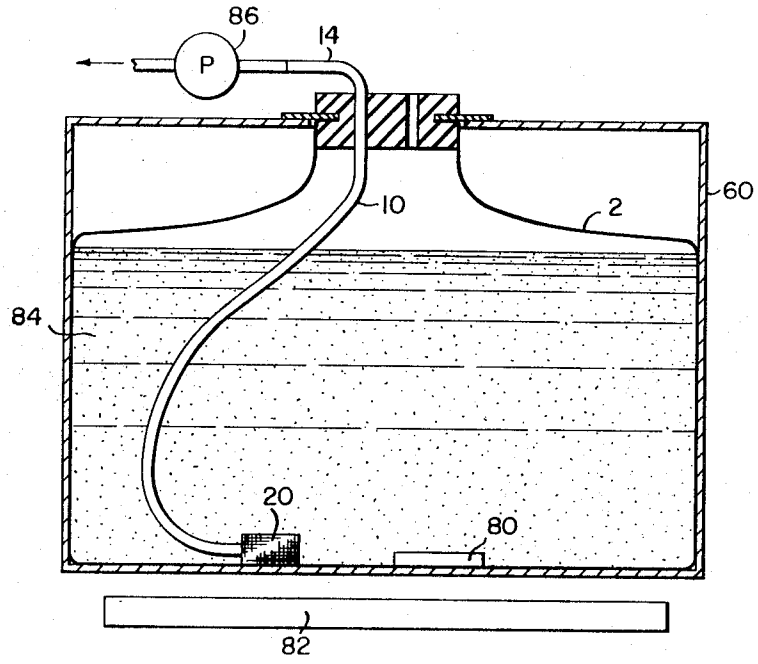

FIG. 3.

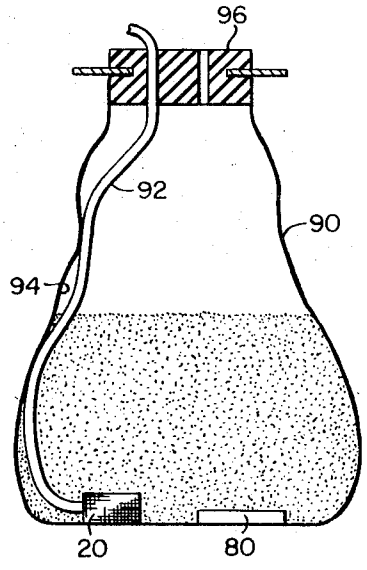

FIG. 4.

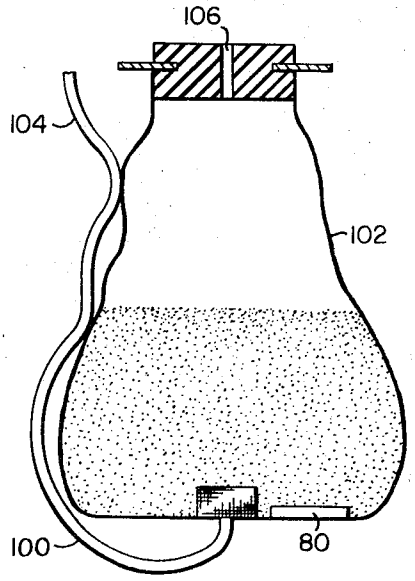

FIG. 5.

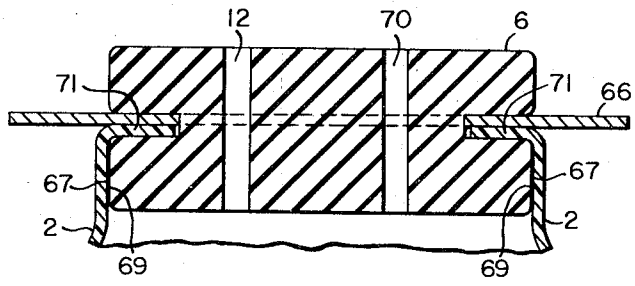

FIG.6.

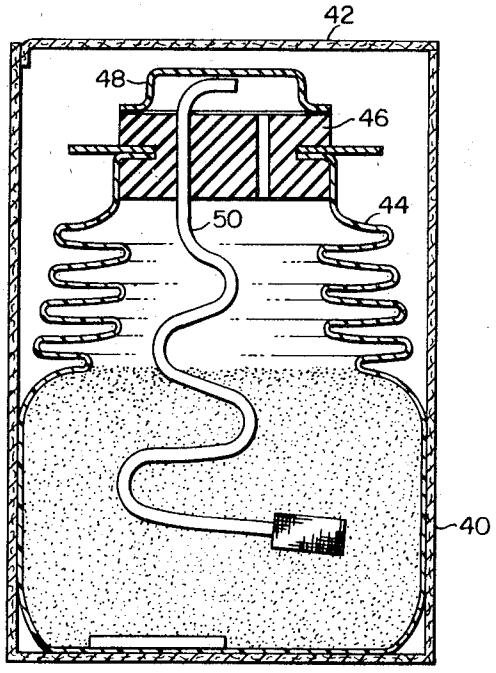

FIG.7.

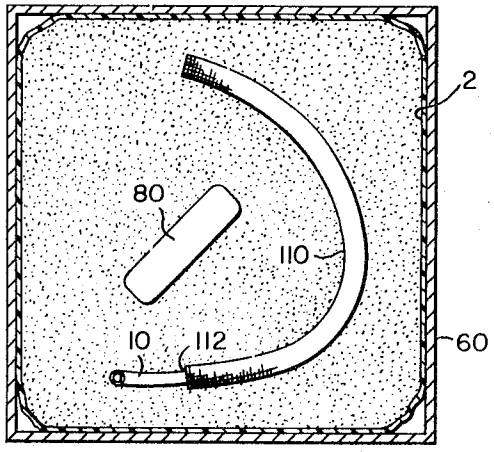

FIG.8.

REAGENT SOLUTION PREPARATION

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a method of preparing sterile chemical reagent solutions and to a container assembly for use in preparing sterile chemical reagent solutions.

2. Description of the Prior Art

A preferred known system for supplying clinical laboratories in hospitals with required sterile chemical reagent solutions is to completely prepare the reagent in the supplier's factory and ship the same to the laboratory. One obvious disadvantage of such a system is that the hospital's supply is totally dependent upon the efficiency of the supplier delivery schedule. As a practical matter, in order to insure a continuous supply of reagents which are required for clinical purposes and are frequently critical to the diagnosis of the state of health of a patient, hospitals generally purchase and store extra quantities of such reagents. One problem with such an approach is that a number of reagent solutions perform effectively when fresh, but deteriorate with time. Not only do chemical precipitates form with the passage of time, but also many solutions will sustain undesired microbiological growth. A long stored solution could, therefore, become contaminated and as a result be the cause of erroneous clinical test results and improper diagnosis of a patient's illness. Even with an extra supply, disruptions in delivery have frequently resulted in exhaustion of supply of one or more reagents.

In addition to the above-noted technical difficulties with such a system, there are significant economic disadvantages. A major portion of the mixed reagent solution consists of a reagent mixing fluid such as distilled water. In packaging and shipping the complete reagent solution, added costs are encountered as a result of the high volume and weight of the mixing fluid. In addition, the receiving clinical laboratory must allocate substantial space for storage of an adequate supply in accordance with usage requirements and the supplier's delivery pattern.

As a result of the problems encountered in the above described method of distribution some laboratories have adopted the practice of preparing their own chemical reagent solutions. While this results in the availability of fresh reagent solutions, it is not free from problems. Preparation in the laboratory requires the time of a specially skilled and supervised technician. Also, the reagent chemicals employed are frequently exposed to unsterile conditions which interfere with the desired reagent solution quality and performance characteristics.

BRIEF SUMMARY OF THE INVENTION

The above-enumerated problems have been solved by the method and container assembly of this invention. In the method of this invention a sterile chemically inert expandable mixing container is provided with a charge of a stable reagent concentrate material. The mixing container is positioned on or within a support member. A predetermined quantity of a mixing fluid is then introduced into the mixing container through an opening in the container. The reagent concentrate material and mixing fluid are then mixed to establish a uniform homogeneous solution and subsequently the reagent solution is filtered to remove particulate material. The mixing is preferably effected by external excitation of an inertly covered magnetic stirrer element positioned within the mixing container.

The container assembly of this invention provides an expandable mixing container having a charge of a reagent concentrate material. The mixing container has a closure provided with at least one fluid passageway therethrough. A tubular reagent discharge conduit has one end positioned within the mixing container and a portion extending into the closure passageway. A filter member to prevent discharge of particulate material is secured to the conduit. An outer container protectively surrounds the inner container. At least one of the containers has a sterile sealing member to prevent communication between the mixing container interior and the ambient air surrounding the outer container.

It is an object of this invention to provide a method of freshly preparing sterile chemical reagent solutions prior to use, by means of relatively unskilled laboratory personnel.

It is another object of this invention to provide a method of preparing sterile chemical reagent solutions in such a manner as to substantially reduce packaging costs, transporting costs, and storage space requirements, while insuring a supply of freshly prepared solutions as needed.

It is another object of this invention to provide such a method which is adapted for use with conventional automatic analysis equipment.

It is another object of this invention to provide for mixing of a reagent concentrate material and mixing fluid by means of a remotely activated magnetic stirrer which is positioned within the sterile expansible container and also to provide for filtration to remove particulate material from the reagent solution, all without destruction of the sterile environment within the shipping and mixing container.

It is another object of this invention to provide a container assembly having an outer protective container and an inner flexible expandable container for sterile charging, shipping and storage of a stable chemical reagent concentrate material as well as sterile mixing of a mixing fluid and the concentrate material to provide a fresh reagent solution.

These and other objects of the invention will be understood from the following description of the invention on reference to the appended drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a partially schematic sectional elevational view of one form of container assembly contemplated by this invention.

FIG. **2** is a partially schematic sectional elevational view of an initial stage of introduction of mixing fluid into the expandable container.

FIG. **3** is a partially schematic sectional view of the filled container during mixing of the reagent.

FIGS. **4** and **5** illustrate modified forms of expandable containers contemplated by this invention.

FIG. **6** shows some forms of closure and container joint means contemplated by this invention.

FIG. **7** shows a modified form of container assembly of this invention.

FIG. **8** shows a schematic sectional plan view of a filled inner container having a modified filter element.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring now more specifically to the drawings, with particular reference to FIG. **1**, a form of container assembly of this invention is there illustrated. An expandable inner container **2** has a quantity of a chemical reagent concentrate **4**, which in the form shown is a dry material. The expandable container **2** is composed of a flexible film and is shown in unexpanded condition.

A closure **6** is secured to the upper end of inner container **2**. A section of flexible reagent delivery tubing **10** is disposed within the inner container **2** and has a portion extending into a bore **12** in closure **6** and an outer end **14** disposed outside of inner container **2**. Secured to the inner end **16** of tubing **10** is a filter member **20** which is adapted to prevent entry of particulate material into delivery tube **10**.

In some instances the reagent concentrate particle size may approximate the filter opening size. In order to provide extra protection against the likelihood of the dry particulate material clogging openings in filter member **20** during handling, an inert protective film soluble in the reagent mixing fluid may be provided over the filter exterior. This film would be dissolved when the mixing fluid is introduced during reagent solution preparation.

Also disposed within inner container 2 is a magnetic stirrer element 22 which, preferably is bar shaped, is adapted to be activated by an external source during mixing of the reagent solution. The magnetic stirrer 22 is preferably covered with a material which is chemically inert to the reagent concentrate material 4. The magnetic stirrer 22 may conveniently be moved in a rotary path by means of an externally disposed rotating magnet.

In the form of expandable container illustrated in FIG. 1, it is contemplated that expansion of the inner container will result at least in part by filling the collapsed container 2 and opening it to its full size. As this occurs, folded regions 26 will unfold to provide a smooth wall surface. In lieu of such an expandable container or in addition thereto, a resilient stretching of the material may be employed to expand responsive to an increase in internal container pressure as mixing fluid is introduced. The material of the inner container must possess chemical inertness with respect to the reagent concentrate and sufficient strength to maintain its integrity during shipping and storage, as well as mixing. Among the preferred materials for use for the inner container are flexible polymer film materials selected from the group consisting of rubbers, olefins and acrylics, as well as combinations thereof.

The expandable inner mixing container 2 is protectively secured within an outer container which, in the form shown in FIG. 1, is a jar or bottle 30 which may be made of glass, plastic or other suitable material. The bottle 30 has a closure 32 sealingly secured thereto. The closure 32 is provided with a compressible gasket element 36 and is threadedly secured to the mouth of bottle 30.

The term "sterile" as used herein shall refer to operational sterility such that there is present no impurity which will cause any meaningful detrimental effect in the results obtained during subsequent usage of the chemical reagent solution. The term shall include, but not be limited to, materials and environments that are culturally sterile in that they are devoid of living organisms as well as materials and environments which are operatively sterile.

The outer container, be it a jar or bottle 30 as shown in FIG. 1 or other variety, is adapted to serve as a shipping and storage container for protectively encompassing the collapsed inner container 2 until reagent preparation is to be initiated. In the form shown in FIG. 1 sterility is maintained by means of the gasketed closure which is sealingly secured to the bottle 30. In lieu of or in addition to a sterility seal on the outer container, a sterility preserving seal may be provided on the inner container. In the form shown in FIG. 7, the exterior container 40 is a boxlike structure with a hinged lid 42. The inner container 44 has a closure 46 provided with a domelike seal 48. This seal 48 may be adhesively secured or otherwise bonded to the closure 46 to prevent contamination of the exterior of container 44. If delivery tube 50 terminates substantially flush with the upper surface of closure 46, the seal may be a disclike member.

Considering now the method of the invention, reference is made to FIGS. 2 and 3. After inner container 2 has been removed from outer container 30, it is seated on a supporting structure. In the form shown in FIG. 2, the supporting structure takes the form of a substantially rigid box 60 provided with a top panel 62 which has an opening. The unexpanded inner mixing container 2 is inserted part way into the box interior 64. Annular washer 66 on closure 6 resists further entry of the container 2 into box 60. FIG. 6 illustrates a means of securing expandable bag 2 to closure 6. If desired, the inner bag 2 may be secured to the closure 6 by adhesive 67, heat sealing or other suitable means without mechanical interlock of flange 71. Such joinder may be effected on the annular side surface 69 of closure 6. Also, mechanical interlock of flange 71 under washer 66 may be employed without other means of joinder.

Next, a sterile reagent mixing fluid will be introduced into inner container 2 through tube 68 which extends through a second passageway 70 in closure 6. Tube 68 may be provided in the assembly shown in FIGS. 1 or 7 or may be provided by the end user. This mixing fluid will frequently be distilled or distilled-deionized water which may be supplied from a reservoir 74 by means of a pump 72. Pump 72 should preferably be of the metering variety and may be controlled by a timer in order to insure the addition of the proper quantity of fluid for mixing with the reagent concentrate material 4. If desired, a microbiological retaining filter may be provided in tube 68 between the pump 72 and passageway 70. As the reagent concentrate material 4 is stable while dry, no concern regarding the freshness of the material 4 need arise until after the fluid has been introduced.

In the stage illustrated in FIG. 3, introduction of the reagent mixing fluid has been completed with the inner container 2 expanding to substantially completely fill the inner space 64 within box 60. As a result of magnetic stirrer 80 being moved under the influence of exteriorly disposed magnetic field generating means 82, effective mixing of the fluid and reagent material 4 is obtained without movement of either inner container 2 or outer container 30. Also, there is no need to open the container and insert a foreign stirrer element with potential loss of sterility. The field generating means 82 may take the form of a magnet or electrically energized coils.

In FIG. 3 the sterile reagent solution 84 has been substantially completely homogenized and is in condition for delivery through tubing 10. This may be accomplished by connecting the outer end 14 of tubing 10 with discharge pump 86. As some reagent solutions tend to produce some precipitate upon standing, filter member 20' is secured to the entry end of tubing 10 in order to prevent the entry of particulate material into tubing 10.

As the homogeneous reagent solution is withdrawn the mixing container 2 will collapse until it reaches a size which will permit withdrawal from box 60. It may be removed and discarded after emptying. This competes the entire shipping, storage, preparation and delivery cycle without loss of sterility.

A preferred form of inner container 90 is shown in FIGS. 4 and 5. In the form shown in FIG. 4 tube 92 has been secured to the exterior surface 94 of inner container 90 at intervals between closure 96 and filter 98. If desired the securement may be substantially continuous. In this position, the likelihood of interfering contact between the moving stirrer 80 and tubing 92 during mixing of the reagent is substantially reduced. As is desired the filter 20 is positioned at the bottom of the inner container at a position at the other extreme from closure 96 in order to permit full withdrawal of the mixed reagent solution. An alternate approach is shown in FIG. 5. Tubing 100 emerges from inner mixing container 102 at the bottom. The tubing 100 then extends upwardly and may be secured to the exterior of the mixing container 102. The upper end 104 may extend through the wall of container 102 and communicate with passageway 106 or alternatively may be employed directly as a reagent withdrawal conduit without entry into container 102.

A modified form of filter member 110 adapted for use with this invention is shown in FIG. 8. In this form, the filter member 110 is elongated and extends over a substantial portion of the base of inner container 2 and is preferably secured thereto. Member 110 is secured to flexible tubing 10 at joint 112. This form of filter assembly facilitates increased delivery flow efficiency, while effecting filtration and avoiding interfering contact with the magnetic stirrer element 80.

It will, therefore, be appreciated that this invention provides a means of sterily packaging a stable reagent concentrate, which may be dry or liquid, and shipping the same to the ultimate user who may by use of unskilled labor provide fresh sterile reagent solutions. This is accomplished while saving packaging and shipping costs, storage space requirements, reagent preparation time and permitting the use of less expensive relatively unskilled labor for skilled labor. The benefits of factory mixing of sterile reagent concentrate materials is retained. The sterility is retained in ultimate mixing within the

expandable mixing container. The emerging homogeneous reagent solution has also been filtered to eliminate particulate material. In addition, the availability of fresh solutions is facilitated as storage of great quantities of the small expandable containers having stable reagent concentrates may be readily employed with this system. Also, the system is compatible with existing automatic analysis equipment.

Whereas particular embodiments of the invention have been described above for purposes of illustration, it will be apparent to those skilled in the art that numerous variations of the details may be made without departing from the appended claims.

Having thus described my invention and certain embodiments thereof, I claim:

1. A method of preparing sterile chemical reagent solutions comprising

providing a sterile expandable mixing container having a quantity of a reagent concentrate material therein,

positioning said mixing container within a support structure which has a substantially rigid multiple walled member of sufficient interior capacity to house said expandable container after introduction of said mixing fluid, introducing said expandable mixing container into said rigid member through an opening in one wall of said rigid member,

providing a closure for said expandable mixing container with said closure having a fluid receiving opening in the form of a passageway therethrough,

introducing a predetermined quantity of a mixing fluid into said mixing container through said closure passageway with said expandible mixing container being enlarged substantially while preventing discharge of mixing fluid or said reagent concentrate material from said container,

mixing said reagent concentrate material and said mixing fluid within said inner container to establish a reservoir of uniform homogeneous reagent solution while preventing discharge of said partially mixed solution therefrom, discharging said reagent solution from said mixing containing after terminating said introduction of said mixing fluid and after mixing to establish said uniform homogeneous reagent solution, and solution to remove particulate material therefrom whereby the introduction of said fluid and the mixing of said fluid and said concentrate material are accomplished within a closed sterile container.

2. The method of claim 1 including

said reagent concentrate material is a dry particulate material,

said mixing fluid is distilled water,

establishing movement of a magnetic stirrer disposed within said expandable container in order to effect said mixing, and

said filtering of said reagent solution occurs prior to delivery from said expandable mixing container.

3. The method of claim 2 including

inserting said mixing container into said rigid container through an opening in one wall of said rigid container,

securing said mixing container to said rigid container adjacent said opening,

providing within said mixing container a discharge tube which has a filter element at an end which extends toward a position closely adjacent the bottom of said container and has the other end extending outwardly through said closure, and

delivering said reagent solution from said mixing container through said discharge tube.

4. A sterile container assembly for chemical reagent concentrates comprising

an expandable inner container made of a flexible film material having a chemical reagent concentrate therein,

closure means having a first passageway and a second passageway therethrough secured to the mouth of said inner container, said closure means being a generally cylindrical stopperlike element having said first and second passageways extending continuously therethrough in direction generally parallel to the central axis of said stopperlike element,

a tubular reagent discharge conduit having one portion extending into said first passageway in said closure means,

said conduit having the other end disposed within said inner container at a position closely adjacent the bottom thereof, said tubular reagent discharge conduit being flexible and being disposed in at least partially folded restricted length position within said expandable inner container,

filter means secured to said conduit closer to said conduit end adjacent the bottom of said container than to said closure means to prevent discharge of particulate material from said conduit,

an outer container protectively surrounding said inner container, and

sterile sealing means to prevent communication between the contaminating elements in the surrounding air and the interior of said inner container,

whereby removal of said inner container from said outer container permits introduction of a mixing fluid into said inner container to create a reservoir of sterile reagent solution.

5. The container assembly of claim 4 including

said inner container is composed of a flexible thermoplastic material,

a stirrer member composed of a magnetic material covered with a material which is inert with respect to said chemical reagent concentrate disposed within said inner container, and

said filter is secured to said second end of said conduit.

6. The container assembly of claim 4 including

said closure means having a passageway therethrough to permit introduction of a mixing fluid into said inner container,

said inner container is made of a flexible polymer film material selected from the group consisting of rubber, olefin and acrylic,

a major portion of said conduit secured to at least one wall of said inner container to prevent interference by said conduit with movement of said stirrer member after the initiation of introduction of a mixing fluid into said inner container, and

said filter element positioned adjacent a portion of said inner container remote from said closure.

7. The container assembly of claim 6 including

said outer container is a substantially rigid jarlike container,

said sealing means has a closure sealingly secured to said outer container, and

said inner container has an expanded size substantially larger than said outer container.

* * * * *