Joseph F. Jennings (Bar No. 145,920)
joe.jennings@knobbe.com
Jared C. Bunker (Bar No. 246,946)
jared.bunker@knobbe.com
Stephanie M. Johnson (Bar No. 304,153)
stephanie.johnson@knobbe.com
KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 Main Street, 14th Floor
Irvine, CA 92614
Telephone: 949-760-0404
Facsimile: 949-760-9502

Boris Zelkind (Bar No. 214,014)
boris.zelkind@knobbe.com
KNOBBE, MARTENS, OLSON & BEAR, LLP
12790 El Camino Real
San Diego, CA 92130
Telephone: 858-707-4000
Facsimile: 858-707-4001

Attorneys for Plaintiff
Rembrandt Diagnostics, LP

IN THE UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

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| REMBRANDT DIAGNOSTICS, LP,<br><br>Plaintiff,<br><br>v.<br><br>ALERE, INC., ALERE TOXICOLOGY SERVICES, INC., AMEDICA BIOTECH, INC., AMEDITECH, INC., INNOVACON, INC., INSTANT TECHNOLOGIES, INC., US DIAGNOSTICS, INC., BRANAN MEDICAL CORPORATION, and DOES 1–10<br><br>Defendants. | Case No. '16CV0698 LAB NLS<br><br>**COMPLAINT FOR PATENT INFRINGEMENT**<br><br>**DEMAND FOR JURY TRIAL** |

Plaintiff Rembrandt Diagnostics, LP ("Rembrandt") complains of Defendants Alere, Inc. ("Alere"), Alere Toxicology Services, Inc. ("Alere Toxicology"), Amedica Biotech, Inc. ("Amedica"), Ameditech, Inc. ("Ameditech"), Innovacon, Inc. ("Innovacon"), Instant Technologies, Inc. ("Instant Technologies"), US Diagnostics, Inc. ("US Diagnostics"), Branan Medical Corporation ("Branan"), and DOES 1–10 (collectively "Defendants"), and alleges as follows:

## JURISDICTION AND VENUE

1. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 100 *et seq*., and more particularly, 35 U.S.C. §§ 271 and 281. This Court has original subject matter jurisdiction of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

2. Defendants are subject to personal jurisdiction in this Court, and venue is proper pursuant to 28 U.S.C. §§ 1391 and 1400(b). Defendants regularly conduct business in this judicial district and have committed the acts of patent infringement complained of herein in this judicial district and directed to this judicial district. Also, Ameditech's and Innovacon's principal place of business is located in this judicial district.

## THE PARTIES

3. Rembrandt is a limited partnership organized and existing under the laws of the Commonwealth of Virginia, having its principal place of business at 401 City Avenue, Suite 900, Bala Cynwyd, PA 19004.

4. Rembrandt is informed and believes, and thereon alleges, that Alere is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 51 Sawyer Rd Suite 200, Waltham, MA 02453.

5. Rembrandt is informed and believes, and thereon alleges, that Alere Toxicology is a wholly-owned subsidiary of Alere, and is a corporation

organized and existing under the laws of the State of Louisiana, having a place of business at 1111 Newton St, Gretna, LA 70053. Rembrandt is informed and believes, and thereon alleges, that Alere Toxicology and Alere have overlapping corporate officers and report their business operations in consolidated financial statements.

6. Rembrandt is informed and believes, and thereon alleges, that Amedica is a wholly-owned subsidiary of Alere, and is a corporation organized and existing under the laws of the State of California, having a place of business at 28301 Industrial Blvd Ste K, Hayward, CA 94545. Rembrandt is informed and believes, and thereon alleges, that Amedica and Alere report their business operations in consolidated financial statements.

7. Rembrandt is informed and believes, and thereon alleges, that Ameditech is a wholly-owned subsidiary of Alere, and is a corporation organized and existing under the laws of the State of California, having a place of business at 10340 Camino Santa Fe Suite F, San Diego, CA 92121. Rembrandt is informed and believes, and thereon alleges, that Alere, Ameditech, and Alere Toxicology have one or more overlapping corporate officers. Rembrandt is informed and believes, and thereon alleges, that Ameditech and Alere report their business operations in consolidated financial statements.

8. Rembrandt is informed and believes, and thereon alleges, that Innovacon is a wholly-owned subsidiary of Alere, and is a corporation organized and existing under the laws of the State of California, having a place of business at 9975 Summers Ridge Rd, San Diego, CA 92121. Rembrandt is informed and believes, and thereon alleges, that Innovacon and Alere report their business operations in consolidated financial statements.

9. Rembrandt is informed and believes, and thereon alleges, that Instant Technologies is a wholly-owned subsidiary of Alere, and is a

corporation organized and existing under the laws of the Commonwealth of Virginia, having a place of business at 400 Port Centre Parkway, Portsmouth, VA 23707. Rembrandt is informed and believes, and thereon alleges, that Instant Technologies and Alere report their business operations in consolidated financial statements.

10. Rembrandt is informed and believes, and thereon alleges, that US Diagnostics is a wholly-owned subsidiary of Alere, and is a corporation organized and existing under the laws of the State of Alabama, having a place of business at 2 Parade St NW, Huntsville, AL 35806. Rembrandt is informed and believes, and thereon alleges, that US Diagnostics and Alere report their business operations in consolidated financial statements.

11. Rembrandt is informed and believes, and thereon alleges, that Branan is a wholly-owned subsidiary of Alere, and is a corporation organized and existing under the laws of the State of Nevada, having a place of business at 140 Technology Drive, Suite 400, Irvine, CA 92618. Rembrandt is informed and believes, and thereon alleges, that Branan, Alere, and Alere Toxicology have overlapping corporate officers and report their business operations in consolidated financial statements.

12. Rembrandt is ignorant of the identity of Defendants sued herein as DOES 1–10, but sues them in that capacity until such information is ascertained. Rembrandt is informed and believes, and thereon alleges, that DOES 1–10 are responsible for some of the acts complained of herein, as well as other acts of infringement. Rembrandt is informed and believes, and thereon alleges, that DOES 1–10 are corporate affiliates and/or agents of one or more of the other Defendants in performing the acts complained of herein.

## GENERAL ALLEGATIONS

### The Asserted Patents

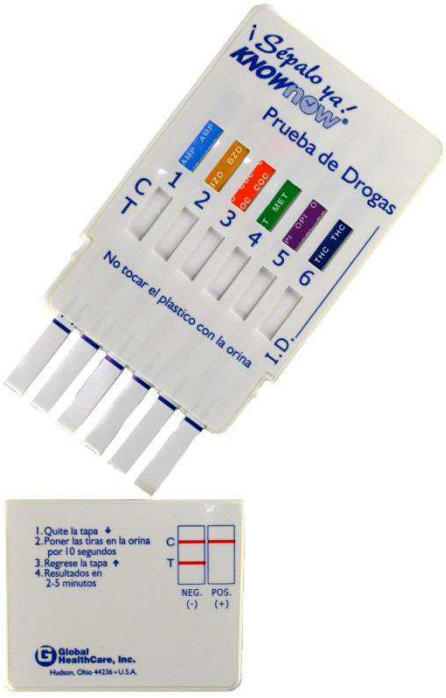
13. On April 15, 2003, the United States Patent and Trademark Office duly and lawfully issued U.S. Patent No. 6,548,019 ("the '019 patent"), entitled "Device and Methods for Single Step Collection and Assay of Biological Fluids." The '019 patent names Dr. Jin Po Lee and Dr. Poyi Tseng as inventors. Rembrandt owns all rights, title, and interest in the '019 patent. A true and correct copy of the '019 patent is attached hereto as Exhibit 1.

14. On January 7, 2014, the United States Patent and Trademark Office duly and lawfully issued U.S. Patent No. 8,623,291 ("the '291 patent"), entitled "Multiple Analyte Assay Device." The '291 patent names Dr. Jin Po Lee as the inventor. Rembrandt owns all rights, title, and interest in the '291 patent. A true and correct copy of the '291 patent is attached hereto as Exhibit 2.

### The Patented Technology

15. The '019 patent describes test cups that includes one or more test strips and can be used to collect and quickly screen a urine sample for the presence of illicit drugs or other substances. For many years, the named inventor Dr. Lee, through his company Syntron Bioresearch, Inc. ("Syntron"), has marketed and sold such test cups under the tradename QuikScreen®. Syntron is a corporation organized and existing under the laws of the State of California, having a place of business in this judicial district at 2774 Loker Avenue West, Carlsbad, CA 92010. At least some of Syntron's test cups are covered by one or more claims of the '019 patent. Shown below is a photograph of a Syntron test cup:


16. The '291 patent describes dip testing devices that hold multiple test strips and can also be used to quickly screen a urine sample for the presence of illicit drugs or other materials. For many years, Dr. Lee, through his company Syntron, has also marketed and sold such dip testing devices. At least some of the dip testing devices are covered by one or more claims of the '291 patent. Shown below is a photograph of a Syntron dip testing device:




17. Syntron is a licensee under the '019 and '291 patents. Syntron has been marking its QuikScreen® test cups or their packaging with the '019 patent

number and its dip testing devices or their packaging with the '291 patent number.

**Defendants' Products**

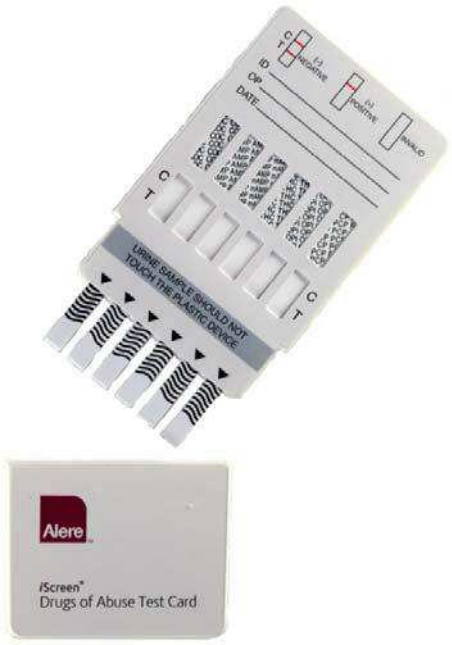
18. Rembrandt is informed and believes, and thereon alleges, that Alere makes, uses, imports, offers to sell, and/or sells in the United States test cups used to collect and quickly screen a urine sample for the presence of illicit drugs or other substances. Rembrandt is informed and believes, and thereon alleges, that Alere sells these test cups to customers in this judicial district. These test cups are marketed and sold under the tradenames "iCup Dx Pro," "iCup A.D.," "AmediCheck," "DrugSmart," and "UScreen." The following pictures show examples of these test cups:

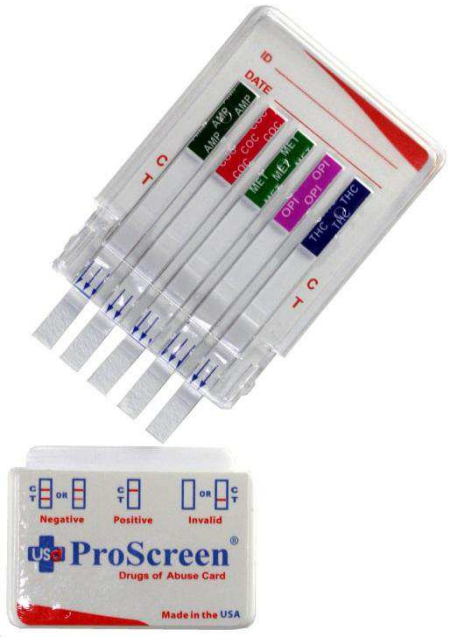




19. Rembrandt is informed and believes, and thereon alleges, that Alere also makes, uses, imports, offers to sell, and/or sells in the United States test cups under additional tradenames, which test cups are substantially the same in design and function as the above test cups. Rembrandt is informed and believes, and thereon alleges, that Alere also offers to sell and sells these test cups to customers in this judicial district.

20. Rembrandt is informed and believes, and thereon alleges, that Alere makes, uses, imports, offers to sell, and/or sells in the United States dip testing devices that hold multiple test strips and can be used to quickly screen a urine sample for the presence of illicit drugs or other materials. Rembrandt is informed and believes, and thereon alleges, that Alere offers to sell and sells these dip testing devices to customers in this judicial district. These dip testing devices are marketed and sold under the tradenames "iScreen" and "ProScreen." The following pictures show examples of these dip testing devices:



21. Rembrandt is informed and believes, and thereon alleges, that Alere also makes, uses, imports, offers to sell, and/or sells in the United States dip testing devices under additional tradenames, which devices are substantially the same in design and function as the above dip testing devices. Rembrandt is informed and believes, and thereon alleges, that Alere also offers to sell and sells these dip testing devices to customers in this judicial district.

22. Rembrandt is informed and believes, and thereon alleges, that Alere Toxicology makes, uses, imports, offers to sell, and/or sells in the United States the "iCup Dx Pro" and "iCup A.D." test cups, as well as the "iScreen" dip testing devices. Rembrandt is informed and believes, and thereon alleges, that Alere Toxicology offers to sell and sells these test cups and dip testing devices to customers in this judicial district. Rembrandt is informed and believes, and thereon alleges, that Alere Toxicology also makes, uses, imports, offers to sell, and/or sells in the United States other test cups and dip testing devices that are substantially the same in design and function as the above test cups and dip testing devices. Rembrandt is informed and believes, and thereon alleges, that Alere controls its wholly-owned subsidiary Alere Toxicology in performing at least some of these acts.

23. Rembrandt is informed and believes, and thereon alleges, that Amedica makes, uses, imports, offers to sell, and/or sells in the United States the "iCup Dx Pro," "Amedicheck," and "DrugSmart" test cups. Amedica is listed as the Applicant and Manufacturer on FDA applications to market "iCup Dx Pro" and "AmediCheck" test cups. Amedica is listed as the Applicant on an FDA application to market a "DrugSmart" test cup. Rembrandt is informed and believes, and thereon alleges, that Amedica sells these test cups to customers in this judicial district. Rembrandt is informed and believes, and thereon alleges, that Amedica also makes, uses, imports, offers to sell, and/or sells in the United States other test cups that are substantially the same in design and function as

the above test cups. Rembrandt is informed and believes, and thereon alleges, that Alere controls its wholly-owned subsidiary Amedica in performing at least some of these acts.

24. Rembrandt is informed and believes, and thereon alleges, that Ameditech makes, uses, imports, offers to sell, and/or sells in the United States the "DrugSmart" test cups, as well as the "ProScreen" dip testing devices. Ameditech is listed as the Applicant on an FDA application to market a "DrugSmart" test cup and as the Applicant on an FDA application to market a "ProScreen" dip testing device. Rembrandt is informed and believes, and thereon alleges, that Ameditech manufactures these test cups and dip testing devices in this judicial district and/or sells these test cups and dip testing devices to customers in this judicial district. Rembrandt is informed and believes, and thereon alleges, that Ameditech also makes, uses, imports, offers to sell, and/or sells in the United States other test cups and dip testing devices that are substantially the same in design and function as the above test cups and dip testing devices. Rembrandt is informed and believes, and thereon alleges, that Alere controls its wholly-owned subsidiary Ameditech in performing at least some of these acts.

25. Rembrandt is informed and believes, and thereon alleges, that Innovacon makes, uses, imports, offers to sell, and/or sells in the United States the "iCup A.D." test cups, as well as the "iScreen" dip testing devices. Innovacon is listed as the Applicant on an FDA application to market an "iCup" test cup and as the Applicant on an FDA application to market an "iScreen" dip testing device. Rembrandt is informed and believes, and thereon alleges, that Innovacon manufactures these test cups and dip testing devices in this judicial district and/or sells these test cups and dip testing devices to customers in this judicial district. Rembrandt is informed and believes, and thereon alleges, that Innovacon also makes, uses, imports, offers to sell, and/or sells in the United

States other test cups and dip testing devices that are substantially the same in design and function as the above test cups and dip testing devices. Rembrandt is informed and believes, and thereon alleges, that Alere controls its wholly-owned subsidiary Innovacon in performing at least some of these acts.

26. Rembrandt is informed and believes, and thereon alleges, that Instant Technologies makes, uses, imports, offers to sell, and/or sells in the United States the "iCup A.D." test cups, as well as the "iScreen" dip testing devices. Instant Technologies is listed in the Test Name field on an FDA application to market an "iCup" test cup and in the Test Name field on an FDA application to market an "iScreen" dip testing device. Rembrandt is informed and believes, and thereon alleges, that Instant Technologies sells these test cups and dip testing devices to customers in this judicial district. Rembrandt is informed and believes, and thereon alleges, that Instant Technologies also makes, uses, imports, offers to sell, and/or sells in the United States other test cups and dip testing devices that are substantially the same in design and function as the above test cups and dip testing devices. Rembrandt is informed and believes, and thereon alleges, that Alere controls its wholly-owned subsidiary Instant Technologies in performing at least some of these acts.

27. Rembrandt is informed and believes, and thereon alleges, that US Diagnostics makes, uses, imports, offers to sell, and/or sells in the United States the "UScreen" test cups, as well as the "ProScreen" dip testing devices. US Diagnostics is listed in the Test Name field on an FDA application to market a "UScreen" test cup and in the Test Name field on an FDA application to market a "ProScreen" dip test device. Rembrandt is informed and believes, and thereon alleges, that US Diagnostics sells these test cups and dip testing devices to customers in this judicial district. Rembrandt is informed and believes, and thereon alleges, that US Diagnostics also makes, uses, imports, offers to sell, and/or sells in the United States other test cups and dip testing devices that are

substantially the same in design and function as the above test cups and dip testing devices. Rembrandt is informed and believes, and thereon alleges, that Alere controls its wholly-owned subsidiary US Diagnostics in performing at least some of these acts.

28. Rembrandt is informed and believes, and thereon alleges, that Branan makes, uses, imports, offers to sell, and/or sells in the United States the "AmediCheck" test cups. Branan is listed as the manufacturer on the packaging of some "AmediCheck Instant Test" cups. Rembrandt is informed and believes, and thereon alleges, that Branan sells these test cups to customers in this judicial district. Rembrandt is informed and believes, and thereon alleges, that Branan also makes, uses, imports, offers to sell, and/or sells in the United States other test cups that are substantially the same in design and function as the above test cups. Rembrandt is informed and believes, and thereon alleges, that Alere controls its wholly-owned subsidiary Branan in performing at least some of these acts.

**Alere Seeks a License to the Asserted '019 Patent**

29. In 2012, representatives of Alere and Alere Toxicology, including Cindy Horton, then Vice President of Sales, met with Dr. Lee, named inventor of the '019 patent, at Syntron's facility in this judicial district. Dr. Lee explained to the Alere representatives how test cups made and sold by the Alere entities were infringing the '019 patent.

30. In June 2012, Ms. Horton sent a draft license agreement to Dr. Lee, seeking permission for Alere and its affiliates to lawfully practice the inventions of the '019 patent.

31. Dr. Lee later presented a counter-proposal to Ms. Horton. Alere did not accept Dr. Lee's counter-proposal.

**FIRST CLAIM FOR RELIEF**

**(Infringement of U.S. Patent No. 6,548,019 by all Defendants)**

32. Rembrandt repeats, realleges, and incorporates by reference the allegations set forth in Paragraphs 1–31 of this Complaint.

33. This is a claim for patent infringement and arises under the Patent Laws of the United States and, in particular, under 35 U.S.C. §§ 271, *et seq*.

34. Rembrandt is informed and believes, and thereon alleges, that Defendants have in the past infringed and are currently infringing the '019 patent in violation of 35 U.S.C. § 271(a) by making, using, importing, offering to sell, and selling in the United States test cups that include one or more test strips and can be used to collect and quickly screen a urine sample for the presence of illicit drugs or other substances, including test cups marketed and sold under the tradenames "iCup Dx Pro," "iCup A.D.," "AmediCheck," "DrugSmart," and "UScreen."

35. Rembrandt is informed and believes, and thereon alleges, that Defendants have in the past infringed and are currently infringing the '019 patent in violation of 35 U.S.C. § 271(b) by marketing and selling the above test cups, knowing and intending that that such test cups would be used by Defendants' customers and end users in a manner that infringes the '019 patent. To that end, Defendants provide instructions and teachings to their customers and end users that such test cups be used to infringe the '019 patent. As a result, Defendants' test cups have been used by their customers and end users in a manner that directly infringes the '019 patent. Rembrandt is informed and believes, and thereon alleges, that Defendants are aware of the '019 patent and intend that their customers and end users directly infringe the '019 patent. Defendants have also induced each other to make, import, offers to sell, and sell the infringing test cups.

36. Rembrandt is informed and believes, and thereon alleges, that Defendants have in the past infringed and are currently infringing the '019 patent in violation of 35 U.S.C. § 271(c) because, among other things, Defendants have offered to sell and sold within the United States the above test cups and components thereof, which are not staple articles or commodities of commerce suitable for substantial non-infringing use, which constitute a material part of the patented inventions, and which are known by Defendants to be especially made or especially adapted for use in an infringement of the '019 patent. As a result, Defendants' test cups have been used by their customers and end users to directly infringe the '019 patent.

37. Rembrandt is informed and believes, and thereon alleges, that Defendants have in the past infringed and are currently infringing, both directly and indirectly and both literally and under the doctrine of equivalents, at least Claim 1 of the '019 patent, because Defendants' test cups each include all of the claim elements, including an assay test strip, a sample fluid container, and a flow control channel inside the sample fluid container. The channel in Defendants' test cups includes a liquid pervious side oriented toward the base of the container, with the liquid pervious side joined to liquid impervious sides. The assay test strip of the Defendants' test cups is positioned within the flow control channel and has a sample loading zone that contacts the sample fluid at the liquid pervious side of the flow control channel. The channel in Defendants' test cups is also oriented such that sample fluid, when added to the container, is delivered to the sample loading zone of the assay test strip through the liquid pervious side of the channel without migration through an intermediate structure. Further, the channel in Defendants' test cups is also oriented such that entry of fluid into the channel creates an ambient pressure within the channel equivalent to the ambient pressure outside the channel, thereby eliminating a pressure gradient along which excess sample fluid could flow into the channel.

38. Defendants have been given notice that they infringe the '019 patent. Defendants are aware of or are willfully blind to the existence of the '019 patent. Rembrandt is informed and believes, and thereon alleges, that Defendants are aware of the '019 patent and their infringement of the '019 patent at least though the discussions with Dr. Lee in 2012 regarding the '019 patent, as well as Alere's request for a license to the '019 patent for Alere and its affiliates. Defendants have also been provided constructive notice of the '019 patent through Syntron's marking its licensed test cups or packaging with the '019 patent number.

39. Upon information and belief, Defendants' infringement of the '019 patent has been and continues to be deliberate and willful.

40. Upon information and belief, Defendants' infringement will continue unless enjoined by this Court.

41. Upon information and belief, Defendants have derived, received, and will continue to derive and receive gains, profits, and advantages from these acts of infringement in an amount that is not presently known to Rembrandt. Due to Defendants' infringement of the '019 patent, Rembrandt has been damaged and is entitled to monetary relief in an amount to be determined at trial, which amount is no less than a reasonable royalty. Pursuant to 35 U.S.C. § 284, Rembrandt is also entitled to an increase of damages up to three times the amount found or assessed at least due to Defendants' willful and deliberate infringement. And because Defendants' infringement presents an exceptional case, Rembrandt is also entitled to an award of its attorney fees under 35 U.S.C. § 285.

42. Unless Defendants are enjoined from infringing the '019 patent, Rembrandt will continue to suffer irreparable injury for which it has no adequate remedy at law.

**SECOND CLAIM FOR RELIEF**

**(Infringement of U.S. Patent No. 8,623,291 by Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1-10)**

43. Rembrandt repeats, realleges, and incorporates by reference the allegations set forth in Paragraphs 1–42 of this Complaint.

44. This is a claim for patent infringement and arises under the Patent Laws of the United States and, in particular, under 35 U.S.C. §§ 271, *et seq*.

45. Rembrandt is informed and believes, and thereon alleges, that Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1–10 have in the past infringed and are currently infringing the '291 patent in violation of 35 U.S.C. § 271(a) by making, using, importing, offering to sell, and selling in the United States dip testing devices that hold multiple test strips and can also be used to quickly screen a urine sample for the presence of illicit drugs or other materials, including dip testing devices marketed and sold under the tradenames "iScreen" and "ProScreen."

46. Rembrandt is informed and believes, and thereon alleges, that Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1–10 have in the past infringed and are currently infringing the '291 patent in violation of 35 U.S.C. § 271(b) by marketing and selling the above dip testing devices, knowing and intending that such dip testing devices would be used by these Defendants' customers and end users in a manner that infringes the '291 patent. To that end, these Defendants provide instructions and teachings to their customers and end users that such dip testing devices be used to infringe the '291 patent. As a result, these Defendants' dip testing devices have been used by their customers and end users in a manner that directly infringes the '291 patent. Rembrandt is informed and believes, and thereon alleges, that these Defendants are aware of the '291 patent and intend

that their customers and end users directly infringe the '291 patent. Defendants have also induced each other to make, import, offer to sell, and sell the infringing dip testing devices.

47. Rembrandt is informed and believes, and thereon alleges, that Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1–10 have in the past infringed and are currently infringing the '291 patent in violation of 35 U.S.C. § 271(c) because, among other things, these Defendants have offered to sell and sold within the United States the above dip testing devices and components thereof, which are not staple articles or commodities of commerce suitable for substantial non-infringing use, which constitute a material part of the patented inventions, and which are known by these Defendants to be especially made or especially adapted for use in an infringement of the '291 patent. As a result, these Defendants' dip testing devices have been used by their customers and end users in a manner that directly infringes the '291 patent.

48. Rembrandt is informed and believes, and thereon alleges, that Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1–10 have in the past infringed and are currently infringing, both directly and indirectly and both literally and under the doctrine of equivalents, at least Claims 1 and 9 of the '291 patent, because their dip testing devices each include all of the claim elements, including a base having adjacent slots, wherein each slot is defined by a floor, raised walls, and an open end. The dip testing devices also have a multiplicity of test strips. The test strips have a test zone and a control zone. The test zone of each test strip contains a binder specific for a different analyte. A single test strip is inserted into each slot of the base such that one end of the test strip protrudes out of the open end of the slot. The protruding freestanding end of each test strip also contains a sample addition pad for direct contact with the fluid to be analyzed.

The dip testing devices also have a cover attached to the upwardmost surface of each raised wall, which retains the assay test strips and includes a transparent window through which the test zone and control zone of the test strips can be viewed. The dip testing devices also have a cap enclosing the protruding end of the assay test strips, which can be removably attached to the open end of the base. Defendants also instruct and teach their customers and end users to perform a method of detecting a multiplicity of analytes, which includes removing the cap of the dip testing devices, inserting the protruding end of the assay test strips into a sample to be analyzed, and observing the effect of the sample on the test zone and control zone of the test strips.

49. Rembrandt is informed and believes, and thereon alleges, that Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1-10 are aware of or are willfully blind to the existence of the ’291 patent. They have been provided constructive notice of the ’291 patent through Syntron’s marking its licensed dip testing devices or packaging with the ’291 patent number.

50. Rembrandt is informed and believes, and thereon alleges, that the infringement of the ’291 patent by Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1–10 has been and continues to be deliberate and willful.

51. Rembrandt is informed and believes, and thereon alleges, that the infringement by Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1–10 will continue unless enjoined by this Court.

52. Rembrandt is informed and believes, and thereon alleges, that Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1-10, have derived, received, and will continue to derive and receive gains, profits, and advantages from these acts of infringement

in an amount that is not presently known to Rembrandt. Due to their infringement of the '291 patent, Rembrandt has been damaged and is entitled to monetary relief in an amount to be determined at trial, which amount is no less than a reasonable royalty. Pursuant to 35 U.S.C. § 284, Rembrandt is also entitled to an increase of damages up to three times the amount found or assessed at least due to Defendants' willful and deliberate infringement. And because Defendants' infringement presents an exceptional case, Rembrandt is also entitled to an award of its attorney fees under 35 U.S.C. § 285.

53. Unless Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1-10 are enjoined from infringing the '291 patent, Rembrandt will continue to suffer irreparable injury for which it has no adequate remedy at law.

**PRAYER FOR RELIEF**

WHEREFORE, Rembrandt prays for judgment in its favor against Defendants, and each of them, as follows:

a) an Order adjudging Defendants to have infringed and willfully infringed the '019 patent;

b) an injunction enjoining Defendants, as well as their officers, agents, servants, employees, attorneys, and those persons in active concert or participation with Defendants, from infringing the '019 patent;

c) an accounting of all gains, profits, and advantages Defendants derived by their infringement of the '019 patent, and for damages adequate to compensate Rembrandt for such infringement of the '019 patent;

d) an Order adjudging Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1-10 to have infringed and willfully infringed the '291 patent;

e) an injunction enjoining Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1-10 as well as

their officers, agents, servants, employees, attorneys, and those persons in active concert or participation with them, from infringing the '291 patent;

f) an accounting of all gains, profits, and advantages Alere, Alere Toxicology, Ameditech, Innovacon, Instant Technologies, US Diagnostics, and DOES 1-10 derived by their infringement of the '291 patent, and for damages adequate to compensate Rembrandt for such infringement of the '291 patent;

g) an award of treble damages and/or for exemplary damages under 35 U.S.C. § 284;

h) an Order declaring this to be an exceptional case under 35 U.S.C. § 285;

i) an award to Rembrandt of its attorney fees under 35 U.S.C. § 285;

j) an award to Rembrandt of pre-judgment and post-judgment interest and costs; and

k) such other and further relief as the Court deems just and proper.

Respectfully submitted,
KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 23, 2016

By: */s/ Joseph F. Jennings*
Joseph F. Jennings
Boris Zelkind
Jared C. Bunker
Stephanie M. Johnson
Attorneys for Plaintiff Rembrandt Diagnostics, LP

**DEMAND FOR JURY TRIAL**

Pursuant to Federal Rules of Civil Procedure 38(b), Plaintiff Rembrandt Diagnostics, LP hereby demands a trial by jury on all issues so triable that are raised herein or that hereinafter may be raised in this action

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 23, 2016

By: */s/ Joseph F. Jennings*
Joseph F. Jennings
Boris Zelkind
Jared C. Bunker
Stephanie M. Johnson
Attorneys for Plaintiff Rembrandt Diagnostics, LP

22842112

# TABLE OF EXHIBITS

**Page #**

# Exhibit 1

US006548019B1

(12) **United States Patent**
**Lee et al.**

(10) **Patent No.: US 6,548,019 B1**
(45) **Date of Patent: Apr. 15, 2003**

(54) **DEVICE AND METHODS FOR SINGLE STEP COLLECTION AND ASSAYING OF BIOLOGICAL FLUIDS**

(75) Inventors: **Jin Po Lee**, 13150 Glen Cir., Poway, CA (US) 92064; **Poyi Tseng**, Taipei (TW)

(73) Assignee: **Jin Po Lee**, Poway, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(86) PCT No.: **PCT/US99/18881**

§ 371 (c)(1),
(2), (4) Date: **Mar. 23, 2000**

(87) PCT Pub. No.: **WO00/29111**

PCT Pub. Date: **May 25, 2000**

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(51) **Int. Cl.**[7] ..... **G01N 21/00**

(52) **U.S. Cl.** ..... **422/58**; 422/102; 422/99; 422/68.1

(58) **Field of Search** ..... 422/58, 68.1, 99, 422/102; 436/518

(56) **References Cited**

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|---|---|---|---|---|
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| 5,523,055 | A * | 6/1996 | Hansen et al. | 422/58 |
| 5,770,458 | A * | 6/1998 | Klimov et al. | 436/518 |

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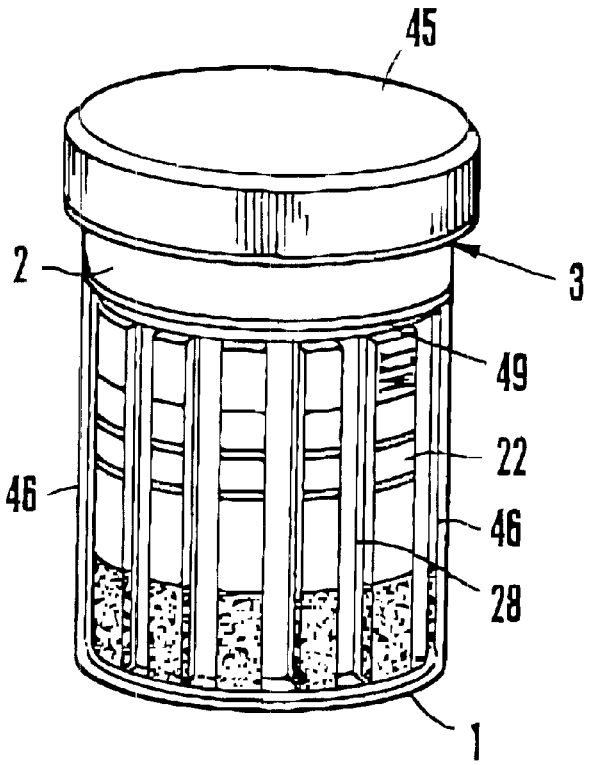
*Primary Examiner*—Jill Warden
*Assistant Examiner*—Sam P. Siefke
(74) *Attorney, Agent, or Firm*—Stacy L. Taylor; Foley & Lardner

(57) **ABSTRACT**

Devices, and methods for the use of same, for collecting and assaying a biological fluid in a single step. One method provides means to control and direct the flow of a sample of the biological fluid directly onto an assay test strip by disposing the assay test strip within a flow control channel in which the internal ambient pressure is maintained in substantial equilibrium with the ambient pressure outside of the flow control channel, such that essentially no pressure gradient is formed within the flow control channel. The devices include the flow control channel, at least one assay test strip and a fluid sample collection container, such as a urine cup, for insertion of the flow control channel therein.

**15 Claims, 2 Drawing Sheets**



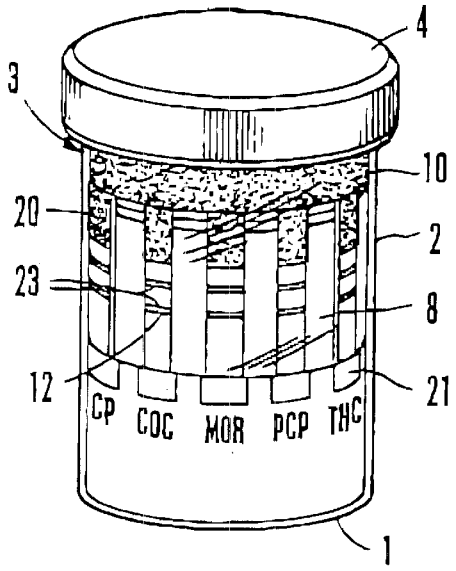



Fig. 1

EXISTING DEVICE

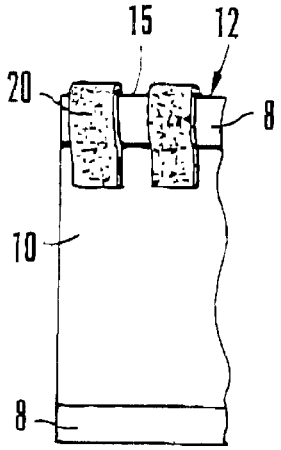



Fig. 2

EXISTING DEVICE

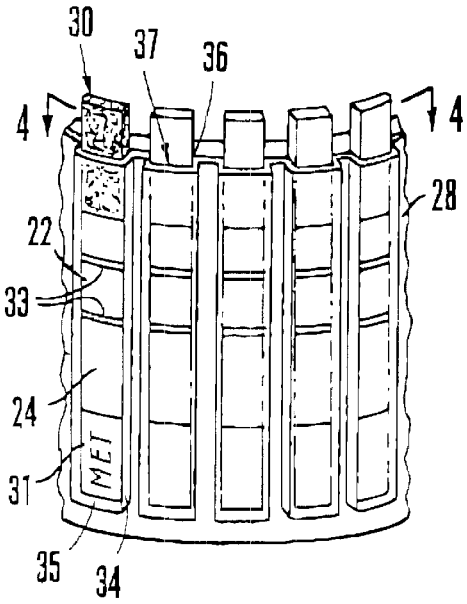



Fig. 3

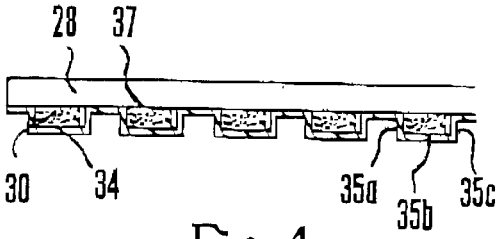



Fig. 4

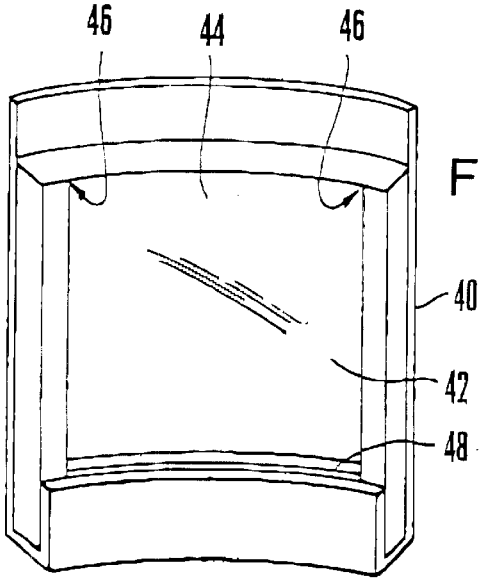



Fig. 5

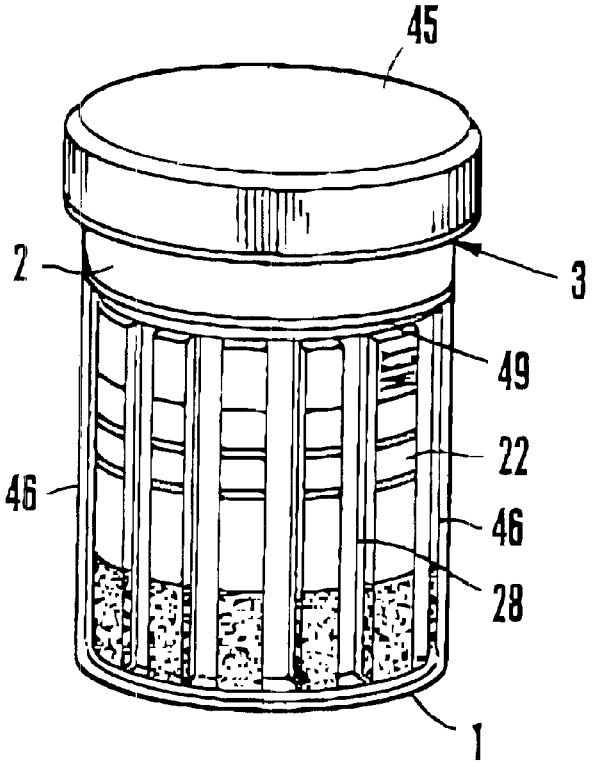



Fig. 6

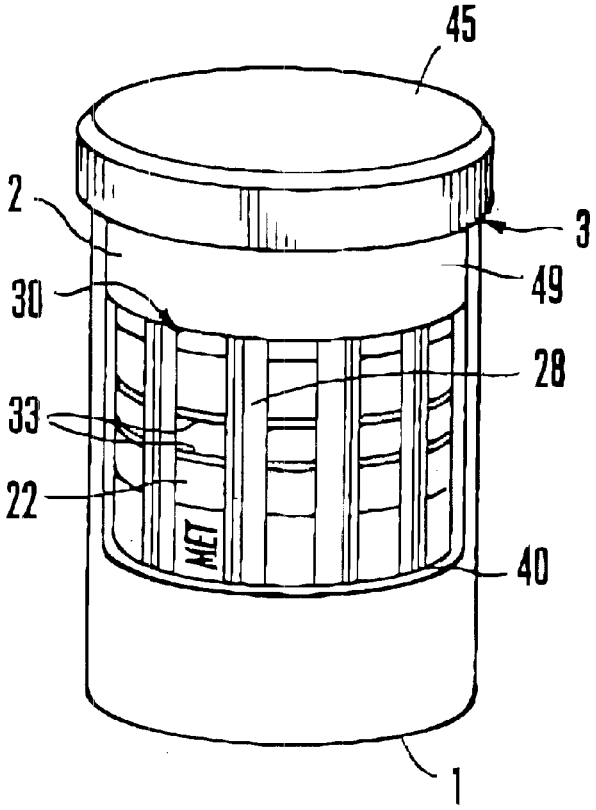



Fig. 7

# DEVICE AND METHODS FOR SINGLE STEP COLLECTION AND ASSAYING OF BIOLOGICAL FLUIDS

## STATEMENT REGARDING RELATED APPLICATIONS

This application is a continuation-in-part of co-owned U.S. patent application Ser. No. 09/192,969, filed on Nov. 16, 1998, entitled "An Assaying Device and Method for [sic] in Field Urinalysis".

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to immunoassay devices and methods for collection and assaying of biological fluids, particularly urine. The invention further relates to means for controlling fluid flow through a wicking membrane.

2. History of the Related Art

With the increasing availability and use of drugs by the general population, employers such as government agencies, sports groups and transportation related companies utilize drug screenings as both conditions of employment and maintenance of safety in the workplace. To have a doctor present at the workplace to perform the drug screenings is both expensive and impractical for an employer. Accordingly, other methods have been developed to perform the drug screenings.

One such method is exemplified in U.S. Pat. No. 5,403,551 entitled "Assaying Device and Container for In Field Analysis of a Specimen and Later Shipment of the Unadulterated Specimen." This device is relatively expensive to manufacture because it requires specialized components (particularly a special fluid collection cup), and is relatively complex to operate by laymen, as well as being subject to leakage and contamination.

## SUMMARY OF THE INVENTION

The invention provides means for controlling assay sample fluid flow through an assay test strip for use in performing immunoassays in a dipstick format. In particular, fluid flow control is accomplished by placing the assay test strip within a flow control channel in which the ambient pressure within the flow control channel is maintained in substantial equilibrium with the ambient pressure outside the flow control channel.

By avoiding the formation of a pressure gradient within the flow control channel along which assay sample fluid would be encouraged to flow into the flow control channel, fluid flow from the sample source into which the dipstick assay test strip is immersed is substantially limited to migration by wicking through the test strip. In this fashion, the risk of oversaturation of the test strip on introduction into an assay sample fluid is minimized. As such, the need for other means of restricting the rate or volume of flow through a dipstick assay test strip, such as a housing with a limited volume sample application port or steps to indirectly introduce sample onto the test strip, is also avoided, thereby reducing manufacturing costs and increasing the speed of assay performance.

The invention further provides a combination assaying device and collection chamber which is capable of easily collecting and testing a biological fluid sample, such as urine, while maintaining the sample unadulterated and secure. In particular, the invention provides a fluid flow control test strip in a chamber on a solid support introduced into a fluid collection chamber, such as a urine cup, wherein the volume capacity of the assay sample fluid collection container is such that the total fluid pressure obtainable within the container is maintained at or below 1 atmosphere



## BRIEF DESCRIPTION OF THE DRAWINGS

The above-mentioned features and objects of the present invention will become more apparent with reference to the following description taken in conjunction with the accompanying drawings wherein like reference numerals denote like elements and in which:

FIG. **1** is a side view of a combination collection cup/dipstick assay means device which is improved upon by the invention.

FIG. **2** is a cut-away view of the dipstick assay means of FIG. **1**.

FIG. **3** is a front view of a flow control dipstick assay means of the invention.

FIG. **4** is a cross-section of FIG. **3** along line **4**—**4** of FIG. **3**.

FIG. **5** is a front view of a holder for the dipstick assay means of FIGS. **3** and **4**.

FIG. **6** is a front view of an assay sample fluid collection device of the invention, into which is inserted the dipstick assay means of FIGS. **3** and **4**, as well as the holder of FIG. **5**.

FIG. **7** is a front view of a further embodiment of an assay sample fluid collection device of the invention in combination with the dipstick assay means of FIGS. **3** and **4**, as well as the holder of FIG. **5**

## DETAILED DESCRIPTION OF THE INVENTION

A. Definitions.

For ease of understanding, the following definitions will apply throughout this description; however, no definition should be regarded as being superceding any art-accepted understanding of the listed terms.

1. The term "analyte" as used herein refers to any substance which is capable of binding either antibodies or antigens. Antigens may comprise, without limitation, chemical compounds, polypeptides, carbohydrates, nucleic acids, lipids, and the like, including viral particles, viral subunits, bacterial and parasite surface antigens, and host proteins that may be diagnostic of the subject's condition.

2. A □test zone□ refers to an area in which a binder (ligand) or analyte is attached, movably or immovably, to the assay test strip portion of an assay device.

3. A "sample loading zone" refers to an area of a assay test strip on which a fluid analyte sample is applied for migration to the test zone.

4. An "assay test strip" of the invention consists of, collectively, test and sample loading zone supporting membranes, as well as any filters present in the dipstick assay means of the invention.

5. An "assay sample fluid" can be any fluid suspected of containing analyte of interest for which a particular assay is specific. Test sample may represent any body fluid, including urine, blood, sweat, lymph, intraperitoneal fluid, crude tissue extract or homogenate, derived from a fetus, neonate, juvenile or adult subject; a non-biological fluid such as water from some ecological niche, e.g., a river or a lake; or a solution used in a laboratory.

6. A "label" is a molecule or compound which directly or indirectly mediates the formation of a signal (such as a color change) which is used in assay to indicate the presence,

absence or concentration range of analyte of interest in a test sample. Labels may include enzymes, fluorescers, liposomes, erythrocyte ghosts, polymer microcapsules, color polymer particles (latex), and preferably includes sols of metal-containing compounds. A wide variety of patents and patent applications provide an extensive literature of different techniques for producing detectable signals in immunoassays. The following list of United States patents is merely illustrative of the type of label which can find application in this invention: U.S. Pat. No. 3,646,346 discloses radioactive label; U.S. Pat. Nos. 3,654,090, 3,791,932, and 3,817,838 disclose enzyme labels; U.S. Pat. No. 3,996,345 discloses fluorescer-quencher labels; U.S. Pat. No. 4,062,733 discloses radioactive label; U.S. Pat. No. 4,067,959 discloses fluorescer or enzyme label; U.S. Pat. No. 4,104,099 discloses chemiluminescent label; and U.S. Pat. No. 4,160,645 discloses non-enzymatic catalyst label. U.S. Pat. No. 3,966,879 discloses an electrophoretic technique employing an antibody zone and U.S. Pat. No. 4,120,945 discloses a radioimmunoassay (RIA) where labeled analyte is initially bound to a solid support through antibody. U.S. Pat. No. 4,233,402 discloses enzyme pair labels; U.S. Pat. No. 4,720,450 discloses chemically induced fluorescent labels; and U.S. Pat. No. 4,287,300 discloses enzyme anionic charge labels.

Labels can also be metal-containing sols; i.e., metal or metal compounds such as metal oxides, metal hydroxides, metal salts, metals or metal-containing compounds mixed with polymers or coated onto polymer nuclei. These metal labels may include dry forms of any of the above-named metal or metal compound sols, and preferably includes colloidal gold in dry form.

7. "Fluid communication" refers to structures which are in contact with, but not necessarily affixed to, one another.

8. "Assay" refers to several different types of assay formats in which an analyte of interest can be detected using an assay test strip. For example, in a sandwich-type immunoassay, analytes of interest in the analyte sample, when present, bind a labeled tracer movably incorporated in the assay test strip (consisting of a porous membrane) at the tracer zone to form a first complex. The tracer is a molecule which binds the analyte of interest and is conjugated to a label, preferably a metal label, and most preferably colloidal gold.

A second immobilized ligand corresponding to the analyte of interest is coupled to the assay test strip at the test zone. First complex and unbound labeled ligand mix with the test sample and be carried along therewith by capillary action (wicking) through the test zone. Analyte sample passes through the assay test strip bringing the first complexes, if any, into contact with the unlabeled ligand immobilized in the test zone to form a second complex of labeled ligand-analyte-immobilized ligand. The first immobilized ligand is immobilized in the test zone by means known in the art, including covalent bonding or attachment to an insoluble protein-coated surface (see, e.g., U.S. Pat. Nos. 4,200,690 and 5,075,078). When the second complex is formed, a visible color pattern appears in the test zone. Labeled ligand not bound to analyte in the test sample continue migration by wicking into the control zone to contact the ligand immobilized there. The labeled ligand can bind the immobilized ligand in the control zone to form a third complex, and thus be captured in the control zone.

9. The term "sample integrity monitoring system" refers to one or more strips on which a determinant indicative of conditions in a fluid sample are provided.

B. Representative Assay Device For Use With the Improvements of the Invention

FIGS. **1** and **2** illustrate features of a combination dipstick assay test strip and urine collection cup device depicted in FIGS. **1** and **2**, which device may be improved by application of the features of the invention. In this device, one or more assay test strips **12** are provided on one side of a two-sided solid support backing **8**. Assay test strip **12** is conventional in design, and includes sample loading zone **20** in fluid communication with a test zone **23** into which are incorporated labels and reagents indicative of the presence or absence of analyte in the assay sample fluid. A printed tag **21** indicative of the identity of the material for which the assay is specific may optionally be included on test strip **12** distal to sample loading zone **20**.

The opposite side of backing **8** is covered with wicking material **10**. Wicking material **10** is brought into contact with assay test strip **12** by either being folded at one end over test strip **12** (FIG. **1**), or by being covered at one end by assay test strip **12** (FIG. **2**). In the latter embodiment, sample loading zone **20** of assay test strip **12** is folded over top edge **15** of backing **8** and layered onto wicking material **10**.

Referring to FIG. **1**, backing **8** is shaped to fit within and follow the inner diameter of a transparent urine collection cup **2**, having mouth **3** and base **1**. In use, backing **8** is inserted into cup **2** so sample loading zone **20** of dipstick **12** is flush with mouth **3** of cup **2**. Urine is collected into cup **2**, then the fluid wicks up wicking material **10** to contact sample loading zone **20** of assay test strip **12**. Cup **2** may then be sealed with cap **4**. Eventually, the fluid migrates through assay test strip **12** to contact the assay reagents incorporated therein. Results of the assay are viewed through the transparent sides of the urine cup.

Although an improvement over prior art assay devices, the representative device of FIGS. **1** and **2** has several limitations. First, it is relatively slow to produce results in comparison to other devices due to the time necessary for assay sample fluid to wick up wicking material **10** toward assay test strip **12** (in many other dipstick assay devices, assay sample fluid is applied directly on, or adjacent to, a sample loading zone).

Second, assay sample fluid may not wick evenly through wicking material **10** if a minimum volume of assay sample fluid is not introduced into cup **2**, or if so much assay sample fluid is introduced that wicking material **10** becomes flooded. Consequently, where the assay device includes multiple assay test strips, different volumes of fluid may be loaded onto each test strip. At times, this limitation has resulted in the failure of the device to produce reliable assay results on one or more of the test strips.

Third, the need to overlap wicking material **10** and sample loading material **20** increases the number of steps, and therefore the cost, necessary for manufacture of the device.

Theoretically, the use of wicking material **10** as a vehicle to deliver assay sample fluid to assay test strip **12** could be eliminated by simply reversing the orientation of sample loading zone **20** in cup **2** so it is adjacent with base **1**, rather than mouth **3**, retaining all other features of the device. In such an orientation, sample loading zone **20** would come into direct contact with assay sample fluid introduced into cup **2**. In practice, however, this alternative fails because test subjects usually provide such quantities of assay sample fluid into urine collection cups that assay test strip **12** rapidly becomes flooded.

These enumerated limitations of the assay device of FIGS. **1** and **2** are overcome by the present invention. In particular, the invention provides an assay device in which

assay fluid sample is introduced directly to the sample loading zone of an assay test strip, wherein the device further includes means to control and direct assay sample fluid flow into the test strip, thereby avoiding oversaturation of the test strip, even in the presence of a substantial volume of assay sample fluid. Where more than one test strip is present in the device of the invention, assay sample fluid is introduced evenly into each strip, even in the presence of very small or very large volumes of assay sample fluid. Advantageously, the invention is relatively simple to manufacture.

C. Assay Devices of the Invention

For ease of understanding, the various embodiments of the invention will be described by reference to their application in a combination assay test strip/assay sample fluid collection cup. However, those of ordinary skill in the art will appreciate that the flow control means of the invention common to each embodiment may be utilized in any test-strip based immunoassay format in which restricting the flow of fluid through the test strip is desired.

Turning to FIG. **3**, an example of the flow control means of the invention is depicted. The dipstick assay device component of the invention **40** consists of assay test strip **22** and a support therefor (backing **28**, described below). In the FIGURE, assay test strip **22** is disposed on one side of a two-sided backing **28**. Backing **28** which is made from a resilient, liquid impermeable material. Typically one such material would be a plastic or plastic coated sheet which is not reactive with any of the components of the biological fluid to be assayed; e.g., urine.

Assay test strip **22** is conventional in design. Therefore, because those of ordinary skill in the art will be abundantly familiar with the design of such assay test strips, they will not be described in detail here. Briefly, assay test strip **22** comprises bibulous membrane **24**, and includes sample loading zone **30** in fluid communication with a test zone **33** into which labels and reagents are incorporated, which labels and reagents are capable of providing an observable signal indicative of the presence or absence of analyte in an assay sample fluid. Optionally, printed tag **31** identifying the material for which the assay is specific is included on test strip **22** distal to sample loading zone **30**.

For further review concerning assay test strip construction, including selection and preparation of test reagents, the following references provide a representative sample of assay test strip designs known in the art: U.S. Pat. No. 5,384,264 (commonly owned); U.S. Pat. Nos. 4,491,645; 4,943,522; 5,252,496; 5,714,389 and 5,602,040, the disclosures of which are incorporated for purposes of reference.

As shown in FIG. **3**, backing **28** is shaped to fit within and follow the inner diameter of a transparent urine collection cup **2** (FIGS. **6** and **7**), having mouth **3** and base **1**. In one embodiment of the invention, backing **8** is inserted into cup **2** so sample loading zone **30** of assay test strip **22** is disposed near base **1** of cup **2**.

Assay sample fluid control in this embodiment of the invention is accomplished by disposing assay test strip **22** within a flow control channel, wherein the ambient pressure within the flow control channel is maintained in substantial equilibrium with the ambient pressure outside of the flow control channel even after placement of the flow control channel into collection container which contains assay sample fluid. The dimensions of the assay sample fluid collection container of the invention are such that the total volume of sample fluid into which the flow control channel is placed is maintained below the depth at which equilibrium in ambient pressure within and without the flow control channel would be lost.

In general principle, an assay sample fluid depth in a column of approximately 10 meters would be required to produce an ambient pressure of substantially more than 1 atmosphere. For most biological fluid assay applications of the inventive flow control means, the total volume of assay sample fluid to be utilized will be well below what would be required to produce such a depth.

The flow control channel of the invention will be formed of five liquid impervious, and one liquid pervious, sides. For example, as shown, collectively, in FIGS. **3** and **4**, flow control channel **34** has five liquid impervious walls **35**, **35**A, **35**B, **35**C and backing **28**, and one liquid pervious side consisting of an opening **36** through which sample loading zone **30** of assay test strip **22** protrudes. In total size, both flow control channel **34** and backing **28** are necessarily smaller than any assay sample fluid collection container into which they are to be placed.

As a further example, the liquid pervious side of the flow control channel may also be formed as an orifice in a liquid impervious side, or the liquid pervious side may consist of a liquid permeable membrane. The liquid pervious side of the flow control channel is necessary to allow the pressure within and without the flow control channel to maintain substantial equilibrium notwithstanding immersion into sample fluid and entry of fluid into the assay test strip disposed within the flow control channel.

By maintaining substantial ambient pressure equilibrium about the flow control channel, no pressure gradient is allowed to form along which fluid outside the flow control channel will flow into the flow control channel. As such, fluid entry into the flow control channel is limited to migration into assay test strip **22**; e.g., by wicking fluid from sample loading zone **30** toward and through test zone **33**.

To this end, flow control channel **34** is preferably disposed over assay test strip **22** (FIG. **4**). Flow control channel **34** has two opposing ends; liquid impervious closed end side **35** and liquid pervious open end **36**. Open end **36** has an opening **37** which is loosely fitted around test strip **22**, whose sample loading zone **30** protrudes beyond opening **37**. In use, the test subject introduces an assay sample fluid (typically urine) into a fluid sample container, such as cup **2**, through mouth **3**. Closed end **35** of flow control channel **34** blocks sample fluid from entering the flow control channel as it is introduced through mouth **3**.

As shown in FIG. **3**, separate flow control channels are provided for each of multiple assay test strips. However, in view of the foregoing teaching concerning the role of ambient pressure equilibrium in flow rate control, those of ordinary skill in the art will appreciate that flow restriction could also be provided by alternative flow control channel designs; e.g., flow control channel **34** may be continuous in width so all test strips are disposed within the same air pocket defined by the flow control channel.

As assay sample fluid collects in cup **2**, it contacts sample loading zone **30** and begins migrating upwards through assay test strip **22**. So long as the volume of fluid introduced into cup **2** is sufficient to contact sample loading zone **30** (which may itself be placed into contact with base **1** of cup **2** to minimize the necessary volume of assay sample fluid), any amount of assay fluid up to the maximum volume capacity of cup **2** may be used in performing an assay with the device of the invention. In devices with multiple assay test strip, the sample loading zone of each is contacted by an equivalent volume of sample assay, thereby avoiding inequal distribution of sample assay fluid among the test strips.

Preferably, test zone **33** will be situated on test strip **22** at least 2 millimeters away from the distalmost end of sample loading zone **30** to isolate test zone **33** from fluid collecting around open end **36** of chamber **34**. Assay test results are viewed through the transparent walls of cup **2**. To ensure privacy of test results, the outside of cup **2** through which results are viewed may be covered, for example, with a piece of removable opaque tape. The assay sample fluid may be discarded after performance of the assay, and the dipstick assay device preserved, within or without cup **2**.

An optional addition to the invention is a holder for holding the assay device in place in cup **2** (FIG. **5**). As shown in FIG. **5**, the holder **40** is curved to follow the inner diameter of cup **2** and is substantially the same height as cup **2**, although it will be appreciated that the holder may be of any configuration which will fit within cup **2** and hold backing **28** as described herein. Holder **40** includes curved portion **42** with a cut-out **44**, defining vertical slots **46** and optional horizontal slot **48** for insertion of backing **28** therein. Curved portion **42** is shown in FIG. **4** as having end **49**, which is optionally closed to protect backing **8** and may be beveled for ease of insertion of holder **40** into cup **2**. In use, backing **28** is inserted into vertical slots **46** and horizontal slot **48** so, on insertion of holder **40** into cup **2**, sample loading zone **30** of assay test strip **22** is oriented toward cup base **1** and end **49** of holder **40** is oriented toward cup mouth **3** (FIG. **6**). The operation of this further embodiment of the invention proceeds as described above.

In an alternative embodiment of the invention (shown in FIG. **7**), backing **28** is placed into holder **40** so sample loading zone **30** is inserted into horizontal slot **48**. In this embodiment, horizontal slot **48** of cut-out **44** (FIG. **5**) includes end **49** (including the optional closure of end **49**, thereby defining a narrow liquid reservoir in the liquid pervious side of flow control channel **34** is enclosed. Holder **40** is placed into cup **2** so closed end **49**, and sample loading zone **30** enclosed therein, are adjacent to mouth **3** of cup **2** (FIG. **7**). Cap **45** (which may be of any design which provides a watertight seal; e.g., a screw-on or snap-fit design) is included to close cup **2**.

The use of this embodiment of the invention proceeds as follows. Assay sample fluid (usually urine) is introduced into cup **2**. When fluid collection is complete, cap **45** is placed onto cup **2** to provide it with a watertight seal. To perform the assay, the laboratory technician inverts cup **2** so assay sample fluid flows into horizontal slot **48**. In this fashion, the combination of horizontal slot **48**, vertical slots **46** and closed end **49** define a fluid reservoir into which sample loading zone **30** of assay test strip **22** becomes immersed on inversion of cup **2** (FIG. **8**). Assay sample fluid then migrates evenly through assay test strip **22** and any other test strips present in the device. Assay results are viewed through the transparent walls of cup **2**.

All of the foregoing embodiments of the invention share the advantage of providing for direct application of sample fluid to the assay test strip (as opposed to having the fluid migrate through an intermediate structure, such as wicking material **10** of FIGS. **1** and **2**). As such, interassay variation derived from differential volume application to multiple test strips is avoided, and the entire assay may be performed more quickly than previously possible, at a lower manufacturing cost.

Although the invention may be utilized to assay any fluid for any analyte of interest, it is especially well-adapted to screening urine for the presence of narcotics. To this end, a five drug panel of assay tests is recommended by the National Institute on Drug Abuse (NIDA), which includes tests for tetrahydrocannabinol and other marijuana metabolites, cocaine metabolites, opiate metabolites, phencyclidine (PCP, Angel Dust), and amphetamines. For a more extensive substance abuse testing panel, the choice of analytes tested can include marijuana metabolites; tetrahydrocannabinol and other marijuana metabolites, cocaine metabolites, opiate metabolites, phencyclidine (PCP, Angel Dust), amphetamines, barbiturates, benzodiazepines, methaqualone, and propoxyphene. The assay test strips for drug tests preferably have the sensitivity equal to the cutoffs recommended by Substance Abuse Mental Health Service Administration (SAMSHA) and NIDA, which most employers use. Binders and reagents for use in constructing assay test strips for use in detecting drugs of abuse are well-known in the art and will not be described in detail here.

Subjects undergoing drug tests are sometimes creative in their efforts to adulterate the analyte samples to evade detection of drugs of abuse likely to be present in the sample. To minimize the effects of such evasion efforts on results obtainable with the assay devices of the invention, a sample integrity monitoring system will be incorporated into the device. Such a system is used to determine whether adulterants have been added to the sample or if its quality is otherwise compromised.

For example, the sample integrity monitoring system may evaulate any or all of the pH, osmolality (the total concentration of solutes in urine, expressed as mOsm/kg and measured as a function of fluid specific gravity) of, or albumin, creatinine, glutaraldehye and nitrite levels in, the sample. In the devices of the invention, the system is comprised of one or more additional test strips (not shown) placed on backing **28**, or test pads integrated into assay test strip **22** adjacent to printed tag **31** (as described in co-pending, commonly owned U.S. patent application Ser. No. 09/364,277, filed Jul. 29, 1999).

It should be apparent to those skilled in the art that the above-described embodiments are merely illustrative of but a few of the embodiments which could be created by one of ordinary skill in the art without departing from the spirit and scope of the present invention.

The invention claimed is:

**1**. A device for collecting and assaying a sample of biological fluid, the device comprising:

(a) a flow control channel defined by at least one liquid pervious side joined to liquid impervious sides, wherein the internal dimensions of the flow control channel are sufficient to permit placement therein of an assay test strip;

(b) an assay test strip within the flow control channel, wherein the assay test strip has a sample loading zone therein, and wherein further the assay test strip is disposed within the flow control channel so the sample fluid contacts the sample loading zone at a liquid pervious side of the flow control channel; and,

(c) a sample fluid container having a base, an open mouth, and walls connecting the base to the mouth;

wherein the flow control channel is disposed inside the sample fluid container with the liquid pervious side oriented the base of the sample fluid container so that the assay sample fluid, when added to the container, is delivered to the sample loading zone of the assay test strip by entry through a liquid pervious side of the flow control channel without migration through an intermediate structure, and wherein entry of fluid into the flow control channel creates an ambient pressure within the flow control channel equivalent to the ambient pressure outside of the flow control channel, thereby eliminating

a pressure gradient along which excess sample fluid could flow into the flow control channel.

**2**. A device according to claim **1**, wherein the sides of the flow control channel are loosely fitted around the assay test strip.

**3**. A device according to claim **1**, wherein one of the liquid impervious sides of the flow control channel is formed as a portion of a liquid impervious backing; and wherein the device farther comprises a holder fittable inside the fluid sample container, the holder having at least one slot formed therein to receive the backing.

**4**. A device according to claim **3**, wherein both the holder and the fluid sample container are curved in shape, and the curvature of the holder follows the curvature of the inner diameter of the fluid sample container.

**5**. A device according to claim **4**, wherein the fluid sample container is a cup.

**6**. A device according to claim **5**, further comprising a watertight cap fittable over the mouth of the cup.

**7**. A device according to claim **3**, wherein the slot formed in the holder is closed on five sides to define a liquid reservoir.

**8**. A device according to claim **7**, wherein the backing is inserted into the holder such that a liquid pervious side of the flow control channel is enclosed in the slot of the holder.

**9**. A device according to claim **1**, further comprising additional assay test strips, wherein the additional assay test strips detect the presence or absence of different analytes in a biological fluid.

**10**. A device according to claim **9**, wherein all of the assay test strips are disposed in a single flow control channel.

**11**. A device according to claim **9**, further comprising additional flow control channels, wherein each assay test strip is disposed in a separate flow control channel.

**12**. A device according to claim **9**, wherein the different analytes are different narcotics.

**13**. A device according to claim **12**, further comprising a sample integrity monitoring system, the system comprising one or more assay test strips into which reagents and labels are incorporated to provide a visually observable signal indicative of the presence of adulterants or contaminants in the biological fluid.

**14**. A device according to claim **9**, wherein the biological fluid is urine.

**15**. A device according to claim **12**, wherein the biological fluid is urine.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,548,019 B1
DATED : April 15, 2003
INVENTOR(S) : Jin Po Lee and Poyi Tseng



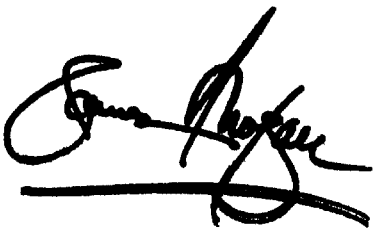
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8,
Line 59, after "oriented" insert the word -- toward --

Column 9,
Line 9, correct the spelling of the word "farther" to -- further --

Signed and Sealed this

Twelfth Day of August, 2003



JAMES E. ROGAN
*Director of the United States Patent and Trademark Office*

# Exhibit 2

US008623291B2

(12) **United States Patent**
**Lee**

(10) **Patent No.: US 8,623,291 B2**
(45) **Date of Patent: *Jan. 7, 2014**

(54) **MULTIPLE ANALYTE ASSAY DEVICE**

(76) Inventor: **Jin Po Lee**, Carlsbad, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1444 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/650,280**

(22) Filed: **Jan. 5, 2007**

(65) **Prior Publication Data**

US 2007/0128072 A1 Jun. 7, 2007

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 10/019,570, filed as application No. PCT/US98/15359 on Jul. 14, 1998, now Pat. No. 7,347,972.

(51) **Int. Cl.**
***G01N 33/48*** (2006.01)

(52) **U.S. Cl.**
USPC ..... **422/401**; 422/420; 422/430; 436/164; 436/165

(58) **Field of Classification Search**
USPC ..... 422/401, 420, 430; 436/164, 165
See application file for complete search history.

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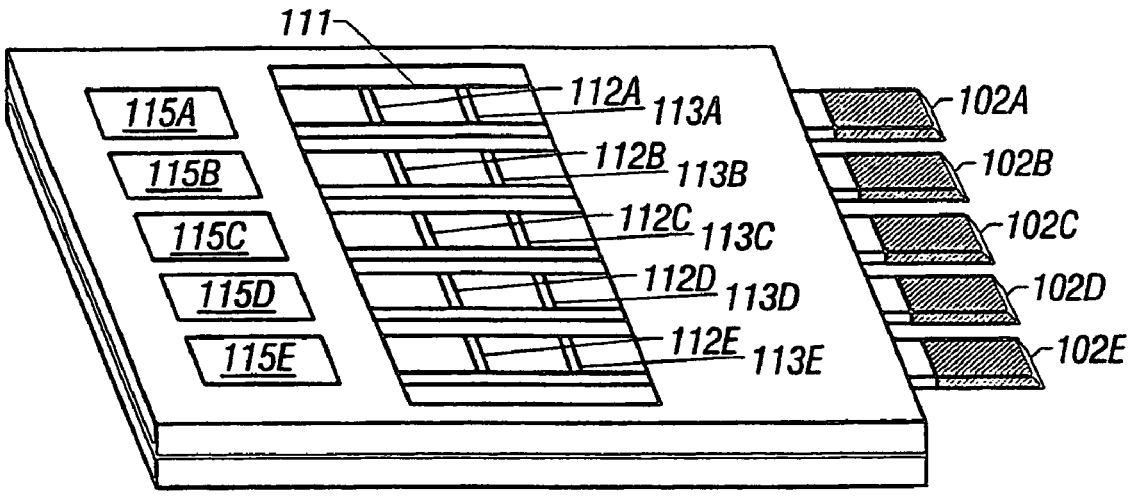
*Primary Examiner* — Lyle Alexander
(74) *Attorney, Agent, or Firm* — Bernd W Sandt

(57) **ABSTRACT**

The present invention relates to an assay device capable of testing for multiple analytes such as drugs using individual test strips for each analyte.

**9 Claims, 6 Drawing Sheets**



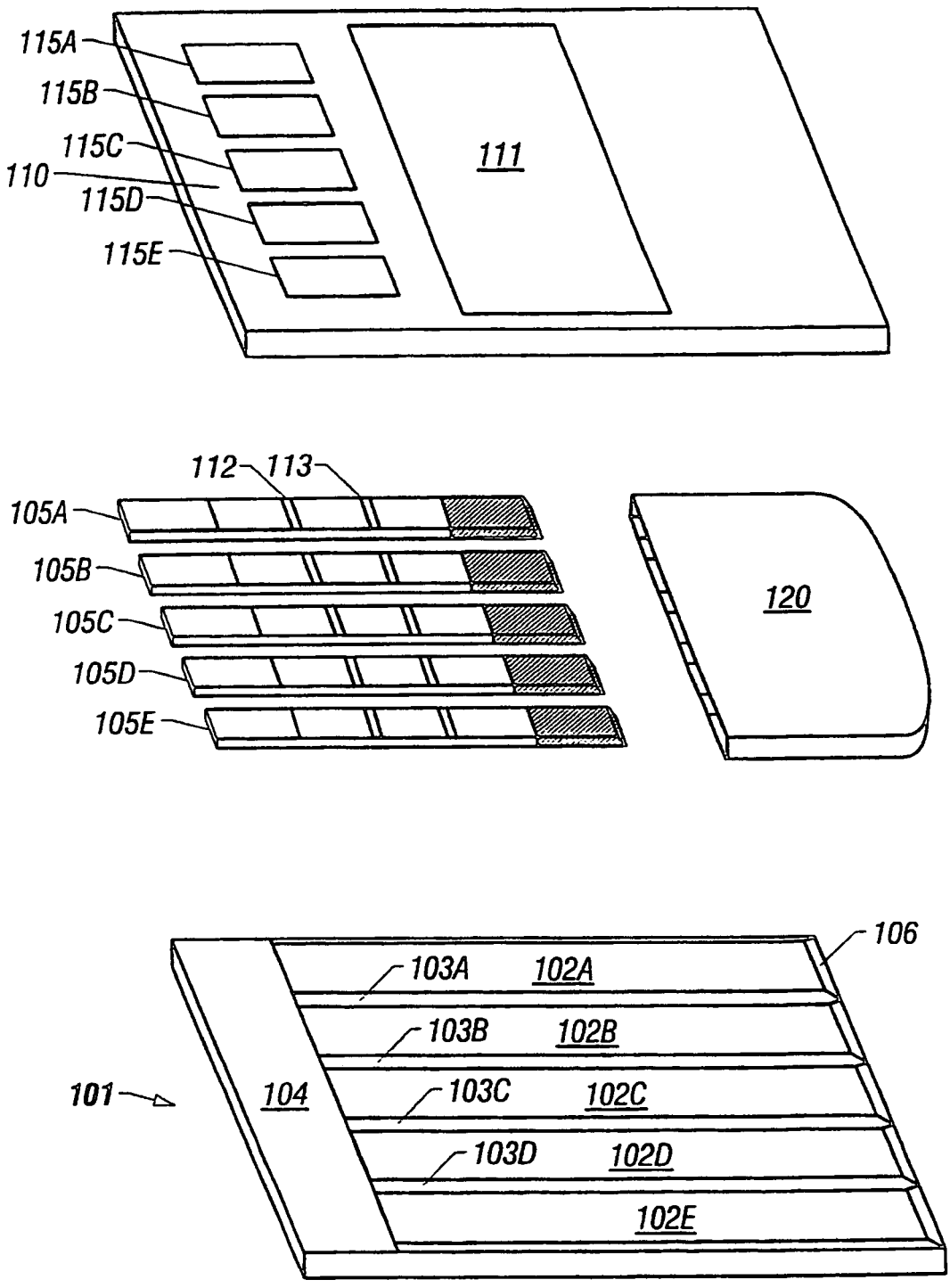

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FIG. 1

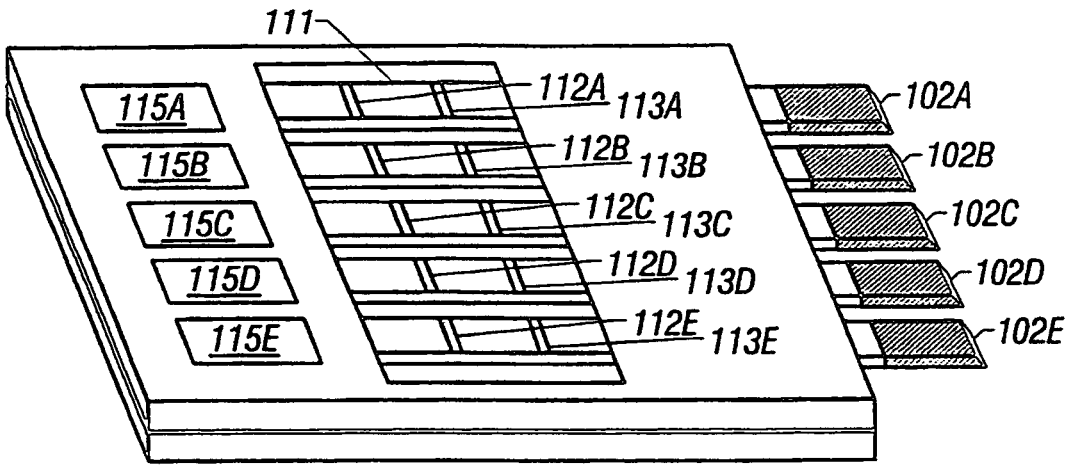
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FIG. 2

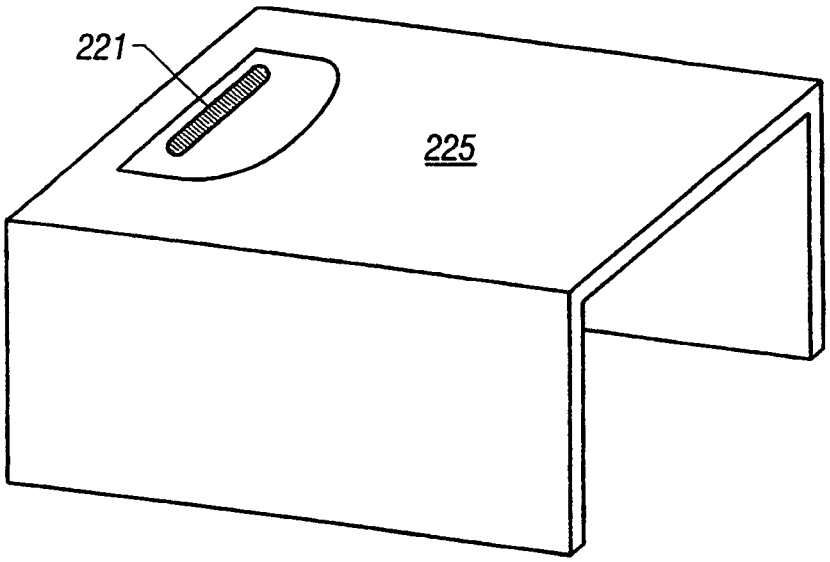


FIG. 3A

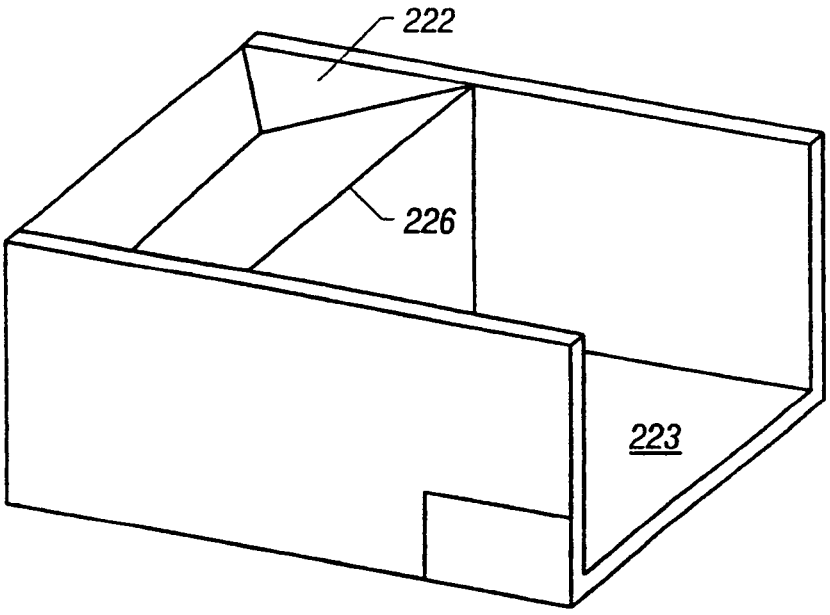


FIG. 3B

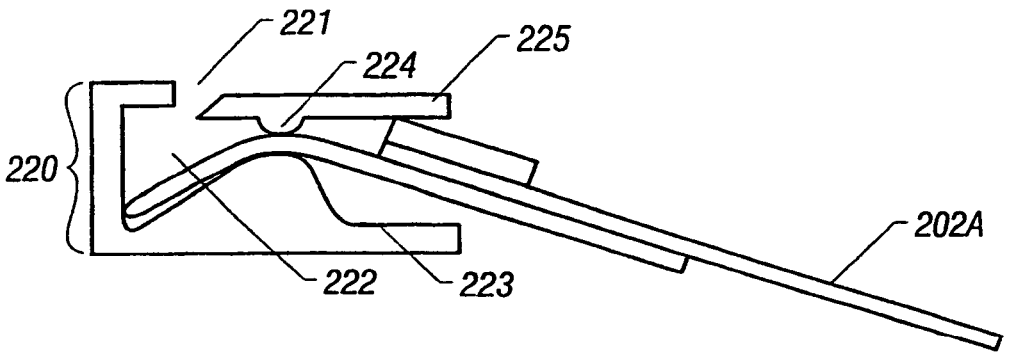


FIG. 3C

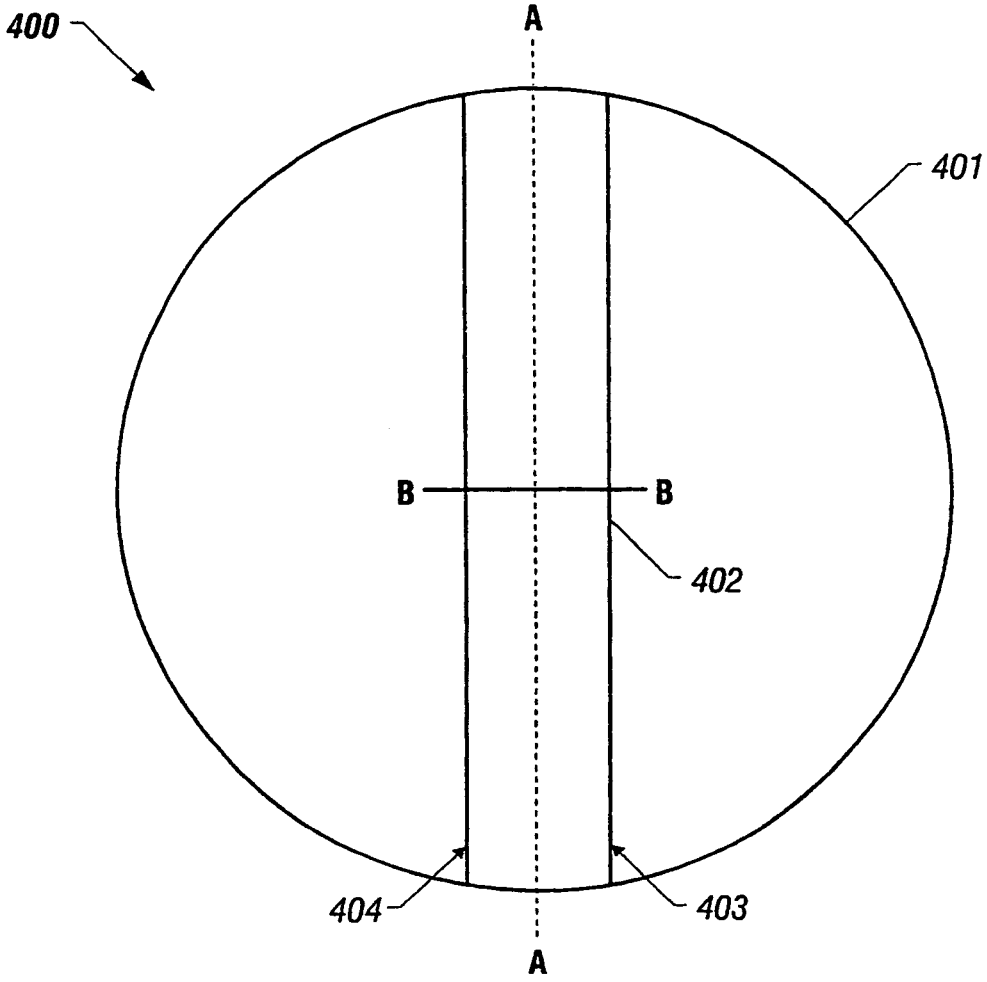


FIG. 4

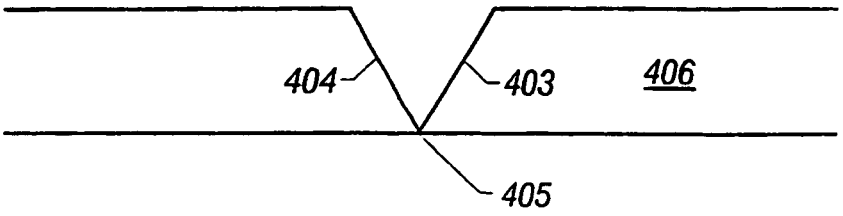


FIG. 5

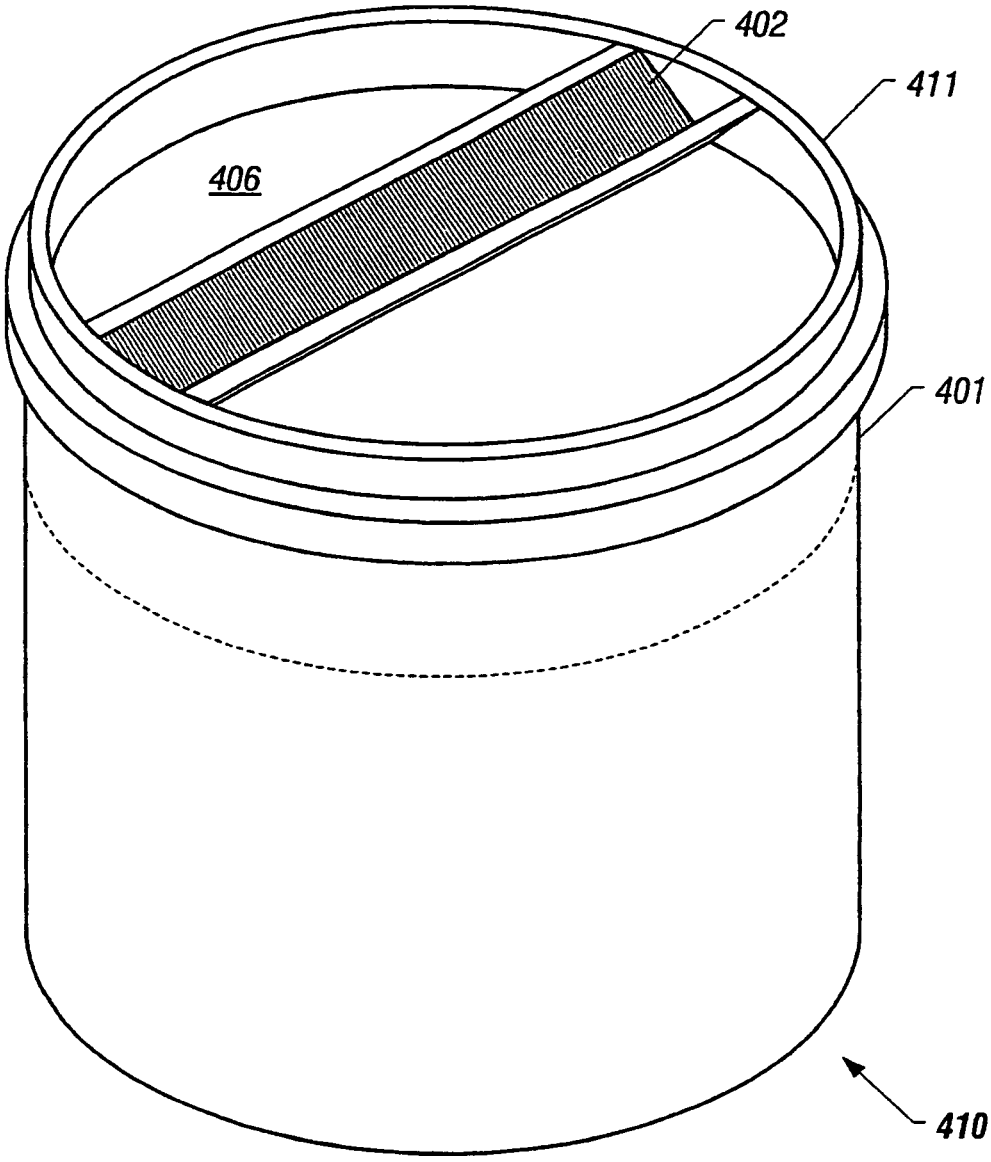


FIG. 6

# MULTIPLE ANALYTE ASSAY DEVICE

This application is a continuation-in-part of Ser. No. 10/019,570 filed Nov. 8, 2001 now U.S. Pat. No. 7,347,972, which is based on PCT application US98/15369 filed Jul. 22, 1998.

## BACKGROUND

1. Field of the Invention

The present invention relates to methods and devices for assaying biological fluid samples. More particularly the invention relates to methods and devices for detecting analytes, such as drugs, in urine.

2. History of the Related Art

In their most simple form, chromatographic analyte devices permit an assay to be performed in a single step (application of an analyte sample to the device) to producer visually observable assay results (such as those indicated by colored bars on the test strip). However a common limitation of such devices is that they can only be used to detect a single analyte, requiring that serial assay procedures be performed to detect additional analytes (for example to test a sample for the presence of a panel of narcotics). Multiple dipping steps such as are commonly used when multiple dipstick assays are separately performed, present not only possible loss of sensitivity of the assay (through reagent mixing or possible loss reagent solutions) but also an esthetic and hygienic problem for the analyst. Repetitive performance of assay procedures is also tedious, which increases the risk that assays will be performed improperly or the results misinterpreted.

## SUMMARY OF THE INVENTION

The present invention provides an assay device, device for separating a fluid analyte sample for use in multiple assay procedures and methods for performing multiple analyte assays. In one embodiment of the assay device, the assay device is a dipstick having multiple analyte test strips, each of which includes a test zone and a control zone. The test strips are enclosed in a housing having an open side through which an end of each test strip protrudes to form a sample loading zone. A protective cap is provided to seal the protruding ends of the test strips from exposure while not in use. Each test strip is separated from the next within the housing by a raised spacer. The portion of the housing which overlies the test and control zones is transparent to permit visually observible results shown in each zone to be viewed.

In cassette form, the assay device has the same structure described above, but the protruding test strips are inserted into a cap which has a sample port for application of sample to the test strips. The cap is retained on the assay device by a close fit over the device housing.

Each test strip provides binders and assay reagents for detection of a different analyte in the sample fluid. In a particularly preferred embodiment of the assay device, the housing may be opened to permit substitution of different test strips to allow each device to be customized for detection of specific analytes of interest. Assay sample integrity determinants consisting of test strips which allow measurement of parameters such as specific gravity and pH may also be included in each device.

The invention also provides a separator device for dividing a fluid assay sample into portions for use in multiple assays without need for contact between the assay operator and the fluid sample. This latter feature of the device increases operator safety and avoids inadvertent contamination of the assay



sample. The separator device may be used to separate any fluid assay sample, but is especially useful in assaying samples for the presence of narcotics, where a positive result on first testing of the sample may necessarily be followed by additional testing of the sample to confirm the result and the identity of the detected narcotic. To this end, the separator device is adapted particularly well to use with the assay device of this invention.

The assay device of the invention makes specimen analysis easier because an analyte sample need only to be applied once to the assay device for testing. In addition, the replaceable nature of the analyte test strips allows the analyst to customize the array of assays to the testing situation. Because the customization can be performed before adding the test sample (e.g., urine), fewer manipulations with the analyte sample are needed to obtain the desired information. In addition, use of the separator device permits further testing of the sample to be performed without risk of adultering the sample in a preliminary assay performed according to the invention.

The invention also provides a method for assaying one or more analytes of interest. The protruding ends of the device are dipped into a fluid analyte sample. Binding of an analyte present in the sample with one or more specific ligands causes formation of specific visual pattern in the test and control zones indicative of the test result. The assay results performed according to the invention may be read visually without use of separate measuring equipment. Thus, performance of assays according to the invention requires only that the user introduce the requisite amount of test sample into the device of the invention, then observe any color changes which appear shortly thereafter in a detection zone of an analyte strip. The method of the invention is especially useful for screening fluid analyte samples (e.g., urine) for the presence or absence of drugs of abuse.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an exploded view of a dipstick assay device of the invention.

FIG. **2** is a top view of a dipstick assay device of the invention.

FIG. **3**A is a top view of the upper half sample port cap of a cassette assay device of the invention, and FIG. **3**B is a top view of the lower half, base portion of the sample port cap, while FIG. **3**C is a side, cut-away view of the intact cap with test strips in place therein.

FIG. **4** is a top view of the separator device of the invention.

FIG. **5** is a cross-sectional view of the separator device taken along line A-A at cut-away point B-B of FIG. **1**.

FIG. **6** is a lateral view of the separator device within a specimen collection cup.

Like numerals refer to like elements in the drawings.

## DETAILED DESCRIPTION OF INVENTION

### A. Definitions

For ease of understanding, the following definitions will apply throughout this description:

1. The term “antigen” as used herein refers to any analyte which is capable of binding antibodies. Antigens may comprise, without limitation, chemical compounds, polypeptides, carbohydrates, nucleic acids, lipids, and the like, including viral particles, viral subunits, bacterial and parasite surface antigens, and host proteins that may be diagnostic of the subject’s condition.

2. A "binder" refers to a ligand for the analyte as in the format of a sandwich assay, or a ligand for both the analyte and the tracer as in the format of a competitive assay. A binder can be chosen from a group of molecules or compounds capable of binding the analyte, such as an antigen to the antibody analyte, or an antibody to the antigen analyte.

3. A "test zone" refers to an area in which a binder or the analyte is attached, movably or immovably, to the test strip portion of an assay device.

4. A "tracer" refers to a ligand for the analyte or the binder labeled with a detectable label, preferably a visually readable particulate label, such as colloidal gold, latex and liposomes including dye, carbon black, and the like.

5. A "sample loading zone" refers to an area of a test strip on which a fluid analyte sample is applied for migration to the test zone.

6. A "test strip" of the invention consists of, collectively, all of the zone supporting membranes and any filters of the assay device.

7. A "fluid analyte sample" can be any fluid suspected of containing analyte of interest for which a particular assay is specific. Test sample may represent any body fluid, including urine, blood, sweat, lymph, intraperitoneal fluid, crude tissue extract or homogenate, derived from a fetus, neonate, juvenile or adult subject; a non-biological fluid such as water from some ecological niche, e.g., a river or a lake; or a solution used in a laboratory.

8. A "label" is a molecule or compound which directly or indirectly mediates the formation of a signal (such as a color change) which is used in assay to indicate the presence, absence or concentration range of analyte of interest in a test sample. Labels may include enzymes, fluorescers, liposomes, erythrocyte ghosts, polymer microcapsules, color polymer particles (latex), and preferably includes sols of metal-containing compounds. A wide variety of patents and patent applications provide an extensive literature of different techniques for producing detectible signals in immunoassays. The following list of United States patents is merely illustrative of the type of label which can find application in this invention: U.S. Pat. No. 3,646,346 discloses radioactive label; U.S. Pat. Nos. 3,654,090, 3,791,932, and 3,817,838 disclose enzyme labels; U.S. Pat. No. 3,996,345 discloses fluorescer-quencher labels; U.S. Pat. No. 4,062,733 discloses radioactive label; U.S. Pat. No. 4,067,959 discloses fluorescer or enzyme label; U.S. Pat. No. 4,104,099 discloses chemiluminescent label; and U.S. Pat. No. 4,160,645 discloses non-enzymatic catalyst label. U.S. Pat. No. 3,966,879 discloses an electrophoretic technique employing an antibody zone and U.S. Pat. No. 4,120,945 discloses a radioimmune assay (RIA) where labeled analyte is initially bound to a solid support through antibody. U.S. Pat. No. 4,233,402 discloses enzyme pair labels; U.S. Pat. No. 4,720,450 discloses chemically induced fluorescent labels; and U.S. Pat. No. 4,287,300 discloses enzyme anionic charge labels.

Labels can also be metal-containing sols; i.e., metal or metal compounds such as metal oxides, metal hydroxides, metal salts, metals or metal-containing compounds mixed with polymers or coated onto polymer nuclei. These metal labels may include dry forms of any of the above-named metal or metal compound sols, and preferably includes colloidal gold in dry form.

9. A "complex" means (depending on the context) any multimolecular complex formed by analyte and one or more ligands, or by labeled ligand and immobilized ligand. In a sandwich-type immunoassay, e.g., the following complexes occur: analyte/labeled ligand duplex first produced in the assay (first complex) and analyte/labeled ligand/immobilized ligand triplex formed second in the assay (second complex).

10. "Fluid communication" refers to structures which are in contact with, but not necessarily affixed to, one another.

11. "Assay" refers to several different types of assay formats in which an analyte of interest can be detected using an assay test strip. For example, in a sandwich-type immunoassay, analytes of interest in the analyte sample, when present, bind a labeled tracer movably incorporated in the test strip (consisting of a porous membrane) at the tracer zone to form a first complex. The tracer is a molecule which binds the analyte of interest and is conjugated to a label, preferably a metal label, and most preferably colloidal gold.

A second immobilized ligand corresponding to the analyte of interest is coupled to the test strip at the test zone. First complex and unbound labeled ligand mix with the test sample and be carried along therewith by capillary action (wicking) through the test zone. Analyte sample passes through the test strip bringing the first complexes, if any, into contact with the unlabeled ligand immobilized in the test zone to form a second complex of labeled ligand-analyte-immobilized ligand. The first immobilized ligand is immobilized in the test zone by means known in the art, including covalent bonding or attachment to an insoluble protein-coated surface (see, e.g., U.S. Pat. Nos. 4,200,690 and 5,075,078). When the second complex is formed, a visible color pattern appears in the test zone. Labeled ligand not bound to analyte in the test sample continue migration by wicking into the control zone to contact the ligand immobilized there. The labeled ligand can bind the immobilized ligand in the control zone to form a third complex, and thus be captured in the control zone.

Within the scope of this invention, the labeled ligand forming the complex in the control zone may be the same as the tracer forming the first and second complexes, or it may be a different labeled ligand. The ligand immobilized in the control zone should have specific affinity for the labeled ligand intended to form the third complex. Formation of the third complex is indicated by a visible pattern in the control zone.

Besides sandwich immunoassay method, other assay methods may be implemented in the devices of the invention. These methods may include competition and inhibition assays. In a competition assay, the analyte and tracer have similar affinity properties and compete for binding with immobilized ligand. Thus, in absence of analyte, the pattern (e.g., band) in the test zone is of maximum intensity. When present, the analyte binds to immobilized ligand to prevent the tracer from getting captured in the test zone. Thus, the intensity of the test band is reduced, depending on the concentration of analyte in the test sample.

In an inhibition assay, the analyte and immobilized ligand in the test zone each have affinity for the tracer. In the absence of analyte in the analyte sample, the tracer is captured by immobilized ligand, and a visible pattern forms in the test zone. When present, the analyte binds the tracer, thereby preventing it from binding to the immobilized ligand in the test zone. The resulting intensity of the test band is reduced depending on the concentration of analyte in the test sample.

B. Dipstick Assay Device

Turning to FIG. **1**, a dipstick form of the assay device is shown in exploded view. The device consists of a housing **100**, which is defined by base **101** and cover **110**. Base **101** can be constructed of any sterilizable material, such as a nonporous plastic (e.g., the commercially available plastic "ABS" supplied by the Monsanto Company of St. Louis, Mo.). Base **101** having a closed end **104** and an open end **106**,

slots **102**A, **102**B, **102**C, **102**D and **102**E separated by rails **103**A, **103**B, **103**C and **103**D for insertion of test strips **105**A, **105**B, **105**C, **105**D and **105**E. A particular advantage of this embodiment of the assay device is its customizability in that test strips specific for different analytes of interest to the user may be inserted into base **101** and that the number of test strips employed may vary (e.g., base **101** may have any number of slots from two upward to accomodate as many test strips as the user may desire).

Referring to FIG. **2**, when inserted into slots **102**A, **102**B, **102**C, **102**D and **102**E, the test strips extend out of base **101** beyond open end **106**. The length to which the test strips protrude from base **101** must be sufficient to allow the test strips to contact a fluid analyte sample, preferably by immersion, and most preferably without allowing the fluid to contact housing **100**. The test strips are conventional in form; therefore, because those of ordinary skill in the art will be abundantly familiar with the design of such test strips, they will not be described in detail here. However, each test strip will have a test zone **112** for binding of analyte (to indicate a positive test result for the presence of analyte in the analyte sample) and a control zone **113** for binding of tracer (to indicate correct operation of the assay). Preferably, the test zones and control zones of each test strip lie in the same location on each test strip so each can be viewed in side-by-side fashion.

Each test strip is typically constructed of a porous membrane which is substantially inert with respect to the analyte and must be porous or absorbent relative to the analyte sample to be tested, e.g., urine. The substance can be either bibulous matrices or nonbibulous matrices that are insoluble in, and maintain their structural integrity when exposed to aqueous solutions or physiological fluids. Bibulous matrices that can be useful for the devices of the present invention include but are not limited to, paper, sponge materials, cellulose, hydrophilic inorganic powders, wood, synthetic resin fleeces, woven and nonwoven fabrics and like materials. Nonlimiting examples of nonbibulous matrices include glass fiber, permeable polymer films and preformed or microporous membranes. The absorbent material is preferably absorbent paper. The absorbent material can be affixed by a double sided adhesive (e.g., two sided adhesive tape) to a solid moisture impervious support. This support can be constructed from, for example, hydrophobic plastic, cellulose acetate, polyethylene, terephthalate, polycarbonate, or polystyrene.

The tracer is prepared according to the means known in the art. For purposes of producing a clearly visible reaction, labels of metal-containing sols are preferred, with labels of colloidal gold or selenium being most preferred. An example of a suitable product is colloidal gold available from Janssen Life Sciences Products. These colloidal metals produce distinctive visual patterns without addition of further reagents; however, fluorescers (such as fluorescein) and enzymes (such as those identified in U.S. Pat. No. 4,275,149), may also be used.

Selections and choices for test binders (e.g., immobilized antigens, antibodies and other test and control binders), as well as suitable means for their attachment to porous test strip membranes, are well-known to those of ordinary skill in the art and will not be stated in detail here. To maximize contact of test sample with the tracer and all test binders, the area occupied by each reagent on the test strip preferably extends from one side of the membrane to the other.

For further review concerning test strip construction, including selection and preparation of test reagents, the following references provide a representative sample of test strip designs known in the art: U.S. Pat. No. 5,384,264 (commonly owned); U.S. Pat. No. 4,491,645; U.S. Pat. No. 4,943,522; U.S. Pat. No. 5,252,496; U.S. Pat. No. 5,714,389 and U.S. Pat. No. 5,602,040, the disclosures of which are incorporated for purposes of reference.

Test strips **105**A, **105**B, **105**C, **105**D and **105**E may be secured within slots **102**A, **102**B, **102**C, **102**D and **102**E by adhesion to the floor of each slot; however, the placement of cover **110** onto base **101** is sufficient to retain the test strips within the base slots. To this end, cover **110** is conveniently constructed of an opaque tape having at least one transparent window **111** formed therein for viewing of test results along test zone **112** and control zone **113**. To secure cover **110** onto base **101**, as well as to secure test strips **105**A, **105**B, **105**C, **105**D and **105**E within slots **102**A, **102**B, **102**C, **102**D and **102**E, cover **110** is pressed into place to form an adhesive attachment between cover **110** and the upper edges of rails **103**A, **103**B, **103**C, and **103**D. To provide additional surface area for adhesion of cover **110** to base **101**, bar **107** separates closed end wall **104** of base **101** from rails **103**A, **103**B, **103**C, and **103**D.

Conveniently, cover **110** is also provided with transparent windows **115**A, **115**B, **115**C, **115**D and **115**E through which labels on test strips **102**A, **102**B, **102**C, **102**D and **102**E can be viewed. The labels (not shown) may be printed with information of use in performing the assay, such as the identity of analyte detectible with each test strip.

In certain instances, it may be desirable to store the assay device after test results are obtained for later viewing. To that end, a five-sided cap **120** is provided for insertion over open end **106** of base **101** (with cover **110** in place) to protect the protruding ends of test strips **102**A, **102**B, **102**C, **102**D and **102**E from contact with other materials, from dessication and from contact with the assay operator. Cap **120** is easily secured onto the assay device by a close fit, such as a friction fit or snap-fit.

### C. Cassette Assay Device

In some instances (e.g., where the analyte sample is believed to contain pathogenic organisms) it is desirable to protect the assay operator from contact with analyte sample after its application to an assay device. To this end, the dipstick assay device may be conveniently modified for use in closed cassette form.

More specifically, cap **220** (FIGS. **3**A and **3**B) is adapted to convert the dipstick assay device into a cassette. Cap **220** is similar in design to cap **120** (FIGS. **1** and **2**), except that sample application slot **221** is formed therein to permit analyte sample to be applied to test strips **202**A, **202**B, **202**C, **202**D and **202**E dropwise; e.g., by pipetting the sample through slot **221** (in FIG. **3**C, only strip **202**A is visible from the side view and the device housing is not shown). To avoid sample overflow, a reservoir **222** may be provided in the inner floor **223** of cap **220** by, for example, providing raised bar **226** on floor **223** (in FIGS. **3**A and **3**B, floor **223** is shown as if split from roof **225** of the cap only for the purpose of permitting reservoir **222** to be viewed in the drawing). A downwardly protruding bar **224** is provided from the inner surface of roof **225** of cap **220** to depress the test strips into reservoir **222** so each test strip has equal access to the analyte sample. After performance of the assay, cap **220** remains in place on the assay device to protect the protruding ends of the test strips from contact with other materials, from dessication and from contact with the assay operator.

### D. Separator Device for Division of Analyte Sample

If a positive result is obtained from use of the assay device of the invention, it is usually necessary to further characterize

the detected compound to better enable its identification; e.g., by mass spectrometry. However, it is rarely practical to ask that more than one assay sample be obtained from a subject. As such, any assay sample which is obtained must be divided into portions of sufficient volume for repeated testing, for example by pouring the original sample into separate specimen containers (at the risk of operator contamination and sample loss). Even where the sample is only to be assayed once, the tendency of subjects to provide abundant urine samples poses a different problem in that too much sample can saturate a test strip and overwhelm the assay reagents. Again, division of the sample is required.

The separator device of the invention provides simple means for dividing a sample while protecting the sample from contamination and the operator from the sample. To these ends, the separator device consists of a ring which is just smaller in diameter than the inner diameter of the open end of a specimen collection cup so, when pressed inside of the open end of the cup, the ring will remain seated there. A collection chamber (for example, a "V" shaped well) extends across the ring and is attached thereto so the ends of the collection chamber are closed by the inner walls of the ring.

In use, an assay fluid is placed within the specimen collection cup to a level below the point where the separator device will be seated. The assay operator presses the separator device into place and seals the specimen collection cup with a cap. The operator inverts the specimen collection cup several times so fluid pours into the collection chamber of the separator device. The balance of the fluid assay remains below the level of the separator device and is therefore protected from contact with reagents or other material placed therein. A test strip (such as the assay device of the invention) is placed into contact with the portion of the assay sample contained within the collection chamber of the separator device; e.g., by dipping an end of the test strip into the collection chamber. After the assay sample is loaded from the collection chamber onto the test strip, the latter is removed and the separator device is carefully lifted from the specimen collection cup for disposal.

Use of the separator device provides the assay operator with a volume of assay sample fluid which is sufficiently limited to avoid saturation of the test strip. For example, where the assay device utilized is the device of this invention, the collection chamber is of a depth and length sufficiently limited so the maximum fluid level achievable in the collection chamber is lower than the level of the assay device housing. The uncontaminated balance of the assay sample still in the specimen collection cup is available for further testing; e.g., for mass spectrometry to determine the identity of any compounds detected in the initial assay of the portion of the sample separated in the separator device. Conveniently, the separator device may be provided in the form of a kit, including the separator device, a sterilized specimen collection cup with cap and forceps for removal of the separator device from the cup after performance of the assay. Such a kit may also be provided with the assay device of the invention.

An example of a separator device is shown in FIGS. **4** through **6**. Although the separator device shown is in the shape of a ring (to correspond to the common cup-like shape of urine collection cups), those of ordinary skill in the art will recognize that the separator device may be of any shape which conforms to a specimen collection container having at least one open end into which the separator device may be seated.

Referring to FIG. **4**, a top view of separator device **400** is provided. Ring **401** has an OD of slightly less than the ID of the specimen collection cup into which the separator device is to be placed. Collection chamber **402** spans ring **401** and is defined by walls **403** and **404**.

Looking through separator device **400** along line A-A from cut-away point B-B (FIG. **5**), it is seen that walls **403** and **404** meet at point **405** to form a V-shaped well. Those of ordinary skill in the art will recognize that collection chamber **402** may take the form of a half-circular, squared or other shaped well, but a V-shape is a convenient well form to manufacture. Collection chamber **402** is closed at both ends of the well by inner surface **406** of ring **401**. Also, it will be appreciated that separator device **400** may be provided with more than one collection chamber.

FIG. **6** shows separator device **400** in place within specimen collection cup **410**. It can be seen from FIG. **6** that the height of ring **401** is restricted so neither it nor collection chamber **402** extend above the level of the open mouth **411** of cup **410** (to avoid interfering with closure of cup **410** by its cap [not shown]). Assay sample fluid **412** remains below separator device **400** in cup **410**.

Separator device **400** may be constructed of any sterilizable material which is acceptable for use with fluid assay samples, the identity of which will be known to those of ordinary skill in the art (e.g., plastics such as polycarbonate and glass). Preferably, the material will be non-porous and hydrophobic.

### E. Methods for Use of the Assay Devices

The method of the invention may be used to detect any analyte present in fluid sample. The invention is especially useful for detection of monoepitopic and polyepitopic antigens and antibodies associated with pathologies, as well as physiological compounds and drugs.

The assay devices of the invention are particularly well suited for use in drug screening assays and for diagnostic testing of organisms. In the former respect, a five drug panel of assay tests is recommended by the National Institute on Drug Abuse (NIDA), which includes tests for tetrahydrocannabinol and other marijuana metabolites, cocaine metabolites, opiate metabolites, phencyclidine (PCP, Angel Dust), and amphetamines. For a more extensive substance abuse testing panel, the choice of analytes tested can include marijuana metabolites; tetrahydrocannabinol and other marijuana metabolites, cocaine metabolites, opiate metabolites, phencyclidine (PCP, Angel Dust), amphetamines, barbiturates, benzodiazepines, methaqualone, and propoxyphene. The analyte test strips for drug tests preferably have the sensitivity equal to the cutoffs recommended by Substance Abuse Mental Health Service Administration (SAMSHA) and NIDA, which most employers use. Binders and reagents for use in constructing test strips for use in detecting drugs of abuse are well-known in the art and will not be described in detail here; however, representative sources of such materials are described in the Examples below.

Subjects undergoing drug tests are often creative in their attempts to adulterate the analyte samples to evade detection of drugs of abuse likely to be present in the sample. To minimize the effects of such evasion efforts on results obtainable with the assay devices of the invention, test strips may be provided in the devices which indicate the integrity and condition of the analyte sample. For example, test strips may be provided to simultaneously assay the analyte sample for for pH, osmolality (the total concentration of solutes in urine, expressed as mOsm/kg and measured as a function of fluid specific gravity), or the presence of albumin.

In test strips for pH, the strip is impregnated with various dyes that respond with different color changes to a pH in the range of 5 to 9. Depending on the acid-base status, urinary pH may range from as low as 4.5 to as high as 8.0. Although this test is done routinely, it neither identifies nor excludes patients with urinary system disease. The test can, however, indicate that the condition of the urine sample has deteriorated.

To test the specific gravity (which is directly proportional to urine osmolality) of an analyte test fluid, analyte test strips are available that measure specific gravity in approximations. For example, U.S. Pat. No. 4,318,709, to Falb et al., issued Mar. 9, 1982, provides a test means for determining the ionic strength or specific gravity of an aqueous test sample, the test means comprising a weakly acidic or weakly basic polyelectrolyte which is at least partially neutralized, and an indicator means capable of producing a detectable response to ion exchange between the polyelectrolyte and the sample. The test device is a carrier matrix incorporated with the test means, and the method for its use involves contacting an aqueous test sample with the device and observing a detectable response. The disclosure of the '709 Patent is incorporated for reference herein.

Normal urine osmolality varies between 50 and 1200 mOsm/kg (specific gravity between 1.002 and 1.035). Any urine having a specific gravity over 1.035 is either contaminated, contains very high levels of glucose, or the patient may have recently received high density radiopaque dyes intravenously for radiographic studies or low molecular weight dextran solutions.

Commercially available analyte test strips also permit simple and rapid testing for protein. Methods based on dye binding techniques have proven especially useful because dye binding methods are readily automated and provide reproducible and accurate results. In general, dye binding techniques use pH indicator dyes that are capable of interacting with a protein, such as albumin, and that are capable of changing color upon interaction with a protein absent any change in pH. When a pH indicator dye interacts with, or binds to, a protein, the apparent pKa (acid dissociation constant) of the indicator dye is altered and the dye undergoes a color transition, producing the so-called "protein-error" phenomenon. In methods utilizing the dye binding technique, an appropriate buffer maintains the pH indicator even at a constant pH to prevent a color transition of the pH indicator dye due to a substantial shift in pH. Due to the "protein-error" phenomena, upon interaction with the protein, the pH indicator dyes undergoes a color transition that is identical to the color change arising because of a change in the pH. Examples of pH indicator dyes used in the dry phase assay of proteins that are capable of interacting with or binding to proteins and exhibiting "protein-error" color transitions include tetrabromophenol blue and tetrachlorophenol-3,4,5,6-tetrabromosulfophthalein. Simple, accurate and inexpensive protein detection assays have been developed for the detection or measurement of protein in urine and serum (See, e.g., U.S. Pat. No. 5,096,833 to Lau et al., incorporated herein for reference).

The method of the invention is performed by applying analyte sample to test strips by immersion (dipstick forms of the device) or by applying the sample dropwise through slot **221** in cap **220** (FIG. **3**; representing cassette forms of the device). After waiting a predetermined time, such as from about 15 seconds to about 60 seconds, test results are viewed through window **111** or **211** (FIGS. **1** and **2**), either visually or by an instrument. A color change in test zone **112** or **212** (FIGS. **1** and **2**) indicates the presence or concentration of analyte in the sample. When no band appears in test zones, or if the control band is neither distinct nor fully formed, the assay is regarded as incompetent to indicate the presence or absence of analyte in the test samples and may be performed again. In addition, the assay can be made quantitative by employing spectrophotometric or calorimetric techniques, as opposed to visual techniques, in order to more reliably and more accurately measure the degree of color transition, and therefore more accurately measure the concentration of analyte in the test sample.

### F. Kits

The invention provides a kit useful for the detection of analytes of interest, having a carrier compartmentalized to receive one or more containers holding the multianalyte assay device of the invention or parts thereof. Preferably, the multianalyte assay device is part of a kit which may be composed of the device, instructions for its use, a sample collection cup, a capillary device for measuring test sample, a pipette for introduction of sample to the device, and a desiccant packet.

Desiccant provides low humidity conditions necessary for preservation of reagents during the shelf life of the device. Alternatively, a desiccant tablet or a desiccant packet may be included in an air-tight protective pouch with the device. Instructions for use of the multianalyte assay device may be printed onto the cover or onto the packaging of the multianalyte assay device or may be printed in literature to be packaged with the multianalyte assay device. The kit may additionally include an attached temperature strip, lids for the specimen cup, and the literature. Components of such a kit for use in performing an assay procedure (e.g., excluding printed instructions) are preferably to be sealed in one or more air-tight packages, such as foil packets.

The following examples are provided to illustrate a use for the invention and do not limit its scope. Unless otherwise noted, all terms and abbreviations used in the examples are standard in the art.

### EXAMPLE 1

#### Assay for Six Drugs of Abuse

Six chromatographic strips for detecting drugs of abuse (methamphetamine, opiates/morphine, marijuana/tetrahydrocannabinol, amphetamine, cocaine/benzoylecgonine, benzodiazepine) each of a size of 5 mm×73 mm were placed in slots of the device of the invention as shown in FIG. **1**. Each strip consisted of a colloidal gold-labeled antibody (specific to the target drug) incorporated into the upstream end of the strip (tracer zone) in the middle of a 30 mm fiberglass matrix, and an antigen-BSA binder immobilized in the center (binder zone) of a 22 mm nitrocellulose membrane lying downstream of, and in fluid communication with, the fiberglass matrix (wherein the antigen is either the drug of interest or an analog thereof having the same immunogenicity). Downstream to the nitrocellulose membrane was a 26 mm long filter paper. The matrix, membrane and filter paper were attached on a vinyl sheet so each was in fluid communication, by overlapping 2 mm of each of their ends.

15 drops (0.7 ml each) of analyte sample (human urine) were applied to the sample port. Results were read after 10 minutes. The presence or absence of a pink-rose color band in the binder zone indicated negative or positive results for the presence of each drug of interest in the analyte sample.

For comparison, additional aliquots of the analyte samples were separately tested for the presence of the same drugs of

abuse by a commercial assay (Syva EMIT EIA II). The second panel of test results correlated with the results obtained according to the invention.

Although the invention has been described with reference to the presently preferred embodiment, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

The invention claimed is:

**1**. A device for assaying a fluid for the presence or absence of different analytes comprising:

(A) a base having adjacent slots therein of sufficient length for insertion of part of a test strip therein, wherein each slot is defined by (a) a floor, (b) raised walls depending upwardly from the floor to separate each adjacent slot from the next, and (C) at least one open end,

(B) a multiplicity of test strips having an upstream and a downstream end, wherein a single test strip is inserted into each slot of the base so the upstream end of each test strip protrudes out of the open end of each slot, and wherein each test strip has a test zone and a control zone therein, and each test zone contains a binder specific for a different analyte; the protruding freestanding end of each test strip containing a sample addition pad for direct contact with the fluid to be analyzed;

(C) a cover attached to the upwardmost surface of each raised wall of the slots of the base and extending to the open end of said base, wherein the cover retains the test strips within the slots and has a first transparent window formed therein through which the test zone and the control zone of each of the test strips can be viewed and

(D) a cap enclosing the protruding ends of the test strips and removably attached to the open end of said base.

**2**. The device according to claim **1** further comprising a second transparent window formed within the cover through which the test strips can be viewed.

**3**. The device according to claim **1** further comprising a multiplicity of test strips inserted into each slot of the base, wherein each test strip has a test zone therein and each test zone contains a binder specific for a different analyte.

**4**. The device according to claim **3** wherein each binder is specific for a different drug of abuse.

**5**. The device according to claim **3** wherein each test zone is visible through the first transparent window of the cover.

**6**. The device according claim **3** each test strip further comprises a label downstream of the test zone, which label identifies the analyte for which the binder is specific.

**7**. The device according to claim **6**, wherein the label on the test strip is visible through the second transparent window of the cover.

**8**. The device according to claim **4** wherein the drug of abuse is from the group consisting of methamphetamine, opiates/morphine, marihuana/tetrahydrocannabinol, amphetamine, cocaine/benzoylecgonine, methadone, PCP, barbituate, trichloroacetic acid and benzodaizepine.

**9**. A method for detecting a multiplicity of analytes which comprises removing the cap from the device of claim **1** and inserting the protruding ends of the test strips into a sample to be analyzed and observing the effect of the sample on the test and control zones of the test strips contained in the device.

* * * * *

JS 44 (Rev. 12/12)

# CIVIL COVER SHEET

'16CV0698 LAB NLS

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

## I. (a) PLAINTIFFS

REMBRANDT DIAGNOSTICS, LP

**(b)** County of Residence of First Listed Plaintiff Montgomery
*(EXCEPT IN U.S. PLAINTIFF CASES)*

**(c)** Attorneys *(Firm Name, Address, and Telephone Number)*
KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 Main Street, 14th Floor
Irvine, CA 92614 (949)760-0404

## DEFENDANTS

Alere, Inc., Alere Toxicology Services, Inc., Amedica Biotech, Inc., Ameditech Inc., Innovacon, Inc., Instant Technologies, Inc., US Diagnostics, Inc., Branan Medical Corporation, and DOES 1-10

County of Residence of First Listed Defendant
*(IN U.S. PLAINTIFF CASES ONLY)*

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

## II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

## III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

*(For Diversity Cases Only)*

| | PTF | DEF | | PTF | DEF |
|---|---|---|---|---|---|
| Citizen of This State | ❒ 1 | ❒ 1 | Incorporated *or* Principal Place of Business In This State | ❒ 4 | ❒ 4 |
| Citizen of Another State | ❒ 2 | ❒ 2 | Incorporated *and* Principal Place of Business In Another State | ❒ 5 | ❒ 5 |
| Citizen or Subject of a Foreign Country | ❒ 3 | ❒ 3 | Foreign Nation | ❒ 6 | ❒ 6 |

## IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

**CONTRACT**
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

**REAL PROPERTY**
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

**TORTS**

**PERSONAL INJURY**
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

**PERSONAL INJURY**
- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

**PERSONAL PROPERTY**
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

**CIVIL RIGHTS**
- ❒ 440 Other Civil Rights
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

**PRISONER PETITIONS**

**Habeas Corpus:**
- ❒ 463 Alien Detainee
- ❒ 510 Motions to Vacate Sentence
- ❒ 530 General
- ❒ 535 Death Penalty

**Other:**
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

**FORFEITURE/PENALTY**
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

**LABOR**
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

**IMMIGRATION**
- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

**BANKRUPTCY**
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

**PROPERTY RIGHTS**
- ❒ 820 Copyrights
- ☒ 830 Patent
- ❒ 840 Trademark

**SOCIAL SECURITY**
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

**FEDERAL TAX SUITS**
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

**OTHER STATUTES**
- ❒ 375 False Claims Act
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 950 Constitutionality of State Statutes

## V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation

## VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. § 271

Brief description of cause:
Patent infringement

## VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

**DEMAND $**

CHECK YES only if demanded in complaint:
**JURY DEMAND:** ☒ Yes ❒ No

## VIII. RELATED CASE(S) IF ANY

*(See instructions):* JUDGE _____ DOCKET NUMBER _____

DATE
03/23/2016

SIGNATURE OF ATTORNEY OF RECORD
/Joseph F. Jennings/

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