ARCHITECT CEA

REF 7K68-27
REF 7K68-22
REF 7K68-35
REF 7K68-32

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CEA
7K68
G6-2827/R04
B7K6R0

Read Highlighted Changes: Revised November 2015.

Package insert instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

WARNING: The concentration of CEA in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the CEA assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining CEA levels serially is changed, additional sequential testing should be carried out. Before changing assays, the laboratory MUST confirm baseline values for patients being serially monitored.

CAUTION: United States Federal Law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to, by, or on the order of a physician.

NAME

ARCHITECT CEA (carcinoembryonic antigen)

INTENDED USE

The ARCHITECT CEA assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of Carcinoembryonic Antigen (CEA) in human serum and plasma. The ARCHITECT CEA assay is to be used as an aid in the prognosis and management of cancer patients in whom changing concentrations of CEA are observed.

SUMMARY AND EXPLANATION OF THE TEST

Carcinoembryonic antigen (CEA), first described in 1965 by Gold and Freedman,[1] is a tumor associated antigen. CEA was characterized as a glycoprotein of approximately 200,000 molecular weight with a β-electrophoretic mobility.[2, 3] Subsequent development of a radioimmunoassay (RIA) by Thomson, et al[4] made it possible to detect the very low concentrations of CEA in blood, other body fluids, and also in normal and diseased tissues.[5-7] Two years later, Hansen, et al[8] developed a modified RIA for CEA.

The result of clinical studies to date indicate that CEA, although originally thought to be specific for digestive tract cancers, may also be elevated in other malignancies and in some nonmalignant disorders.[9-15]

CEA testing can have significant value in the monitoring of patients with diagnosed malignancies in whom changing concentrations of CEA are observed. A persistent elevation in circulating CEA following treatment is strongly indicative of occult metastatic and/or residual disease.[16-20]

A persistently rising CEA value may be associated with progressive malignant disease and a poor therapeutic response.[21-23] A declining CEA value is generally indicative of a favorable prognosis and a good response to treatment.[21, 23, 24] Patients who have low pretherapy CEA levels may later show elevations in the CEA level as an indication of progressive disease.[25]

Clinical relevance of the CEA assay has been shown in the follow-up management of patients with colorectal, gastric, breast, lung, prostatic, pancreatic, and ovarian carcinoma.[18, 24, 26-31] Follow-up studies of patients with colorectal, breast, and lung carcinoma suggest that the preoperative CEA level has prognostic significance.[32-35]

CEA testing is not recommended as a screening procedure to detect cancer in the general population; however, use of the CEA test as an adjunctive test in predicting prognosis and as an aid in the management of cancer patients has been widely accepted.

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT CEA assay is a two-step immunoassay to determine the presence of CEA in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex.

1. Sample and anti-CEA coated paramagnetic microparticles are combined. The CEA present in the sample binds to the anti-CEA coated microparticles.
2. After washing, anti-CEA acridinium-labeled conjugate is added to create a reaction mixture.
3. Following another wash cycle, Pre-Trigger and Trigger Solutions are added to the reaction mixture.
4. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of CEA in the sample and the RLUs detected by the ARCHITECT iSystem optics.

For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

REAGENTS

Kit Contents

ARCHITECT CEA 7K68

NOTE: Some kit sizes are not available in all countries or for use on all ARCHITECT iSystems. Please contact your local distributor.

REF	7K68-27	7K68-22	7K68-35	7K68-32
Σ	100	400	500	2000
MICROPARTICLES	1 x 6.6 mL	4 x 6.6 mL	1 x 27.0 mL	4 x 27.0 mL
CONJUGATE	1 x 5.9 mL	4 x 5.9 mL	1 x 26.3 mL	4 x 26.3 mL

MICROPARTICLES anti-CEA (mouse, monoclonal) coated Microparticles in TRIS buffer with protein (bovine) stabilizer. Minimum concentration: 0.1% solids. Preservative: Antimicrobial Agents.

CONJUGATE anti-CEA (mouse, monoclonal) acridinium-labeled Conjugate in phosphate buffer with protein (bovine) stabilizer. Minimum concentration: 0.8 µg/mL. Preservative: Antimicrobial Agents.

Other Reagents

MULTI-ASSAY MANUAL DILUENT 1 x 100 mL ARCHITECT Multi-Assay Manual Diluent, REF 7D82-50, containing phosphate buffered saline solution. Preservative: antimicrobial agent.

PRE-TRIGGER SOLUTION ARCHITECT Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide.

TRIGGER SOLUTION ARCHITECT Trigger Solution containing 0.35 N sodium hydroxide.

WASH BUFFER ARCHITECT Wash Buffer containing phosphate buffered saline solution. Preservatives: antimicrobial agents.

NOTE: Bottle and volume varies based on order.

Warnings and Precautions

- IVD
- For *In Vitro* Diagnostic Use

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[36-39]

Safety Data Sheets are available at www.abbottdiagnostics.com or contact your local representative.

For a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

Reagent Handling

- Do not use reagent kits beyond the expiration date.
- **Do not pool reagents within a kit or between kits.**
- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.
- **Septums MUST be used to prevent reagent evaporation and contamination and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
  - To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.
  - Once a septum has been placed on an open reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
  - Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.

For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

Reagent Storage

- When stored and handled as directed, reagents are stable until the expiration date.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened/ Opened*	2-8°C	Until expiration date	May be used immediately after removal from 2-8°C storage.
On board	System temperature	30 days	Discard after 30 days. For information on tracking onboard time, refer to the ARCHITECT System Operations Manual, Section 5.

* Reagents may be stored on or off the ARCHITECT iSystem. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** For information on unloading reagents, refer to the ARCHITECT System Operations Manual, Section 5.

Indications of Reagent Deterioration

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

INSTRUMENT PROCEDURE

The ARCHITECT CEA assay file must be installed on the ARCHITECT iSystem from an ARCHITECT iSystem Assay CD-ROM prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.

For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.

For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

Verified specimen types to be used with this assay:

Specimen Types	Collection Tubes
Human serum	Serum
	Serum separator tubes
Human plasma	Heparin (sodium and lithium)
	Potassium EDTA

- Other specimen collection tube types have not been tested with this assay.
- Plasma specimens collected in lithium or sodium heparin have been shown to exhibit an average of 7% to 8% higher results compared to corresponding serum results.
- When serial specimens are being evaluated, the same type of specimen should be used throughout the study.
- The instrument does not provide the capability to verify specimen type. It is the responsibility of the operator to verify that the correct specimen types are used in the assay.

Specimen Conditions

- Do not use specimens with the following conditions:
  - grossly hemolyzed
  - obvious microbial contamination
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy may exhibit increased clotting time. If the specimen is centrifuged before a complete clot forms, the presence of fibrin may cause erroneous results.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for specimen collection tubes.
- ARCHITECT CEA Calibrators and Controls should be mixed by gentle inversion prior to use.
- For optimal results, specimens should be free of fibrin, red blood cells, or other particulate matter. **Centrifuge serum and plasma specimens containing fibrin, red blood cells, or particulate matter prior to use to ensure consistency in the results.**
- Specimens must be mixed THOROUGHLY after thawing, by vortexing. Thawed samples containing red blood cells or particulate matter, **or which are hazy or cloudy in appearance** must be centrifuged prior to use to ensure consistency in the results.

- Inspect all specimens for bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

Specimen Storage

Specimen Type	Storage Temperature	Maximum Storage Time
Serum/Plasma	2-8°C	≤ 7 days

If testing will be delayed more than 24 hours, serum or plasma should be removed from the clot, serum separator, or red blood cells.

If testing will be delayed more than 7 days, specimens should be stored/frozen at - 20°C or colder.

Avoid multiple freeze/thaw cycles.

Specimen Shipping

- Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

PROCEDURE

Materials Provided

7K68 ARCHITECT CEA Reagent Kit

Materials Required but not Provided

- ARCHITECT CEA Assay file obtained from the ARCHITECT iSystem e-Assay CD-ROM found on www.abbottdiagnostics.com.
- 7K68-02 ARCHITECT CEA Calibrators
- 7D82-50 ARCHITECT Multi-Assay Manual Diluent
- ARCHITECT Pre-Trigger Solution
- ARCHITECT Trigger Solution
- ARCHITECT Wash Buffer
- ARCHITECT Reaction Vessels
- ARCHITECT Sample Cups
- ARCHITECT Septum
- ARCHITECT Replacement Caps
- Pipettes or pipette tips (optional) to deliver the volumes specified on the patient or control order screen.

For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

Materials Available but not Provided:

- 7K68-12 ARCHITECT CEA Controls

Assay Procedure

- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. After the first time the microparticles have been loaded, no further mixing is required.
  - **Invert the microparticle bottle 30 times.**
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
  - Once the microparticles have been resuspended, place a septum on the bottle. For instructions about placing septums on bottles, refer to the **Reagent Handling** section of this package insert.
- Load the reagent kit on the ARCHITECT iSystem.
  - Verify that all necessary reagents are present.
  - Ensure that septums are present on all reagent bottles.
- Order tests.
  - For information on ordering patient specimens and controls and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- Minimum sample cup volume is calculated by the system and printed on the Orderlist report. To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.

  Maximum number of replicates sampled from the same sample cup: 10
  - Priority:

    Sample volume for first test: 60 µL

    Sample volume for each additional test from same sample cup: 10 µL
  - ≤ 3 hours on board:

    Sample volume for first test: 150 µL

    Sample volume for each additional test from same sample cup: 10 µL
  - > 3 hours on board: Additional sample volume is required. Refer to the ARCHITECT System Operations Manual, Section 5 for information on sample evaporation and volumes.
  - If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
- Prepare ARCHITECT CEA Calibrators and Controls.
  - Mix calibrator(s) and controls by gentle inversion before use.
  - Hold bottles **vertically** and dispense recommended volumes into each respective sample cup.
  - Recommended volumes:

    for each calibrator: 5 drops

    for each control: 4 drops
- Load samples.
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN.
- For additional information on principles of operation, refer to the ARCHITECT System Operations Manual, Section 3.
- For optimal performance, it is important to perform routine maintenance as described in the ARCHITECT System Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

Specimen Dilution Procedures

Specimens with a CEA value exceeding 1500 ng/mL are flagged with the code ">1500.00" and may be diluted using either the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol

The system performs a 1:10 dilution of the specimen and automatically calculates the concentration of the specimen before dilution and reports the result.

Manual Dilution Procedure

Suggested dilution: 1:100

An additional 1:10 dilution may be made if needed. It is recommended that dilutions not exceed 1:1000.

1. Add 20 µL of the patient specimen to 1980 µL of ARCHITECT Multi-Assay Manual Diluent.
2. The operator must enter the dilution factor in the Patient or Control order screen. All assays selected for that order will be diluted. The system will use this dilution factor to automatically calculate the concentration of the sample before dilution and report the result. The dilution should be performed so that the diluted result reads > 4 ng/mL.

For detailed information on ordering dilutions, refer to the ARCHITECT System Operations Manual, Section 5.

A comparison of the Automated Dilution Protocol to the Manual Dilution Procedure yielded recoveries between 86% and 97%.

Calibration

- Test Calibrators 1 and 2 in duplicate. The calibrators should be priority loaded.

  A single sample of each control level must be tested to evaluate the assay calibration. Ensure that assay control values are within the ranges specified in the respective control package insert.
- Calibration Range: 0 - 500 ng/mL.
- The assay protocol allows for the range to be extended to 1500 ng/mL.
- Once an ARCHITECT CEA calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:
  - A reagent kit with a new lot number is used or
  - Controls are out of range.
- For detailed information on how to perform an assay calibration, refer to the ARCHITECT System Operations Manual, Section 6.

Quality Control Procedures

The recommended control requirement for the ARCHITECT CEA assay is that a single sample of each control level be tested once every 24 hours each day of use. If the quality control procedures in your laboratory require more frequent use of controls to verify test results, follow your laboratory-specific procedures.

Ensure that assay control values are within the concentration ranges specified in the package insert.

Verification of Assay Claims

For protocols to verify package insert claims, refer to the ARCHITECT System Operations Manual, Appendix B.

The ARCHITECT CEA assay belongs to method group 1.

RESULTS

Calculation

The ARCHITECT CEA assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve.

Flags

- The default result unit for the ARCHITECT CEA assay is ng/mL.
- Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the ARCHITECT System Operations Manual, Section 5.

LIMITATIONS OF THE PROCEDURE

- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits such as ARCHITECT CEA that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.[40, 41]

  ARCHITECT CEA reagents contain a component that reduces the effect of HAMA reactive specimens. Additional clinical or diagnostic information may be required to determine patient status.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference, and anomalous values may be observed. Additional information may be required for diagnosis.[42]
- The ARCHITECT CEA assay should not be used as a cancer screening test.
- Patients with confirmed carcinoma frequently have a pretreatment CEA level in the same range as healthy individuals. Elevations in circulating CEA levels may be observed in smokers as well as patients with nonmalignant disease. For these reasons, a serum or plasma CEA level, regardless of value, should not be interpreted as absolute evidence for the presence or absence of malignant disease. The CEA level should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

EXPECTED VALUES

The distribution of ARCHITECT CEA values determined in 1,141 specimens is shown in the following table.*

Distribution of ARCHITECT CEA Values

		Percent (%)			
	Number of Subjects	0 - 3 (ng/mL)	>3 - 5 (ng/mL)	>5 - 10 (ng/mL)	>10 (ng/mL)
Healthy Subjects					
Smokers	159	74.2	18.2	6.9	0.6
Non-smokers	149	83.2	11.4	5.4	0.0
Total	308	78.6	14.9	6.2	0.3
Nonmalignant Disease					
Ulcerative Colitis	50	72.0	20.0	4.0	4.0
Rectal Polyps	78	83.3	10.3	5.1	1.3
Pulmonary	60	61.7	20.0	13.3	5.0
Cirrhosis	110	47.3	30.0	15.5	7.3
Hepatitis	60	70.0	16.7	11.7	1.7
Renal	20	60.0	15.0	15.0	10.0
Malignant Disease					
Colorectal	150	24.0	10.7	10.7	54.7
Gastric	37	62.2	5.4	10.8	21.6
Pulmonary	110	47.3	19.1	9.1	24.5
Mammary	117	62.4	11.1	10.3	16.2
Ovarian	41	78.0	7.3	2.4	12.2

* Representative data; results in individual laboratories may vary.

In this study, 93.5% of healthy subjects (n=308) had CEA values of 5.00 ng/mL or less.

It is expected that each laboratory establish its own expected reference range for the population of interest.

The distribution table above for malignant disease is derived primarily from patients representing both active (clinical evidence of disease progression) and inactive (no clinical evidence of disease progression) disease states. When changing CEA assay methods in the course of monitoring a patient, additional sequential testing should be carried out to confirm baseline values.

SPECIFIC PERFORMANCE CHARACTERISTICS

Precision

The Architect CEA assay precision is ≤ 8%. Precision was determined as described in the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) Protocol EP5-T2.[43] Five samples, consisting of two serum based panels and three CEA controls, were assayed at three laboratories in replicates of two at two separate times per day for twenty days (n=80 for each sample), using a single lot of reagents and a single calibration. Data from this study are summarized in the following table.*

Reproducibility of ARCHITECT CEA

Sample	Lab	Mean CEA (ng/mL)	Within Run SD	Within Run %CV	Total SD	Total %CV
Low Control	1	5.05	0.180	3.6	0.202	4.0
	2	4.79	0.098	2.1	0.178	3.7
	3	4.86	0.110	2.3	0.162	3.3
Medium Control	1	20.17	0.512	2.5	0.641	3.2
	2	19.08	0.515	2.7	0.629	3.3
	3	19.99	0.605	3.0	0.685	3.4
High Control	1	99.45	3.074	3.1	3.182	3.2
	2	93.97	2.082	2.2	2.559	2.7
	3	99.51	2.898	2.9	3.072	3.1
Panel 1	1	417.34	9.587	2.3	10.483	2.5
	2	395.70	11.313	2.9	13.995	3.5
	3	419.93	11.591	2.8	13.870	3.3
Panel 2	1	1294.72	40.660	3.1	46.508	3.6
	2	1185.03	21.570	1.8	26.286	2.2
	3	1309.28	29.760	2.3	38.030	2.9

* Representative performance data are shown. Results obtained at individual laboratories may vary.

Recovery

Known amounts of CEA were added to normal human serum and plasma samples. The concentration of CEA was determined using the ARCHITECT CEA assay and the resulting percent recovery was calculated.*

Recovery

Sample Type	Endogenous Level (ng/mL)	CEA Added (ng/mL)	CEA Observed (ng/mL)	Percent Recovery
Serum				
1	0.86	94.76	91.00	95.1
2	1.07	4.49	5.56	100.0
3	0.94	94.76	94.53	98.8
4	1.11	4.49	5.85	105.6
				Average % Recovery: 99.9%
EDTA				
1	0.81	94.76	91.77	96.0
2	0.70	94.76	92.29	96.7
3	1.10	4.49	5.77	104.0
4	1.72	4.49	6.21	100.0
				Average % Recovery: 99.2%
Heparin				
1	0.93	94.76	94.60	98.8
2	1.26	4.49	6.10	107.8
3	0.92	94.76	95.24	99.5
4	1.17	4.49	5.92	105.8
				Average % Recovery: 103.0%

* Representative data; results in individual laboratories may vary.

$$\% \text{ Recovery} = \frac{\text{Observed (ng/mL) - Endogenous Level (ng/mL)}}{\text{CEA Added (ng/mL)}} \times 100$$

Analytical Sensitivity

The sensitivity of the ARCHITECT CEA assay was calculated to be better than 0.5 ng/mL at the 95% level of confidence (n = 18 runs). Sensitivity is defined as the concentration at two standard deviations above the mean RLU for the ARCHITECT CEA MasterCheck Level 0 and represents the lowest measurable concentration of CEA that can be distinguished from zero.

Specificity

The specificity of the ARCHITECT CEA assay was determined by testing sera containing the compounds listed below. These compounds showed less than 10% interference in the ARCHITECT CEA assay at the levels indicated.

Test Compound	Test Concentration
Bilirubin	22 mg/dL
Hemoglobin	550 mg/dL
Total Protein	1.8 to 13.2 g/dL
Triglycerides	3300 mg/dL

Carryover

No detectable carryover (less than 12 PPM) was observed when a sample containing 43,630 ng/mL of CEA was assayed.

High Dose Hook

High dose hook is a phenomenon whereby very high level specimens may read within the dynamic range of the assay. For the ARCHITECT CEA assay, no high dose hook effect was observed when samples containing up to approximately 60,000 ng/mL of CEA were assayed.

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Key to Symbols

	Consult instructions for use
	Manufacturer
	Sufficient for
	Temperature limitation
	Use by/Expiration date
CONJUGATE	Conjugate
CONTROL NO.	Control Number
DISTRIBUTED IN THE USA BY	Distributed in the USA by
GTIN	Global Trade Item Number
INFORMATION FOR USA ONLY	Information needed for United States of America only
IVD	*In Vitro* Diagnostic Medical Device
LOT	Lot Number
MICROPARTICLES	Microparticles
MULTI-ASSAY MANUAL DILUENT	Multi-Assay Manual Diluent
PRE-TRIGGER SOLUTION	Pre-Trigger Solution
PRODUCT OF IRELAND	Product of Ireland
REACTION VESSELS	Reaction Vessels
REAGENT LOT	Reagent Lot
REF	List Number
REPLACEMENT CAPS	Replacement Caps
SAMPLE CUPS	Sample Cups
SEPTUM	Septum
SN	Serial number
TRIGGER SOLUTION	Trigger Solution
WASH BUFFER	Wash Buffer

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Revised November 2015.

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