510(k) SUMMARY AND SUBSTANTIAL EQUIVALENCE COMPARISON

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92

JUL 3 1 2012

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Name of the Device	HCY POC Test
Trade Name	HCY POC Test
Common Usual Name	SMART Homocysteine Assay
Device Classification Name	HCY POC Assay
Product Code	LPS; Test, Homocysteine
Panel	Clinical Chemistry (75)
Submission Type	510K
Regulation Number	21CFR 862.1377
Device Class	Class II (Assay)
Predicate Device	Diazyme Homocysteine Assay k071971
Establishment Registration	2032900

Executive Summary

Detailed performance characteristics and comparison analysis are given in this filing and demonstrate substantial equivalence to predicate device that is currently being marketed. The performance characteristics of the Diazyme HCY POC Test Kit are substantially similar to that of the

approved predicate device DIAZYME HOMOCYSTEINE 2 REAGENT ENZYMATIC ASSAY KIT (k071971). Performance data and risk analysis indicates that differences should not affect the safety and effectiveness of the HCY POC Test and offers POL users an *in vitro* diagnostic device system to measure HCY in human serum/plasma samples.

Description of the Device:

Diazyme HCY POC Test Kit contains reagents intended for use with the SMART analyzer for the quantitative determination of Homocysteine (HCY) in human serum or plasma. Diazyme HCY POC Test is based on a novel enzyme cycling method as published in the Journal of Clinical Chemistry. In this assay, oxidized HCY is first reduced to free HCY which then reacts with a co-substrate, S-adenosylmethionine (SAM) catalyzed by a HCY S-methyltransferase to form methionine (Met) and S-adenosylhomocysteine (SAH). SAH is assessed by coupled enzyme reactions including SAH hydrolase, adenosine (Ado) deaminase and glutamate dehydrogenase, wherein SAH is hydrolyzed into adenosine (Ado) and HCY by SAH hydrolase. The formed HCY that is originated from the co-substrate SAM is cycled into the HCY conversion reaction by HCY S-methyltransferase. This forms a co-substrate conversion product-based enzyme cycling reaction system with significant amplification of detection signals. The formed Ado is immediately hydrolyzed into inosine and ammonia which reacts with glutamate dehydrogenase with concomitant conversion of NADH to NAD+. The concentration of HCY in the sample is indirectly proportional to the amount of NADH converted to NAD+ (ΔA340nm).

Diazyme Homocysteine POC Controls were cleared in previous FDA filing k042448.

SMART Analyzer (k092911) is a compact cuvette based spectrophotometer (10 inches x 5.5 inches x 5.5 inches) machine for point-of-care testing designed to analyze readings from single use reagent cuvette. The instrument only uses the Diazyme Reagent System (DRS) cuvette and caps and performs assay with a preprogrammed Radio Frequency ID (RFID) card. The DRS cuvette is supplied prefilled with Reagent 1 (R1) and the DRS cap is supplied prefilled with Reagent 2 (R2). The DRS cuvette and caps are kept separate until use. Users are instructed (see proposed labeling) to add 20µl of sample to the DRS cuvette prefilled with R1 containing proper amount of detergent for whole blood lysis. Users are then instructed to snap in place DRS cap and insert into analyzer. The instrument warms the cuvette to 37°C and after a predefined period adds the reagent R2 found in the DRS cap. The reagents and samples are mixed magnetically and absorbance readings are taken at 700nm. The lot specific RFID card contains reagent addition time, mixing time, reading time and calibration curve.

The Diazyme HCY POC Test system thus consists of the following:

- HCY POC Test Kit. Reagents are provided in prefilled tubes, cuvettes and cuvette caps. The DRS cuvette and cuvette caps can only work with the SMART analyzer.
- HCY POC Test Control Kit. Controls are provided for quality control of the HCY POC Test.

Indication (s) for use

Diazyme's HCY POC Test Kit is intended to be used with the SMART analyzer in a Point-of-Care setting for the *in vitro* quantitative determination of total L-homocysteine in serum or plasma. The assay can assist in the diagnosis and treatment of patients suspected of having hyperhomocysteinemia and homocystinuria. For in vitro diagnostic use only.

Table 1 Summary of Assay Kit Components

Candidate device
Kit can ONLY be used with SMART Analyzers
Reagent 1 20 DRS cuvettes (prefilled) • NADH and substrates, same as the predicate
Reagent 2 20 DRS caps (prefilled) • Enzymes and stabilizers, same as the predicate
Calibrator
1 x preprogrammed lot specific RFID card in each kit
Control Set
Control (serum based, read to use), same as the predicate

Performance Characteristics:

Precision/Reproducibility

Precision study at manufacture site

The precision of the Diazyme HCY POC Assay was evaluated according to Clinical and Laboratory Standards Institute (CLSI) EP5-A guideline with some modifications. In the study, three serum controls containing 7.3, 11.87, and 29.32μmol/L HCY were tested in duplicate, two runs per day, over ten working days. The first five days used Lot 1, HT00209, and subsequent five days used Lot 2, HT00309. This was performed on three different SMART Analyzers. The results indicated good precision and are summarized in the following table:

	7.3μmol/L HCY	11.87μmol/L HCY	29.32μmol/L HCY
No. of Points	40	40	40
Mean (μM)	7.5	11.8	29.0
Within CV%	3.2%	1.8%	2.8%
Total CV%	3.4%	3.5%	3.3%

Conclusion: Within precisions for three levels of HCY serum samples are 3.2% for 7.5μmol/L HCY, 1.8% for 11.87μmol/L HCY, and 2.8% for 29.0μmol/L HCY. Total precisions (CV) for three levels of HCY serum samples are 3.4% for 7.5μmol/L HCY, 3.5% for 11.87μmol/L HCY, and 3.3% for 29.0μmol/L HCY. These results meet precision criteria.

Precision studies at three POL sites

The precision was also evaluated in three physician office laboratories (POL) by intended users such as nurses and office assistances to test systemic and random error on two Diazyme HCY SMART analyzers. Two serum specimens were used at each site. At each POL site, the two serum specimens were run in 4 replicates per day for 5 days. The results indicated good precision and are summarized in the following table:

The results are summarized in the following tables:

	Sample 1 Site 1	Sample 2 Site 2	Sample 3 Site 3	Sample 4 Site 1 and 2	Sample 5 Site 3
No. of Points	20	20	20	40	20
Mean (μmol/L)	4.89	10.68	13.71	29.83	42.92
Within CV%	3.1%	2.8%	2.8%	3.5%	2.6%
Total CV%	5.2%	3.7%	4.1%	6.0%	3.2%

(3) Additional precision study was evaluated at three physician office laboratories (POL) with multiple users at each site. A total of 9 serum samples containing HCY levels ranging from low to high were used for the precision study. At each site, 3 serum samples were tested by three different people. Each sample was run 4 times for 5 days.

The results are summarized in the following tables:

Site 1:

	Sample 1	Sample 2	Sample 3
No. of Points	20	20	20
Mean (μmol/L)	11.05	25.82	42.73
Within run CV	6.7%	6.2%	5.60%
Total CV	7.0%	5.3%	6.4%

Site 2:

	Sample 1	Sample 2	Sample 3
No. of Points	20	20	20
Mean (μmol/L)	10.26	25.18	41.99
Within run CV%	6.9%	5.2%	3.8%
Total CV%	6.6%	5.5%	4.4%

Site 3:

	Sample 1	Sample 2	Sample 3
No. of Points	20	20	20

Mean (μmol/L)	11.63	26.34	31.63
SD (μmol/L)	0.4941	1.9883	1.8298
Within run CV%	4.2%	7.5%	5.8%
Total CV%	6.0%	6.8%	5.5%

Conclusion: For the 9 serum samples containing HCY from 10.26 μmol/L to 42.73 μmol/L, a CV% of less than 8% was obtained at the three POL sites.

Linearity/assay reportable range:

Ten levels of linearity set were prepared by diluting a serum control containing 50μmol/L HCY with saline according to Clinical and Laboratory Standards Institute (CLSI) **EP6-A**. The samples prepared were tested using the Diazyme's HCY POC Assay in triplicate. After linear regression, an equation of Recovered HCY = 0.9749 * Expected HCY + 0.751 and correlation coefficient R^2 of 0.9992 were obtained.

The linearity of Diazyme HCY SMART Assay is linear 3 – 50 μmol/L.

Traceability, Stability, Expected values (controls, calibrators, or methods):

Calibrator

HCY POC Test calibration is traceable to the higher order NIST SRM 1955.

Calibration Radio Frequency Identification Card (RFID card)
HCY POC Test utilizes a RFID card that is preprogrammed with a reagent lot specificcalibration curve and is supplied in each kit. When RFID card is inserted into SMART analyzer slot (assay procedure step), the lot specific calibration curve is automatically utilized for assay test. RFID cards are programmed at the manufacturer site and are subject to the same quality control checks as the reagents and controls.

Lot specific calibrator values to be generated for RFID card calibration curve programming are traced to reference Diazyme Homocysteine calibrator values (k071971) and are value assigned as follows:

- To construct Diazyme HCY SMART Assay RFID card calibration curve, 5 levels of calibrators used in the predicate device (k071971) are tested with the Diazyme HCY POC Test reagents on SMART analyzers to obtain the rate of absorbance change. The calibrator value and the mean of absorbance change are programmed into cards by using a card writer.

- After creation of the RFID card it is used for in process and final QC testing (Step 3: Final calibration values). Tests include NIST SRM 1955, Diazyme Homocysteine Controls, and serum samples.

Stability

Two lots of the Diazyme HCY POC Assay reagents were used for this study. The reagents from each lot were kept 2-8°C refrigerator. In the study, two levels of serum control samples containing 7.31 μM, and 29.53 μM homocysteine were tested. At indicated time, the Diazyme HCY POC Assay reagents were removed from storage and tested. The real time data so far showed that the HCY POC Test is stable for at least 10 months at 2-8°C storage. The real time stability testing is on-going.

LoB, LoD,LoQ

The LoB, LoD, and LoQ of the Diazyme HCY POC Test Kit were determined according to CLSI EP17-A.
LoB = 0.06 μmol/L
LoD = 0.32 μmol/L
LoQ = 3.00 μmol/L.

Interference

Common endogenous substance interference

The level of interference from the substances normally present in the serum was determined by using Diazyme Homocysteine SMART Enzymatic Assay to test 12μM and 29μM HCY serum samples spiked with various concentrations of substances following Clinical and Laboratory Standards Institute EP7-A "Interference Testing in Clinical Chemistry": dose-response guidelines.

Interference	Concentration
Ascorbic Acid	10mmol/L
Unconjugated Bilirubin	40mg/dL
Conjugated Bilirubin	40mg/dL
Hemoglobin	500mg/dL
Triglyceride	1000mg/dL
Glutathione	500 μM
Methionine	20 μM
Cysteine	1000 μM
Pyruvate	500 μM
Cystathionine	100 μM
Hydroxylamine	1000 μM
Carbamezapine	130 μM
Methotrexate	2.0 mM
Phenytoin	200 μM
6-azauridine triacetate	1000 μM
S-adenosyl-methionine	20 μM
Carbamezapine-10, 11-epoxide	60 μM
Ethosuximide	1800 μM

Primidone	200 µM
Valporic Acid	3.5 mM
Sodium Nitrate	500 µM

Conclusion: The following substances normally present in serum produced less than 10% deviation when tested at levels equal to the concentrations listed below

Comparison Studies

Method comparison with predicate device

To demonstrate accuracy, the Diazyme HCY Enzymatic SMART Assay was tested with individual serum samples and run in parallel with the Diazyme HCY Two Reagent Enzymatic Assay on the Olympus AU400.

Serum samples were used for the comparison experiment. To ensure the concentrations of HCY distributed across the reportable dynamic range, additional HCY samples used for the study were spiked with stock solution of HCY to targeted concentrations.

The regression results are summarized in the following table:

	application
n	74
Slope	0.9612
Intercept	0.5246
Correlation coefficient	0.9696
Range of values	4.17-49.50 µmol/L

The method comparison study was performed externally at the three POL sites. One Hundred and Twenty (120) serum specimens are used in total (40 samples at each site). The Diazyme HCY POC reagents were used to test individual serum samples with comparison to Diazyme Enzymatic HCY Assay on Olympus AU400 (k061971).

The regression results are summarized in the following table

SMART HCY	Site 1	Site 2	Site 3	All combined
n	40	40	40	120
Slope	1.0890	1.0041	1.0600	1.0552
Intercept	-0.7438	-0.6251	-1.1564	-0.8860
R^2	0.9830	0.9645	0.9819	0.9765

Range	5.43-48.95	3.88-45.43	4.81-49.86	3.88-49.86

Matrix comparison

To evaluate the anticoagulant effects of EDTA plasma and Li Heparin Plasma of the HCY levels, 40 sample sets serum/EDTA plasma/Li Heparin were tested on SMART analyzer using HCY POC Test Kits.

Results: Slope = 1.0197 and 0.9632 for EDTA plasma and Li Heparin respectively, and R^2 = 0.9889 and 0.99 for EDTA plasma and Li Heparin respectively.

Conclusion: There is no matrix effect between serum, EDTA plasma and Li Heparin Plasma.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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JUL 31 2012

Re: k121053
Trade Name: Diazyme Homocysteine POC Test
Regulation Number: 21 CFR §862.1377
Regulation Name: Urinary Homocysteine (non-quantitative) test system
Regulatory Class: Class II
Product Codes: LPS
Dated: July 11, 2012
Received: July 13, 2012

Dear Dr. Datta:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at (301) 796-5760. For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/Medical Devices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance...

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-5680 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm

Sincerely yours,

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (If Known): K121053

Device Name: Diazyme Homocysteine POC Test Kit

Indications for Use:

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Prescription Use X (Part 21 CFR 801 Subpart D) AND/Or Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Ruth Chesler

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) 121053