April 12, 2018

Siemens Healthcare Diagnostics Inc.
Darius Daruwala
Senior Specialist, Regulatory Affairs
511 Benedict Avenue
Tarrytown, NY 10591

Re: K172201
Trade/Device Name: Atellica IM Folate Assay
Regulation Number: 21 CFR 862.1295
Regulation Name: Folic acid test system
Regulatory Class: Class II
Product Code: CGN
Dated: February 28, 2018
Received: March 1, 2018

Dear Darius Daruwala:

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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. 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 Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR

Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kellie B. Kelm -S

for Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K172201

Device Name
Atellica™ IM Folate Assay

Indications for Use *(Describe)*
The Atellica™ Folate assay is for in vitro diagnostic use in the quantitative determination of folate in serum or red blood cells using the Atellica IM Analyzer. Folic acid measurements are used in the diagnosis and treatment of anemias.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of 21 CFR 807.92 and the Safe Medical Device Act of 1990.

The assigned 510(k) Number is: K172201

1. Date Prepared

April 12, 2018

2. Applicant Information

Contact: Darius Daruwala
Regulatory Affairs Senior Specialist

Address: Siemens Healthcare Diagnostics Inc.
511 Benedict Avenue
Tarrytown, NY 10591

Phone: 914-524-2812

Fax: 914-524-3579

Email: darius.daruwala@siemens.com

3. Regulatory Information

Table 1. Regulatory Information for Atellica™ IM Folate Assay

Trade Name	Atellica™ IM Folate Assay
Model Numbers	10995572 (1-pack); 10995573 (5-pack)
Common Name	Immunoassay, Folate
Classification Name	Folic Acid Test System
FDA Classification	Class II
Review Panel	Clinical Chemistry (75)
Product Code	CGN
Regulation Number	862.1295

4. Predicate Device Information

ADVIA Centaur Folate

Predicate Device Name: ADVIA Centaur Folate

510(k) Number: K010050

5. Intended Use / Indications for Use

Atellica™ IM Folate

The Atellica™ IM Folate assay is for *in vitro* diagnostic use in the quantitative determination of folate in serum or red blood cells using the Atellica™ IM Analyzer. Folic acid measurements are used in the diagnosis and treatment of anemias.

6. Device Description

Table 3. Summary of Ingredients of the Atellica™ IM Folate Assay Components

Component	Volume	Ingredients
Atellica™ IM Folate Primary Reagent ReadyPack (included in assay kit)		
Atellica™ IM Folate Lite Reagent	10.0 mL/pack	Folate labeled with acridinium ester (~9.8 ng/mL) in buffer; bovine serum albumin; sodium azide (0.1%); preservatives
Atellica™ IM Folate Solid Phase Reagent	20.0 mL/pack	Purified avidin (~20 µg/mL) covalently coupled to paramagnetic particles in buffer; human serum albumin; preservatives
Atellica™ IM Folate Binding Protein	10.0 mL/pack	Purified folate binding protein (~1.0 µg/mL) covalently coupled to biotin in buffer; bovine serum albumin; preservatives
Atellica™ IM Folate Calibrator (included in assay kit)		
Atellica™ IM Folate Low and High Calibrators	3.0 mL/vial	After reconstitution, low or high levels of N-5-methyltetrahydrofolic acid; buffer; human serum albumin; sodium azide (< 0.1%); preservatives
Atellica IM Folate DTT/Releasing Agent (sold separately)		
Atellica IM Folate DTT	8.0 mL/vial	Dithiothreitol (~95 mg/mL in liquid form)
Atellica IM Folate Releasing Agent	4.0 mL/vial	Sodium hydroxide (~1.1 N)
Atellica IM RBC Folate (sold separately)		
RBC Folate Ascorbic Acid	~0.30 g/vial	Lyophilized ascorbic acid
RBC Folate Ascorbic Acid Diluent	30.0 mL/vial	Bovine serum albumin; buffer; sodium azide (<0.1%)

7. Purpose of the Submission

The purpose of this submission is a premarket notification for a new device: Atellica™ IM Folate assay.

8. Substantial Equivalence Information

Predicate Device Name: ADVIA Centaur Folate Assay
510(k) Number: K010050

Table 4. Comparison of Atellica™ IM Folate Assay to Predicate

Item	Atellica™ IM Folate Assay (Candidate Device)	ADVIA Centaur Folate Assay (Predicate Device) (K010050)
Intended Use	For *in vitro* diagnostic use in the quantitative determination of folate in serum or red blood cells using the Atellica™ IM analyzer. Folic acid measurements are used in the diagnosis and treatment of anemias.	For *in vitro* diagnostic use in the quantitative determination of folate in serum or red blood cells using the ADVIA Centaur system.
Instrument	Atellica IM	ADVIA Centaur
Measurement	Quantitative	Same
Methodology	Chemiluminescence	Same
Assay Protocol	Competitive immunoassay	Same
Traceability/ Standardization	Internal standards. Values have been assigned to correlate to the Predicate device.	Same
Specimen Type	Human Serum, Red Blood Cells (RBC)	Same
Lower Limit of Measuring Range	LoQ	Analytical Sensitivity
Sample Volume	100 µL	150 µL
Reagents	Lite Reagent: Folate labeled with acridinium ester (~9.8 ng/mL) in Buffer; bovine serum albumin; sodium azide (0,1%) and preservatives. Solid Phase Reagent: Buffered avidin (~20 µg/mL) covalently coupled to paramagnetic particles in buffer; human serum albumin and preservatives. Folate Binding Protein: Purified folate binding protein (~1.0 µg/mL) covalently coupled to biotin in buffer; bovine serum albumin and preservatives	Same
Measuring Range	Serum: 0.56 – 24 ng/mL RBC: 0.98 – 17.51 ng/mL	0.35 – 24 ng/mL 0.35 – 24 ng/mL
Calibration	2-point calibration	Same

9. Standard/Guidance Document References

The following recognized standards from Clinical Laboratory Standards Institute (CLSI) were used as a basis of the study procedures described in this submission:

- § Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition (CLSI EP05-A3, 2014; Recognition Number 7-251)
- § Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (CLSI EP06-A, 2003; Recognition Number 7-193)
- § Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition (CLSI EP07-A2, 2005; Recognition Number 7-127)
- § Measurement Procedure Comparison And Bias Estimation Using Patient Samples -- Third Edition (CLSI EP9-A3, 2013; Recognition Number 7-245)
- § Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline -- Second Edition (CLSI EP17-A2, 2013; Recognition Number 7-233)
- § Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition (CLSI EP28-A3c – formerly C28-A3c, 2010; Recognition Number 7-224)
- § Medical devices – Application of risk management to medical devices (ANSI/AAMI/ISO 14971:2007/(R)2010; Recognition Number 5-70)

10. Performance Characteristics

10.1 Precision

A 20-day precision study was performed according to CLSI EP5-A3. Four human serum and five whole blood samples and two levels of controls were tested.

		Mean		Repeatability			Within-Lab		
				SD[b]		CV[c]	SD		CV
Sample	N[a]	(ng/mL)	(nmol/L)	(ng/mL)	(nmol/L)	(%)	(ng/mL)	(nmol/L)	(%)
Serum Control 1	80	2.82	6.39	0.09	0.20	3.3	0.17	0.39	6.1
Serum Control 2	80	5.43	12.30	0.14	0.32	2.5	0.35	0.79	6.4
Serum 1	80	1.42	3.22	0.05	0.11	N/A[d]	0.08	0.18	N/A
Serum 2	80	4.13	9.35	0.10	0.23	2.4	0.24	0.54	5.9
Serum 3	80	6.19	14.02	0.18	0.41	2.9	0.36	0.82	5.9
Serum 4	80	9.23	20.91	0.24	0.54	2.6	0.60	1.36	6.5
Whole Blood Sample 1	80	94.89	214.93	4.56	10.33	N/A	6.55	14.84	N/A
Whole Blood Sample 2	80	153.11	346.79	4.40	9.97	2.9	11.21	25.39	7.3
Whole Blood Sample 3	80	362.58	821.24	9.82	22.24	2.7	19.99	45.28	5.5
Whole Blood Sample 4	80	563.94	1277.32	19.34	43.81	3.4	35.18	79.68	6.2
Whole Blood Sample 5	80	899.24	2036.78	45.66	103.42	5.1	62.92	142.51	7.0
Whole Blood Control 1	80	77.24	174.95	2.68	6.07	N/A	5.48	12.41	N/A
Whole Blood Control 2	80	257.52	583.28	6.51	14.75	2.5	16.84	38.14	6.5

a Number of samples tested
b Standard deviation
c Coefficient of variation
d Not applicable; there is no CV requirement at these concentrations

10.2 Linearity

Serum:
A linearity study was performed according to CLSI EP06-A using 9 samples spanning the assay range, which were prepared using high and low human serum pools. The mean was taken from each sample tested in triplicate. As presented below, the bias from the linear fit estimate was <10%. The assay is linear from 0.56 to 24 ng/mL.

Sample	Expected Dose (ng/mL)	Observed Dose (ng/mL)	Recovery (Observed vs Expected)	Linear Fit Estimate	Deviation from Linear Fit (%)	Deviation from Linear Fit (ng/mL)
A	0.46	0.46	100%	0.21	116.71	0.25
B	1.26	1.12	89%	0.98	13.93	0.14
C	2.05	1.81	88%	1.75	3.38	0.06
D	2.84	2.57	90%	2.52	1.99	0.05
E	3.63	3.63	100%	3.29	10.44	0.34
F	8.83	7.99	90%	8.34	-4.17	-0.35
G	14.03	12.28	87%	13.38	-8.27	-1.11
H	19.24	18.09	94%	18.43	-1.85	-0.34
I	24.44	24.44	100%	23.48	4.07	0.96

The weighted linear regression equation is presented below.

Observed = 0.971(Expected) – 0.237 ng/mL

RBC:
A linearity study was performed according to CLSI EP06-A using 11 samples spanning the assay range. Using a previously cleared red blood cell Folate device's values as expected values when analyzing the results obtained from the Atellica IM rFOL method results in a linear relationship between the measuring interval 0.98 to 17.51 ng/mL.

Sample	Expected Dose (ng/mL)	Observed Dose (ng/mL)	Recovery (Observed vs Expected)	Linear Fit Estimate	Deviation from Linear Fit (%)	Deviation from Linear Fit (ng/mL)
P01	0.98	1.37	139%	1.50	-8.7%	0.13
P02	6.73	7.38	110%	6.77	9.0%	-0.61
P03	9.58	9.82	103%	9.38	4.7%	-0.44
P04	11.49	11.06	96%	11.13	-0.6%	0.07
P05	12.81	11.60	91%	12.34	-6.0%	0.74
P06	13.82	12.07	87%	13.27	-9.1%	1.21
P07	14.96	14.03	94%	14.32	-2.0%	0.29
P08	15.28	14.99	98%	14.61	2.6%	-0.39
P09	16.05	15.46	96%	15.31	1.0%	-0.15
P10	16.63	15.89	96%	15.85	0.3%	-0.04
P11	17.51	17.45	100%	16.65	4.8%	-0.80

The linear regression equation is presented below.

Observed = 0.917(Expected) – 0.596 ng/mL

10.3 Dilution Recovery

Five human serum samples were diluted 1:2 using Atellica IM Folate diluent and assayed for recovery. All samples were run in triplicate. The recoveries ranged from 102.6%–110.0% with a mean of 105.4%.

10.4 Spiking Recovery

Five samples were created by adding a fixed volume of Folate stock solution into human serum pools. Five control samples were created by pipetting an equal volume of DI H2O into each of the patient sample control for dilution. The percent recovery was calculated with Observed concentration vs. Expected concentration. The recoveries ranged from 87%–116% with a mean of 104%.

10.5 Method Comparison

Method Comparison studies were done with 105 human serum and 100 human whole blood samples distributed over the assay range to demonstrate equivalence to the Predicate (ADVIA Centaur Folate). The Atellica IM Folate assay shows good correlation in sample results compared to the Predicate. The regression equations from the analysis are presented below.

Atellica IM FOL (y) vs ADVIA Centaur FOL (x) (Weighted Deming regression):

Specimen Type	Comparison Assay (x)	N	r	Regression Equation	Sample Range
Serum	ADVIA Centaur FOL	105	0.99	y = 0.94x - 0.01 ng/mL	0.64–22.78 ng/mL
RBC hemolysate	ADVIA Centaur FOL	100	0.93	y = 1.06x – 2.52 ng/mL	229.66-2264.56 ng/mL

10.6 Collection Tube Comparison

Specimen equivalency was determined using weighted Deming linear regression in accordance to CLSI Document EP09-A3. The following results were obtained:

Specimen (y)	Reference Specimen (x)	Regression Equation	Sample Interval	N
K2 EDTA, Whole Blood	Lithium Heparin Whole Blood	y = 1.02x – 32.86 ng/mL	432.70 - 1103.69 ng/mL	90

10.7 Reference Intervals

Reference intervals for the Atellica IM Folate assay were verified to confirm the already established ranges on ADVIA Centaur Assay according to CLSI EP28-A3c. A total of 30 serum and 25 RBC (whole blood with tested percent hematocrit) samples from apparently healthy individuals were analyzed. Based on a 95% confidence interval, the following reference intervals were verified.

Category	N	Median (ng/mL)	95th Percentile Range (ng/mL)
Serum folate			
Normal	305	12.51	> 5.38
RBC folate			
Normal	286	425	280 - 791

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference interval for the diagnostic evaluation of patient results.

10.8 Detection Limits

The limit of blank (LoB), limit of detection (LoD), and the limit of quantitation (LoQ) were determined as described in CLSI protocol EP17-A2. The LoB is defined as the highest measurement result that is likely to be observed for a blank sample. The LoD is defined as the lowest concentration of Folate that can be detected with 95% probability. The LoQ is defined as the lowest concentration of Folate that can be detected at a total CV of 20%.

The Atellica IM Folate assay has an LoB of 0.19 ng/mL, an LoD of 0.38 ng/mL, and an LoQ of 0.56 ng/mL for serum and an LoB of 0.00 ng/mL, an LoD of 0.21 ng/mL, and an LoQ of 0.56 ng/mL for RBC hemolysate.

10.9 Interference

Interference studies were performed according to CLSI EP07-A2 to evaluate the performance of the Atellica IM Folate assay in the presence of endogenous and other interfering substances. Two human sample pools were tested. One sample pool had approximately 4.0 ng/mL Folate. The second sample pool had approximately 12.0 ng/mL Folate. These sample pools were spiked with potential interferents. There was no indication

of interference (< 10% effect) up to the interferent levels claimed. Results are presented below.

	Interferent	Concentrations Showing no Significant Interference
Endogenous	Conjugated Bilirubin	20 mg/dL
	Lipemia (intralipid)	2000 mg/dL
	Unconjugated Bilirubin	20 mg/dL
	Biotin, serum	50 ng/mL
	Biotin, whole blood	75 ng/mL
Exogenous	Acetaminophen	200 mg/dL
	Acetylsalicylic Acid	1000 mg/dL
	Ibuprofen	50 mg/dL
	Acetylcysteine	566 mg/dL
	Ampicillin-Na	1000 mg/dL
	Cefoxitin	660 mg/dL
	Cyclosporine	5 mg/dL
	Doxycyclin	50 mg/dL
	Levodopa	20 mg/dL
	Methyldopa	20 mg/dL
	Metronidazole	200 mg/dL
	Phenylbutazone	40 mg/dL
	Rifampicin	60 mg/dL
	Theophylline	10 mg/dL
	Ascorbic Acid	44 mg/dL

10.10 Cross-Reactivity

Cross reactivity was evaluated in the Atellica IM Folate immunoassay using a normal human serum sample and blank assay diluent for each test compound. An aliquot of each sample was spiked with test compound so that the final test sample contained the compound at the required concentration. A second aliquot of the base pool is spiked with just the diluent to serve as a control sample. Multiple replicates of the test and control samples were processed. Cross-reactivity was calculated as the % difference between the mean test and control sample results, with respect to the test compound concentration. Results are presented below.

Cross-Reactant	Cross-Reactant Concentration (ng/mL)	Maximum Observed Cross-Reactivity (%)
Amethopterin	150	≤2%
Aminopterin	75	≤1%
Folinic Acid	25	≤4%

10.11 Traceability and Stability

Traceability

The Atellica IM FoI assay is traceable to an internal standard manufactured using highly purified material (N-5-methyl tetrahydrofolate). Assigned values for calibrators are traceable to this standardization.

Stability

Shelf-life:
Unopened Atellica IM Folate reagents and calibrators are stable until expiration date printed on the carton when stored at 2-8 °C.

On-board:
The onboard stability of the Atellica IM Folate reagents is 14 days with a pack calibration interval of 7 days, and a lot calibration interval of 14 days.

10.12 Proposed Labeling

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

11. Conclusion

Based on the results of comparative testing, the new Atellica IM Folate assay is substantially equivalent in principle and performance to the currently-marketed predicate device, the ADVIA Centaur Folate assay, cleared under 510(k) k010050.