DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

AXIS-SHIELD DIAGNOSTICS LIMITED
CLAIRE DORA
REGULATORY AFFAIRS MANAGER
THE TECHNOLOGY PARK
LUNA PLACE
DUNDEE DD2 1XA
Great Britain

July 26, 2016

Re: K160757
Trade/Device Name: ADVIA Centaur Active-B12 (Holotranscobalamin) (AB12) Assay,
ADVIA Centaur Active-B12 (AB12) Quality Control,
ADVIA Centaur Active-B12 (AB12) Master Curve Materials (MCM)
Regulation Number: 21 CFR 862.1810
Regulation Name: Vitamin B12 test System
Regulatory Class: II
Product Code: CDD, JJX
Dated: June 23, 2016
Received: June 27, 2016

Dear Claire Dora:

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 Parts 801 and 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.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney C. 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)*
K160757

Device Name
ADVIA Centaur® Active-B12 (Holotranscobalamin)(AB12) assay
ADVIA Centaur® Active-B12 (AB12) Quality Control
ADVIA Centaur® Active-B12 (AB12) Master Curve Material (MCM).

Indications for Use *(Describe)*

The ADVIA Centaur® Active-B12 (Holotranscobalamin)(AB12) assay is for in vitro diagnostic use in the quantitative measurement of holotranscobalamin (holoTC) in human serum using the ADVIA Centaur XP system. Active-B12 (holotranscobalamin) is used as an aid in the diagnosis and treatment of vitamin B12 deficiency.

Quality Control
The ADVIA Centaur® Active-B12 (AB12) quality control is for in vitro diagnostic use to monitor the precision and accuracy of the ADVIA Centaur AB12 (Holotranscobalamin) assay using the ADVIA Centaur systems.

Master Curve Material (MCM)
The ADVIA Centaur® Active-B12 (AB12) Master Curve Material (MCM) is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur AB12 (Holotranscobalamin) assay using the ADVIA Centaur systems.

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

The assigned 510(k) number is k160757

Submission correspondent:

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510k summary prepared date: 22nd July 2016

Device Name:
ADVIA Centaur® Active-B12 (Holotranscobalamin) (AB12) Assay
Quality Control
Master Curve Material (MCM)

Reagents:
Classification Name: Vitamin B12 test system
Trade Name ADVIA Centaur® Active-B12 (Holotranscobalamin) (AB12) assay
Common Name: B12 test
Governing Regulation: 21CFR 862.1810
Device Classification: Class II
Classification Panel: Clinical Chemistry
Product Code: CDD

Quality Control:
Classification Name: Single (Specified) Analyte Control
Trade Name: ADVIA Centaur® Active-B12 (AB12) quality control material
Common Name: Control
Governing Regulation: 862.1660
Device Classification: Class I, reserved
Classification Panel: Clinical Chemistry
Product Code: JJX

Master Curve Material:

Classification Name: Single (Specified) Analyte Control
Trade Name: ADVIA Centaur® Active-B12 (AB12) Master Curve Material (MCM)
Common Name: Control
Governing Regulation: 862.1660
Device Classification: Class I, reserved
Classification Panel: Clinical Chemistry
Product Code: JJX

Legally marketed device to which equivalency is claimed:

ARCHITECT Active-B12 (Holotranscobalamin) Assay (K112443)

Intended Use of Device:

The ADVIA Centaur® Active-B12 (Holotranscobalamin) (AB12) assay is for in vitro diagnostic use in the quantitative measurement of holotranscobalamin (holoTC) in human serum using the ADVIA Centaur XP system. Active-B12 (holotranscobalamin) is used as an aid in the diagnosis and treatment of vitamin B12 deficiency.

Quality Control
The ADVIA Centaur® Active-B12 (AB12) quality control is for in vitro diagnostic use to monitor the precision and accuracy of the ADVIA Centaur AB12 (Holotranscobalamin) assay using the ADVIA Centaur systems.

Master Curve Material (MCM)
The ADVIA Centaur® Active-B12 (AB12) Master Curve Material (MCM) is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur AB12 (Holotranscobalamin) assay using the ADVIA Centaur systems.

Description of Device:

The ADVIA Centaur AB12 assay is a fully automated, two-step direct immunoassay using chemiluminescent technology. The assay utilizes an acridinium ester-labeled anti-transcobalamin antibody as the Lite Reagent. The Solid Phase consists of biotinylated anti-holotranscobalamin antibody coupled to streptavidin-coated magnetic latex microparticles.

Comparison of Technological Characteristics:

The ADVIA Centaur AB12 assay and the ARCHITECT Active-B12 are both automated immunoassays for the quantitative measurement of holotranscobalamin (holoTC) in human serum.

The ADVIA Centaur System and ARCHITECT i System share similar detection methods both utilizing chemiluminescent microparticle immunoassay (CMIA) technology.
Both assays also demonstrated substantial equivalence in terms antibodies employed, detection method and the units of measure.

Comparison of the subject device with the predicate device:

Similarities

Parameter	ADVIA Centaur®AB12	ARCHITECT Active-B12
Intended use	For *in vitro* diagnostic use in the quantitative measurement of holotranscobalamin (holoTC) in human serum using the ADVIA Centaur XP system. Active-B12 (holotranscobalamin) is used as an aid in the diagnosis and treatment of vitamin B12 deficiency.	For the quantitative determination of Holotranscobalamin in human serum on the ARCHITECT *i* System. Active-B12 (Holotranscobalamin) is used as an aid in the diagnosis and treatment of vitamin B12 deficiency.
Assay Technology	Chemiluminescent microparticle immunoassay (CMIA)	Chemiluminescent microparticle immunoassay (CMIA)
Substrate / Signal Generation	Acridinium Tracer	Acridinium Tracer
Specimen type	Serum and Serum Separator	Serum and Serum Separator
Conjugate antibody	Murine monoclonal antibody 3-11	Murine monoclonal antibody 3-11
Storage conditions	Reagent Pack must be stored at 2-8ºC.	Reagent Pack must be stored at 2-8ºC.
Unit of Measure	pmol/L	pmol/L
Cross- Reactivity	≤ 10% with; Apotranscobalamin (500 pmol/L) Haptocorrin (5000 pmol/L)	≤ 10% with; Apotranscobalamin (500 pmol/L) Haptocorrin (5000 pmol/L)
Assay dilution protocol	1:2 autodilute with ADVIA Centaur Multi-Diluent 13	1:2 autodilute or manual with ARCHITECT *i* Multi-Assay manual diluent
Sensitivity	Limit of Quantitation of ≤ 5.0 pmol/L	Limit of Quantitation of ≤ 5.0 pmol/L

Differences

Parameter	ADVIA Centaur®AB12	ARCHITECT Active-B12
Calibration	2-point Calibration using 2 level calibrators	6-point calibration curve. 4PLC Y-weighted
Expected Values in Asymptomatic Population	The mean holoTC concentration for the group was established at 81.91 pmol/L with a 95% central reference interval from 28.96 to 168.90 pmol/L	The mean Holotranscobalamin concentration was 71.9 pmol/L with a range from 20.6 to 196.7 pmol/L. The central 95% of the population defined the expected range of 25.1 to 165.0 pmol/L
Imprecision	Within-Laboratory (Total) %CV ≤ 4.7% Within-run %CV ≤ 3.2%	Total %CV ≤ 5.8% Within-run %CV ≤ 4.4%
Interference	≤ 10% with; Bilirubin at 40 mg/dL Unconjugated bilirubin at 60 mg/dL Haemoglobin at 500 mg/dL Triglyceride at 1000 mg/dL Rheumatoid Factor at 200 IU/mL Total protein at 12 g/dL Biotin at 100 mg/dL Human IgG at 12 g/dL Cholesterol at 500 mg/dL Silwet L720 at 0.2 mg/dL Methotrexate at 91 mg/dL Perimethamine at 75 µg/mL	≤ 10% with; Bilirubin at 20 mg/dL Haemoglobin at 200 mg/dL Triglycerides at 850 mg/dL Rheumatoid Factor at 70 IU/mL Total protein at 10 g/dL
Cross- Reactivity	No detectable cross-reactivity with; Apotranscobalamin at 500 pmol/L Haptocorrin at 5000 pmol/L	No detectable carryover with; Apotranscobalamin at 500 pmol/L Haptocorrin at 5000 pmol/L
Measurable Range	5.0 to 146.0 pmol/L	5.0 to 128.0 pmol/L
Calibration Range	0 to 146.0 pmol/L	0 to 128.0 pmol/L
Linearity	5.0 to 146.0 pmol/L	5.0 to 128.0 pmol/L
On-board Reagent Stability	Reagents can be stored onboard the Centaur XP instrument for a maximum of 44 days.	Reagents can be stored onboard the ARCHITECT instrument for a maximum of 30 days.
Calibration Frequency	44 days	30 days
Sample Stability	Separated specimens are stable for 16 hours at room temperature, 3 days at 2-8ºC For longer storage, specimens may be frozen for 3 months at -20 ºC or colder. Avoid more than 1 freeze/thaw cycle. Do not store in a frost-free freezer	Up to 16 hours at room temperature Up to 3 days at 2-8ºC (for longer than 3 days store at -20ºC or colder for up to 6 months). Avoid more than 3 freeze-thaw cycles.

Summary of Non-Clinical Performance:

The ADVIA Centaur AB12 assay demonstrated substantially equivalent performance to the ARCHITECT Active-B12 assay. A summary of the non-clinical performance data included in this 510(k) submission has been presented.

Linearity

Linearity was evaluated according to the CLSI protocol EP6-A.Two samples containing high levels of active-B12 were mixed with a pool of artificial serum matrix. The resulting sample mixtures were assayed for active-B12. The ADVIA Centaur AB12 assay is linear from 5.00-146.00 pmol/L.

Dilution Linearity

Five samples containing high levels of active-B12 (96.64–135.51 pmol/L) were diluted 1:2 (1 part sample plus 1 part diluent) with Multi-Diluent 13 and assayed for recovery and parallelism correcting the diluted sample by the dilution factor. Representative data from the study is shown below.

Sample	Dilution	Observed (pmol/L)	Expected (pmol/L)	Recovery %
Sample 1	1:2	91.41	96.64	94.59
Sample 2	1:2	112.61	114.20	98.61
Sample 3	1:2	126.19	135.51	93.12
Sample 4	1:2	110.09	121.17	90.86
Sample 5	1:2	121.29	132.63	91.45

Measuring Interval

The ADVIA Centaur AB12 assay measures active-B12concentrations from 5.00-146.00 pmol/L.

Detection Capability

The limit of blank (LoB), limit of detection (LoD), and the limit of quantitation (LoQ) were determined as described in CLSI Document EP17-A2. The ADVIA Centaur AB12 assay has an LoB of 0.74 pmol/L, an LoD of 1.08 pmol/L and an LoQ of 5.00 pmol/L.

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 active-B12 that can be detected with 95% probability. The LoQ is defined as the lowest concentration of active-B12 that can be detected at a total CV of 8%.

High Dose Hook

Patient samples with high active-B12 levels can cause a paradoxical decrease in the Relative Light Units (RLUs) (high-dose hook effect). In the ADVIA Centaur AB12 assay, patient samples with active-B12 levels as high as 1867.80 pmol/L are not subject to a hook effect and will assay greater than 146.00 pmol/L.

Cross-reactivity

Cross-reactivity was tested in the presence and absence of active-B12 according to CLSI EP7-A2 using the ADVIA Centaur AB12 assay. Populations evaluated in the study included other B12 proteins apotranscobalamin and haptocorrin. Percent cross-reactivity is calculated as:

$$\% \text{ cross-reactivity} = \frac{\text{concentration of spiked sample - concentration of unspiked sample}}{\text{concentration of cross-reactant}} \times 100$$

The following results were obtained:

Cross-reactant	Concentration (pmol/L)	Cross-reactivity (%)
Apotranscobalamin	250	0.2
	500	-0.1
Haptocorrin	2500	-0.4
	5000	-0.4

Interference

Potential interference in the ADVIA Centaur AB12 assay is designed to be less than or equal to 10%. Interfering substances at the levels indicated in the table below were tested as described in CLSI Document EP7-A2 using the ADVIA Centaur AB12 assay.

Endogenous and exogenous potential interferents	Highest concentration at which no significant interference (≤10%) was observed
*Biotin	100 mg/dL
Cholesterol	500 mg/dL
Conjugated Bilirubin	40 mg/dL
Hemoglobin	500 mg/dL
Human IgG	12 g/dL
Methotrexate	91 mg/dL
Perimethamine	75 µg/mL
Rheumatoid Factor	200 IU/mL
Silwet L720	0.2 mg/dL
Total Protein	12 g/dL
Unconjugated Bilirubin	60 mg/dL

Endogenous and exogenous potential interferents	Highest concentration at which no significant interference (≤10%) was observed
Triglyceride	1000 mg/dL

Precision

Precision was evaluated according to the CLSI protocol EP5-A2.
Five serum precision panel members were prepared with active-B12 concentrations spanning the measuring interval. Each sample was tested in replicates of 2 in two runs per day over 20 days. One ADVIA Centaur XP system was used and 2 reagent lots giving a total of 80 observations per sample for each reagent lot. Representative data from the study is shown in the following table.

A summary of the imprecision data is summarized below:

			Repeatability		Within-Lab	
Specimen	N	Mean (pmol/L)	SD (pmol/L)	CV (%)	SD (pmol/L)	CV (%)
Sample 1	80	16.82	0.30	1.8	0.79	4.7
Sample 2	80	38.12	1.12	2.9	1.66	4.4
Sample 3	80	74.24	1.64	2.2	3.06	4.1
Sample 4	80	104.76	1.92	1.8	4.16	4.0
Sample 5	80	123.10	3.92	3.2	5.61	4.6

Summary of Clinical Performance:

The ADVIA Centaur AB12 assay demonstrated substantially equivalent performance to the ARCHITECT Active-B12 assay as indicated by method comparison and reference range studies.

Method Comparison

For 104 serum samples in the range of 5.56 – 142.58 pmol/L, the relationship of the ADVIA Centaur AB12 assay (y) and the Abbott ARCHITECT Chemiluminescent Microparticle Immunoassay (CMIA) Active-B12 (Holotranscobalamin) assay (x) is described using Passing-Bablok regression. Representative data from the study is shown below:

ADVIA Centaur AB12 = 0.97 (CMIA) - 0.99 pmol/L (intercept), r = 0.95.

Expected Values

The ADVIA Centaur AB12 assay results were obtained on 241 apparently healthy males (n = 103) and females (n = 138). The age range was 21 - 67 years. The mean holoTC concentration for the group was established at 81.91 pmol/L with a 95% central reference interval from 28.96–168.90 pmol/L according to EP28-A3c.

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results. Consider these values as guidelines only.

Conclusion

The results presented in this 510(k) premarket submission demonstrate that the candidate assay (ADVIA Centaur® Active-B12 (Holotranscobalamin)(AB12) assay, K160757) performance is substantially equivalent to the predicate assay (ARCHITECT Active-B12 (Holotranscobalamin) assay,K112443).

The similarities and differences between the candidate assay and the predicate assay are presented in the tables starting on page 3/8.