



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

August 4, 2016

Axis-Shield Diagnostics Ltd
Dr. Claire L. Dora
Regulatory Affairs Manager
The Technology Park, Luna Place
Dundee, DD2 1XA, UK

Re: K153551

Trade/Device Name: ADVIA Centaur® Anti-CCP IgG (aCCP) Assay
ADVIA Centaur® Anti-CCP IgG (aCCP) Quality Controls
ADVIA Centaur® Anti-CCP IgG (aCCP) Master Curve Materials

Regulation Number: 21 CFR 866.5775

Regulation Name: Rheumatoid Factor Immunological Test System

Regulatory Class: II

Product Code: NHX, JJX

Dated: July 18, 2016

Received: July 19, 2016

Dear Dr. 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,

Kelly Oliner -S

FOR
Leonthena R. Carrington, MS, MBA, MT(ASCP)
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known)
K153551

Device Name

ADVIA Centaur® anti-CCP IgG (aCCP) Assay
ADVIA Centaur® anti-CCP IgG (aCCP) Quality Control
ADVIA Centaur® anti-CCP IgG (aCCP) Master Curve Material (MCM)

Indications for Use (Describe)

The ADVIA Centaur® anti-CCP IgG (aCCP) assay is for in vitro diagnostic use in the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma (K2-EDTA and lithium heparin) using the ADVIA Centaur XP system. Detection of anti-CCP antibodies is used as an aid in the diagnosis of Rheumatoid Arthritis (RA) and should be used in conjunction with other clinical information. Autoantibody levels represent one parameter in a multi-criteria diagnostic process, encompassing both clinical and laboratory-based assessments.

Quality Control:

The ADVIA Centaur® Anti-CCP IgG (aCCP) quality control material is for in vitro diagnostic use to monitor the precision and accuracy of the ADVIA Centaur aCCP assay using the ADVIA Centaur systems.

Master Curve Material (MCM):

The ADVIA Centaur® Anti-CCP IgG (aCCP) Master Curve Material (MCM) is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur aCCP assay.

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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

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: K153551.

Submission correspondent:

Dr Claire Dora
Regulatory Affairs Manager
Axis-Shield Diagnostics Ltd.
The Technology Park
Dundee
DD2 1XA,
Scotland, UK

Device Name:

ADVIA Centaur® anti-CCP IgG (aCCP) assay
ADVIA Centaur® anti-CCP IgG (aCCP) Quality Control
ADVIA Centaur® anti-CCP IgG (aCCP) Master Curve Material (MCM)

Reagents:

Classification Name: Antibodies, ANTI-CYCLIC CITRULLINATED PEPTIDE (CCP)
Trade Name: ADVIA Centaur® anti-CCP IgG (aCCP) assay
Common Name: Anti-CCP test
Governing Regulation: 866.5775
Device Classification: Class II
Classification Panel: Immunology
Product Code: NHX

Quality Control:

Classification Name: Single (Specified) Analyte Control
Trade Name: ADVIA Centaur® anti-CCP IgG (aCCP) quality control material
Common Name: Control
Governing Regulation: 862.1660
Device Classification: Class I
Classification Panel: Clinical Chemistry
Product Code: JJX

Master Curve Materials:

Classification Name: Single (Specified) Analyte Control
Trade Name: ADVIA Centaur® anti-CCP IgG (aCCP) Master Curve Material (MCM)
Common Name: Control
Governing Regulation: 862.1660
Device Classification: Class I
Classification Panel: Clinical Chemistry
Product Code: JJX

Legally marketed device to which equivalency is claimed:

ARCHITECT Anti-CCP Assay (K083868)

Intended Use of Device:

The ADVIA Centaur® anti-CCP IgG (aCCP) assay is for in vitro diagnostic use in the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma (K2-EDTA and lithium heparin) using the ADVIA Centaur XP system. Detection of anti-CCP antibodies is used as an aid in the diagnosis of Rheumatoid Arthritis (RA) and should be used in conjunction with other clinical information. Autoantibody levels represent one parameter in a multi-criteria diagnostic process, encompassing both clinical and laboratory-based assessments.

Quality Control:

The ADVIA Centaur® Anti-CCP IgG (aCCP) quality control material is for in vitro diagnostic use to monitor the precision and accuracy of the ADVIA Centaur aCCP assay using the ADVIA Centaur systems.

Master Curve Material (MCM):

The ADVIA Centaur® Anti-CCP IgG (aCCP) Master Curve Material (MCM) is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur aCCP assay.

Description of Device:

The ADVIA Centaur aCCP assay is a fully automated, two-step immunoassay using chemiluminescent technology. The assay utilizes an acridinium ester-labeled anti-human IgG as the Lite Reagent. The Solid Phase consists of biotinylated CCP coupled to streptavidin which is then coated onto magnetic latex microparticles.

Comparison of Technological Characteristics:

The ADVIA Centaur aCCP assay and the ARCHITECT Anti-CCP are both automated immunoassays for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma. 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 and units of measure.

Comparison of the subject device with the predicate device:

Similarities		
Parameter	Submission device ADVIA Centaur® aCCP	Predicate device ARCHITECT Anti-CCP
Intended use	Intended for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma using the ADVIA Centaur XP system. Detection of anti-CCP antibodies is used as an aid in the diagnosis of Rheumatoid Arthritis (RA) and should be used in conjunction with other clinical information. Autoantibody levels represent one parameter in a multi-criteria diagnostic process, encompassing both clinical and laboratory-based assessments.	Intended for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma on the ARCHITECT <i>i</i> System. Detection of anti-CCP antibodies is used as an aid in the diagnosis of Rheumatoid Arthritis (RA) and should be used in conjunction with other clinical information. Autoantibody levels represent one parameter in a multicriterion diagnostic process, encompassing both clinical and laboratory-based assessments.
Assay Technology	Automated. Chemiluminescent Microparticle Immunoassay (CMIA)	Automated. Chemiluminescent Microparticle Immunoassay (CMIA)
Substrate / Signal Generation	Acridinium Tracer	Acridinium Tracer
Specimen type	Human serum and serum separator tubes. Human plasma collected in lithium heparin and potassium EDTA tubes	Human serum and serum separator tubes. Human plasma collected in lithium heparin and potassium EDTA tubes
Capture antibody	Cyclic citrullinated peptide (CCP), second generation.	Cyclic citrullinated peptide (CCP), second generation.
Conjugate antibody	Mouse anti-human IgG: acridinium-labeled.	Mouse anti-human IgG: acridinium-labeled.
Storage conditions	Intended Storage of 2-8 °C.	Intended Storage of 2-8 °C.
Calibrator Range	0.0-200.0 U/mL	0.0-200.0 U/mL
Suggested Cut-Off	5.0 U/mL	5.0 U/mL
Interference	No interference from Total Protein (12 g/dL) Rheumatoid Factor (200 IU/mL)	No interference from Total Protein (12 g/dL) Rheumatoid Factor (200 IU/mL)
Cross- Reactivity	No significant cross-reactivity of the CCP antigen with any of these other autoantibodies (SSA, SSB, Sm, RNP, Scl-70, TPO, Jo-1, ds-DNA, and Ribosomal P).	No significant cross-reactivity of the CCP antigen with any of these other autoantibodies (SSA, SSB, Sm, RNP, Scl-70, TPO, Jo-1, ds-DNA, and Ribosomal P).
Assay dilution protocol	Manual-dilution (1:10)	Manual-dilution (1:10)

Similarities		
Parameter	Submission device ADVIA Centaur® aCCP	Predicate device ARCHITECT Anti-CCP
Sample Stability	Separated specimens are stable for up to 22 hours at room temperature or up to 7 days at 2-8 °C. Avoid more than 2 freeze-thaw cycles.	Specimens may be stored for up to 7 days at 2-8°C or 22 hours at 30°C after the date of collection. For longer storage, store specimens at -20°C or colder. Avoid more than three freeze/thaw cycles.

Differences		
Parameter	Submission device ADVIA Centaur® Anti-CCP	Predicate device ARCHITECT Anti-CCP
Calibration	Semi-quantitative assay. 10-point master calibration curve (4PL, Y-weighted) generated and stored on the lot-specific aCCP master curve card. The ADVIA Centaur aCCP assay utilizes a 2-point operator-initiated calibration. The assay calibration covers 0 to 200 U/mL	Semi-quantitative assay. 6-point calibration curve (4PLC, Y-weighted) generated and stored on the instrument. The ARCHITECT Anti-CCP Standard Calibrators A-F (0.0, 5.0, 25.0, 50.0, 100.0, 200.0 U/mL)
Expected Values in Asymptomatic Population	The median was established at 0.74 U/mL. (Mean 95% Confidence Limits of 0.25 -1.87 U/mL) in a representative study	Specimen values ranged from < 0.5 U/mL to 2.5 U/mL in a representative study
Imprecision	Within-Lab % CV was designed to be < /= 7.0% for CCP concentrations < 50.00 U/mL and < /=10% for levels >= 50 U/mL. Within Lab %CV ranged from 3.0 to 4.3% from 2.37 to 111.53 U/mL.	Within-run CV of 2.0% to 4.7% and total CV of 2.8 to 7.7% from 2.7 to 195.3 U/mL.
Assay dilution protocol	No auto-dilution capabilities. Manual dilution only (1:10)	Auto-dilution (1:6)
Sensitivity	Limit of Detection ≤ 0.40 U/mL	Limit of Detection ≤ 0.5 U/mL
Interference	No interference from: Biotin (500 ng/dL) Bilirubin – Conj & unconj (40 mg/dL) Haemoglobin (1000 mg/dL) Triglycerides (2450 mg/dL) Intralipid (1500 mg/dL) Caprine IgG (6 g/dL) HAAA	No interference from Bilirubin (20 mg/dL) Red blood cells (0.4%) Haemoglobin (800 mg/dL) Triglycerides (3000 mg/dL)
Cross- Reactivity	No significant cross-reactivity of the CCP antigen with any of these other autoantibodies (M2, Chromatin).	No significant cross-reactivity of the CCP antigen with any of these other autoantibodies (ANA, AMA).
Measurable Range	0.40 – 200.0 U/mL	0.5 – 200.0 U/mL
On-board Reagent Stability	Reagents can be stored on-board for a maximum of 60 days	Reagents can be stored on-board for a maximum of 30 days

Summary of Non-Clinical Performance:

The ADVIA Centaur aCCP assay demonstrated substantially equivalent performance to the ARCHITECT Anti-CCP 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. Three samples containing high levels of anti-CCP IgG were mixed with a pool of negative serum. The resulting sample mixtures were assayed for anti-CCP IgG. The ADVIA Centaur aCCP assay is linear from 0.40-200.00 U/mL.

Dilution Linearity

Two samples containing high levels of anti-CCP IgG (140.63 and 180.08 U/mL) were diluted 1:10 (1 part sample plus 9 parts diluent) with Multi-Diluent 1 and assayed for recovery and parallelism. Representative data from the study is shown below.

Sample	Dilution	Observed (U/mL)	Expected (U/mL)	Recovery %
1	-	140.63		
	1:10	151.70	14.06	107.87
2	-	180.08		
	1:10	190.20	18.01	105.62

Measuring Interval

The ADVIA Centaur aCCP assay measures anti-CCP IgG concentrations from 0.40-200.0 U/mL.

Detection Capability

The ADVIA Centaur aCCP assay is designed to have a Limit of Detection (LoD) of less than 1.50 U/mL. The LoD was determined as described in CLSI Document EP17-A2.

The LoD is defined as the lowest concentration of anti-CCP IgG that can be detected with greater than or equal to 95% probability. The LoD was determined to be 0.40 U/mL.

High Dose Hook

Patient samples with high anti-CCP IgG levels can cause a paradoxical decrease in the Relative Light Units (RLUs) (high-dose hook effect). In this assay, patient samples with anti-CCP IgG levels as high as 3000.00 U/mL will assay greater than 200.00 U/mL.

Cross-reactivity

Cross-reactivity was tested in the presence and absence of anti-CCP IgG according to CLSI EP7-A2 using the ADVIA Centaur aCCP assay. Populations evaluated in the study included Sm, RNP, SSB, Scl-70, Jo-1, Ribosomal P, M2, TPO, ds-DNA, SSA and Chromatin. The study showed no clinically significant cross-reactivity of the CCP antigen with any of these auto-antibodies.

Interference

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

Serum specimens that are...	Have an insignificant effect on the assay up to ...
hemolyzed	1000 mg/dL of hemoglobin
icteric	40 mg/dL of unconjugated bilirubin
icteric	40 mg/dL of conjugated bilirubin
lipemic	1500 mg/dL of lipemia (Intralipid)
lipemic	2450 mg/dL of triglycerides

The following substances at the levels indicated caused no significant interference in anti-CCP IgG measurement.

Substances	Concentrations
Biotin	500 ng/dL
Caprine IgG ^a	6 g/dL
Total Protein	12 g/dL
Rheumatoid Factor	200 IU/mL

^aCaprine IgG was used to avoid interference with human IgG sensitive to CCP.

Precision

Precision was evaluated according to the CLSI protocol EP5-A2. Assay precision was designed to have Within-Laboratory %CV less than or equal to 7.0% for levels less than 50.00 U/mL and less than or equal to 10% for levels greater than 50.00 U/mL.

Six serum precision panels were prepared with anti-CCP IgG concentrations spanning the measuring interval. Each sample was tested in replicates of 2 in two runs per day over 20 days. One ADVIA Centaur system was used and one reagent lot giving a total of 80 observations per sample. Representative data from the study is shown in the following table.

Specimen Type	N	Mean (U/mL)	Repeatability		Within-Lab	
			SD (U/mL)	CV (%)	SD (U/mL)	CV (%)
Sample 1	80	2.37	0.09	3.9	0.10	4.3
Sample 2	80	3.75	0.12	3.1	0.13	3.6
Sample 3	80	6.73	0.22	3.3	0.25	3.6
Sample 4	80	42.01	1.09	2.6	1.27	3.0
Sample 5	80	55.34	1.73	3.1	2.01	3.6
Sample 6	80	111.53	3.30	3.0	3.64	3.3

Specimen Collection Comparison

The ADVIA Centaur aCCP assay was evaluated using different specimen matrices and collection tube types.

A clinical specimen collection study was performed. Any negative anti-CCP IgG values were excluded. The specimen anti-CCP IgG values ranged from 0.41-180.82 U/mL. Linear regression analysis was performed and no significant difference between tube types was observed. The following results were obtained:

Serum Vs.	n	Slope	Intercept	r
Serum Separator Tube	50	1.01	0.05	1.00
K2-EDTA	51	0.98	0.03	1.00
Lithium heparin	49	1.00	0.11	0.98

Summary of Clinical Performance:

The ADVIA Centaur anti-CCP IgG assay demonstrated substantially equivalent performance to the ARCHITECT Anti-CCP assay as indicated by a clinical concordance and method comparison study.

Method Comparison

253 samples (143 samples confirmed positive for RA, and 110 samples where other auto-antibodies may be present) were tested. The diagnostic concordance between the ADVIA Centaur aCCP and the Abbott ARCHITECT anti-CCP assays is 96.84% (Confidence Interval (CI) 93.89 – 98.39%). The following results were obtained:

ARCHITECT anti-CCP assay			
ADVIA Centaur aCCP assay	Positive	Negative	Total
Positive	121	4	125
Negative	4	124	128
Total	125	128	253

Overall % Agreement (95% Confidence Interval (CI)) 96.84% (93.89-98.39%).
Positive % Agreement (95% Confidence Interval (CI)) 96.80% (92.06-98.75%).
Negative % Agreement (95% Confidence Interval (CI)) 96.88% (92.24-98.78%).

Clinical Sensitivity and Specificity

Clinical sensitivity and specificity were determined using 767 patients samples. The following results were obtained:

ADVIA Centaur aCCP assay	Clinical Diagnosis		
	Positive	Negative	Total
Positive	209	13	222
Negative	98	447	545
Total	307	460	767

Clinical Sensitivity (Exact 95% Confidence Interval (CI)) 68.08% (62.5–73.3%).
Clinical Specificity (Exact 95% Confidence Interval (CI)) 97.17% (95.22–98.49%).

The sensitivity assessment of the ADVIA Centaur aCCP assay was conducted on 307 confirmed-positive RA subjects that were classified according to the American College of Rheumatology criteria.

The specificity assessment of the ADVIA Centaur aCCP assay was conducted on 22 subgroups of non-RA subjects (n=460) with potentially cross-reacting conditions.

Conclusion:

Based on the performance characteristics the ADVIA Centaur aCCP assay is substantially equivalent to the predicate device.

The results presented in this 510(k) premarket submission demonstrate that the candidate assay (ADVIA Centaur® anti-CCP IgG (aCCP) assay, K153551) performance is substantially equivalent to the predicate assay (ARCHITECT Anti-CCP Assay (K083868))
The similarities and differences between the candidate assay and the predicate assay are presented in the tables starting on page 3/10.