

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k083868

B. Purpose for Submission:

New Device

C. Measurand:

Human IgG autoantibodies to cyclic citrullinated peptide (CCP)

D. Type of Test:

Semi-quantitative chemiluminescent microparticle immunoassay (CMIA)

E. Applicant:

Axis-Shield Diagnostic Limited

F. Proprietary and Established Names:

ARCHITECT Anti-CCP

G. Regulatory Information:

1. Regulation section:

21 CFR § 866.5775, Rheumatoid Factor Immunological Test System

21 CFR § 862.1150, Calibrator

21 CFR § 862.1660, Quality control material (assayed and unassayed).

2. Classification:

Class II (Device)

Class II (Calibrator)

Class I (Quality control)

3. Product code:

NHX, Antibodies, anti-cyclic citrullinated peptide (CCP)

JIX, Calibrator, multi-analyte mixture

JJY, Multi-analyte controls, all kinds (assayed)

4. Panel:

Immunology (82)

Clinical Chemistry (75)

Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

Reagents:

The ARCHITECT Anti-CCP assay is a chemiluminescent microparticle immunoassay (CMIA) 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* 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.

Calibrators:

The ARCHITECT Anti-CCP Calibrators are for the calibration of the ARCHITECT *i* System when used for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma.

Controls:

The ARCHITECT Anti-CCP Controls are for the estimation of test precision and the detection of systematic analytical deviations of the ARCHITECT *i* System (reagents, calibrators and instrument) when used for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma.

2. Indication(s) for use:

Same as Intended Use

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

ARCHITECT *i*2000 and *i*2000SR and *i*1000SR, which are platforms of the ARCHITECT *i* system family

I. Device Description:

Each ARCHITECT Anti-CCP Reagent Kit (100 tests, 500 tests) contains 1 bottle of each of Microparticles, Conjugate, and Sample Diluent:

Microparticles – 1 Bottle (6.5 mL or 26.5 mL) CCP coated microparticles in phosphate buffer with surfactant and protein (bovine) stabilizer. Minimum concentration: 0.05% solids. Preservative: sodium azide;

Conjugate – 1 Bottle (5.8 mL or 25.8 mL) Mouse anti-human IgG: acridinium-labeled conjugate in MES buffer with surfactant and protein (bovine) stabilizer. Minimum concentration: 10 ng/mL. Preservatives: Nipasept and Sarafloxacin

Sample Diluent – 1 Bottle (9.8 mL or 50.0 mL) Phosphate buffer with surfactant and protein (bovine) stabilizer. Preservative: sodium azide.

J. Substantial Equivalence Information:

1. Predicate device name(s):

AxSYM Anti-CCP Assay

2. Predicate 510(k) number(s):

k063347

3. Comparison with predicate:

Similarities:

Parameter	Submission device ARCHITECT Anti-CCP	Predicate device AxSYM Anti-CCP
Intended use	Semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma. 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	Same

Parameter	Submission device ARCHITECT Anti-CCP	Predicate device AxSYM Anti-CCP
	information. Autoantibody levels represent one parameter in a multicriterion diagnostic process, encompassing both clinical and laboratory-based assessments.	
Capture antibody	Cyclic citrullinated peptide (CCP), second generation.	Same
Storage conditions	The ARCHITECT Anti-CCP Reagent Pack, Calibrator Pack and Control Pack must be stored at 2-8°C.	Same
Calibration	Semi-quantitative assay. 6-point calibration curve (4PLC, Y-weighted) generated and stored on the instrument. Calibrators A-F (0, 5, 25, 50, 100, 200 U/mL)	Same
Calibrator Range	0-200 U/mL	Same
Suggested Cut-Off	5 U/mL	Same

Differences:

Parameter	Submission device ARCHITECT Anti-CCP	Predicate device AxSYM Anti-CCP
Assay Technology	Chemiluminescent Microparticle Immunoassay (CMIA)	Microparticle Enzyme Immunoassay (MEIA).
Substrate / Signal Generation	Acridinium Tracer	4-Methylumbelliferyl phosphate
Assay dilution protocol	Auto-dilution (1:6) Manual-dilution (1:10)	Auto-dilution (1:10) Manual-dilution (1:10)
Sensitivity	Limit of Detection is 0.5 U/mL	Limit of Blank is 1.0 U/mL.
Measurable Range	0.5 – 200 U/mL	0 – 200 U/mL

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach

CLSI EP7-A2 – Interference Testing in Clinical Chemistry

CLSI EP9-A2 – Method Comparison and Bias Estimation Using Patient Samples

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation

L. Test Principle:

The ARCHITECT Anti-CCP assay is a two-step immunoassay with an automated sample pretreatment for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma, using CMIA (chemiluminescent microparticle immunoassay) technology.

CCP coated paramagnetic microparticles and prediluted sample are combined. Anti-CCP antibodies present in the sample bind to the CCP coated microparticles. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of anti-CCP antibody in the sample and the RLUs detected by the ARCHITECT *i* System optics.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Testing was performed in accordance with CLSI EP5-A2.

Precision of the Architect Anti-CCP assay was evaluated on the ARCHITECT *i* system analyzers *i2000*, *i2000SR* and *i1000SR*. Samples included two patient samples, 1 positive control and 4 QC panel samples and were assayed in duplicate in two runs for 20 days (n=80 for each control/sample). A calibration curve for each reagent lot was generated on each instrument during run 1 on day 1. The study results are summarized in the table below:

Imprecision of the Architect Anti-CCP Assay on Architect *i* analyzers

Instrument No.	Sample	N	Mean (U/mL)	Within-Run		Between-Run		Between-Day		Total	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
ARCHITECT <i>i2000</i>	Positive Control	80	24.5	0.73	3.0	0.27	1.1	0.23	0.9	0.81	3.3
	QC Panel 2	80	10.9	0.30	2.7	0.53	4.9	0.00	0.0	0.61	5.6
	QC Panel 3	80	28.6	0.63	2.2	1.82	6.4	0.33	1.2	1.95	6.8
	QC Panel 4	80	66.7	1.40	2.1	3.61	5.4	1.09	1.6	4.03	6.0
	QC Panel 5	80	135.3	6.36	4.7	5.04	3.7	0.00	0.0	8.11	6.0
	Sample 1	80	2.8	0.07	2.6	0.09	3.1	0.01	0.4	0.11	4.0
	Sample 2	80	181.4	6.67	3.7	6.56	3.6	2.53	1.4	9.69	5.3
ARCHITECT <i>i2000SR</i> (1)	Positive Control	80	26.7	0.68	2.6	0.28	1.1	0.00	0.0	0.74	2.8
	QC Panel 2	80	11.3	0.26	2.3	0.52	4.6	0.00	0.0	0.58	5.2
	QC Panel 3	80	30.3	0.60	2.0	1.53	5.1	0.34	1.1	1.68	5.5
	QC Panel 4	80	72.7	1.92	2.6	4.46	6.1	0.00	0.0	4.85	6.7
	QC Panel 5	80	154.1	5.02	3.3	10.7	6.9	0.00	0.0	11.82	7.7
	Sample 1	80	2.7	0.07	2.4	0.08	2.8	0.04	1.6	0.11	4.0
	Sample 2	80	195.3	7.20	3.7	9.77	5.0	0.00	0.0	12.14	6.2
ARCHITECT <i>i1000SR</i> (1)	Negative Control	80	0.03	0.04	144.7	0.00	0.0	0.02	77.4	0.05	164.1
	Positive Control	80	25.03	0.83	3.3	0.00	0.0	0.71	2.9	1.10	4.4
	Panel 1	80	11.52	0.46	4.0	0.00	0.0	0.16	1.4	0.49	4.2
	Panel 2	80	66.62	2.85	4.3	0.00	0.0	1.12	1.7	3.06	4.6
	Panel 3	80	142.84	7.48	5.2	2.07	1.4	3.51	2.5	8.51	6.0

Instrument No.	Sample	N	Mean (U/mL)	Within-Run		Between-Run		Between-Day		Total	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
ARCHITECT i1000SR (2)	Negative Control	80	0.09	0.03	27.4	0.01	12.3	0.01	8.7	0.03	31.2
	Positive Control	80	28.32	0.80	2.8	0.00	0.0	0.66	2.3	1.04	3.7
	Panel 1	80	11.54	0.33	2.8	0.18	1.5	0.20	1.7	0.42	3.7
	Panel 2	80	67.64	1.63	2.4	1.22	1.8	0.81	1.2	2.19	3.2
	Panel 3	80	140.17	6.34	4.5	2.87	2.0	1.47	1.0	7.11	5.1

To cover the assay range, an additional seven patient samples were analyzed later in duplicate in 4 runs for 5 days (n=40 for each sample) on one of each of the instrument platforms. The results are summarized in the table below:

Imprecision of the Architect Anti-CCP Assay on Architect *i* analyzers

Instrument No.	Sample	N	Mean (U/mL)	Within-Run		Between-Run		Between-Day		Total	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
ARCHITECT i2000	Additional Sample 1	40	2.4	0.06	2.6	0.00	0.0	0.02	0.8	0.07	2.8
	Additional Sample 2	40	2.2	0.09	4.0	0.01	0.4	0.00	0.0	0.09	4.0
	Additional Sample 3	40	4.2	0.07	1.7	0.06	1.3	0.05	1.3	0.10	2.5
	Additional Sample 4	40	4.6	0.10	2.1	0.06	1.3	0.00	0.0	0.11	2.5
	Additional Sample 5	40	4.5	0.09	1.9	0.08	1.8	0.00	0.0	0.12	2.6
	Additional Sample 6	40	164.5	4.55	2.8	1.90	1.2	1.53	0.9	5.16	3.1
	Additional Sample 7	40	201.6	5.65	2.8	2.48	1.2	0.00	0.0	6.17	3.1
ARCHITECT i2000SR (2)	Additional Sample 1	40	2.4	0.058	2.4	0.02	0.7	0.01	0.2	0.06	2.5
	Additional Sample 2	40	2.2	0.062	2.8	0.05	2.2	0.00	0.0	0.08	3.5
	Additional Sample 3	40	4.1	0.048	1.2	0.00	0.0	0.05	1.3	0.07	1.7
	Additional Sample 4	40	4.5	0.13	2.8	0.05	1.1	0.00	0.0	0.14	3.0
	Additional Sample 5	40	4.5	0.07	1.6	0.08	1.7	0.10	2.2	0.14	3.2
	Additional Sample 6	40	153.6	4.77	3.1	1.91	1.2	0.00	0.0	5.14	3.3

Instrument No.	Sample	N	Mean (U/mL)	Within-Run		Between-Run		Between-Day		Total	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
	Additional Sample 7	40	185.1	6.46	3.5	3.76	2.0	2.75	1.5	7.96	4.3
ARCHITECT i1000SR (3)	Additional Sample 1	40	2.6	0.06	2.5	0.01	0.4	0.08	3.0	0.10	3.9
	Additional Sample 2	40	2.3	0.06	2.5	0.00	0.0	0.05	2.1	0.08	3.3
	Additional Sample 3	40	4.3	0.11	2.4	0.00	0.0	0.13	2.9	0.16	3.8
	Additional Sample 4	40	4.7	0.10	2.2	0.05	1.1	0.10	2.2	0.15	3.3
	Additional Sample 5	40	4.6	0.09	1.9	0.03	0.6	0.08	1.7	0.12	2.6
	Additional Sample 6	40	163.3	6.13	3.8	0.00	0.0	0.00	0.0	6.13	3.8
	Additional Sample 7	40	192.9	6.79	3.5	2.91	1.5	0.00	0.0	7.39	3.8

b. *Linearity/assay reportable range:*

Linearity:

The linearity of the Architect Anti-CCP assay was assessed with four samples on all three instruments. Samples were serially diluted to cover the assay measuring range. Data were analyzed in accordance with CLSI EP6-A. The ARCHITECT Anti-CCP assay linear range was determined as 0.1 U/mL to 246.5 U/mL. The data is summarized in the table below:

Instrument	Test Range (U/ml)	Slope (95% CI)	Y-intercept (95% CI)	R ²	%CV Range
i2000	0.1 - 6.7	0.95 (0.91 to 1.00)	0.31 (0.14 to 0.47)	0.9966	1.2 to 2.7
	0.0 - 48.7	0.99 (0.98 to 1.01)	0.52 (0.09 to 0.95)	0.9996	1.4 to 3.4
	0.0 - 98.5	0.98 (0.95 to 1.01)	0.20 (-1.34 to 1.74)	0.9987	1.2 to 3.8
	0.1 - 244.4	0.91 (0.88 to 0.95)	-1.9 (-6.9 to 3.1)	0.9982	0.8 to 3.9
i2000SR	0.1 - 6.5	0.96 (0.93 to 1.00)	0.25 (0.10 to 0.39)	0.9973	1.3 to 3.9
	0.0 - 48.5	1.00 (0.99 to 1.02)	0.34 (-0.10 to 0.78)	0.9996	0.7 to 3.4
	0.1 - 94.6	1.00 (0.99 to 1.01)	0.41 (-0.22 to 1.04)	0.9998	1.0 to 4.3
	0.1 - 257.4	0.98 (0.95 to 1.01)	-1.85 (-6.19 to 2.48)	0.9985	1.8 to 3.2
i1000SR	0.2 - 7.1	0.99 (0.93 to 1.04)	0.34 (0.12 to 0.56)	0.9952	0.3 to 2.7
	0.2 - 47.5	1.01 (0.99 to 1.02)	0.27 (-0.17 to 0.72)	0.9996	1.7 to 4.0
	0.0 - 94.6	1.00 (0.98 to 1.02)	-0.22 (-1.20 to 0.76)	0.9995	1.9 to 4.6
	0.2 - 272.3	0.97 (0.94 to 1.01)	-0.97 (-6.62 to 4.67)	0.9977	2.3 to 8.8

The assay measurement (reportable) range is 0.5 U/ml to 200.0 U/mL.

ORDAC (Over Range Detection and Correction):

The automatic auto-dilution protocol for samples >50 U/mL was assessed using twelve anti-CCP serum samples with 4 samples for each assay range (50 to 150 U/mL, 160 to 200 U/mL, and 200 to 1200 U/mL). Samples were tested neat, auto-diluted and manually diluted (1:10 with negative control) in the

ARCHITECT Anti-CCP assay in replicates of 5. The auto-dilution is a 1:6 dilution of the sample performed onboard the ARCHITECT instrument using ARCHITECT wash buffer. For samples >50.0 U/mL (range 58.7 to 785.0 U/mL), the autodiluted samples had a mean difference of $\pm 10\%$ when compared to the expected value calculated from the manual dilution. The overall mean % difference was calculated for all samples as detailed in the table below:

Range	Sample	Neat mean	Auto dilution mean	Autodilute *6	Manual dilution mean	Manual *10	% Diff for Manual vs Neat	% Diff for Auto vs Neat	% Diff for Auto vs Manual
200 - 1200	1	305.8*	76.1	456.4	45.3	453.0	N/A	N/A	0.7
	2	485.9*	84.0	504.1	48.3	482.7	N/A	N/A	4.4
	3	1477.6*	132.8	796.8	74.4	743.8	N/A	N/A	7.1
	4	245.8*	122.4	734.6	78.5	785.0	N/A	N/A	-6.4
160 - 200	5	169.2	36.7	220.2	21.0	209.9	24.1	30.1	4.9
	6	170.7	32.0	192.0	18.8	187.9	10.1	12.5	2.2
	7	187.8	35.7	213.9	20.7	207.0	10.2	13.9	3.3
	8	169.7	32.8	196.8	19.5	194.6	14.7	15.9	1.1
50 - 150	9	58.7	10.9	65.3	6.1	61.4	4.5	11.1	6.3
	10	62.0	11.7	70.1	6.9	69.2	11.6	13.1	1.3
	11	61.4	12.0	72.0	6.9	69.0	12.3	17.3	4.4
	12	132.8	27.9	167.2	16.5	165.2	24.4	25.9	1.2
Overall % Difference:							14.0	17.5	2.6

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

There is no recognized standards for anti-CCP. Values for calibrators and controls are arbitrary assigned.

Calibrators: the stability performance of the ARCHITECT Anti-CCP Calibrators was established in k063347.

Unopened calibrators can be stored at 2 – 8°C for up to 27 months.

In-use/open calibrators can be stored at 2 – 8°C for up to 27 months.

Controls: the stability performance of the ARCHITECT Anti-CCP Controls was established in k063347.

Unopened control vials can be stored at 2 – 8°C for up to 27 months.

In-use/open control vials can be stored at 2 – 8°C for up to 27 months.

Reagents storage conditions:

Unopened reagents can be stored at 2 – 8°C for up to 14 months.

Open reagents can be stored, if returning to 2 – 8°C between time points, for up to 14 months.

Onboard the ARCHITECT i instrument reagents can be stored for a maximum of 30 days.

The calibration curve is valid for 30 days.

The recommended minimum quality control requirement for the ARCHITECT Anti-CCP assay is that a single sample of each control be tested every 24 hours, each day of use.

Sample storage conditions:

The sponsor presented a study supporting the storage of specimens for up to 7 days at 2 – 8°C or 22 hours at 30°C after the date of collection. For longer storage, the recommended storage temperature is -20°C or colder.

d. Detection limit:

The limit of blank (LoB) and limit of detection (LoD) was determined in accordance with CLSI document EP17-A. To determine the Limit of Blank (LoB), Calibrator A (0.0 U/mL) was used. The mean concentration (U/mL) result and standard deviation (SD) for 60 replicates of Calibrator A were calculated. To determine Limit of Detection (LoD)/Limit of Quantitation (LoQ) one lot of ARCHITECT Anti-CCP Reagents, Calibrators and kit Controls were run in duplicate followed by 5 low level anti-CCP negative samples in replicates of 4, on 5 individual days. The results are summarized in the table below:

LoB/LoD/LoQ Data Summary:

	<i>i</i> 2000 Instrument/ reagent lot combination	<i>i</i> 2000 _{SR} Instrument/ reagent lot combination	<i>i</i> 1000 _{SR} Instrument 1	<i>i</i> 1000 _{SR} Instrument 2
Limit of Blank (U/mL)	0.02	0.01	0.01	0.01
Limit of Detection (U/mL)	0.09	0.11	0.03	0.02
Limit of Quantitation (U/mL)	0.09	0.11	0.03	0.02

The ARCHITECT Anti-CCP assay was designed to have a limit of detection of ≤ 0.5 U/mL. The values for LoB (0.02 U/mL) and LoD (0.11 U/mL) have been quoted in the ARCHITECT Anti-CCP Reagent insert as representative data.

d. Hook effect:

A study was performed on one each of *i*2000, *i*2000SR and *i*1000SR instruments to assess high dose hook effect. No high dose hook effect was observed for any of the three instruments when a sample containing approximately 2000 U/mL of anti-CCP antibody was assayed.

e. Analytical specificity:

Interference of endogenous compounds: A study was done in accordance with CLSI document EP7-A2. Five serum specimens with anti-CCP levels across the assay range (0.5 to 200.0 U/mL) were supplemented with the potentially interfering compounds at several concentrations. There was no interference observed at the following concentrations:

Potential Interfering Substance	Concentration
Bilirubin	20 mg/dL
Hemoglobin	800 mg/dL
Total Protein	12 g/dL

Triglyceride	3000 mg/dL
Rheumatoid factor	200 IU/mL
Red Blood Cells	0.4%

Cross reactivity: A study was performed according to CLSI Document EP7-A2. Samples were spiked with different concentrations of the interferent autoantibodies. An anti-CCP negative serum samples was used as a negative control sample. The results are summarized in the following table:

Sample	Interferent Autoantibodies	Concentration of autoantibodies tested (U/mL)	% Difference from control
1	Sm/RNP	9.07	0.8
2	Sm/RNP	9.51	-0.3
3	SCL-70	6.38	6.3
4	SCL-70	5.37	8.0
5	TPO	2.13	9.3
6	TPO	5.26	3.8
7	ANA	3.87	5.5
8	ANA	2.97	3.0
9	Jo-1	2.72	3.7
10	Jo-1	2.22	3.0
11	ds-DNA	42.8	6.0
12	ds-DNA	53	-0.9
13	ds-DNA	>200	5.8
14	Jo-1	82.5	4.4
15	Jo-1	93	-5.4
16	Ribosomal P	48	2.5
17	SCL-70	110	3.7
18	Sm/RNP	>100	-1.2
19	Sm/RNP	RNP 2.5 OD @ 1:100 High positive Sm	9.2
20	SSa/SSb/AMA	SSA 87 SSB 30 AMA 40	2.9

- e. Assay cut-off:
A 5.0 U/mL cut-off was selected to maintain consistency with the other Anti-CCP assays including the predicate for the ARCHITECT Anti-CCP. Result of ≥ 5.0 U/ml is considered positive and a result of <5.0 U/ml is considered negative.
2. Comparison studies:
 - a. Method comparison with predicate device was performed according to CLSI EP9-2A. Results are shown in the table below:

Analyzers	Range (U/mL)	n	Slope (95% CI)	Intercept (95% CI)	r (95% CI)
i2000SR vs. AxSYM	0.5 to 1200	370	1.10 (1.06 to 1.13)	-2.03 (-3.84 to -1.07)	0.95 (0.93 to 0.96)
	0.5 to 200	234	0.93 (0.90 to 0.96)	-0.19 (-0.45 to 0.30)	0.94 (0.93 to 0.95)
i2000 vs. i2000SR	0.5 to 200	62	0.978 (0.96 to 1.00)	0.130 (-0.05 to 0.27)	0.99 (0.98 to 0.99)
i1000SR vs. i2000SR	0.5 to 1200	96	0.99 (0.98 to 1.02)	0.01 (-0.18 to 0.12)	1.00

Using a cut-off of 5.0 U/mL for the ARCHITECT Anti-CCP assay, the concordance results between ARCHITECT and AxSYM are summarized in the following tables:

All Specimens (n = 995)		AxSYM Anti-CCP Result	
		POS	NEG
ARCHITECT <i>i</i> 2000SR Anti-CCP Result	POS	356	3
	NEG	4	632
% Positive agreement		98.9%	
% Negative agreement		99.5%	
% Total Agreement		99.3%	

A Receiver Operator Characteristic (ROC) analysis was performed between the ARCHITECT Anti-CCP and AxSYM Anti-CCP assays using the 995 specimens. The area under the curve (AUC) for the ARCHITECT Anti-CCP assay was 0.873 (95% Confidence Interval: 0.849-0.897) and 0.872 (95% Confidence Interval: 0.848-0.896) for the AxSYM Anti-CCP assay.

b. Matrix comparison:

Study was performed on *i*2000, *i*2000SR and *i*1000SR instruments. The aim was to determine the type of anticoagulant collection tubes that can be used with the ARCHITECT Anti-CCP assay. 18 matched serum/plasma negative samples were spiked with different concentrations of anti-CCP positive sample (concentration approximately 4340 U/mL): 5 U/mL, 5 – 10 U/mL, and 10 - 200 U/mL. Samples were tested in replicates of five. The percent difference of anti-CCP concentration from the same samples obtained in the control collection tube (Serum) versus the other collection tube types tested (plastic serum separator (SST), plastic K2EDTA plasma, and plastic Lithium Heparin plasma separator) met the sponsor's design claim criteria:

- $\pm 15\%$ for samples with anti-CCP concentrations > 10.0 U/mL (i.e. above 2x the diagnostic cut-off)
- $\pm 10\%$ for samples with anti-CCP concentrations > 5.0 U/mL and < 10.0 U/mL (i.e. 1x to 2x the diagnostic cut-off)
- ± 0.5 U/mL samples with anti-CCP concentrations < 5.0 U/mL (i.e. below 1x the diagnostic cut-off).

The ARCHITECT Anti-CCP assay is therefore able to test specimens collected in the following blood collection tubes: serum, serum separator (SST), K2EDTA plasma, and Lithium Heparin plasma separator.

3. Clinical studies:

a. Clinical Sensitivity:

The clinical sensitivity was determined for confirmed RA individuals (n=496). Using a cut-off of 5.0 U/mL, the % clinical sensitivity was calculated to be 70.6% as indicated below:

Specimen Category	Total (n)	Anti-CCP Positive (n)	%Sensitivity (95% CI)
Confirmed RA	496	350	70.6 (66.3%-77.4%)

The clinical sensitivity is comparable to that of the predicate device, AxSYM Anti-CCP which is 70.8% (95% CI 66.5%-74.7%)

b. Clinical specificity:

The clinical specificity was determined for 499 non-RA specimens (299 from patients with other rheumatic and non-rheumatic disorders and 200 asymptomatic apparently healthy individuals). The other non-RA diseases tested were ankylosing spondylitis, autoimmune thyroiditis/Hashimoto's disease, Crohn's disease, dermatomyositis, Epstein Barr Virus (EBV), Lyme disease, osteoarthritis, polymyalgia rheumatica, polymyositis, psoriatic arthritis, reactive arthritis/Reiter's syndrome, scleroderma, Sjogrens syndrome, systemic lupus erythematosus (SLE) and ulcerative colitis. Using a 5.0 U/mL cut-off, the ARCHITECT Anti-CCP % clinical specificity calculations for total non-RA, non-RA asymptomatic, and non-RA other disease specimens is summarized in the table below:

Specimen Category	Total (n)	Anti-CCP Positive (n)	% Specificity
Non-RA (Normals)	200	1	99.5
Non-RA other diseases	299	8	97.3
Total Non-RA	499	9	98.2

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Reference interval was established by testing 199 asymptomatic apparently healthy males(n=126) and females (n=73), 19 to 67 years old. Specimen values ranged from < 0.5 U/mL to 2.5 U/mL. No differences attributed to gender or age was observed.

N. Proposed Labeling:

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

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.