510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k082953

B. Purpose for Submission:

New device

C. Measurand:

Digoxin

D. Type of Test:

Quantitative

E. Applicant:

Biokit S.A.

F. Proprietary and Established Names:

ARCHITECT *i*Digoxin Reagents

ARCHITECT *i*Digoxin Calibrators

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
KXT	Class II	862.3320	91, Toxicology
DLJ	Class II	862.3200	91, Toxicology

H. Intended Use:

1. Intended use(s):

    See Indications for Use below.

2. Indication(s) for use:

The ARCHITECT *i*Digoxin assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of digoxin in human serum or plasma on the ARCHITECT *i* System with STAT protocol capability. The measurements obtained are used to aid in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to help ensure appropriate therapy.

The ARCHITECT *i*Digoxin Calibrators are for the calibration of the ARCHITECT *i* System with STAT protocol capability when used for the quantitative determination of digoxin in human serum or plasma.

For *in vitro* diagnostic use

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

ARCHITECT *i* System

I. Device Description:

The ARCHITECT *i*Digoxin assay is an *in vitro* chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of digoxin in human serum or plasma on the ARCHITECT *i* System with STAT protocol capability. The measurements obtained are used to aid in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to help ensure appropriate therapy.

Each *i*Digoxin Reagent kit contains 1 bottle of each component of Microparticles, Conjugate and Assay Diluent.

• Microparticles - 1 bottle (6.6 mL) Anti-digoxin (mouse, monoclonal) coated microparticles in TRIS buffer with protein (bovine) stabilizer. Preservative: ProClin 300.

• Conjugate – 1 bottle (5.9 mL) Digoxigenin acridinium-labeled conjugate in citrate buffer. Preservative: ProClin 300.

• Assay Diluent - 1 bottle (10.0 mL) Assay Diluent containing goat serum with EDTA disodium. Preservative: ProClin 300 and ProClin 950.

The ARCHITECT *i*Digoxin Calibrators are for the calibration of the ARCHITECT *i* System with STAT protocol capability when used for the quantitative determination of digoxin in human serum or plasma.

Each digoxin calibrator kit contains 6 bottles of ARCHITECT *i*Digoxin Calibrators (4.0 mL each). Calibrators A-F contain normal human serum and digoxin except Calibrator A has no digoxin as shown below.

Cal A 0.0 ng/mL

Cal B 0.5 ng/mL

Cal C 1.0 ng/mL

Cal D 2.0 ng/mL

Cal E 3.0 ng/mL

Cal F 4.0 ng/mL

The normal human serum used in the calibrators has been tested by an FDA approved method and found to be nonreactive for HIV-1/2 Antibody, HCV Antibody, HTLV-1/2 Antibody, HBc Antibody and HBsAg.

J. Substantial Equivalence Information:

1. Predicate device name(s):

    The ARCHITECT *i*Digoxin device is compared to the Aeroset Multigent Digoxin

2. Predicate K number(s):

    k023058

3. Comparison with predicate:

REAGENTS

Similarities

Reagents	Device	Predicate
Intended use	The ARCHITECT *i* Digoxin assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of digoxin in human serum or plasma on the ARCHITECT *i* System with STAT protocol capability. The measurements obtained are used to aid in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to help ensure appropriate therapy.	The MULTIGENT Digoxin assay is used for the quantitative in vitro measurement of digoxin in human serum or plasma on the ARCHITECT c 8000® System and the AEROSET System.
Specimen type	Human serum or plasma	Human serum or plasma.

Differences

Reagents	Device	Predicate
Platform	ARCHITECT *i* System	ARCHITECT c 8000® System and the AEROSET System
System Methodology	Chemiluminescent Microparticle Immunoassay (CMIA).	Homogeneous particle-enhanced turbidimetric immunoassay (PETIA)
Components	1 bottle Microparticles: 6.6 mL 1 bottle Conjugate: 5.9 mL 1 bottle Assay Diluent: 10.0 mL	2 bottles R1: 45 mL 2 bottles R2: 17 mL

CALIBRATORS

Similarities

Calibrators	Device	Predicate
Intended use	The ARCHITECT *i* Digoxin Calibrators are for the calibration of the ARCHITECT *i* System with STAT protocol capability when used for the quantitative determination of digoxin in human serum or plasma.	The MULTIGENT. Digoxin Calibrators are intended for in vitro diagnostic use with the AEROSET® System and the ARCHITECT® c8000. System for the calibration of the MULTIGENT. Digoxin Assay.
Standardization	Internal Reference Calibrators are manufactured gravimetrically using USP Reference Standard Digoxin. The ARCHITECT *i* Digoxin Calibrators are matched to the internal Reference Calibrators.	MULTIGENT. Digoxin Calibrators are gravimetrically prepared using weighing equipment calibrated to standards that are traceable to NIST weight standards. Digoxin used to prepare calibrators is traceable to digoxin USP.
Traceability	USP Reference Standard Digoxin	Digoxin USP

Differences

Calibrators	Device	Predicate
Platform	ARCHITECT *i* System	ARCHITECT c 8000® System and the AEROSET System
System Methodology	Chemiluminescent Microparticle Immunoassay (CMIA).	Homogeneous particle-enhanced turbidimetric immunoassay (PETIA)
Calibration Range/Levels	A: 0.00 ng/mL (0.00 nmol/L) B: 0.05 ng/mL (0.64 nmol/L) C: 1.00 ng/mL (1.28 nmol/L) D: 2.00 ng/mL (2.56 nmol/L) E: 3.00 ng/mL (3.84 nmol/L) F: 4.00 ng/mL (5.12 nmol/L)	1: 0.00 ng/mL (0.00 nmol/L) 2: 0.05 ng/mL (0.64 nmol/L) 3: 1.00 ng/mL (1.28 nmol/L) 4: 2.00 ng/mL (2.56 nmol/L) 5: 3.00 ng/mL (3.84 nmol/L) 6: 5.00 ng/mL (6.40 nmol/L)
Components	6 bottles of 4.0 mL each.	Cal 1: 1 bottle of 4.8 mL. Cal 2 – 6: 1 bottle of 1.8 mL.
Matrix	Calibrators A-F contain normal human serum Calibrators B-F contain digoxin.	The MULTIGENT Digoxin Calibrators contain buffer spiked with digoxin.

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

Clinical Laboratory Standards Institute; Evaluation of Precision Performance of Quantitative Measurement Methods (CLSI EP5-A2 guideline)

Clinical and Laboratory Standards Institute; Protocols for Determination of Limits of Detection and Limits of Quantitation (CLSI EP17-A guideline)

Clinical and Laboratory Standards Institute; Interference Testing in Clinical Chemistry (CLSI EP7-A2)

L. Test Principle:

The ARCHITECT *i*Digoxin assay is a one-step STAT immunoassay for the quantitative measurement of digoxin in human serum or plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex. Sample, anti-digoxin coated paramagnetic microparticles, assay diluent, and digoxigenin acridinium-labeled conjugate are combined to create a reaction mixture. The anti-digoxin coated microparticles bind to digoxin present in the sample and to the digoxigenin acridinium-labeled conjugate. After washing, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). An indirect relationship exists between the amount of digoxin in the sample and the RLUs detected by the ARCHITECT *i* System optics

M. Performance Characteristics (if/when applicable):

All performance characteristics were established on the ARCHITECT i2000$_{SR}$ system.

1. Analytical performance:

   a. *Precision/Reproducibility:*

      Precision was performed with the ARCHITECT *i*Digoxin assay based on the National Committee for Clinical Laboratory Standards (CLSI EP5-A2 guideline).

      Two ARCHITECT *i 2000$_{SR}$* Systems were used along with 2 lots of reagents and 2 lots of calibrators. The assay was run twice a day for 20 days using 3 Multi-constituent Controls and 3 human serum based panels in replicates of 2.

      The 3 human serum based panels were prepared by adding digoxin concentrations into a pool of human sera at final concentrations targeted at 0.80, 2.00 and 3.60 ng/mL.

The table below summarizes the precision study results and is included in the reagent package insert.

Sample	Instrument	Reagent Lot	n	Mean (ng/mL)	Within Run		Total	
					SD	%CV	SD	%CV
Level1	1	1	80	0.81	0.020	2.5	0.024	3.0
	2	2	80	0.82	0.020	2.4	0.027	3.3
Level 2	1	1	80	1.72	0.032	1.9	0.053	3.1
	2	2	80	1.73	0.030	1.7	0.040	2.3
Level 3	1	1	80	2.88	0.069	2.4	0.075	2.6
	2	2	80	2.89	0.055	1.9	0.059	2.0
Panel 1	1	1	80	0.66	0.024	3.6	0.029	4.4
	2	2	80	0.68	0.017	2.5	0.025	3.7
Panel 2	1	1	80	1.70	0.039	2.3	0.059	3.5
	2	2	80	1.72	0.026	1.5	0.035	2.0
Panel 3	1	1	80	3.53	0.064	1.8	0.118	3.3
	2	2	80	3.57	0.056	1.6	0.087	2.4

b. *Linearity/assay reportable range:*

Five pooled serum samples (1.80, 2.40, 3.00, 3.60 and 3.90 ng/mL) were diluted manually with the ARCHITECT iDigoxin Calibrator A. Each sample was diluted to have 11 concentration levels. Each sample was diluted using the ARCHITECT iDigoxin Calibrator A. The concentration of digoxin was determined using the ARCHITECT *i*Digoxin assay and the resulting percent deviation from linearity or concentration difference was calculated. For diluted samples reading above 1.0 ng/mL, the percent deviation from linearity ranged from 4.0 to 8.8%. For diluted samples below 1.0 ng/mL, the concentrations were within 0.1 ng/mL of the expected results. The regression equations for the five samples are shown in the table below. The linear range of the assay is 0.3 to 4.0 ng/mL.

Sample A (1.80 ng/mL)	$y = 0.9940x + 0.07$
Sample B (2.40 ng/mL)	$y = 0.9845x + 0.07$
Sample C (3.00 ng/mL)	$y = 0.9943x + 0.05$
Sample D (3.60 ng/mL)	$y = 0.9599x + 0.05$
Sample E (3.90 ng/mL)	$y = 0.9925x + 0.04$

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

Internal Reference Calibrators are manufactured gravimetrically using

purified synthetic Digoxin from US Pharmacopeia (USP) Reference Standard Digoxin. The ARCHITECT *i*Digoxin Calibrators are manufactured using normal human serum and matched to the internal Reference Calibrators.

The normal human serum used in the calibrators has been tested by an FDA approved method and found to be nonreactive for HIV-1/2 Antibody, HCV Antibody, HTLV-1/2 Antibody, HBc Antibody and HBsAg.

Real time stability testing is ongoing. Based on accelerated stability results, the data support an expiration date of 9 months for ARCHITECT *i*Digoxin Calibrator Kits at 2-8ºC.

Open-vial real time stability testing for the calibrators is ongoing. Testing currently supports a storage time of 4 months at 2-8ºC.

d. *Detection limit:*

A study was conducted to determine the limit of the blank (LoB) and the limit of detection (LoD) for the ARCHITECT *i*Digoxin assay using the ARCHITECT i2000$_{SR.}$ System following CLSI guideline 17-A. The determinations were performed using one blank, assayed 60 times and four samples containing low concentrations of digoxin assayed 15 times. The limit of blank obtained was 0.07 ng/mL and limit of detection was 0.09 ng/mL.

A functional sensitivity study was performed using a series of seven samples ranging from 0.05 to 0.5 ng/mL which were prepared by diluting Calibrator B with Calibrator A. These samples were tested in replicates of ten two times per day for five days using one reagent and calibrator lot for a total of 100 replicates per panel. The total % CVs were calculated and plotted against the mean concentration. A reciprocal curve was fitted through the data, and the functional sensitivity value was calculated as the concentration corresponding to the 20% CV level of the fitted curve. At the upper 95% confidence limit, the lowest ARCHITECT i Digoxin assay value exhibiting a 20% CV was calculated to be 0.1 ng/mL, which is below the reportable range of the ARCHITECT i Digoxin assay.

The measuring range is 0.3 to 4.0 ng/mL.

e. *Analytical specificity:*

A study was conducted to evaluate the potential interference from triglycerides, hemoglobin, bilirubin, protein (low and high level), HAMA and Rheumatoid Factor (RF) in the ARCHITECT *i*Digoxin assay using the ARHITECT i *2000$_{SR}$* system.

Interference testing was performed on the ARCHITECT *i* System. Testing

was performed based on guidance from the Clinical and Laboratory Standards Institute document CLSI Document EP7-A2.

No influence from the endogenous interfering substances tested was observed during the study.

Five serum specimens with digoxin levels ranging from 0.35 to 2.84 ng/mL were supplemented with the following potentially interfering compounds. The mean recovery observed during the study ranged from 99.1% to 104.8%. The following table is included in the reagent package insert. Results are shown below:

Potentially Interfering Compound	Interferent Concentration	% Recovery Range (Individual)
Bilirubin	20 mg/dL	98.9-103.1
Hemoglobin	750 mg/dL	100.0-103.2
Triglycerides	2500 mg/dL	98.4-105.6
HAMA	1000 ng/mL	98.1-101.6
Rheumatoid Factor	500 IU/mL	97.1-102.5
Low Protein	3 g/dL	94.3-106.8
High Protein	12 g/dL	97.6-109.8

Cross-reactivity was tested for the major digoxin active metabolites (digoxigenin bis-digitoxoside, digoxigenin mono-digitoxoside, digoxigenin), related compounds (acetyldigoxin, digitoxin, digitoxigenin, ouabain, deslanoside, lanatoside C, proscillaridin) and other therapeutic agents that may be co-administered to determine whether these compounds affect the quantitation of digoxin concentrations using the ARCHITECT i Digoxin assay. The compounds were spiked into a serum pool (control) containing no digoxin and into two therapeutic levels (approximately 0.8 ng/mL and 2.0 ng/mL) of digoxin. The samples were assayed and the digoxin concentrations of the spiked samples were compared to the control serum. The data are summarized in the following table.

Test Compound	Test Compound Conc. (ng/mL)	Digoxin Concentration (Conc.) (ng/mL)					
		0.0	0.8			2.0	
		Conc. Difference	Conc. Difference	Cross React. (%)		Conc. Difference	Cross React. (%)
Digoxigenin bis-digitoxoside	1.30	2.03	1.86	143.1		_c*	_c*
Digoxigenin mono-digitoxoside	1.00	1.49	0.69	69.0		0.96	96.0
Digoxigenin	0.80	0.15	0.02	2.5		-0.05	-6.3
Acetyldigoxin	2.50	2.70	2.34	93.6		_c*	_c*
Digitoxin	25	0.04	0.07	0.3		-0.09	-0.4
Digitoxigenin	15	0.00	0.04	0.3		-0.08	-0.5
Ouabain	860	1.38	0.28	0.0		0.22	0.0
Deslanoside	2.25	2.03	1.65	73.3		1.66	73.8
Lanatoside C	1.55	1.98	1.14	73.5		0.96	61.9
Proscillaridin	340	0.21	0.26	0.1		0.08	0.0
Spironolactone	500	0.35	0.04	0.0		0.21	0.0
Canrenone	1000	0.00	0.01	0.0		0.05	0.0
Canrenoic Acid	1000	0.36	0.08	0.0		-0.04	0.0
Hydrocortisone	2000	0.12	0.02	0.0		0.01	0.0
Methylprednisolone	7000	0.02	0.08	0.0		-0.05	0.0
Prednisolone	1000	0.15	0.02	0.0		0.37	0.0
Dexamethasone	5000	0.36	0.19	0.0		0.10	0.0
Progesterone	250	0.05	0.06	0.0		-0.12	0.0
Amiloride	50	0.00	0.36	0.7		-0.04	-0.1
Amrinone	7000	0.15	-0.11	0.0		0.11	0.0
Clorazepate	1500	0.00	0.04	0.0		-0.09	0.0
Nabumetone	37,000	0.00	0.12	0.00		-0.04	0.0
Phenytoin	80,000	0.00	0.16	0.0		-0.03	0.0
Triamterene	500	0.00	-0.25	-0.1		-0.03	0.0

_c*: Not determined. The value obtained is outside the assay range

In addition, the labeling contains the following information:

"The sera from patients in specific patient populations (i.e., patients with renal and/or hepatic failure, newborn infants, and pregnant women) have been reported to contain an unidentified component that gives positive results for digoxin with a number of immunoassays. This component has been called digoxin-like immunoreactive factor (DLIF) or substance (DLIS). The presence of DLIF in a sample can result in falsely elevated digoxin assay

results. The amount of DLIF in these patient samples is extremely variable, but in some cases these levels have been shown to approach concentrations that are in the therapeutic range of digoxin. As with any assay employing mouse antibodies, the possibility exists for interference by HAMA in the sample, which could falsely elevate or depress results. The manufacturer of Digoxin Immune Fab has stated that no immunoassay technique is suitable for quantitating digoxin in serum from patients on antibody fragment therapy. According to the manufacturer's insert, DIGIBIND will interfere with digitalis immunoassay measurements."

"It has been reported in the literature that one in ten patients converts 40% or more of oral digoxin to an inactive reduction product (dihydrodigoxin) via bacteria in the gut. There is little or no cross-reactivity reported for dihydrodigoxin."

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

A study was performed using 200 serum and plasma (heparin and EDTA) samples with values ranging from 0.34 ng/mL to 3.93 ng/mL using the ARCHITECT iDigoxin Reagents on the Architect i2000_{SR} vs. predicate Multigent Digoxin on the Aeroset system. The results are shown in the table below:

Regression method	Number of observations	Slope (95% CI)	Intercept (95% CI)	Correlation coefficient
Passing-Bablok	200	0.921 (0.906 to 0.937)	-0.040 (0.061 to -0.018)	0.993

b. *Matrix comparison:*

Three plasma tube types and one serum specimen tube were collected from 20 individuals. Serum tubes without additives were used as the control. Human serum and plasma specimens were collected in the following tube types:

- serum no additive

- potassium EDTA (K-EDTA)

- sodium heparin (Na-heparin)

- lithium heparin (Li-heparin)

Each of the 20 sets of serum/plasma tubes were spiked with digoxin to achieve 10 different spiking concentrations (0.30, 0.40, 0.60, 0.80, 1.20, 1.60, 2.00, 2.80, 3.20 and 3.60 ng/mL). Two tubes of each collecting tube type were used for each spiking level. The results are provided in the following table:

Tube type	N	Mean % recovery vs. Serum
Serum no additive	20	Control
K-EDTA	20	98.3
Na-Heparin	20	97.9
Li-Heparin	20	97.5

3. Clinical studies:

   a. *Clinical Sensitivity:*

      Not applicable

   b. *Clinical specificity:*

      Not applicable

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

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   The Expected Values for ARCHITECT *i*Digoxin have been established based on bibliography references.

   The statement presented in the package insert is as follows:

   "The ARCHITECT *i*Digoxin assay accurately quantitates digoxin concentrations in human serum or plasma at concentrations up to 4.0 ng/mL. Numerous studies have shown a relationship between serum levels of digoxin and its concentration in myocardial and other tissues. Optimum therapeutic effects usually are observed

when serum levels are in the range from 0.8 to 2.0 ng/mL based on radioimmunoassay, although some clinical benefit may be realized at serum or plasma concentrations below 0.8 ng/mL. The risk of toxicity increases at serum or plasma levels above 2.0 ng/mL. Symptoms of digoxin toxicity may include gastrointestinal disturbances such as anorexia, nausea, vomiting and diarrhea, central nervous system disturbances manifested by blurred or yellow vision, headache, weakness, dizziness, apathy, and confusion, and cardiac rhythm disturbances and tachycardia. There is some evidence that children may tolerate slightly higher serum or plasma concentrations than adults. It is important to note that the distinction between adequate digitalization and toxicity in patients cannot be made on the basis of digoxin concentrations alone. Most studies show a significant overlap between the toxic and nontoxic groups. Additional factors to consider when evaluating the correct therapeutic dosage for each patient are lean body weight, age, renal function, concomitant disease states, concurrent medications, and other clinical factors."

The literature references are provided in the package insert for the statements above.

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.