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

A. 510(k) Number:

k060818

B. Purpose for Submission:

Notification of intent to manufacture and market a new device

C. Measurand:

Sex Hormone Binding Globulin (SHBG)

D. Type of Test:

chemiluminescent microparticle immunoassay (CMIA)

E. Applicant:

BIOKIT S.A.

F. Proprietary and Established Names:

Proprietary Name - Architect® SHBG
Established name - Sex hormone binding globulin

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
JIT	Class II	21 CFR 862.1150	75 Chemistry
CDZ	Class I, reserved	21 CFR 862.1680	75 Chemistry
JJX	Class I, reserved	21 CFR 862.1660	75 Chemistry

H. Intended Use:

1. Intended use(s):

See Indications for use below.

2. Indication(s) for use:

Indications for Use:

Reagents

The ARCHITECT® SHBG assay is a chemiluminescent immunoassay (CMIA) for the quantitative determination of sex hormone binding globulin (SHBG) in human serum and plasma on the Architect *i* system.
The Architect SHBG assay is intended for use as an aid in the diagnosis of androgen disorders.

Calibrators

The ARCHITECT® SHBG Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of SHBG in human serum and plasma.

Controls

ARCHITECT® SHBG Controls are for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of SHBG in human serum and plasma.

For *in vitro* diagnostic use.

3. Special conditions for use statement(s):

For professional use only.

4. Special instrument requirements:

ARCHITECT® *i* instrument system platforms

I. Device Description:

Reagents:
Each SHBG Reagent kit contains 1 or 4 bottle(s) of each component of Microparticles, Conjugate and Assay Diluent
Microparticles: 1 or 4 bottle(s) (6.6 mL each) Anti-SHBG (mouse, monoclonal) coated microparticles in TRIS buffer. Preservative: sodium azide. Conjugate: 1 or 4 bottle(s) (5.9 mL each) Anti-SHBG (mouse, monoclonal) acridinium-labeled conjugate in phosphate buffer with protein (mouse, bovine) stabilizer. Preservative: sodium azide.

Assay Diluent: 1 or 4 bottle(s) (8.0 mL each) SHBG Assay Diluent containing phosphate buffer with protein (mouse, bovine) stabilizer.
Preservative: sodium azide.

Calibrators:
Calibrator A contains phosphate buffered saline with protein (goat) stabilizer.
Calibrators B to F contain SHBG (human, purified) in phosphate buffered saline with protein (goat) stabilizer.
Preservatives: sodium azide and ProClin® 300.
Each SHBG Calibrator kit contains 6 bottles of ACHITECT Calibrators (2.0mL fill volume per bottle) with the following targeted concentrations:

Cal A - 0.0 nmol/L
Cal B - 2.0 nmol/L
Cal C - 6.0 nmol/L
Cal D - 25.0 nmol/L
Cal E - 125.0 nmol/L
Cal F - 250.0 nmol/L

J. **Substantial Equivalence Information:**

1. Predicate device name(s):

Elecsys®SHBG Immunoassay System

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

k031717

3. Comparison with predicate:

Comparisons	**ARCHITECT® SHBG assay kit**	**Elecsys®SHBG Immunoassay System**
Similarities		
Product Type	Immunoassay	Immunoassay
Methodology	Chemiluminescent Microparticle Immunoassay (CMIA)	Chemiluminescence a solid phase enzyme immunoassay
Intended Use	The ARCHITECT® SHBG assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of sex	Immunoassay for the in vitro quantitative determination of sex hormone-binding globulin in human serum and

Comparisons	**ARCHITECT® SHBG assay kit**	**Elecsys®SHBG Immunoassay System**
	hormone binding globulin (SHBG) in human serum and plasma on the ARCHITECT *i* System.	plasma. The ECLIA is intended for use on the Roche Elecsys® 1010/2010 and MODULAR ANALYTICS E170 (Elecsys module) immunoassay analyzers.
Assay Protocol	Two-step direct sandwich immunoassay	Sandwich principle
Specimen Type	Human serum or plasma (Lithium Heparin, Sodium Heparin, Ammonium Heparin, Potassium EDTA)	Human Serum and Lithium Heparin Plasma
Interpretation of Results	Standard Curve	Standard Curve
Interferences	Non significant interferences with: Hemoglobin, bilirubin, triglycerides, protein	Non significant interferences with: Bilirubin, hemolysis, lipemia, biotin
Measuring Range	0.1 – 250 nmol / L	0.350 – 200 nmol / L
Analytical Sensitivity	0.1 nmol / L	0.35 nmol / L
Analytical Specificity	Non detectable cross-reactivities were found for: AFP, cortisol, 11-Deoxycortisol, Estradiol, testosterone, 5-dihydrotestosterone, TG, TBG and transferrin.	Non detectable cross-reactivities were found for: AFP, CBG, DHT, estradiol, fibrinogen, human IgA, human IgG, plasminogen, TBG, testosterone, TG, transferrin and TSH.

Comparisons	**ARCHITECT® SHBG assay kit**	**Elecsys®SHBG Immunoassay System**
Differences		
Platform	ARCHITECT *i* System	ROCHE Elecsys® 1010/1020 Analyzer and MODULAR ANALYTICS E170
Components	**Microparticles** 1or 4 Bottle(s) (6.6 mL each) Anti-SHBG(mouse monoclonal) coated microparticles in TRIS buffer. Preservative: sodium azide. **Conjugate** 1or 4 Bottle(s) (5.9 mL each) Anti-SHBG(mouse,monoclonal) acridinium-labeled conjugate in phosphate buffer with protein (mouse, bovine) stabilizer. Preservative: sodium azide. **Assay Diluent** 1or 4 Bottle(s) (8.0 mL each) SHBG Assay Diluent containing phosphate buffer with protein (mouse, bovine) stabilizer. Preservative: sodium azide.	**Microparticles** 1 bottle of 6.5mL. Streptavidin-coated microparticles, 0.72 mg/mL; binding capacity: 470 ng biotin/mg microparticles. Preservative. **R1 – Anti-SHBG-Ab~biotin** - 1 bottle (10.0 mL) Biotinylated monoclonal anti-SHBG antibody (mouse) 1.25 mg/L; phosphate buffer 100 mmol/L, pH 7.2. Preservative. **R2 –Anti-SHBG-Ab~Ru** 1 bottle, 10 mL Monoclonal anti-SHBG antibody (mouse) labeled with ruthenium complex 1.25 mg/L; phosphate buffer 100mmol/L, pH 7.2. Preservative

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

STANDARDS
Title and Reference Number
Interference Testing in Clinical Chemistry; Approved Guideline (CLSI EP 7-A)
Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (CLSI EP5-A)

GUIDANCE			
Document Title	**Office**	**Division**	**Web Page**
Points to Consider Guidance Document on Assayed and Unassayed Quality Control Material; Draft	**OIVD**		**http://www.fda.gov/cdrh/ode/99.html**

L. Test Principle:

Chemiluminescent Microparticle Immunoassay (CMIA)

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision evaluations were performed with the ARCHITECT SHBG assay based on CLSI EP5-A. Precision testing was carried out at four different sites. Multiple ARCHITECT SHBG control lots and three serum samples were assayed using one lot of reagent in duplicate, twice a day during 20 days at one site in one instrument. In addition, two lots of reagents were assayed for 10 days in three other instruments at different sites. Each reagent lot used a single calibration curve.

Precision Protocol

	Site 1	Site 2	Site 3	Site 4
Instrument	I2000	I2000sr	I2000	I2000sr
Reagent Lot	Lot 1/Lot 2 10 days/10 days	Lot 1/Lot 2 10 days/10 days	Lot 1/Lot 2 10 days/10 days/5 days	Lot 1/Lot 2 10 days/20 days

Site 1

Panel	N	Mean (nmol/L)	Run to Run SD	Run to Run %CV	Within Run SD	Within Run %CV	Total SD	Total %CV
Low Control	320	8.8	0.50	5.68	0.33	3.81	0.79	8.98
Medium Control	320	25.1	1.48	5.89	1.08	4.30	1.75	6.98
High Control	320	162.9	13.29	8.16	9.48	5.82	17.51	10.75
Human Serum High	160	145.1	19.40	13.37	8.41	5.79	21.26	14.64
Human Serum Medium	160	16.5	1.70	10.29	0.95	5.73	1.70	10.29
Human Serum Low	160	45.3	4.06	8.96	1.64	3.62	6.49	14.33

Site 2

Panel	N	Mean (nmol/L)	Run to Run SD	Run to Run %CV	Within Run SD	Within Run %CV	Total SD	Total %CV
Low Control	320	9.0	0.49	5.44	0.49	5.44	0.57	6.26
Medium Control	320	25.4	1.44	5.66	1.44	5.66	1.49	5.86
High Control	320	163.4	10.05	6.15	10.05	6.15	12.08	7.39
Human Serum High	160	158.9	11.94	7.52	9.74	6.13	12.12	7.63
Human Serum Medium	160	17.7	0.84	4.73	0.76	4.30	0.88	4.95
Human Serum Low	160	50.1	2.88	5.74	2.88	5.74	3.05	6.08

Site 3

Panel	N	Mean (nmol/L)	Run to Run SD	Run to Run %CV	Within Run SD	Within Run %CV	Total SD	Total %CV
Low Control	320	8.5	0.48	5.60	0.40	4.76	0.89	10.48
Medium Control	320	24.2	1.50	6.22	1.09	4.51	1.63	6.72
High Control	320	147.3	9.15	6.21	5.06	3.44	12.28	8.34
Human Serum High	160	143.3	9.74	6.80	6.20	4.33	9.077	6.82
Human Serum Medium	160	17.1	0.88	5.13	0.68	3.97	0.91	5.31
Human Serum Low	160	47.9	2.73	5.70	2.16	4.51	2.76	5.76

Site 4

Panel	N	Mean (nmol/L)	Run to Run SD	Run to Run %CV	Within Run SD	Within Run %CV	Total SD	Total %CV
Low Control	320	9.0	0.66	7.29	0.45	4.98	1.18	13.15
Medium Control	320	24.2	1.27	5.23	1.24	5.12	1.31	5.40
High Control	320	149.0	7.90	5.30	7.70	5.16	8.72	5.85
Human Serum High	160	144.3	8.17	5.66	5.72	3.97	9.53	6.61
Human Serum Medium	160	16.5	1.79	10.87	1.79	10.87	1.85	11.23
Human Serum Low	160	47.2	2.75	5.83	2.51	5.32	2.75	5.83

Data generated in the four sites was evaluated together and the precision results were summarized using SAS.

Panel	N	Mean nmol/L	Run to Run SD	Run to Run %CV	Within Run SD	Within Run %CV	Total SD	Total %CV
Low Control	1280	8.8	0.53	5.97	0.42	4.80	0.88	9.97
Medium Control	1280	24.7	1.42	5.75	1.22	4.94	1.55	6.26
High Control	1280	155.6	10.14	6.51	8.30	5.33	12.91	8.29
Human Serum Low	640	16.9	1.15	6.77	0.86	5.06	1.15	6.77
Human Serum Medium	640	47.6	3.13	6.57	2.34	4.92	4.04	8.48
Human Serum High	640	147.9	15.36	10.4	9.06	6.12	16.49	11.15

b. Linearity/assay reportable range:

The reportable range of the ARCHITECT SHBG assay is 0.1 to 250 nmol/L.

A study was conducted to verify that SHBG supplemented into human serum can be accurately recovered by the ARCHITECT® SHBG assay. 10 human serum samples of known concentration were spiked with additional SHBG resulting in samples ranging from 9.4 – 249 nmol/L. The recovery by the ARCHITECT SHBG assay ranged from 93 – 103%. The sponsor's minimum acceptance criteria for spiked recovery was 90-110%.

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

Calibrators and controls are produced from in house master lots of calibrators and controls. These materials are traceable to the World Health Organization's international standard - NIBSC code 95/560.

Calibrators:

The ARCHITECT® SHBG Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of SHBG in human serum and plasma. Calibrator A contains phosphate buffered saline with protein (goat) stabilizer. Calibrators B to F contain SHBG (human, purified) in phosphate buffered saline with protein (goat) stabilizer.

Preservatives: sodium azide and ProClin® 300.

Each SHBG Calibrator kit contains 6 bottles of ACHITECT Calibrators (2.0mL fill volume per bottle) with the following concentrations:

Cal A - 0.0 nmol/L
Cal B - 2.0 nmol/L
Cal C - 6.0 nmol/L
Cal D - 25.0 nmol/L
Cal E - 125.0 nmol/L
Cal F - 250.0 nmol/L

Controls:

The ARCHITECT® SHBG Controls are for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of SHBG in human serum and plasma. The controls contain SHBG (human, purified) in phosphate buffered saline with protein (goat) stabilizer. Preservatives: sodium azide and ProClin® 300.

Each SHBG control kit contains 3 bottles of controls (4.0 mL fill volume per bottle) with the following target concentrations:

Control Low - 9.0 nmol/L (target) 5.9 to 12.2 nmol/L (range)
Control Medium - 25.0 nmol/L (target) 16.3 to 33.8 nmol/L (range)
Control High - 150.0 nmol/L (target) 90.0 to 210.0 nmol/L (range)

Stability was determined using real time and accelerated studies based upon an in-house protocol for the calibrators and controls. Protocols and acceptance criteria were reviewed and found to be acceptable.

d. Detection limit:

The analytical sensitivity (Limit of Blank) of the ARCHITECT SHBG assay was determined by testing ARCHITECT SHBG Calibrator A (0.0 µg/dL) in replicates of 20, on each of 3 instruments (*i*2000 and *i*2000 SR), using 2 lots of reagents (n = 6 runs). Analytical sensitivity was defined as the concentration at two standard deviations (SD) from the mean of ARCHITECT SHBG Calibrator A rates, and represents the lowest measurable concentration of analyte that can be distinguished from zero. The analytical sensitivity was determined by using the corresponding calibration curve for each run. The analytical sensitivity of the ARCHITECT SHBG assay was calculated to be 0.02 nmol/L.

The potential for High dose hook testing was evaluated on the Architect i2000 SR using two lots of reagents. High Dose Hook effect was tested on two sets of samples with spiked SHBG with concentrations ranging from 78 to 10000 nmol/L. The matrix of one set was calibrator A and the other was a human serum pool. Both sets of samples were tested in triplicate with two lots of reagents. Samples exceeding the calibration range were tested using dilution.

Reported concentrations for samples with a SHBG concentrations greater than Calibrator F (250 nmol/L) were listed as higher than 250 nmol/L. No High Dose Hook effect was observed up to 10000 nmol/L.

e. Analytical specificity:

A study was conducted to evaluate the potential cross-reactivity of the ARCHITECT SHBG assay when tested with the following structurally similar compounds: AFP (alpha fetoprotein), Cortisol, 11-Deoxycortisol, Estradiol, Testosterone, 5-dihydrotestosterone, TG (thyroglobulin), TBG (thyroxin binding globulin) and Transferrin. Aliquots of Calibrator A, containing essentially no residual SHBG, were supplemented with each potential cross-reactant at the concentrations listed in the table below. Each sample was tested in replicates of four using the ARCHITECT SHBG assay based on CLSI Protocol EP7-A.

Compound	Concentration Cross Reactant
AFP	400 ng/mL
Cortisol	100000 ng/mL
11-Deoxycortisol	4000 ng/mL
Estradiol	3600 pg/mL
Testosterone	20000 ng/mL
5-dihydrotestosterone	20000 ng/mL
TG	300 ng/mL
TBG	200 µg/mL
Transferrin	4 mg/mL

No cross-reactivity was observed in the ARCHITECT SHBG with samples containing AFP, Cortisol, 11- Deoxycortisol, Estradiol, Testosterone, 5-dihydrotestosterone, TG, TBG and Transferrin at the tested concentrations.

A study was conducted to evaluate the potential interference from hemoglobin, bilirubin, triglycerides and protein (low and high level) on the ARCHITECT SHBG assay.

Interference testing was performed on the Architect instrument using two lots of reagents based on CLSI Protocol EP7-A. Ten (10) human serum and 10 EDTA plasma based samples (SHBG values covering the assay range), were used to prepare the test panel. Human specimens were spiked with the interferent and non spiked samples were used as the control. All samples were analyzed in four replicates.
The sponsor defined non-interference as SHBG recovery within 90-110%.
There is no significant interference with added hemoglobin at 500 mg/dL.
There is no significant interference with added bilirubin at 20 mg/dL.
There is no significant interference with added triglyceride at 4000 mg/dL.
There is no significant interference with protein at 4 g/dL

There is no significant interference with protein at 12 g/dL in serum samples. There is a significant interference with protein at 12 g/dL in plasma samples. (A limitation is included in the assay labeling)
The following table shows the mean value results to be included in the ARCHITECT SHBG package insert (PI):

	Serum Mean Value	**Plasma Mean Value**	**Mean (Serum and Plasma) Claim in PI**
500 mg/dL Hemoglobin	102	97	**99**
20 mg/dL Bilirubin	99	99	**99**
4000 mg/dL Triglycerides	102	104	**103**
Protein Low	105	103	**104**
Protein High	98	80	**95**

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison was performed testing samples on Architect i2000 SR and i2000 using two lots of reagents at three sites. 626 samples were analyzed. Samples were collected retrospectively. One aliquot of each sample were analyzed with the Architect SHBG at three different sites. Another aliquot of these samples were also analyzed on the Roche Elecsys E170 SHBG.

The results of the study yielded to following comparison data for the ARCHITECT SHBG assay:

Device =1.06(Predicate) + 1.34; r^2=0.922 n=626.

b. Matrix comparison:

20 unlinked, non-surplus fresh whole blood specimens from 20 different donors (10 males and 10 females) were collected in the following tube types: Serum clot tube (no additive) – control tube, Serum separator tubes, K-EDTA, Li-Heparin, Na-Fluoride/K-Oxalate, Na-Citrate, NH4-Heparin, Na-Heparin
The samples were analyzed in triplicate with one lot of SHBG reagents on the ARCHITECT instrument. The sponsor defined non-interference as the mean

concentration difference of the donor cohort for each test condition should be less than or equal to 10% compared to the control condition. A statement was added to the labeling stating that NaF and citrate samples should not be used.

Test Condition	N	Mean of difference of all samples [%]
Serum no additive	20	Control Condition
SST	20	-1.1
K-EDTA	20	-8.5
Li-Heparin	20	-2.1
Na-Fluoride/K-Oxalate	20	-18.3
Na-Citrate	20	-19.9
NH4-Heparin	20	-2.9
Na-Heparin	20	-2.6

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):

   Not Applicable

4. Clinical cut-off:

   Not Applicable

5. Expected values/Reference range:

Studies were conducted to establish the reference interval for a given population using the ARCHITECT SHBG assay.

A total of 319 samples were analyzed with one lot of reagents. 152 serum samples from females and 167 from males were used for the study.

The following table summarizes the values established as reference interval at the 2.5th and 97.5th percentiles.

Adults	Male	Female
N	167	152
Mean	33.6	56.8
90%CI	31.4 -35.7	52.23 – 61.4
Median	30.4	48.2
CI*	28.2 -33.0	43.4 – 53.2
Range	79.1	142.5
IQR	21.6	44.7
Percentile Distribution		
2.5^{th}	11.2	11.7
25^{th}	19.9	32.3
50^{th}	30.4	48.2
75^{th}	41.5	77.0
97.5	78.1	137.2

CI males 91.2% Females 91.2%

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.