

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

A. 510(k) Number:

k070810

B. Purpose for Submission:

Clearance of a new device

C. Measurand:

Theophylline

D. Type of Test:

Quantitative

E. Applicant:

Biokit S.A.

F. Proprietary and Established Names:

ARCHITECT i Theophylline Reagents and Calibrators

G. Regulatory Information:

1. Regulation section:

21 CFR § 862.3880, Theophylline test system
21 CFR § 862.3200, Calibrator, Drug Specific

2. Classification:

Class II

3. Product code:

LGS, Theophylline test system
DLJ, Calibrator, Drug Specific

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

The ARCHITECT i Theophylline assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of theophylline in human serum or plasma on the ARCHITECT i System with STAT protocol capability. Theophylline is used in the treatment of bronchospasm associated with bronchial asthma, chronic bronchitis and pulmonary emphysema. The measurements obtained are used in the diagnosis and treatment of

theophylline overdose or in monitoring levels of theophylline to help ensure appropriate therapy.

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

2. Indication(s) for use:
See intended use above.
3. Special conditions for use statement(s):
For prescription use only
4. Special instrument requirements:
ARCHITECT Instrument System platforms

I. Device Description:

The ARCHITECT *i* Theophylline assay is a one-step STAT immunoassay for the quantitative determination of theophylline in human serum or plasma using CMIA technology, with flexible assay protocols, referred to as Chemiflex. Sample, anti-theophylline coated paramagnetic microparticles, and theophylline acridinium-labeled conjugate are combined to create a reaction mixture. The antitheophylline coated microparticles bind to theophylline present in the sample and to the theophylline 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 theophylline in the sample and the RLUs detected by the ARCHITECT *i* System optics.

J. Substantial Equivalence Information:

1. Predicate device name(s):
AxSYM Theophylline II assay
2. Predicate 510(k) number(s):
k953016
3. Comparison with predicate:

Similarities
<ul style="list-style-type: none"> - Both assays are Immunoassays. - The device and the predicate have similar Methodology: while the device uses the Chemiluminescent Microparticle Immunoassay (CMIA), the predicate device uses Fluorescence Polarization Immunoassay (FPIA). - Both assays have similar Intended Use - The measurements obtained are used in the diagnosis and treatment of theophylline overdose or in monitoring levels of theophylline to ensure appropriate therapy. - Both assays are intended to be used in Clinical Laboratories with Competitive Immunoassay Protocol. - Both assays interpret results with Standard Curve. Both assays have a Measurement range between 0.82 µg/mL and 40 µg/mL. - Internal Reference Calibrators are manufactured gravimetrically using USP Reference Standard Theophylline. The ARCHITECT i Theophylline Calibrators are matched to the internal Reference Calibrators. - Calibrator levels: both have 6 different calibrator levels.

Differences
<ul style="list-style-type: none"> - The device, the ARCHITECT i Theophylline, is intended to be run in the ARCHITECT i System and the predicate, the AxSYM Theophylline II, is intended to be run in the AxSYM System. - The device has a 2 components reagent and the predicate has a 3 components reagent. The composition and vial volumes are also different. - Specimen Type: both assays can use serum samples. They differ in the plasma tube types. The device: Serum or Plasma (collected in lithium heparin, potassium EDTA, sodium citrate, sodium fluoride/potassium oxalate and sodium heparin tubes). The predicate device: Serum or Plasma (collected in sodium heparin, citrate, EDTA or oxalate collection tubes) - Calibrator Matrix: Device: normal human serum, Predicate: Recalcified human plasma

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

- 1) Points to Consider Guidance Document on Assayed and Unassayed Quality Control Material; Draft
- 2) CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods
- 3) CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach
- 4) CLSI EP7-A, Interference Testing in Clinical Chemistry
- 5) CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples
- 6) CLSI EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantitation

L. Test Principle:

The ARCHITECT i Theophylline assay is a one-step STAT immunoassay for the quantitative determination of theophylline in human serum or plasma using CMIA technology, with flexible assay protocols, referred to as Chemiflex. Sample, anti-theophylline coated paramagnetic microparticles, and theophylline acridinium-labeled conjugate are combined to create a reaction mixture. The antitheophylline coated microparticles bind to theophylline present in the sample and to the theophylline 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 theophylline 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:*

A study was conducted to determine the total precision of the ARCHITECT i Theophylline assay. The sponsor's acceptance criterion was a total CV of $\leq 10\%$. Precision was performed with the ARCHITECT i Theophylline assay based on the CLSI EP5-A2. Two ARCHITECT i Systems were used along with 2 lots of reagents and 2 lots of calibrators. Each reagent lot used a single calibration curve along the study. The assay was run twice a day for 20 days using 3 Multiconstituent Controls (MCC) and 2 serum (panel) levels in replicates of 2. The 2 human serum based samples were prepared by adding theophylline concentrations into a pool of human sera at final concentrations targeted at 7 and 26 $\mu\text{g/mL}$. The following tables show the mean of the reported theophylline concentration for each control and panel. Also the values for the total, within run, between run and between day %CV were calculated.

Instrument: iSR03055

Reagent & Calibrator lot: 025061000 023061000

Days	20									
Runs	2									
Replicates per run	2									
Level	MCC level 1		MCC level 2		MCC level 3		Panel 7 µg/mL		Panel 26 µg/mL	
Theophylline (µg/mL)	5		15.2		30.4		7.5		26.4	
Preliminary SD	-		-		-		-		-	
Mean	4.8		14.5		28.2		7.5		26.4	
	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Total	0.28	5.5%	0.83	5.4%	1.40	4.6%	0.44	5.9%	1.67	6.3%
Within run	0.21	4.1%	0.57	3.8%	0.96	3.2%	0.29	3.9%	1.09	4.1%
Between run	0.00	0.0%	0.37	2.4%	0.92	3.0%	0.19	2.5%	0.83	3.2%
Between day	0.18	3.7%	0.47	3.1%	0.44	1.4%	0.26	3.5%	0.96	3.6%

Instrument: iSR03064

Reagent & Calibrator lot: 026061000 024061000

Days	20									
Runs	2									
Replicates per run	2									
Level	MCC level 1		MCC level 2		MCC level 3		Panel 7 µg/mL		Panel 26 µg/mL	
Theophylline (µg/mL)	5		15.2		30.4		7.5		26.4	
Preliminary SD	-		-		-		-		-	
Mean	5.0		15.4		31.2		7.9		29.3	
	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Total	0.24	4.8%	0.78	5.1%	1.75	5.8%	0.44	5.9%	1.85	7.0%
Within run	0.16	3.2%	0.49	3.2%	1.20	3.9%	0.24	3.3%	1.08	4.1%
Between run	0.12	2.4%	0.36	2.4%	1.00	3.3%	0.29	3.9%	1.32	5.0%
Between day	0.13	2.7%	0.49	3.2%	0.79	2.6%	0.22	3.0%	0.73	2.8%

b. *Linearity/assay reportable range:*

A study was conducted to evaluate the recovery of dilutions of the ARCHITECT iTheophylline assay. The sponsor's acceptance criterion was a recovery of $\pm 10\%$. The study was performed with the ARCHITECT iTheophylline assay using CLSI EP6-A. Five pooled serum samples, (frozen), and Calibrator F were diluted manually with the ARCHITECT iTheophylline Calibrator A. Each specimen sample was diluted to have 11 concentration levels. Each sample was diluted using the ARCHITECT iTheophylline Calibrator A in different proportions. The recovery of assay was evaluated by comparing observed versus expected values across the expected range.

Sample A Dilution number	Mean Measured Concentration (µg/mL) (n=2)	% CV	Dilution factor	% Recovery Dilution
1	11.3	0.3	-	
2	10.7	4.4	1.11	105
3	9.5	1.9	1.25	105
4	8.4	3.7	1.43	106
5	7.6	1.3	1.67	112
6	5.8	4.0	2.00	103
7	4.7	4.3	2.50	104
8	3.4	2.9	3.33	100
9	2.4	1.2	5.00	106
10	1.2	10.0	10.00	106
11	0.0	-		
Mean				105

Sample B Dilution number	Mean Measured Concentration (µg/mL) (n=2)	% CV	Dilution factor	% Recovery Dilution
1	16.2	5.8	-	
2	14.1	4.2	1.11	97
3	12.4	1.5	1.25	96
4	11.6	3.5	1.43	102
5	9.6	4.0	1.67	99
6	8.0	3.8	2.00	99
7	6.6	0.5	2.50	102
8	4.9	0.3	3.33	101
9	3.2	0.5	5.00	99
10	1.6	6.0	10.00	99
11	0.0	-		
Mean				99

Sample C Dilution number	Mean Measured Concentration (µg/mL) (n=2)	% CV	Dilution factor	% Recovery Dilution
1	18.5	1.9		
2	16.7	3.9	1.11	100
3	15.6	1.5	1.25	105
4	14.3	5.5	1.43	111
5	11.4	7.3	1.67	103
6	9.5	4.7	2.00	103
7	8.3	3.5	2.50	112
8	5.8	4.3	3.33	104
9	3.9	8.0	5.00	105
10	1.9	8.7	10.00	103
11	0.0	-		
Mean				105

Sample D Dilution number	Mean Measured Concentration (µg/mL) (n=2)	% CV	Dilution factor	% Recovery Dilution
1	31.2	0.6		
2	29.8	0.5	1.11	106
3	25.5	3.6	1.25	102
4	21.9	0.0	1.43	100
5	18.7	0.2	1.67	100
6	15.4	1.9	2.00	99
7	13.2	1.0	2.50	106
8	9.6	2.3	3.33	102
9	6.3	3.6	5.00	101
10	3.2	8.5	10.00	103
11	0.0	-		
Mean				102

Sample E Dilution number	Mean Measured Concentration (µg/mL) (n=2)	% CV	Dilution factor	% Recovery Dilution
1	34.5	1.8	-	
2	32.9	6.1	1.11	106
3	29.9	8.7	1.25	108
4	24.4	1.6	1.43	101
5	21.7	2.1	1.67	105
6	17.5	2.9	2.00	101
7	15.2	1.8	2.50	110
8	10.9	3.1	3.33	105
9	7.3	2.7	5.00	106
10	3.4	3.4	10.00	99
11	0.0	-		
Mean				105

Calibrator F Dilution number	Mean Measured Concentration (µg/mL) (n=2)	% CV	Dilution factor	% Recovery Dilution
1	38.4	*	-	
2	35.4	2.8	1.11	102
3	31.8	5.9	1.25	104
4	27.0	3.5	1.43	100
5	25.3	6.4	1.67	110
6	19.9	2.2	2.00	104
7	17.1	6.9	2.50	111
8	12.0	2.9	3.33	104
9	8.2	0.6	5.00	107
10	3.9	3.5	10.00	102
11	0.0	-		
Mean				105

Dilution number 6 is the dilution 1:2

* One of the replicates was out of range

Grand Mean % Recovery for samples =	103
Grand Mean % Recovery of 1:2 dilution for samples =	101

Mean % Recovery for Calibrator F =	105
Recovery of 1:2 dilution for Calibrator F =	104

All samples and Calibrator F % Recovery	
Grand Mean	104
Grand Mean Dilution (1:2)	101

A recovery study was conducted to verify that theophylline supplemented into human serum can be accurately recovered by the ARCHITECT iTheophylline assay. The sponsor's acceptance criterion for the mean recovery is 100% +/- 10%. Five pooled serum samples (frozen) were supplemented with known theophylline concentrations and tested in duplicates using the ARCHITECT iTheophylline assay. The 5 human serum sample pools used for the study had endogenous levels of theophylline ranging from 1.2 to 10.8 µg/mL. Additional theophylline pools were prepared and added to the sample pools above. Target

values of the concentrations of these pools were 5, 10, 20 and 30 µg/mL.

Sample Pool	Endogenous Concentration (µg/mL)	% CV	Spiked Theophylline (µg/mL)	% CV	Expected (µg/mL)	Observed (µg/mL)	% CV	% Recovery	Mean % Recovery
1	1.2	3.0	5.8	2.5	7.0	6.6	0.5	94.3	98.0
			11.9	2.0	13.1	13.4	5.3	102.3	
			23.5	3.3	24.7	23.8	1.7	96.4	
			31.7	5.1	32.9	32.5	2.1	98.8	
4	3.8	1.6	5.8	2.5	9.6	9.7	2.5	101.0	101.0
			11.9	2.0	15.7	16.1	1.5	102.5	
			23.5	3.3	27.3	27.0	2.0	98.9	
			31.7	5.1	35.5	36.1	6.2	101.7	
6	5.2	3.9	5.8	2.5	11.0	10.9	3.8	99.1	99.9
			11.9	2.0	17.1	16.4	0.5	95.9	
			23.5	3.3	28.7	28.7	13.4	100.0	
			31.7	5.1	36.9	38.6	4.5	104.6	
9	8.0	6.9	5.8	2.5	13.8	13.6	0.0	98.6	98.5
			11.9	2.0	19.9	19.4	4.5	97.5	
			23.5	3.3	31.5	31.3	0.2	99.4	
			31.7	5.1	39.7	* 40.2	1.4		
11	10.8	5.2	5.8	2.5	16.6	16.8	5.2	101.2	99.6
			11.9	2.0	22.7	22.7	3.9	100.0	
			23.5	3.3	34.3	33.5	1.6	97.7	
			31.7	5.1	* 42.4	* 42.0	0.9		
Grand mean:									99.4

* These values are above the calibration range and were removed from the data analysis.

The results from the two studies support an assay range claim is 0.05 µg/mL (the limit of detection) to 40 µg/mL. Specimens with a theophylline value exceeding 40.0 µg/mL are reported as "> 40.0 µg/mL" and may be diluted with the Manual Dilution Procedure as it is described in the ARCHITECT i Theophylline Reagent Package Insert.

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
 The ARCHITECT i Theophylline Calibrators are for the calibration of the ARCHITECT i System with STAT protocol capability when used for the quantitative determination of theophylline in human serum or plasma. Each i Theophylline calibrator kit contains 6 bottles of ARCHITECT i Theophylline Calibrators (4.0 mL each). Calibrator materials A-F contain normal human serum. Calibrator materials B-F contain theophylline with sodium azide as a preservative:

Cal A 0 µg/mL
 Cal B 2.5 µg/mL
 Cal C 5.0 µg/mL
 Cal D 10.0 µg/mL
 Cal E 20.0 µg/mL
 Cal F 40.0 µg/mL

Internal Reference Calibrators are manufactured gravimetrically using purified synthetic Theophylline from the US Pharmacopeia (USP) Reference Standard Theophylline (Ref. 1653004). The ARCHITECT i Theophylline Calibrators are matched to the Internal Reference Calibrators with a maximum allowed error of $\pm 1.5\%$ when compared to the reference material.

The sponsor's accelerated stability studies support a stability of 13.66 months, as samples up to this time are within the sponsor's acceptance criteria of $\pm 15\%$ of the assigned value. The sponsor will claim a stability of 9 months.

d. Detection limit:

The sponsor determined the limit of detection for the assays using CLSI EP17-A, using proportions of false positives less than 5% and false negatives less than 5%. The limit of detection and limit of the blank were performed on 2 instruments and one lot of reagents and calibrators were used for each instrument. A panel of 4 samples with a low theophylline concentration and 1 sample with 0 $\mu\text{g/mL}$ was used. The samples with theophylline were prepared by diluting calibrator B (2.5 $\mu\text{g/mL}$) into calibrator A (0 $\mu\text{g/mL}$) to achieve concentrations of 0.1, 0.5, 0.8, and 1.0 $\mu\text{g/mL}$. Three runs were performed for each reagent lot. Each run consisted of 20 replicates of Calibrator A (0 $\mu\text{g/mL}$) and 5 replicates of each panel member. A total of 60 replicates of Calibrator A and 15 replicates of each panel member were analyzed. Results are summarized below:

Limit of the Blank (LoB), Lot 02506I000 (VL1):	0.003 $\mu\text{g/mL}$
Limit of the Blank (LoB), Lot 02606I000 (VL2):	0.004 $\mu\text{g/mL}$
Final Limit of the Blank :	0.004 $\mu\text{g/mL}$

Limit of Detection (LoD), Lot 02506I000 (VL1):	0.044 $\mu\text{g/mL}$
Limit of Detection (LoD), Lot 02606I000 (VL2):	0.052 $\mu\text{g/mL}$
Final Limit of Detection:	0.05 $\mu\text{g/mL}$

Results obtained are based on the highest obtained value with the two lots.

e. Analytical specificity:

A study was conducted to evaluate the potential cross-reactivity of the

ARCHITECT iTheophylline assay when tested with structurally similar compounds as:

Caffeine
8-Chlorotheophylline
1,3-Dimethyl uric acid
Dyphylline
1-Methyl uric acid
1-Methylxanthine
Theobromine
Paraxanthine
3-Methylxanthine

A pool of sera containing undetectable theophylline was split into 3 different groups. One was spiked with theophylline to reach a target concentration of 7 µg/mL, the second group was spiked with theophylline to reach a target concentration of 28 µg/mL and the third group was not spiked with theophylline.

The three different groups of sera were used to spike the following possible interferants: Caffeine, 8-Chlorotheophylline, 1,3-Dimethyl uric acid, Dyphylline, 1-Methyl uric acid, 1-Methylxanthine, Theobromine, Paraxanthine, 3-Methylxanthine. Therapeutic interferants were dissolved at concentrations 20 times greater than the desired testing concentrations. Therapeutic concentrates were spiked into the 3 samples above to prepare the test sample. An equal volume of the interferant diluent was spiked to the samples to prepare the control sample. Each sample was tested in replicates of three using the ARCHITECT iTheophylline assay. The testing was based on guidance from the Clinical and Laboratory Standards Institute, document CLSI Protocol EP7-A. The % recovery specification is a mean % recovery of 100% ± 10%. The specificity of the ARCHITECT i Theophylline assay is designed to have a cross-reactivity concentration less than 0.82 µg/mL when tested with the compounds in the following table. The interferants of 1-Methylxanthine and 3-Methylxanthine did not meet specification requirements and are addressed in the reagent package insert.

Therapeutic Interferent (µg/mL)	Sample	Expected	Observed	Difference (0 µg/mL only)	% Recovery	Mean % Recovery
Caffeine (10)	1	0.2	0.3	0.1		101.0
	2	7.3	7.5		102.5	
	3	28.0	27.9		99.5	
8-Chlorotheophylline (10)	1	0.2	0.3	0.1		99.5
	2	7.3	7.4		101.5	
	3	28.0	27.4		97.6	
1,3-Dimethyl uric acid (100)	1	0.2	0.8	0.6		102.5
	2	7.3	7.7		105.1	
	3	28.0	28.0		99.9	
Dyphylline (100)	1	0.2	0.7	0.5		103.2
	2	7.3	7.8		106.5	
	3	28.0	28.0		99.8	
1-Methyl uric acid (100)	1	0.2	0.2	0.0		95.2
	2	7.5	7.4		98.3	
	3	29.0	26.7		92.2	
1-Methylxanthine (40)	1	0.2	1.4	1.2		114.4
	2	7.1	8.8		124.1	
	3	27.4	28.6		104.6	
Theobromine (100)	1	0.2	0.3	0.1		105.3
	2	7.3	7.6		104.3	
	3	27.3	29.0		106.3	
Paraxanthine (50)	1	0.2	0.3	0.1		103.8
	2	7.3	7.5		102.7	
	3	28.0	29.4		104.9	
3-Methylxanthine (8)	1	0.2	1.5	1.3		109.8
	2	7.3	8.4		115.0	
	3	28.0	29.3		104.5	

A second 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 Theophylline assay. Interference testing was performed on the Architect i System using one lot of reagents. Testing was performed based on guidance from the Clinical and Laboratory Standards Institute document CLSI Protocol EP7-A2. Five human serum samples with theophylline concentrations targeted at 2.5, 5, 10, 20 and 35 µg/mL were used to prepare the interfering panel. These human serum samples were spiked with the interferant for the test sample and interferant diluent was spiked into the samples to prepare the control sample. The tables in the result section identify the final interferant concentration. All samples were analyzed in three replicates. No influence from the endogenous interferants listed below was observed during the study. Results are summarized below:

Interferent	Sample	Expected (µg/mL)	Observed (µg/mL)	% Recovery	Grand Mean % Recovery
Hemoglobin 500 mg/dL	1	3.0	2.9	97.9	94.2
	2	5.7	5.4	95.7	
	3	11.6	10.9	94.0	
	4	21.8	21.1	96.9	
	5	30.8	26.7	86.6	
Bilirubin 20 mg/dL	1	2.9	2.8	96.9	98.8
	2	5.3	5.2	98.9	
	3	11.0	10.7	97.3	
	4	20.7	21.5	103.9	
	5	29.7	28.8	97.0	
Triglycerides 2000 mg/dL	1	2.8	2.8	101.5	102.4
	2	5.3	5.2	99.0	
	3	10.9	11.3	103.5	
	4	21.3	20.8	97.5	
	5	27.3	30.1	110.4	
Protein 10 g/dL	1	2.7	2.9	96.9	95.7
	2	5.0	5.4	97.5	
	3	10.5	10.7	95.8	
	4	19.9	21.8	96.7	
	5	29.2	31.5	91.6	
Protein 3 g/dL	1	3.0	3.0	100.6	96.2
	2	5.5	5.6	101.3	
	3	11.2	11.2	100.1	
	4	22.5	20.8	92.5	
	5	34.4	29.8	86.6	
RF 500 IU/mL	1	2.7	2.7	99.0	100.0
	2	5.0	5.2	103.0	
	3	10.5	10.4	98.8	
	4	19.9	20.5	102.8	
	5	29.2	28.1	96.3	
HAMA 1000 ng/mL	1	2.8	2.8	99.0	100.6
	2	5.1	5.2	100.6	
	3	11.1	10.8	96.9	
	4	19.9	20.4	102.6	
	5	29.3	30.5	104.1	

f. *Assay cut-off:*
Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

A study was conducted to evaluate the correlation of the ARCHITECT iTheophylline Reagent on the ARCHITECT i System and another commercially available diagnostic kit. The method comparison was performed by testing samples on the ARCHITECT i System and on the AxSYM based on CLSI EP9-A2. One hundred ninety-eight (198) serum samples covering the possible concentration range from 1.4 to 39.5 with the ARCHITECT iTheophylline assay and from 1.4 to 37.6 with the commercially available diagnostic kit were analyzed.

Passing & Bablock regression analysis gave the following relationship:
Device = 0.9917(Predicate) + 0.0836; r = 0.9938.

b. *Matrix comparison:*

A study was conducted to evaluate the use of different anticoagulants (K-EDTA, Na-Citrate, Na-Fluoride/K-Oxalate, Na-Heparin, and Li-Heparin) and determine which tubes can be used when determining the theophylline level of a patient. Serum tubes without additives were used as the control.

One hundred twenty (120) fresh (less than 24 hours from the time of draw) blood from 20 different donors, were analyzed in triplicates with one lot of Theophylline reagent. Each of the 20 sets of serum/plasma tubes were spiked with theophylline at 10 different concentrations: 2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, and 35 µg/mL. Two tubes of each collecting tube were used for each spiking level. The sponsor's acceptance criterion was the recovery compared to the serum tube to be within ±10%. Results are summarized below:

Test Condition	N	Mean % recovery vs. Serum	Acceptance Criteria met?
Serum no additive	20	Control Condition	
K-EDTA	20	100.8	Yes
Na-Citrate	20	101.2	Yes
Na-Fluoride/K-Oxalate	20	100.5	Yes
Na-Heparin	20	101.1	Yes
Li-Heparin	20	100.6	Yes

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:

The expected values for the ARCHITECT i Theophylline have been established based on bibliographic references.

The statement presented in the package insert is as follows:

Strong correlations have been shown between theophylline serum levels for both therapeutic and toxic effects. In most patients, theophylline serum concentrations of 10 to 20 µg/mL effectively suppress chronic asthmatic and other

bronchospastic symptoms.⁽¹³⁻¹⁶⁾ Serum concentrations of 5 to 10 µg/mL theophylline reportedly control apneic spells in neonates without causing apparent side effects.⁽¹³⁻¹⁶⁾ Peak concentrations above 20 µg/mL are often associated with toxicity.⁽¹³⁻¹⁶⁾ Adverse effects associated with serum concentrations above 20 µg/mL include nausea, headache, diarrhea, and at higher levels, vomiting, gastrointestinal bleeding, seizures and cardiac arrhythmias.⁽⁴⁾

4. Jacobs MH, Senior RM, Kessler G. Clinical experience with theophylline. Relationships between dosage, serum concentration, and toxicity. *JAMA* 1976;235(18):1983-6.

13. Hendeles L, Weinberger M. Theophylline: therapeutic use and serum concentration monitoring. In: Taylor WJ, Finn AL, editors. *Individualizing Drug Therapy: Practical Applications of Drug Monitoring* New York, NY: Gross, Townsend, Frank; 1981:Vol 1, 31–65.

15. Bierman CW, Williams PV. Therapeutic monitoring of theophylline: rationale and current status. *Clin Pharmacokinet* 1989;17(6):377–84.

16. Glynn-Barnhart A, Hill M, Szeffler SJ. Sustained release theophylline preparations: practical recommendations for prescribing and therapeutic drug monitoring. *Drugs* 1988;35:711–26.

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.