

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

A. 510(k) Number:
k090358

B. Purpose for Submission:
New device

C. Measurand:
Valproic acid

D. Type of Test:
Quantitative immunoassay and calibrators

E. Applicant:
Abbott Laboratories

F. Proprietary and Established Names:
ARCHITECT *i*Valproic Acid Immunoassay and ARCHITECT *i*Valproic Acid
Calibrators (A-F)

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
<u>Enzyme</u> <u>Immunoassay,</u> <u>Valproic Acid</u> <u>(LEG)</u>	<u>Class II</u>	<u>21 CFR 862.3645,</u> <u>Neuroleptic drugs</u> <u>radioreceptor assay test</u> <u>system.</u>	<u>91 CLINICAL</u> <u>TOXICOLOGY</u> <u>(TX)</u>
<u>Calibrators</u> <u>(DLJ)</u>	<u>Class II</u>	<u>21 CFR 862.3200,</u> <u>Clinical toxicology</u> <u>calibrator</u>	

H. Intended Use:

1. Intended use(s):

Reagents

The ARCHITECT *i*Valproic Acid assay is an *in vitro* chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of valproic acid, an anticonvulsant drug, in human serum or plasma on the ARCHITECT *i* System with *STAT* protocol capability. The measurements obtained are used in monitoring levels of valproic acid to help ensure appropriate therapy.

Calibrators

The ARCHITECT *i*Valproic Acid Calibrators are for the calibration of the

ARCHITECT i System with STAT protocol capability when used for the quantitative determination of valproic acid in human serum or 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:

Evaluations represented in the 510(k) were performed on the ARCHITECT i2000_{SR} with STAT protocol capability.

I. Device Description:

The assay consists of the following reagents:

Anti-valproic acid (mouse, monoclonal) coated goat anti-mouse microparticles in buffer with protein (bovine) stabilizer and preservative; valproic acid acridinium-labeled conjugate in buffer with surfactant and preservative; ARCHITECT i Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide; ARCHITECT i Trigger Solution containing 0.35 N sodium hydroxide; ARCHITECT i Wash Buffer containing phosphate buffered saline solution and antimicrobial agent.

Calibrator:

The ARCHITECT iValproic Acid Calibrator set is a six-level set (0, 9, 18, 36, 75, 150 µg/mL or Calibrators A to F) of single analyte (valproic acid) calibrators, in a human serum matrix, with sodium azide. The human serum used in the calibrators is nonreactive for HBsAg, HIV-1 Ag or HIV-1 RNA, anti-HCV, HCV RNA, and anti-HIV-1/HIV-2.

J. Substantial Equivalence Information:

1. Predicate device name(s):

AxSYM Valproic Acid assay

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

k941615

3. Comparison with predicate:

Characteristics	Device	Predicate
Methodology	Chemiluminescent Microparticle Immunoassay (CMIA)	Fluorescence Polarization Immunoassay (FPIA)

Characteristics	Device	Predicate
Intended Use	The ARCHITECT <i>i</i> Valproic Acid assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of valproic acid, an anticonvulsant drug, in human serum or plasma on the ARCHITECT <i>i</i> System with <i>STAT</i> protocol capability. The measurements obtained are used in monitoring levels of valproic acid to help ensure appropriate therapy.	The AxSYM Valproic Acid assay is a reagent system for the quantitative measurement of valproic acid, an anticonvulsant drug, in serum or plasma. The measurements obtained are used in monitoring levels of valproic acid to ensure appropriate therapy.
Where Used	Clinical Laboratories	Clinical Laboratories
Assay Protocol	Competitive	Competitive
Interpretation of Results	Standard Curve	Standard Curve
Measuring Range	2.00 µg/mL–150.00 µg/mL	0.70 µg/mL–150.00 µg/mL
Specimen Type	Serum or Plasma (collected in lithium heparin, sodium heparin, potassium EDTA, or sodium EDTA, collection tubes)	Serum or Plasma (collected in heparin, citrate, EDTA, or oxalate collection tubes)
Antibody	Anti-valproic acid (mouse, monoclonal) coated goat anti-mouse (GAM) microparticles in TRIS buffer with protein (bovine) stabilizer. Preservative: ProClin 950.	Valproic Acid Antiserum (Sheep, Polyclonal) in Phosphate buffer with protein stabilizers. Preservative: Sodium Azide.

Calibrator	Device	Predicate
Intended Use	The ARCHITECT <i>i</i> Valproic Acid Calibrators are for the calibration of the ARCHITECT <i>i</i> System with <i>STAT</i> protocol capability when used for the quantitative determination of valproic acid in human serum or plasma.	The AxSYM Valproic Acid Standard Calibrators are for the standard calibration of the AxSYM System when used for the quantitative measurement of valproic acid in human serum or plasma.
Levels	6 levels	6 levels
Matrix	Human serum	Human serum

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

CLSI Documents:

1. EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods
2. EP9-A2: Method Comparison and Bias Estimation Using Patient Samples
3. EP17-A: Protocol for Demonstration, Verification, and Evaluation of Limits of Detection and Quantitation
4. EP7-A: Interference Testing in Clinical Chemistry

L. Test Principle:

The ARCHITECT iValproic Acid assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of valproic acid in human serum or plasma. Anti-valproic acid coated paramagnetic microparticles, and valproic acid acridinium-labeled conjugate are combined to create a reaction mixture. The anti-valproic acid coated microparticles bind to valproic acid present in the sample and to the valproic acid 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 valproic acid 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:*

Precision was evaluated at the manufacturer's site on three ARCHITECT *i* 2000SR instruments using three lots of reagents and one lot of calibrators. The assay was run twice a day for 20 days using three levels of Abbott Immunoassay-MCC (Liquid) and four levels of patient serum panels in replicates of two, resulting in a total of 80 replicates for each control and panel. Results are shown below.

Sample	Instrument	Reagent Lot	n	Mean (ug/mL)	Within-Run		Between-Run		Total	
					SD	%CV	SD	%CV	SD	%CV
Level 1	1	1	80	38.50	1.10	2.86	0.820	2.130	1.38	3.58
	2	2	80	37.16	0.89	2.38	0.299	0.805	1.00	2.69
	3	3	80	36.51	1.11	3.05	0.485	1.328	1.23	3.37
Level 2	1	1	80	79.79	2.96	3.71	1.530	1.918	3.83	4.80
	2	2	80	75.55	1.91	2.52	0.513	0.679	2.32	3.07
	3	3	80	76.39	3.10	4.05	0.000	0.000	3.10	4.06
Level 3	1	1	80	142.61	3.91	2.74	1.422	0.997	4.16	2.92
	2	2	80	140.97	4.91	3.48	0.000	0.000	5.39	3.82
	3	3	80	141.43	4.63	3.27	3.375	2.386	5.73	4.05

Sample	Instrument	Reagent Lot	n	Mean (ug/mL)	Within-Run		Between-Run		Total	
					SD	%CV	SD	%CV	SD	%CV
Panel 1	1	1	80	21.30	0.85	3.97	0.151	0.709	1.00	4.69
	2	2	80	21.03	0.53	2.52	0.143	0.680	0.67	3.19
	3	3	80	20.18	0.58	2.87	0.362	1.794	0.72	3.57
Panel 2	1	1	80	52.28	1.75	3.34	0.000	0.000	1.96	3.75
	2	2	80	49.70	1.53	3.07	0.477	0.960	1.66	3.34
	3	3	80	49.68	1.34	2.70	0.323	0.650	1.55	3.12
Panel 3	1	1	80	103.23	3.82	3.70	0.000	0.000	4.10	3.97
	2	2	80	99.54	2.80	2.81	0.000	0.000	3.02	3.03
	3	3	80	100.83	3.00	2.98	0.000	0.000	3.45	3.42
Panel 4	1	1	80	119.28	3.98	3.33	1.335	1.119	4.38	3.67
	2	2	80	115.71	3.85	3.33	1.119	0.967	4.01	3.47
	3	3	80	116.88	4.03	3.45	0.000	0.000	4.49	3.84

Additionally, precision at the lower end of the assay range was evaluated. Results are tabulated below.

			Within-Run		Between-Run		Total	
Sample	N	Mean (µg/mL)	SD	%CV	SD	%CV	SD	%CV
Panel 1 (~3.00 ug/mL target)	50	2.79	0.131	4.7	0.000	0.0	0.134	4.8
Panel 1 (~8.00 ug/mL target)	50	7.52	0.212	2.8	0.078	1.0	0.240	3.2
Panel 1 (~15.00 ug/mL target)	50	14.70	0.355	2.4	0.130	0.9	0.398	2.7

b. Linearity/assay reportable range:

The claimed measurement range of the ARCHITECT *i* Valproic Acid assay is 2.0 µg/mL to 150.00 µg/mL.

Recovery:

A study was conducted to demonstrate that valproic acid supplemented into human serum can be accurately recovered by the ARCHITECT *i* Valproic Acid assay. A total of 10 human serum and plasma specimens (5 serum and 5 plasma) and the ARCHITECT *i* Valproic Acid Calibrator A (recalcified nonreactive human plasma) were supplemented with a valproic acid stock solution of concentrations of 0, 15, 30, 75 and 113 µg/ml (determined independently of the new assay). The samples were tested in duplicate using

the ARCHITECT *i*Valproic Acid assay. The percent recovery was calculated by the equation:

$$\% \text{ Recovery} = (\text{Observed } (\mu\text{g/mL}) / \text{Expected } (\mu\text{g/mL})) \times 100$$

The expected concentrations were based on the gravimetric preparation using USP valproic acid material of known concentration. Results from serum samples are shown below. Overall, similar results were observed for the plasma samples evaluated.

Spike level Known concentrations (ug/mL)	Observed Mean (μg/mL)	Avg (n=5) % Recovery
15	0.01	92%
30	14.46	98.6%
75	31.74	98.4%
113	75.97	101.6%

To demonstrate linearity across the assay range, five individual serum samples and five individual plasma samples were each spiked with a concentrated valproic acid stock solution to target sample concentration values greater than 140ug/mL but less than 160 ug/mL. Each sample was diluted using the ARCHITECT *i*Valproic Acid Calibrator A to 11 concentrations spanning the entire assay range. Recovery relative to the high sample concentration determined using the ARCHITECT *i*Valproic Acid assay are shown below for a representative serum sample. Overall, similar results were observed for plasma samples:

Dilution factor	Expected concentration (ug/mL) based on dilution of the high sample measured on the ARCHITECT <i>i</i> Valproic Acid	Observed concentrations (ug/mL)	Percent recovery
1		148.53	---
1.11	133.81	131.02	98%
1.33	111.68	106.76	96%
1.67	88.94	87.60	98%

2	74.27	72.03	97%
4	37.13	34.66	93%
10	14.85	14.45	97%
20	7.43	7.73	104%
40	3.72	3.84	103%
80	1.86	2.06	111%

Validation of the manual dilution procedure:

A study was conducted to verify the use of ARCHITECT iMulti-Assay Manual Diluent as the manual diluent for routine 1:10 dilutions of a sample tested with the ARCHITECT iValproic Acid assay. Five high serum and five plasma sample sets containing valproic acid concentrations were tested in replicates of four. Average percent recovery was equal to 104%.

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

The ARCHITECT iValproic Acid Calibrators are traceable to United States Pharmacopeia (USP) valproic acid.

The stability of the calibrators was established through real time testing, conducted at multiple time points. The sponsor's protocol was reviewed and found to be acceptable. Three lots of calibrators and one lot each of reagents were used to test multiple levels of serum panels and control material. At time point zero, all calibrator bottles were opened and closed, and then stored at 2-8°C for the duration of the study. The serum panels were stored at -70°C or colder. No trends in recovery of serum samples were observed throughout the real-time month testing interval.

d. *Detection limit:*

The limit of blank (LoB) and limit of detection (LoD) of the ARCHITECT i Valproic Acid assay were determined based on CLSI Protocol EP17. These evaluations were performed using one blank (60 replicates) and five low level valproic acid samples (15 replicates each). Analysis yielded LoB = 0.27 µg/mL and LoD = 0.51 µg/mL. Three instruments, three lots of reagents, three lots of calibrators and one control lot were used for this study. Results support the low end range claim of 2 ug/mL.

e. *Analytical specificity:*

The following compounds were tested for cross-reactivity or interference in serum samples containing 0 ug/mL, 50 ug/mL and 100 ug/mL valproic acid. Measurements were compared to those of control samples without cross-reactant. Results are shown below and in the package insert:

		Valproic Acid 50 µg/mL	Valproic acid 100 µg/mL
Test Compound	Test compound concentration µg/mL	% Cross Reactivity	% Cross Reactivity
3-keto-valproic acid	150	4.6%	0.47%
3-hydroxy-valproic acid	10	2.5%	11.7%
4-hydroxy-valproic acid	60	1.65%	0.82%
4-ene-valproic acid (2-n-propyl-4-pentenoic acid)	10	33.1%	68.8%
2-propyl glutarate	50	1.94%	0.06%
5-hydroxy-valproic acid	25	7.04%	-5.44%
2-propyl-glutaric acid	400	0.12%	0.32%
2-n-propyl-3-hydroxy-pentanoic acid	100	1.16%	5.64%
2-n-propyl-5-hydroxy-pentanoic acid	100	7.8%	4.14%
2-propyl-4-pentenoic acid	10	25.30%	17.2%
2-propyl-2-pentenoic acid	10	21.3%	6%

The drugs listed below were spiked into normal human serum pools containing valproic acid at 0, 50 and 100 µg/mL. Control samples were serum spiked with valproic acid, without any additional added drug. The drugs and concentrations tested and results are tabulated below. The results are reported as %Recovery to indicate the level of cross-reactivity.

Test compound name	Test compound concentration (ug/mL)	Valproic Acid Concentration (ug/mL)		
		0	50	100
		test sample minus control sample conc (ug/mL)	% Recovery (test/control)x 100	% Recovery (test/control)x 100
Clonazepam*	1.2	-0.01	103.4	98.8
Acetyl Cysteine	150	-0.03	102.6	95.1
Ampicillin-Na	1000	0.74	101	100.8
Ascorbic acid	300	0.05	106.2	101
Cyclosporine	5	0.1	99.7	103.6

Test compound name	Test compound concentration (ug/mL)	Valproic Acid Concentration (ug/mL)		
		0	50	100
		test sample minus control sample conc (ug/mL)	% Recovery (test/control)x 100	% Recovery (test/control)x 100
Cefoxitin-Na	2500	0.14	101.2	99.5
Heparin	5	0.09	99.5	103.5
Levodopa	20	0.05	97.2	98.7
Methyldopa				
+1,5	20	-0.03	101.4	97.7
Metronidazole	200	-0.01	98	103.4
Phenylbutazone	400	0.07	102.5	104.9
Doxycycline HCl	50	-0.17	104.6	101.9
Acetylsalicylic Acid	1000	3.77	113.9	99.9
Rifampicin	60	0.03	102.5	101.6
Acetaminophen	200	-0.18	101.6	100.6
Ibuprofen	500	0.31	109.8	106.5
Theophylline	100	0.04	101.4	100.6

Interference from endogenous compounds was evaluated based on the CLSI Protocol EP7-A2. Serum specimens with valproic acid levels were targeted at 50 and 100 µg/mL and supplemented with the compounds listed below.

Substance (high concentration)	Percent Recovery for 50 µg/mL Valproic acid	Percent Recovery for 100 µg/mL Valproic acid
Triglycerides (3000 mg/dL)	101	102
Hemoglobin (500 mg/dL)	99	98
Bilirubin (20 mg/dL)	-108	105
Protein (13 g/dL)	99	100

Evaluation of Other Potentially Interfering Compounds

The ARCHITECT *i* Valproic Acid assay is designed to have a mean recovery of 100 ± 10% in the presence of HAMA and rheumatoid factor (RF). In a study, the ARCHITECT *i* Valproic Acid assay was evaluated by testing specimens with HAMA and RF to further assess the clinical specificity. Five specimens positive for HAMA and five specimens positive for RF were evaluated for percent recovery with valproic acid spiked into each specimen to target concentrations of 50 and 100 µg/mL. The mean percent recovery for HAMA specimens ranged

from 103% to 104% and for RF specimens ranged from 103% to 109%. The package insert notes that specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may show either falsely elevated or depressed values when tested with assay kits that employ mouse monoclonal antibodies.

f. Assay cut-off:

Not applicable. This is a quantitative assay.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison was performed based on guidance from the CLSI EP9A-2. Two ARCHITECT i 2000SR instruments, three lots each of ARCHITECT iValproic Acid reagents and calibrators, and one lot of ARCHITECT iValproic Acid controls were used. Two ARCHITECT i 2000_{SR} instruments, three lots each of ARCHITECT iValproic Acid reagents and calibrators, and one lot of ARCHITECT iValproic Acid controls were used. A total of 152 serum specimens containing valproic acid that spanned the measurement range of the assay were measured. No other selection criteria were applied. Results ranged from 3.13 to 144.10 with the ARCHITECT iValproic Acid and from 3.32 to 145.06 with the AxSYM Valproic Acid assay. Results of Passing-Bablok regression analysis are shown below

N = 152	Slope (95% Confidence Interval)	Intercept (95% Confidence Interval)	Correlation Coefficient
	0.978 (0.956 to 1.003)	0.651 (-0.472 to 1.684)	0.986

A bias analysis was also performed by the sponsor on the same specimens. The average bias exhibited by ARCHITECT vs. AxSYM in this study was -0.386% (95% confidence interval -1.181% to 0.410%). Within the typical therapeutic range of valproic acid therapy (50 to 100 µg/mL, as read in the AxSYM), the average bias was -0.353% (95% confidence interval of -1.442% to 0.736%).

b. Matrix comparison:

A study was conducted to evaluate different anticoagulant tube types that can be used with the ARCHITECT iValproic Acid assay. Donors were drawn with the following matched, FDA-cleared tube types of serum and plasma: human serum, no additive (control); human plasma 2K-EDTA Sodium Heparin, 3K-EDTA

Lithium Heparin, 2Na-EDTA. Valproic acid was spiked into the matched sets ranging from 5-130 ug/mL.

Serum Control Concentrations(ug/ml)	Percents recovery for each sampe				
	2K-EDTA	2Na-EDTA	Sodium heparin	Lithium heparin	3K-EDTA
5.1	102	103	105	108	100
5.4	99	99	98	94	99
39.4	101	99	100	105	96
40.3	99	98	101	100	101
61.4	102	100	101	101	101
63.0	98	97	101	97	102
90.6	97	99	100	96	101
83.4	101	101	103	100	102
124.9	98	95	99	97	100
129.2	98	99	96	97	105

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 sponsor cites the following references regarding a therapeutic range of 50 to 100 µg/mL for Valproic Acid.

- Pinder RM, Brogden RN, Speight TM, *et al.* Sodium valproate: a review of its pharmacological properties and therapeutic efficacy in epilepsy. *Drugs* 1977;13:81-123.
- Simon D, Penry JK. Sodium di-n-propylacetate (DPA) in the treatment of epilepsy. *Epilepsia* 1975;16:549-73.
- Bruni J, Wilder BJ. Valproic acid. Review of a new antiepileptic drug. *Arch Neurol* 1979;36:393-8.

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.