

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

A. 510(k) Number:

k123271

B. Purpose for Submission:

New Device

C. Measurand:

Phenobarbital

D. Type of Test:

Quantitative immunoassay

E. Applicant:

Microgenics Corporation

F. Proprietary and Established Names:

Abbott Phenobarbital Assay

G. Regulatory Information:

1. Regulation section:

21 CFR 862.3660, Phenobarbital Test System

2. Classification:

Class II

3. Product code:

DLZ, Enzyme immunoassay, phenobarbital

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

See indication(s) for use below.

2. Indication(s) for use:

The Abbott Phenobarbital Assay is for in vitro diagnostic use for the quantitative measurement of phenobarbital in human serum or plasma on the ARCHITECT cSystems. The measurements obtained are used in the diagnosis and treatment of phenobarbital overdose and in monitoring levels of phenobarbital to help ensure appropriate therapy.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

For use on the ARCHITECT c8000 clinical chemistry analyzer

I. Device Description:

The Phenobarbital Assay kit is supplied ready-to-use in liquid form, for storage at 2 to 8°C. Each Phenobarbital Assay kit is packaged in a rectangular cardboard box divided into three sections. One section will contain three bottles of Antibody Reagent (R1), one section will contain three bottles of Microparticle Reagent (R2), and the last section will contain the package insert. Each kit is sufficient for 300 tests.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Abbott Aerose[®] Phenobarbital Assay

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

k993031

3. Comparison with predicate:

Similarities		
Comparison	Device	Predicate
Proprietary name	Abbott Phenobarbital Assay	Abbott Aeroset® Phenobarbital Assay (k993031)
Intended Use	The Abbott Phenobarbital assay is for in vitro diagnostic use for the quantitative measurement of phenobarbital in human serum or plasma on the ARCHITECT cSystems. The measurements obtained are used in the diagnosis and treatment of phenobarbital overdose and in monitoring levels of phenobarbital to help ensure appropriate therapy.	Same
Sample Matrix	Human Serum or Human Plasma	Same
Storage	2-8°C	Same
Calibrator	Liquid Ready-to-Use, six levels (0.0, 5.0, 10.0, 20.0, 40.0, and 80.0 µg/mL)	Same

Differences		
Comparison	Device	Predicate
Reagents	Liquid Ready-to-Use (Antibody reagent and Phenobarbital-coated microparticle reagent)	Liquid Ready-to-Use (Antibody reagent and Phenobarbital-labeled enzyme reagent)
Assay Range	2.0 to 80.0 µg/mL	0.5 to 80.0 µg/mL

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

CLSI EP5-A2: Evaluation of Precision Performance of Clinical Chemistry Devices
 CLSI EP17-A2: Protocol for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

The Phenobarbital assay is a homogeneous particle-enhanced turbidimetric inhibition immunoassay (PETINIA) used for the analysis of phenobarbital in serum or plasma. The assay is based on competition between drug in the sample and drug coated onto a

microparticle for antibody binding sites of the phenobarbital antibody reagent (mouse). The phenobarbital-coated microparticle reagent is rapidly agglutinated in the presence of the anti-phenobarbital antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically, and is directly proportional to the rate of agglutination of the particles. When a sample containing phenobarbital is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration dependent classic agglutination inhibition curve can be obtained, with maximum rate of agglutination at the lowest phenobarbital concentration and the lowest agglutination rate at the highest phenobarbital concentration.

M. Performance Characteristics (if/when applicable):

Performance was established on the Abbott ARCHITECT c8000 Clinical Chemistry Analyzer. The data summarized below is the data generated on the ARCHITECT c8000 System.

1. Analytical performance:

a. *Precision/Reproducibility:*

The inter-assay precision study was performed on one Abbott ARCHITECT c8000 systems clinical analyzer with two reagent lots. Three serum based control levels and 6 serum samples (pooled patient serum samples and negative serum pools spiked with phenobarbital concentrations at 5 levels (5, 10, 20, 40 and 80µg/ml)) were used for the precision study. Each phenobarbital sample was assayed in replicates of two, twice a day for 20 days for a total of 40 runs resulting in a total of 80 replicates for each instrument/lot. Results are summarized below.

Abbott Phenobarbital Assay: Precision

Sample	Instrument/ Reagent Lot	Mean (µg/mL)	Within Run		Total	
			SD	%CV	SD	%CV
Level 1	1	4.06	0.07	1.7	0.18	4.3
	2	4.37	0.13	3.0	0.28	6.4
Level 2	1	9.29	0.11	0.33	0.76	1.2
	2	9.62	0.16	1.6	0.23	2.4
Level 3	1	24.02	0.33	1.4	0.52	2.2
	2	24.57	0.32	1.3	0.62	2.5
Level 4	1	48.79	0.79	1.6	1.33	2.7
	2	46.80	0.51	1.1	1.34	2.9
Level 5	1	74.29	1.20	1.6	1.96	2.6
	2	73.09	0.70	1.0	2.76	3.8
Patient 1	1	2.51	0.08	3.3	0.12	4.9
	2	2.62	0.06	2.4	0.15	5.7
Patient 2	1	4.35	0.09	2.0	0.15	3.5
	2	4.60	0.15	3.3	0.23	5.0
Patient 3	1	11.01	0.12	1.1	0.73	6.7
	2	10.89	0.17	1.6	0.25	2.2
Patient 4	1	25.93	0.31	1.2	0.79	3.1

	2	26.71	0.42	1.6	0.68	2.5
Patient 5	1	47.72	1.01	2.1	1.44	3.0
	2	45.78	0.33	0.7	1.33	2.9
Patient 6	1	77.22	1.00	1.3	1.34	1.7
	2	75.70	0.67	0.9	1.97	2.6

An additional precision study was performed at an external site on one lot of reagents to confirm the observed precision with spiked samples.

Sample	Mean ($\mu\text{g/mL}$)	Within Run		Total	
		SD	%CV	SD	%CV
Level 1	4.10	0.07	1.8	0.183	4.5
Level 2	9.83	0.18	1.8	0.230	2.3
Level 3	23.65	0.34	1.4	0.513	2.2
Level 4	54.59	1.44	2.6	1.82	3.3
Level 5	77.03	1.00	1.3	1.57	2.0

b. Linearity/assay reportable range:

The claimed assay range is 2.0 $\mu\text{g/mL}$ to 80.0 $\mu\text{g/mL}$. The high sample contained human serum spiked with a phenobarbital reference standard. The high sample was diluted with negative serum for 10 concentrations across the entire assay range (and included samples extending above and below the assay range). Each dilution was tested in replicates of four. Regression analysis of each dilution showed that the samples were linear throughout the claimed range ($y=1.0555x-0.5813$, $R^2=0.998$).

The recovery of all serum samples relative to the expected concentration based on the standard material and dilution factors, ranged between 92.7 – 109.4%

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

The calibrators used in this submission were cleared under k120936. The controls used in this submission were cleared under k032826.

d. Detection limit:

CLSI EP17-A2 was followed to determine the limit of blank (LoB). The samples were run with two lots of reagents on one instrument. Testing consisted of 4 replicates of five phenobarbital-free human serum samples tested each day for 3 days. Calculations were performed according to CLSI EP17-A2. The LoB was determined at 0.29 $\mu\text{g/mL}$.

CLSI EP17-A2 was followed to determine the limit of detection (LoD). The Samples were run with two lots of reagents on one instrument. Testing consisted of 4

replicates of six low level samples at phenobarbital concentrations of 0.25, 0.50, 0.82, 1.21, 1.61 and 2.00µg/mL tested each day per day for 3 days. The LoD was determined at 0.41µg/mL.

CLSI EP17-A2 was followed to determine the limit of quantitation (LoQ). The samples were run with two lots of reagents. Testing consisted of 3 replicates of five low level samples at phenobarbital concentrations of 0.25, 0.50, 1.00, 2.50 and 5.00µg/mL tested twice per day for 7 days. Results from one lot of reagents yielded bias (SD) ≤ 0.12 ug/mL when these five samples were compared to the reference value. LoQ is based on an inter-assay precision of 7% CV at 2.0 ug/ml. The sponsor concluded that LoQ is 2.0 ug/mL.

LoQ (ug/mL)	Measuring Range (ug/mL)
2.0	2.0-80

e. Analytical specificity:

Serum samples spiked with two levels of phenobarbital near the upper and lower therapeutic ranges were supplemented with the below interfering compounds. Each test and control sample were run in duplicates and the percent cross reactivity (% cross reactivity) was calculated (Measured concentration minus Expected concentration) divided by Drug Concentration Tested multiplied by 100. All % recovery results were within 100%±10%.

Abbott Phenobarbital Assay: Cross Reactivity

Compound	Test Conc (µg/mL)	% Cross reactivity
Amitriptyline	25	0.3
Amobarbital	30	2.9
Butobarbital	100	-0.1
Carbamazepine	500	0.0
Carbamazepine-10,11-epoxide	500	0.0
Chlordiazepoxide	500	0.0
Chlorpromazine	60	-0.2
Clorazepate	500	0.0
Diazepam	60	0.2
Ethosuximide	500	0.0
Ethotoin	200	0.1
5-Ethyl-5-phenylhydantoin (Nirvanol)	200	0.4
Glutethimide	200	0.1
5-9p-Hydroxyphenyl)-5-phenylhydantoin	100	0.2
Imipramine	5	4.3

Mephenytoin	200	0.2
Methsuximide	150	0.0
Nortriptyline	10	-0.8
Pentobarbital	100	0.4
PEMA	500	0.0
Phensuximide	500	0.0
Phenytoin	200	0.0
Primidone	200	0.3
Promethazine	30	1.0
Secobarbital	50	-0.2
Valproic Acid	1000	0.0
p-hydroxyphenobarbital	22	0.1
Aprobarbital	100	-0.1
Barbital	100	0.3
Thiopental	100	0.3

The sponsor also conducted an interference study to evaluate the effects of the following compounds and concentrations with their phenobarbital assay. All samples in this evaluation recovered within $\pm 10\%$ of the expected phenobarbital value.

Compound	Concentration ($\mu\text{g/mL}$)	%Recovery
Bilirubin, unconjugated	60mg/dL	100.1
Bilirubin, conjugated	30mg/mL	102.1
Hemoglobin	800mg/dL	100.0
Triglyceride	1250mg/dL	94.8
Cholesterol	500mg/dL	109.7
Human serum albumin (HSA)	7.5g/dL	99.0
γ -Globulin (IgG)	12g/dL	97.0
HAMA	400ng/mL	100.7
Rheumatoid Factor (RF)	500IU/mL	93.6

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The Phenobarbital assay (On-test) for the ARCHITECT c8000 System was compared to the Abbott Aeroset® Phenobarbital Assay by testing 118 serum specimens commercially obtained (all natural) with phenobarbital concentrations ranging from 5 to 80ug/mL. Correlation studies were performed using a modified CLSI guideline EP9-A2 and analysis was based on a single measurement of each sample. Results are summarized below.

Comparative Methods	N	Passing-Bablok		R
		Slope (95% CI)	Intercept (95% CI)	
On-test vs Abbott	118	1.003 (0.981-1.022)	0.363 (-0.106-0.981)	0.9949

b. *Matrix comparison:*

The suitability of additional matrices, anticoagulants, or collection tubes was evaluated using drug-free paired donor samples to compare serum in glass (method used in method comparison) with the matrices listed below. Twenty-two to twenty-five samples were spiked with phenobarbital into each paired matrix sample at multiple concentrations spanning the assay range. A singlet set of data was evaluated and the slope, intercept and correlation coefficient determined.

Comparative Method	N	Range	Deming's Regression		R
			Slope	Intercept	
X: Serum in glass Y: Serum in plastic	25	4.14 – 76.26	0.982	0.189	0.9989
X: Serum in glass Y: SST	25	4.14 - 76.26	0.982	0.189	0.9989
X: Serum in glass Y: Plasma w/NaF/K Oxalate	22	5.52 – 77.98	1.022	-0.425	0.9988
X: Serum in glass Y: Plasma w/Na Heparin in glass	25	3.64- 71.50	0.984	0.389	0.9975
X: Serum in glass Y: Plasma w/Na Heparin in plastic	25	4.20 – 77.23	0.976	0.098	0.9962
X: Serum in glass Y: Plasma w/Li Heparin w/ gel in plastic	25	4.48- 71.00	0.983	-0.067	0.9986
X: Serum in glass Y: Plasma w/Li Heparin w/o gel in plastic	25	4.48- 71.00	1.006	0.920	0.9982
X: Serum in glass Y: Plasma w/K3 EDTA in glass	25	4.40 – 75.16	1.035	-0.277	0.9985
X: Serum in glass Y: Plasma w/K3 EDTA in	25	3.98- 73.67	0.995	0.613	0.9987

plastic					
X: Serum in glass	25	4.40 – 75.16	0.991	0.318	0.9981
Y: Plasma w/K2 EDTA in plastic					
X: Serum in glass	25	4.01 – 72.69	1.009	-0.122	0.9984
Y: Plasma w/Na Citrate in Glass					
X: Serum in glass	25	4.01 – 72.69	1.027	-0.274	0.9993
Y: Plasma w/ Na Citrate in Plastic					

Out of approximately 300 samples tested, greater than 98% of individual samples recoveries were within $\pm 10\%$ of the expected concentration, and no trends were observed.

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 sponsor has referenced the following expected values from literature¹ in the package insert:

The desired therapeutic effect is usually achieved in the serum concentration range of 15 to 40 $\mu\text{g/mL}$ (65 to 172 umol/L). Concentrations of 35 to 80 $\mu\text{g/mL}$ (151 to 345 umol/L) are associated with slowness, ataxia, and nystagmus. Concentrations of 65 to 117 $\mu\text{g/mL}$ (280 to 504 umol/L) are associated with coma with reflexes. Concentrations of >100 $\mu\text{g/mL}$ (>430 umol/L) are associated with coma without reflexes. For effective treatment, some patients may require serum levels outside these ranges. Therefore, the expected range is provided only as a guide, and individual patient results should be interpreted in light of other clinical signs and symptoms.

1. Goldman L, Ausiello D, editors. Cecil Medicine, 23rd ed. Philadelphia, PA: Elsevier Saunders; 2008:2994.

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.