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

A. 510(k) Number:

k101574

B. Purpose for Submission:

New assay, calibrator and control

C. Measurand:

Gabapentin

D. Type of Test:

Quantitative, Homogeneous Enzyme Immunoassay (EIA)

E. Applicant:

ARK Diagnostics, Inc.

F. Proprietary and Established Names:

ARK™ Gabapentin Assay, Calibrators, and Controls

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.3350, Diphenylhydantoin test system

   21 CFR 862.3200, Clinical toxicology calibrator

   21 CFR 862.3280, Clinical toxicology control material

2. Classification:

   Class II (assay), Class II (calibrator), and Class I, reserved, (control)

3. Product code:

   OTF (assay), LAS (controls), DLJ (calibrator)

4. Panel:

   91 Toxicology

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:
   The ARK™ Gabapentin Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of gabapentin in human serum or plasma on automated clinical chemistry analyzers.

   Gabapentin concentrations can be used as an aid in management of patients treated with gabapentin.

   The ARK™ Gabapentin Calibrator is intended for use in calibration of the ARK Gabapentin Assay.

   The ARK™ Gabapentin Control is intended for use in quality control of the ARK Gabapentin Assay.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   The assay has been validated on the Hitachi 917 automated clinical chemistry analyzer.

I. Device Description:

The ARK Gabapentin Assay consists of reagents R1 anti- gabapentin polyclonal rabbit antibody with substrate and R2 gabapentin labeled with bacterial G6PDH enzyme. The ARK Gabapentin Calibrator consists of a six – level set (target values: 0.0, 1.5, 4.0, 10.0, 20.0, and 40 µg/mL) to calibrate the assay, and the ARK Gabapentin Control consists of a three – level (target values: 2.5, 8.0, and 25.0 µg/mL) set used for quality control of the assay. The calibrator and control materials both consist of a synthetic protein matrix containing gabapentin, buffer, bovine serum albumin, and preservatives (≤0.09% sodium azide).

J. Substantial Equivalence Information:

1. Predicate device name(s):

ARK Topiramate Assay

2. Predicate 510(k) number(s):
k083799

3. Comparison with predicate:

Characteristic	**Device** ARK™ Gabapentin Assay	**Predicate -** k083799 ARK™ Topiramate Assay
Intended Use	The ARK™ Gabapentin Assay is intended for the quantitative determination of gabapentin in human serum or plasma on automated clinical chemistry analyzers.	The ARK™ Topiramate Assay is intended for the quantitative determination of topiramate in human serum or plasma on automated clinical chemistry analyzers.
Indications for Use	Gabapentin concentrations can be used as an aid in management of patients treated with gabapentin.	The results obtained are used in the diagnosis and treatment of topiramate overdose and in monitoring levels of topiramate to help ensure appropriate therapy.
Sample	Serum or plasma	Same
Methodology	Homogenous enzyme immunoassay (EIA)	Same
Reagent Components	Two (2) reagent system: Anti- gabapentin Antibody/Substrate Reagent (R1) containing rabbit polyclonal antibodies to gabapentin, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers Enzyme Reagent (R2) containing gabapentin labeled with bacterial G6PDH, buffer, bovine serum albumin, sodium azide, and stabilizers	Two (2) reagent system: Anti-topiramate Antibody/Substrate Reagent (R1) containing rabbit polyclonal antibodies to an epitope of topiramate, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, preservatives, and stabilizers Enzyme Reagent (R2) containing topiramate epitope labeled with bacterial G6PDH, buffer, bovine serum albumin, preservatives, and stabilizers
Platform required	Automated clinical chemistry – Hitachi 917 – analyzer	Same
Testing environment	Routine clinical laboratory	Same

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

CLSI documents:

Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)

Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach (EP6-A)

Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)

Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP09-A2)

Protocols for Determination of Limits of Detection and Limits of Quantitation (EP17-A)

L. Test Principle:

The ARK Gabapentin Assay is a homogeneous immunoassay based on competition between drug in the specimen and gabapentin labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for binding to the antibody reagent. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly proportional to the drug concentration. Active enzyme converts the coenzyme nicotinamide adenine dinucleotide (NAD) to NADH that is measured spectrophotometrically as a rate of change in absorbance. Endogenous serum G6PDH does not interfere with the results because the coenyzme NAD functions only with the bacterial enzyme used in the assay.

M. Performance Characteristics (if/when applicable):

Performance was validated on the Hitachi 917 instrument.

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   Precision studies were performed on a Hitachi 917 analyzer over twenty (20) non-consecutive days. Multiple calibrations were performed during this interval to provide variation, although each calibration was performing in a stable manner. Samples evaluated included tri-level ARK Gabapentin Controls and three pooled human serum samples. Each sample (calibrator/control matrix and pooled human serum) was assayed in quadruplicate twice a day, with each run separated by at least two hours. Calculations were conducted according to CLSI Guideline EP5-A2. The

within run, between day, total SD, and percent CVs were calculated. Results are summarized below:

			Within Run		Between Day		Total	
Sample	**N**	**Mean (µg/mL)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**
Control Low	160	2.5	0.08	3.3	0.10	3.9	0.14	5.6
Control Mid	160	7.9	0.21	2.6	0.26	3.3	0.35	4.4
Control High	160	24.6	0.48	1.9	0.65	2.7	0.88	3.6
Low Patient Pool	160	2.2	0.11	4.7	0.11	4.8	0.17	7.7
Mid Patient Pool	160	7.3	0.58	2.4	0.25	3.4	0.33	4.6
High Patient Pool	160	24.9	0.54	2.2	0.97	3.9	1.17	4.7

ARK performed an additional precision study supplementing both the calibrator/control matrix and the serum matrix with gabapentin to obtain a target concentration of 36 µg/mL. The human serum matrix was comprised of pooled human specimens containing gabapentin and then further supplemented to the target level. Samples were tested twice a day (at least two hours separation per day) for five separate days. A total of 40 replicate measurements were made. Total precision ranged 2.8 to 3.4% CV, meeting the acceptance criterion, ≤10%.

			Within Run		Between Day		Total	
Sample	**N**	**Mean (µg/mL)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**
Calibrator/ Control Matrix	40	35.4	0.77	2.2	0.95	2.68	1.22	3.4
Pooled Human Serum	40	35.9	0.58	1.6	0.49	1.37	0.99	2.8

b. Linearity/assay reportable range:

The manufacturer's claimed assay reportable range is 0.75 to 40µg/mL.

To evaluate linearity, pure gabapentin (USP) was added to pooled human

serum in order to obtain a concentration of 48µg/mL and confirmation of this concentration was made by LC/MS/MS. Dilutions of this concentration (48 µg/mL) were made proportionally with pooled human serum negative for gabapentin to create samples ranging from 0.75 µg/mL – 48 µg/mL). The averaged results of multiple runs and replicates (n=6) for each sample using the ARK assay were used in the calculations. The results at each separate level were averaged and compared to the target concentration (based on spiked concentrations of USP materials) and the percentage recovery was calculated. The following table represents the data in terms of % recoveries:

% Recovery=[100 X mean recovered concentration]/Theoretical concentration

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	Recovery (%)
0.75	0.73	97.3
1.0	1.0	100.0
2.4	2.4	100.0
3.2	3.3	103.1
4.8	4.9	102.1
8.0	8.0	100.0
12.0	11.9	99.2
24.0	23.6	98.3
32.0	31.8	99.4
40.0	39.7	99.3
48.0	48.1	100.2

Regression analysis of the data yields the equation: y (observed result) = 0.9959 (Target concentration) + 0.0121, r^2= 0.9999

Trueness/Recovery:

Serum samples were prepared by adding a pure gabapentin solution (USP) into human serum negative for gabapentin. The results of the six replicates were averaged and compared to the theoretical concentration (spiked serum samples) percentage recovery was calculated.

$$\% \text{ Recovery} = 100 \times \frac{\text{Mean recovered concentration}}{\text{Theoretical concentration}}$$

Results are shown in the following table:

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	Percent Recovery
1.0	0.99	98.5
2.0	2.07	103.3
3.5	3.55	101.3

9.0	8.98	99.7
16.0	16.03	100.2
22.0	22.00	100.0
28.0	27.85	99.5
35.0	35.59	101.7
40.0	41.49	103.7

High Sample Carryover

The impact of high gabapentin concentration specimens on the measurement of gabapentin in specimens with lower concentrations (high sample carryover) was evaluated by assaying a series of high 100.0 µg/mL spiked serum samples followed by a series of low 2.0µg/mL spiked serum samples. No carryover was observed from the High 100.0 µg/mL sample to the Low 2.0 µg/mL sample.

Manual Dilution Protocol

The manufacturer recommends that samples with concentrations exceeding 40.0µg/mL should be diluted 4-fold with zero calibrator. Samples spiked with gabapentin and patient samples containing gabapentin (with initial concentrations ranging from 38.8 to 100µg/mL) were diluted 4-fold with zero calibrator and results using the ARK method were compared to the target level (for spiked samples) and the LC-MS/MS determined level (for neat samples). The percentage recovery ranged from 90.9 to 110.8%.

ARK performed an additional study by supplementing aliquots of neat specimens with gabapentin. Three specimens were supplemented with 50µg/mL gabapentin and tested after diluting them by a factor of 4. The percentage recovery ranged from 100.5 to 104.4% which was calculated based on the theoretical LC-MS/MS values for each sample.

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

Traceability and Value Assignment of Calibrator and Control Materials:

There is no internationally recognized standard for gabapentin.

ARK gabapentin calibrator materials are prepared by gravimetric dilution of high purity gabapentin (USP>99.9% purity) into a synthetic proteinaceous matrix free of gabapentin containing buffer, bovine serum albumin, and preservative. Each calibrator level (B-F) is then qualified by testing multiple times and comparing to a master calibrator lot with values to be within 5% at each positive calibrator.

ARK gabapentin control materials are prepared by gravimetric dilution of

gabapentin in buffer, bovine serum albumin and preservative. Quality control (QC) ranges are established using three runs with four replicates tested per run (n=12 for each control level) and the mean gabapentin level of each control is calculated. Control ranges were set at ± 15% around the mean level tested. The package insert notes that each laboratory should establish its own ranges for each new lot of controls.

Specimen Stability:

Stability of stored specimens (frozen and refrigerated storage) and the effect of freezing/thawing on the measurement of gabapentin by the ARK™ Gabapentin Assay were evaluated. Testing of fresh specimens is preferred, however, clarified serum specimens were shown to be stable for up to four weeks frozen at ≤10ºC and for up to one week when refrigerated (2-8ºC). The manufacturer's acceptance criteria for this evaluation are recovery within ±10%. Specimens were shown to withstand 3 freeze-thaw cycles when stored at -20ºC.

The ARK Gabapentin Calibrator and the ARK Gabapentin Control are comprised of a synthetic proteinaceous matrix with buffer, bovine serum albumin and preservatives. To evaluate recovery and matrix equivalence, synthetic calibrator/control matrix (Calibrator A) and pooled human serum were each supplemented with gabapentin to achieve 1.0, 2.0, 3.5, 9.0, 16.0, 22.0, 28.0, 35.0, and 40 µg/mL levels. Multiple replicates and runs were performed and the mean recovery (of replicates) was calculated for each level and each matrix. All levels tested in the calibrator matrix recovered within 90.2% of the serum gabapentin levels. Recoveries (percentage of nominal level) were acceptable for both matrices, falling within 10% of the expected spike level – calibrator/control matrix (90.2% - 104.1%) and serum matrix (98.5% to 103.0%).

Calibration stability on the analyzer:

ARK provided a study on calibration stability on the analyzer. This study supports the stable operation of the assay over an extended period based on one calibration. Up to 84 days of calibration curve stability and in-use stability of reagents, calibrators and controls were observed for the study as tested.

Calibrator and Control material stability:

1. The calibrator and control are stable until the expiration date (18 months) printed on the vial when stored unopened at 2-8ºC. Once opened vials may be stored at 2-8°C for up to 12 months.

2. Real time stability studies are ongoing for both unopened and opened calibrators and controls. Stability testing protocols and acceptance

criteria were reviewed and found to be acceptable.

d. *Detection limit:*
Accuracy and precision studies were performed to determine the manufacturer's claimed lower limit of quantitation (LOQ). These studies were conducted using the CLSI Guideline EP 17-A. Three gabapentin levels were tested below the lowest positive calibrator concentration (1.0µg/mL). Samples were prepared by gravimetric addition of gabapentin (USP >99% purity) to human serum negative for gabapentin to give concentrations of 0.50, 0.75, and 1.00 µg/mL. Eight replicates of each sample were tested in each of five runs to give 40 replicates of each sample per reagent lot. A total of three reagent lots were used for the study. The LOQ was chosen at 0.75 µg/mL where the precision was 7.6 %CV and the recovery was 91.0 %.

e. *Analytical specificity:*

Studies included testing for interference from endogenous compounds, metabolite, and commonly co-administered, and other anti-epileptic drugs.

Serum samples with clinically high concentrations of the potential interfering substances were tested by ARK Gabapentin assay in the presence of varying amounts of gabapentin. Specifically, serum samples containing low (2.0µg/mL) and high (20.0µg/mL) levels of gabapentin were tested. Each sample containing interferent was assayed, along with a serum control of gabapentin. No significant interference (defined by the manufacturer as ≤10% differences in detecting gabapentin) was observed.

Endogenous Interferences

		Percentage Recovery	
Interfering Substance	Interferent Concentration	2 µg/mL Gabapentin	20 µg/mL Gabapentin
Albumin	12 g/dL	102.1	98.2
Bilirubin conjugated	70 mg/dL	95.2	98.3
Bilirubin unconjugated	70 mg/dL	106.6	98.4
Cholesterol	313 mg/dL	94.5	100.9
Gamma-globulin	12 g/dL	103.2	99.7
Hemoglobin	1000 mg/dL	102.5	101.6
Intralipid®	1500 mg/dL	97.0	99.2
Rheumatoid Factor	1100 IU/mL	97.0	97.1
Triglycerides	618 mg/dL	96.4	97.2
Uric Acid	30 mg/dL	106.6	97.9

L-Amino Acid Interference:

The L-amino acids listed below were tested for cross-reactivity. These amino acids were spiked into two separate samples each containing low and high gabapentin concentrations of 2.0 µg/mL and 20.0 µg/mL, respectively. The samples were analyzed and the gabapentin concentrations of samples containing interferent were compared to the serum control. All L-amino acids tested resulted in <10% error in detecting gabapentin at the concentrations tested.

Compound	Concentration (µg/mL)	Percentage Recovery	
		Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)
L-Arginine	100	96.9	104.4
L-Asparagine	100	95.1	101.8
L-Aspartic Acid	25	93.9	102.0
L-Cysteine	25	92.6	101.9
L-Glutamic Acid	100	95.7	101.4
L-Glycine	100	98.0	100.8
L-Histidine	100	92.2	102.5
L-Isoleucine	100	92.2	101.9
L-Leucine	100	96.3	101.5
L-Methionine	25	93.3	100.9
L-Phenylalanine	50	94.4	99.6
L-Serine	50	95.1	99.3
L-Threonine	100	95.6	100.7
L-Tyrosine	100	93.9	99.0
L-Alanine	150	98.9	97.0
L-Lysine	150	97.8	98.2
L-Proline	150	96.0	98.3
L-Valine	150	97.5	97.7
L-Tryptophan	150	98.0	99.1
L-Glutamine	350	97.3	96.9

Drugs that Cross-React – Pregabalin

Pregabalin was analyzed from 15 to 100 µg/mL in the presence of either Low (2 µg/mL) or High (20 µg/mL) concentration of gabapentin and assayed along with a serum control of gabapentin. Interference was observed only at the low concentration of gabapentin. Recovery of gabapentin ranged from 108.9 to 156.9. The manufacturer notes in the package insert that care should be taken when interpreting ARK Gabapentin results if pregabalin is also being administered to the patient. The results are shown below:

	Percent Cross-Reactivity		Percent Recovery	
Pregabalin (µg/mL)	Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)	Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)
100	1.10	1.95	156.9	109.7
50	1.18	2.06	130.6	105.1
15	1.13	-1.47	108.9	98.9

In addition, a cross reactivity study was performed to evaluate the interference effect of serum pre-gabalin on gabapentin level measurements. The complete

list of interferents tested and results are included in the package insert.

Drug Interference:
Gabapentin did not cross-react with other anti-epileptic or co-administered drugs tested. A high concentration of each compound shown below was spiked into normal human serum with known levels of gabapentin (approximately 2 and 20 µg/mL) and assayed along with a serum control of gabapentin. Measurement of gabapentin resulted in ≤10% error in the presence of drug compounds at the levels tested.

		Percentage Recovery	
Compound	Concentration (µg/mL)	Gabapentin (2 µg/mL)	Gabapentin(20 µg/mL)
γ-Aminobutyric Acid	100	97.8	99.2
L-2-Aminobutyric Acid	100	98.6	99.2
Acetaminophen	200	98.7	98.1
Acetazolamide	100	99.2	98.6
Acetylsalicylic acid	1000	100.6	100.4
Amikacin	100	100.2	98.7
Amitriptyline	20	98.2	97.9
Amoxapine	40	98.9	99.6
Amphotericin B	100	98.2	98.2
Ampicillin	100	100.8	100
Ascorbic Acid	100	97.3	98.3
Baclofen	100	103.3	100.6
Buproprion	40	106.9	100.6
Caffeine	100	99.8	99.8
Carbamazepine	120	99.4	98.9
Carbamazepine- 10, 11 epoxide	120	98.9	98.9
10-Hydroxy carbamazepine	100	102.8	100.4
Chloramphenicol	250	101.4	96.7
Chlorpromazine	20	103.1	100.8
Citalopram	20	102.8	100.8
Clobazam	100	96.3	108
Clonazepam	20	101.2	101.4
Cyclosporin A	40	95.1	97.2
Diazepam	20	102.6	100.5
Digoxin	80	103	101.8
Doxepin	20	103.9	101.2
Erythromycin	200	97.9	98.9
Ethanol	4000 (0.4%)	105.2	99.3
Ethotoin	100	97.1	97.5
Ethosuximide	250	95.8	99.6
Felbamate	250	98.2	99.1
Fluoxetine	20	103.8	101.2
Furosemide	100	95.2	98
Gentamicin	100	100	100.4

Haloperidol	20	102.5	101.7
Heparin	200 U/mL	94.8	96.2
Ibuprofen	500	96.5	96.9
Imipramine	20	101.2	101.1
Kanamycin B	200	96.7	101.3
Lamotrigine	250	102.9	95.9
Levetiracetam	400	97.4	96
Lidocaine	100	97.7	98.7
Lincomycin	1000	102.4	100.4
Mephenytoin	100	100.6	99.6
Mesoridazine	40	106.2	96.2
Methicillin	250	101.5	98
Naproxen	600	100.2	97.3
Neomycin	1000	97.8	102.1
Niacin	100	98.9	100.3
Nitrazepam	20	96.5	97.5
Nortriptyline	20	101.6	97.1
Olanzapine	20	99.9	98.5
Oxcarbazepine	200	100.9	100.8
Paroxetine	40	102.4	96
2-phenyl-ethyl--malonamide (PEMA)	1000	105.8	98.7
Penicillin V	100	95.8	99
Perphenazine	100	102.4	99
Phenobarbital	200	100.3	98.3
Phenytoin	200	96.9	93.6
Primidone	100	93	99.1
Procainamide	100	95.9	95.9
Prochlorperazine	40	97.8	98.7
Ranitidine	100	97.2	98.3
Rifampin	100	95.3	102.4
Risperidone	20	101.8	103.2
Sertraline	100	98.5	97.5
Spectinomycin	100	98.3	102.1
Stiripentol	100	95.9	96.7
Sulfamethoxazole	400	97.5	98
Theophylline	200	103	100.5
Thioridazine	20	102.6	102.5
Tobramycin	100	94.6	100.3
Tiagabine	200	91.6	97.9
Topiramate	250	96.9	96.9
Trimethoprim	40	96.7	99
Valproic Acid	600	96.7	96.9
Vancomycin	250	100.3	99.8
Vigabatrin	150	101.3	99.9
Zonisamide	400	98.6	104.1

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed according to CLSI Guideline EP9-A2. Banked samples from patients tested for gabapentin concentrations were used. Inclusion criteria for the samples measured were based on gabapentin concentration. No exclusion criteria were used for selection of specimens. The large majority of specimens were in a serum matrix. (See also matrix comparison, below.)

Results of samples obtained with the ARK assay in three separate laboratories were compared to those obtained with two different reference methods (HPLC and LC/MS/MS). Results of the Passing – Bablok regression analysis for these studies are shown below:

Method comparison summary:

Comparative Method	Number of Samples and range	Slope (95% CI)	Intercept (95% CI)	Mean Bias of ARK vs comparative method	Correlation coefficient (r^2)
Study 1: ARK vs LC/MS/MS	N=183 Range: 1.0 – 39.0 µg/mL	Y=0.96 (0.92 - 0.99)	-0.06 (-0.28 to 0.18)	-0.46 (-0.69 to -0.24)	0.96 (0.95 to 0.97)
Study 2: ARK vs HPLC	N=64 Range: 1.8 - 29.4 µg/mL	Y=1.08 (1.03 - 1.13)	-0.08 (-0.35 to 0.25)	0.76 (0.39 to 1.12)	0.97 (0.95 to 0.98)
Study 3: ARK vs LC/MS/MS	N=43 Range: 1.4 – 14.0 µg/mL	Y=1.12(1.08 – 1.18)	0.31 (0.05 to 0.55)	1.08 (0.87 to 1.31)	0.97 (0.94 to 0.98)

b. Matrix comparison:

Serum versus Plasma:

Anticoagulated plasma and serum were evaluated to evaluate equivalency of these matrices for measurement of gabapentin with the ARK™ Gabapentin Assay. Samples with sufficient volume left for testing from the method comparison study were utilized. Of the original 187 specimens, one hundred forty-six (146) had sufficient volume to perform this study. Fibrinogen levels were measured to distinguish plasma from serum. Seven specimens were identified as plasma and 139 specimens were identified as serum.

Anticoagulant matrix comparison study:

Anticoagulated plasma and serum were evaluated to determine equivalency of these matrices for measurement of gabapentin with the ARK™ Gabapentin Assay. Matched samples for serum and plasma were collected from eight (8) subjects. Blood was collected in three different anticoagulant tubes: lithium heparin, potassium EDTA, sodium heparin, and a serum tube to produce a matched set. Each sample matrix was spiked with a gabapentin stock solution to give gabapentin concentrations of 0.75, 2.0, 20.0, and 30.0 µg/mL (for a total of 32 samples per anticoagulant). The mean, standard deviation and %CV for six replicates were calculated for each sample. Percentage recovery of gabapentin in anticoagulated samples compared to the serum control was calculated for each subject. Percent recoveries for the 0.75 µg/mL samples ranged from 87.6 – 104.9% for plasma relative to serum values. Percent recoveries for levels 2.0 to 30.0 µg/mL ranged from 93.6 to 109.3% for plasma relative to serum values.

In addition, ARK performed an additional matrix comparison study using four additional samples containing approximately 36 µg/mL. The percentage recovery in plasma compared to that in serum ranged from 96.6% to 101.5%. Regression analyses were prepared for each anticoagulant tube type with results shown below:

Lithium Heparin Plasma vs Serum: $y=1.00x + (-0.04)$, $r^2 = 1.00$, N=36

Potassium EDTA Plasma vs Serum: $y=0.99x + (-0.03)$, $r^2=1.00$, N=36

Sodium Heparin Plasma vs Serum: $y=1.00x + (-0.03)$, $r^2=1.00$, N=36

3. Clinical studies:

   a. Clinical Sensitivity:

   Not applicable. Not typically submitted for this type of assay.

   b. Clinical specificity:

   Not applicable. Not typical for this type of assay.

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

The sponsor provided a discussion with balanced and representative literature discussing clinical use of gabapentin measurements.

4. Clinical cut-off**:**

See expected values below.

5. Expected values/Reference range:

The following is included in the package insert:

A therapeutic range for gabapentin has not been well established. A reference range of 2 μg/mL to 20 μg/mL[1,2] has been proposed. Studies[2] have suggested that optimal responses to gabapentin in patients with difficult-to-treat partial seizures are achieved at concentrations >2 μg/mL or in a range of 4 to 11 μg/mL, while others proposed a higher range of 6 to 21 μg/mL. It has been reported that toxicity with gabapentin tends to occur with increasing frequency when serum concentrations exceed 25 μg/mL. Interindividual variability may be influenced by dose-related saturable drug absorption, and hence, variable pharmacokinetic properties.

The reference range of drug concentrations which is quoted should only imply a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur in the specific patient populations studied. Generally, clinicians using reference ranges such as these should be aware that, because of individual variation, patients may achieve therapeutic benefit with serum drug concentrations outside of these ranges and may experience toxicity with levels below the lower limit of the reference range. Because gabapentin has a relatively short half-life, sampling time in relation to dose ingestion is important for the interpretation of the drug concentration. Sampling time should be standardized such that trough serum concentrations are measured just before the next dosage, preferably in the morning.

References:

1. Wilson, E.A et al. 1998. High dose gabapentin in refractory partial epilepsy: clinical observations in 50 patients. *Epilepsy* Res **29**: 161 – 166.

2. Patsalos, P.N. et al. 2008. Antiepileptic drugs – best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* **49**: 1239 – 1276.

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.