

510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is k153596.

807.92 (a)(1): Name: ARK Diagnostics, Inc.

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Date prepared: August 9, 2016

807.92 (a)(2): Device name- trade name and common name, and classification

Trade name: ARK™ Oxcarbazepine Metabolite Assay
ARK™ Oxcarbazepine Metabolite Calibrator
ARK™ Oxcarbazepine Metabolite Control

Common Name: Homogeneous Enzyme Immunoassay

Classification: 21 CFR 862.3645 POX Neuroleptic drugs radioreceptor assay test system; Class II; 21 CFR 862.3200 DLJ; 21 CFR 862.3280 LAS

807.92 (a)(3): Identification of the legally marketed predicate device

Emit® 2000 Carbamazepine Assay	K010814
ARK™ Topiramate Calibrator	K083799
ARK™ Topiramate Control	K083799

807.92 (a)(4): Device Description

The ARK Oxcarbazepine Metabolite Assay is a homogeneous immunoassay based on competition between drug in the specimen and Oxcarbazepine Metabolite 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 coenzyme NAD functions only with the bacterial enzyme used in the assay.

The ARK Oxcarbazepine Metabolite Assay consists of reagents R1 anti-Oxcarbazepine Metabolite polyclonal antibody with substrate and R2 Oxcarbazepine Metabolite labeled with bacterial G6PDH enzyme. The ARK Oxcarbazepine Metabolite Calibrator consists of a six-level set to calibrate the assay, and the ARK Oxcarbazepine Metabolite Control consists of a three-level set used for quality control of the assay.

807.92 (a)(5): Intended Use / Indications for Use

The ARK™ Oxcarbazepine Metabolite Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of Oxcarbazepine Metabolite in human serum on automated clinical chemistry analyzers. The measurements obtained are used in monitoring levels of Oxcarbazepine Metabolite to help ensure appropriate therapy.

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

The ARK™ Oxcarbazepine Metabolite Control is an assayed quality control material intended for use in quality control of the ARK Oxcarbazepine Metabolite Assay.

For prescription use only. Caution: Federal Law restricts this device to sale by or on the order of a licensed practitioner.

Summary and Explanation

Oxcarbazepine [10, 11-dihydro-10-oxo-5H-dibenzo[b,f]azepine-5-carboxamide] and eslicarbazepine [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide] are prodrugs that are metabolized to an active metabolite (10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide). Oxcarbazepine Metabolite is often called 10-monohydroxy derivative (MHD) or referred to as licarbazepine. Oxcarbazepine (*Trileptal*, Novartis) is metabolized to two enantiomers (S)-MHD and (R)-MHD at a metabolite ratio of approximately 4:1, respectively.

Eslicarbazepine acetate (*Aptiom*, Sunovion Pharmaceuticals) is prescribed as adjunctive therapy for partial-onset seizures associated with epilepsy in adults. Eslicarbazepine acetate is [(S)-10-Acetoxy-10,11-dihydro-5Hdibenz[b,f]azepine-5-carboxamide] and metabolism to (S)-MHD is favored such that the metabolite ratio of (S)-MHD to (R)-MHD is approximately 19:1.

ARK Oxcarbazepine Metabolite Calibrator

The ARK Oxcarbazepine Metabolite Calibrator is traceable to certified Oxcarbazepine Metabolite powder. The purity of Oxcarbazepine Metabolite in the certified raw material is determined by NMR and elemental analysis as performed by the supplier of the certified powder.

Bulk solutions of the ARK Oxcarbazepine Metabolite Calibrator are prepared volumetrically using a stock solution prepared by gravimetric addition of powder to solvent. The concentration of Oxcarbazepine Metabolite in the respective bulk solution must agree within 5% of its corresponding master calibrator.

Value Assignment: Testing is performed with the ARK Oxcarbazepine Metabolite Assay on the Beckman Coulter AU480[®] automated analyzer. Two calibrated runs are performed using the Master Calibrator. In each run, five replicates of Master Lot (reference) and Test Lot are tested as matched pairs for each calibrator level. Mean values for ten replicates are calculated. Test lot mean values are expected to match the Master lot mean values within 5% allowance.

REF	Product Description	Quantity/Volume	
5032-0002-00	ARK Oxcarbazepine Metabolite Calibrators* Oxcarbazepine Metabolite, buffer, bovine serum albumin, and sodium azide	Dropper vials	
	A	0.0 µg/mL	1 X 4 mL
	B	2.0 µg/mL	1 X 2 mL
	C	5.0 µg/mL	1 X 2 mL
	D	12.0 µg/mL	1 X 2 mL
	E	25.0 µg/mL	1 X 2 mL
	F	50.0 µg/mL	1 X 2 mL

*To convert results from µg/mL to µmol/L Oxcarbazepine Metabolite, multiply µg/mL by 3.933. Oxcarbazepine Metabolite levels become 7.9, 19.7, 47.2, 98.3, and 196.6 µmol/L for Calibrators B to F respectively.

ARK Oxcarbazepine Metabolite Control

The ARK Oxcarbazepine Metabolite Control is traceable to certified Oxcarbazepine Metabolite powder. The purity of Oxcarbazepine Metabolite in the certified raw material is determined by NMR and elemental analysis as performed by the supplier of the certified powder.

Bulk solutions of the ARK Oxcarbazepine Metabolite Control are prepared volumetrically using a stock solution prepared by gravimetric addition of powder to solvent. ARK manufactures the controls to contain Oxcarbazepine Metabolite within 10% of the target levels.

Value Assignment: Testing is performed with the ARK Oxcarbazepine Metabolite Assay on the Beckman Coulter AU480[®] automated analyzer, calibrated with the master calibrator lot. Three calibrated runs are performed using four replicates of each level per run. The expected control ranges are set according to mean values. Each laboratory should establish the mean value for each control level and its own ranges for each new lot of controls.

REF	Product Description	Quality Control
5032-0003-00	ARK Oxcarbazepine Metabolite Control* (4 mL) Oxcarbazepine Metabolite, buffer, bovine serum albumin, and sodium azide (target level)	Expected Range (Mean µg/mL)
	LOW (3.0 µg/mL)	2.4 – 3.6
	MID (10.0 µg/mL)	8.5 – 11.5
	HIGH (30.0 µg/mL)	25.0 – 35.0

*To convert results from µg/mL to µmol/L Oxcarbazepine Metabolite, multiply µg/mL by 3.933. Oxcarbazepine Metabolite levels become 11.8, 39.3 and 118.0 µmol/L for LOW, MID and HIGH respectively.

807.92 (a)(6): Technological Similarities and Differences to the Predicate

SUBSTANTIAL EQUIVALENCE COMPARATIVE CHART

Characteristic	Device	Predicate
	ARK™ Oxcarbazepine Metabolite Assay	Emit® 2000 Carbamazepine Assay K010814
Intended Use	The ARK™ Oxcarbazepine Metabolite Assay is intended for the quantitative determination of Oxcarbazepine Metabolite in human serum on automated clinical chemistry analyzers.	The Emit® 2000 Carbamazepine Assay is a homogeneous enzyme immunoassay intended for use in the quantitative analysis of carbamazepine in human serum or plasma.
Indications for Use	The measurements obtained are used in monitoring levels of Oxcarbazepine Metabolite to help ensure appropriate therapy.	The results obtained helps physicians individualize dosage regimens.
Sample	Serum	Serum or plasma
Methodology	Homogenous enzyme immunoassay (EIA)	Homogenous enzyme immunoassay (EIA)
Reagent Components	Two (2) reagent system: Anti- Oxcarbazepine Metabolite Antibody/Substrate Reagent (R1) containing rabbit polyclonal antibodies to Oxcarbazepine Metabolite, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers Enzyme Reagent (R2) containing Oxcarbazepine Metabolite labeled with bacterial G6PDH, buffer, bovine serum albumin, sodium azide, and stabilizers	Two (2) reagent system: Antibody/Substrate Reagent (R1) containing mouse monoclonal antibodies to carbamazepine, glucose-6-phosphate, nicotinamide adenine dinucleotide. Enzyme Reagent (R2) containing carbamazepine labeled with bacterial G6PDH, buffer. Sodium azide, buffer, preservatives, and stabilizers
Platform required	Automated clinical chemistry analyzer	Automated clinical chemistry analyzer
Testing environment	Routine clinical laboratory	Routine clinical laboratory
Reagent condition and storage	Liquid, 2-8° C	Liquid, 2-8° C

Calibrators: Similarities and Differences		
Item	Candidate Device (ARK Oxcarbazepine Calibrator)	Predicate Device (ARK Topiramate Calibrator; k083799)
Intended Use/Indications for Use	ARK Oxcarbazepine Metabolite Calibrator is intended for use in calibration of the ARK Oxcarbazepine Metabolite Assay.	The ARK Topiramate Calibrator is intended for use in calibration of the ARK Topiramate Assay.
Matrix	Synthetic protein matrix (buffer, bovine serum albumin, preservatives)	Same
Levels	6	Same

Controls: Similarities and Differences		
Item	Candidate Device (ARK Oxcarbazepine Control)	Predicate Device (ARK Topiramate Control; k083799)
Intended Use/Indications for Use	The ARK Oxcarbazepine Metabolite Control is an assayed quality control material intended for use in quality control of the ARK Oxcarbazepine Metabolite Assay.	The ARK Topiramate Control is intended for use in quality control of the ARK Topiramate Assay.
Matrix	Synthetic protein matrix (buffer, bovine serum albumin, preservatives)	Same
Levels	3 (LOW, MID, HIGH)	Same

**807.92 (b)(1) and 807.92 (b)(2):
Brief Description of Nonclinical and Clinical Data**

The following performance characteristics were obtained on the Beckman Coulter AU480[®] automated clinical chemistry analyzer. Unless otherwise stated, a metabolite S:R ratio of 9:1 was used to evaluate performance.

Limit of Quantitation (LOQ)

The LOQ of the ARK Oxcarbazepine Metabolite Assay was determined according to CLSI EP17-A2 and is defined as the lowest concentration for which acceptable inter-assay precision and recovery is observed ($\leq 20\%$ CV with $\pm 15\%$ recovery). The LOQ was determined to be 1.0 $\mu\text{g/mL}$, and may depend on analyzer-specific performance.

Recovery

Analytical recovery throughout the measurement range was assessed by adding concentrated Oxcarbazepine Metabolite into human serum negative for Oxcarbazepine Metabolite. The S:R ratio of each enantiomer was varied. The mean of six (6) replicate measurements of Oxcarbazepine Metabolite was tabulated as a function of the enantiomer ratio.

Theoretical Concentration ($\mu\text{g/mL}$)	Mean Recovered Concentration ($\mu\text{g/mL}$)			
	S:R 1:1	S:R 4:1	S:R 9:1	S:R 19:1
1.0	0.77	0.93	0.98	0.95
4.0	3.78	3.92	3.94	3.86
8.0	7.47	8.18	8.16	7.82
15.0	14.10	15.80	14.91	15.42
20.0	19.03	21.69	19.81	21.02
35.0	33.74	34.71	33.52	36.16
45.0	42.89	46.88	44.63	49.46

Linearity

Linearity studies were performed as suggested in CLSI/NCCLS Protocol EP6-A. A 60.0 µg/mL serum sample was prepared and dilutions were made proportionally with human serum negative for Oxcarbazepine Metabolite. Oxcarbazepine Metabolite concentrations ranged from 1.0 to 50.0 µg/mL. Linearity at specific dilutions was considered acceptable if the percent difference was ±10% between the predicted 1st and 2nd order regressed values or ≤ 0.20 µg/mL below 2.0 µg/mL. A linear relationship was demonstrated between 1.0 and 50.0 µg/mL ($y = 1.0388x - 0.0693$). Results are shown below.

Estimated Value (µg/mL)	Results (µg/mL)	1st Order Predicted Results	2nd Order Predicted Results	Difference
1.00	1.00	0.97	1.11	0.14 µg/mL
3.00	3.19	3.05	3.11	2.2 %
5.00	5.14	5.12	5.12	0.0 %
10.00	10.26	10.32	10.18	-1.3 %
20.00	21.01	20.71	20.41	-1.4 %
30.00	29.88	31.09	30.80	-0.9 %
40.00	41.92	41.48	41.36	-0.3 %
50.00	52.13	51.87	52.07	0.4 %

Assay Range

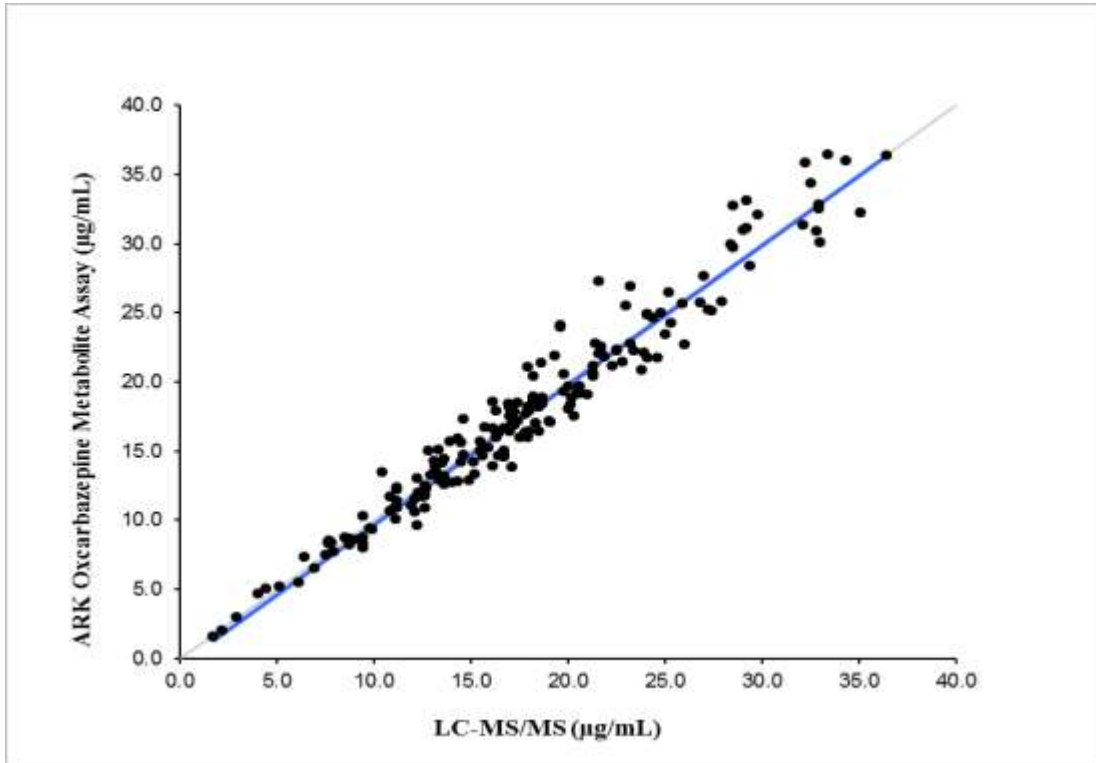
The measurement range of the ARK Oxcarbazepine Metabolite Assay is 1.0 to 37.0 µg/mL based on clinical concentrations tested. Report results below this range as <1.0 µg/mL or below the analyzer-specific lower LOQ established in your laboratory. Report results above this range as >37.0 µg/mL or test a diluted specimen having a concentration within the measurement range.

Specimens testing initially above the measurement range may be diluted in Calibrator A and retested. Multiply the assay result by the dilution factor to obtain the concentration of Oxcarbazepine Metabolite in the undiluted specimen.

Method Comparison

Correlation studies were performed using CLSI Protocol EP9-A3. Results from the ARK Oxcarbazepine Metabolite Assay were compared with results from LC-MS/MS. The Oxcarbazepine Metabolite concentrations ranged from 1.7 µg/mL to 36.4 µg/mL. Results of the Passing-Bablok regression analysis for the study are shown below (with 95% confidence limits).

Slope	1.01	(0.98 to 1.04)
y-intercept	- 0.38	(- 0.84 to 0.12)
Correlation Coefficient (r ²)	0.95	(0.94 to 0.97)
Number of Samples	190	



Precision

Precision was determined as described in CLSI Protocol EP5-A3. Tri-level controls and three human serum pooled specimens containing Oxcarbazepine Metabolite were used in the study. Each level was assayed in quadruplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The within-run, between-day, total SD, and percent CVs were calculated. Acceptance criterion: $\leq 10\%$ CV.

Sample	N	Mean ($\mu\text{g/mL}$)	Within Run		Between Day		Total	
			SD	CV (%)	SD	CV (%)	SD	CV (%)
ARK Control								
LOW	160	3.0	0.12	4.0	0.12	4.1	0.17	5.7
MID	160	10.1	0.37	3.6	0.33	3.2	0.48	4.8
HIGH	160	30.2	0.99	3.3	1.19	3.9	1.54	5.1
Human Serum								
LOW	160	3.1	0.12	3.9	0.12	4.0	0.17	5.5
MID	160	10.1	0.38	3.8	0.36	3.6	0.55	5.5
HIGH	160	30.4	1.10	3.6	1.11	3.7	1.55	5.1

Interfering Substances

Interference studies were conducted using CLSI Protocol EP7-A2 as a guideline. Clinically high concentrations of the following potentially interfering substances in serum with known levels of Oxcarbazepine Metabolite (approximately 3 and 30 $\mu\text{g/mL}$) were evaluated. Each sample was assayed using the ARK Oxcarbazepine Metabolite Assay, along with a serum control of Oxcarbazepine Metabolite. Measurement of Oxcarbazepine Metabolite resulted in $\leq 10\%$ error in the presence of interfering substances at the levels tested.

Interfering Substance	Interferent Concentration	Percentage Recovery	
		3 $\mu\text{g/mL}$ Oxcarbazepine Metabolite	30 $\mu\text{g/mL}$ Oxcarbazepine Metabolite
Human Albumin	12 g/dL	102.2	95.1
Bilirubin - conjugated	70 mg/dL	108.6	100.2
Bilirubin - unconjugated	70 mg/dL	102.7	92.4
Cholesterol	602 mg/dL	96.5	103.5
Human IgG	12 g/dL	93.1	93.1
Hemoglobin	1000 mg/dL	105.7	100.7
Rheumatoid Factor	1000 IU/mL	101.0	103.9
Triglycerides	1000 mg/dL	96.6	94.3
Uric Acid	30 mg/dL	107.5	95.5

Specificity

MHD-Glucuronide and Dihydro-dihydroxy-carbamazepine (synonymous with dihydroxy-derivative of oxcarbazepine or DHD) are secondary metabolites of Oxcarbazepine Metabolite (MHD). Oxcarbazepine and Eslicarbazepine acetate are parent drugs for MHD. Carbamazepine and its metabolites (Dihydro-carbamazepine and Carbamazepine-epoxide) are compounds structurally similar to MHD. All were tested for crossreactivity at the concentrations listed in the presence of MHD (20 µg/mL) in serum. MHD-Glucuronide levels may appear in serum greater than MHD in cases of renal impairment¹⁶. MHD-Glucuronide and DHD levels are not crossreactive.

The parent drug oxcarbazepine crossreacted 22.2% (as did Eslicarbazepine Acetate), although neither Oxcarbazepine nor Eslicarbazepine Acetate are expected to be present with MHD at a significant level due to rapid renal clearance. Carbamazepine and its metabolites also crossreacted in the assay; the possibility of co-therapy or transition of therapy should be considered.

Metabolite	Level Tested (µg/mL)	Percent Cross-Reactivity	Percent Interference
MHD Glucuronide	20	1.6	1.6
	40	0.0	-0.1
	100	1.5	7.4
	200	1.0	10.5
(DHD) Dihydro-dihydroxy carbamazepine	5.0	-11.3	-2.9
Oxcarbazepine	20.0	22.2	22.6
Eslicarbazepine acetate	20.0	22.1	22.4
Carbamazepine	20.0	20.4	20.7
Dihydro – Carbamazepine	5.0	6.0	1.5
Carbamazepine-epoxide	10.0	13.6	6.9

Drug Interference

Other anti-epileptic or coadministered drugs tested did not crossreact with Oxcarbazepine Metabolite-selective antibody. A high concentration of each compound was spiked into normal human serum with known levels of Oxcarbazepine Metabolite (approximately 3 and 30 µg/mL) and assayed along with a serum control of Oxcarbazepine Metabolite. Measurement of Oxcarbazepine Metabolite resulted in ≤10% error in the presence of drug compounds at the levels tested.

#	Compound	Concentration ($\mu\text{g/mL}$)	Percentage Recovery	
			Oxcarbazepine metabolite (3 $\mu\text{g/mL}$)	Oxcarbazepine metabolite (30 $\mu\text{g/mL}$)
1	Acetaminophen	200	95.6	97.1
2	Acetazolamide	100	99.9	90.3
3	Acetylsalicylic acid	1000	95.1	96.0
4	Amikacin	100	91.7	92.0
5	Amitriptyline	10	105.1	101.1
6	Amoxapine	10	99.3	98.0
7	Amphotericin B	100	93.6	93.2
8	Ampicillin	100	96.5	100.2
9	Ascorbic acid	100	92.8	91.1
10	Baclofen	100	91.1	93.5
11	Bupropion	10	109.6	98.8
12	Caffeine	100	98.3	91.7
13	Chloramphenicol	250	93.7	90.3
14	Chlorpromazine	10	98.3	99.7
15	Citalopram	10	102.9	99.3
16	Clobazam	100	98.3	103.2
17	Clonazepam	10	104.6	99.2
18	Cyclosporin A	40	91.2	90.2
19	Diazepam	20	103.1	100.3
20	Digoxin	10	97.3	97.0
21	Doxepin	10	107.4	102.9
22	Erythromycin	200	94.5	94.7
23	Ethanol	4000 (0.4%)	91.6	100.7
24	Ethotoin	100	98.4	96.2
25	Ethosuximide	250	103.2	105.1
26	Felbamate	250	93.0	93.8
27	Fluoxetine	20	94.9	99.2
28	Furosemide	100	95.2	92.8
29	Gabapentin	200	92.2	104.3
30	Gentamicin	100	95.8	91.2
31	Haloperidol	10	101.2	97.4
32	Ibuprofen	500	103.3	91.6
33	Imipramine	10	109.4	100.4
35	Kanamycin A	200	93.8	109.0
35	Lamotrigine	400	91.5	97.9
36	Levetiracetam	400	97.7	94.7
37	Lidocaine	100	96.8	97.7
38	Lincomycin	1000	90.7	100.4
39	Mephenytoin	100	100.7	97.3
40	Mesoridazine	10	97.8	99.4
41	Methicillin	250	93.5	96.2

#	Compound	Concentration ($\mu\text{g/mL}$)	Percentage Recovery	
			Oxcarbazepine metabolite (3 $\mu\text{g/mL}$)	Oxcarbazepine metabolite (30 $\mu\text{g/mL}$)
42	Naproxen	600	102.2	95.7
43	Neomycin	1000	95.6	102.9
44	Niacin	100	93.0	93.9
45	Nitrazepam	20	106.3	98.5
46	Nortriptyline	10	104.4	102.0
47	Olanzapine	10	105.8	100.5
48	Paroxetine	10	96.7	98.3
49	2-phenyl-2-ethyl-malonamide (PEMA)	1000	94.6	93.9
50	Penicillin V	100	95.4	93.8
51	Perphenazine	50	104.9	100.9
52	Phenobarbital	200	90.2	94.7
53	Phenytoin	200	100.1	99.6
54	Pregabalin	200	91.5	90.2
55	Primidone	100	95.0	92.4
56	Procainamide	100	93.3	92.4
57	Prochlorperazine	10	105.2	101.6
58	Ranitidine	100	102.1	100.6
59	Rifampin	100	93.3	92.7
60	Risperidone	10	100.6	97.7
61	Sertraline	100	98.9	93.4
62	Spectinomycin	100	97.2	97.9
63	Stiripentol	100	93.8	99.7
64	Sulfamethoxazole	400	100.5	97.5
65	Theophylline	200	100.5	100.8
66	Thioridazine	10	103.9	98.0
67	Tobramycin	100	94.5	101.3
68	Tiagabine	200	91.6	93.5
69	Topiramate	250	92.8	91.7
70	Trimethoprim	40	101.2	93.6
71	Valproic Acid	600	92.7	93.0
72	Vancomycin	250	101.3	92.6
73	Vigabatrin	150	103.2	96.9
74	Zonisamide	400	92.1	91.4

Sample Stability

Serum specimens were shown to be stable for at least forty-eight (48) hours at room temperature (22 °C), fourteen (14) days when refrigerated (2-8 °C), frozen (-20 °C) for at least 3 months and after three (3) successive freeze/thaw cycles based on supporting data.

Calibration Curve Stability

A stored calibration was effective for at least 15 days based on supporting data.

807.92 (b)(3): Conclusions from Nonclinical Testing

As summarized above, the ARK Oxcarbazepine Metabolite Assay, the ARK Oxcarbazepine Metabolite Calibrator and the ARK Oxcarbazepine Metabolite Control are substantially equivalent to the ARK™ Topiramate Assay system. The ARK Oxcarbazepine Metabolite Assay system was shown to be safe and effective for its intended use based on performance studies.