510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K213875

B Applicant

Microgenics Corporation

C Proprietary and Established Names

DRI™ Tricyclics Serum Tox Assay

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LFH	Class II	21 CFR 862.3910 - Tricyclic Antidepressant Drugs Test System	TX - Clinical Toxicology

II Submission/Device Overview:

A Purpose for Submission:

New device (assay)

B Measurand:

Nortriptyline

C Type of Test:

Qualitative/Semiquantitative - Enzymatic Immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The DRI™ Tricyclics Serum Tox Assay is a homogenous enzyme immunoassay intended for the qualitative and/or semiquantitative determination of the presense of tricyclic antidepressants (TCAs) in human serum, plasma, or urine of patients at a cutoff concentration of 300 ng/mL in patients suspected of drug overdose.

The semi-quantitative mode is for the purpose of enabling laboratories to determine an appropriate dilution of the specimen for confirmation by a confirmatory method sych as Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) or permitting laboratories to establish quality control procedures.

The assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) is the preferred confirmatory method.

Clinical and professional judgment should be applied to any drug of abuse test result, particulary when preliminary positive results are used.

For In Vitro Diagnostic Use Only.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Architect c4000 Clinical Chemistry Analyzer

IV Device/System Characteristics:

A Device Description:

The DRI ^{TM} Tricyclics Serum Tox Assay is a homogeneous enzyme immunoassay used to detect tricyclic antidepressants in serum, plasma, or urine. The DRI ^{TM} Tricyclics Serum Tox assay is supplied as a two liquid reagent kit (Reagent A and Reagent E). They are bottled separately within the same kit, as described below:

• **Antibody/Substrate Reagent (Reagent A) 1 bottle of 25 mL (1 x 25 mL):** Contains polyclonal anti-tricyclics antibodies (sheep), glucose-6- phosphate (G6P), and nicotinamide adenine dinucleotide (NAD) in Tris buffer with sodium azide as a preservative.
• **Enzyme Conjugate Reagent (Reagent E) 1 bottle of 8 mL (1 x 8 mL):** Contains glucose-6-phosphate dehydrogenase (G6PDH) labeled with nortriptyline in Tris buffer with sodium azide as a preservative.

B Principle of Operation:

The test is based on the competition of an enzyme, glucose-6-phosphate dehydrogenase (G6PDH), labeled-drug and the drug from the sample for a fixed amount of specific antibody binding sites. In the absence of the drug from the sample, the specific antibody binds the enzyme-labeled drug and the enzyme activity is inhibited. This phenomenon creates a direct relationship between drug concentration in the sample and the enzyme activity. The enzyme activity is determined spectrophotometrically at 340 nm by measuring its ability to convert nicotinamide adenine dinucleotide (NAD) to NADH.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Tricyclic Serum Tox Eia Assay

B Predicate 510(k) Number(s):

K983268

C Comparison with Predicate(s):

Device & Predicate Device(s):	K213875	K983268
Device Trade Name	DRI ™ Tricyclics Serum Tox Assay	Tricyclic Serum Tox EIA Assay
General Device Characteristic Similarities		
Intended Use/Indications For Use	Intended to be used for qualitative and semiquantitative determination of tricyclic antidepressants in serum, plasma or urine of patients suspected of drug overdose.	Same
Measurand	Nortriptyline	Same
Sample Matrix	Serum, Plasma, Urine	Same
Cut-Off	300 ng/mL	Same

General Device Characteristic Differences		
Antibody	Sheep polyclonal antibodies	Monoclonal antibodies

VI Standards/Guidance Documents Referenced:

- Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline–Third Edition. (Clinical and Laboratory Standards Institute (CLSI) EP05-A3).
- Interference Testing in Clinical Chemistry (CLSI EP07-ED3).
- Measurement Procedure Comparison and Bias Estimation Using Patient Samples (CLSI EP09c-ED3).
- Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline (CLSI EP25-A).
- Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures. (CLSI EP35-ED1).
- User Protocol for Evaluation of Qualitative Test Performance Approved Guideline – Second Edition (CLSI EP12-A2).

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Repeatability

Samples were prepared by spiking Nortriptyline into drug-free serum and drug-free urine at the cutoff as well as 25%, 50%, 75%, and 100% above and below the cutoff and tested in duplicate (n=2) twice per day for 20 days (total n=80 for each level), in both qualitative and semi-quantitative modes. The results are shown below.

Table #1 – Serum:

Spiked Concentration (ng/mL)*	% of Cutoff	Total Precision (n=80) – Serum				
		# of Determinants	Qualitative Immunoassay Results (Negative/ Positive)	Semi-quantitative Immunoassay Results (Negative/ Positive)	Semi-quantitative SD results	Semi-quantitative CV% results
0	-100	80	80/0	80/0	N/A	N/A
75	-75	80	80/0	80/0	4.40	5.36
150	-50	80	80/0	80/0	4.19	2.42
225	-25	80	80/0	80/0	4.22	1.68
300	100	80	10/70	19/61	17.29	5.34

Spiked Concentration (ng/mL)*	% of Cutoff	Total Precision (n=80) – Serum				
		# of Determinants	Qualitative Immunoassay Results (Negative/ Positive)	Semi-quantitative Immunoassay Results (Negative/ Positive)	Semi-quantitative SD results	Semi-quantitative CV% results
375	+25	80	0/80	0/80	16.59	3.92
450	+50	80	0/80	0/80	19.15	3.94
525	+75	80	0/80	0/80	47.37	8.25
600	+100	80	0/80	0/80	43.10	6.28

**Approximate concentrations*

Table #2 – Urine:

Spiked Concentration (ng/mL)*	% of Cutoff	Total Precision (n=80) - Urine				
		# of Determinants	Qualitative Immunoassay Results (Negative/ Positive)	Semi-quantitative Immunoassay Results (Negative/ Positive)	Semi-quantitative SD results	Semi-quantitative CV% results
0	-100	80	80/0	80/0	N/A	N/A
75	-75	80	80/0	80/0	4.62	5.96
150	-50	80	80/0	80/0	7.19	4.45
225	-25	80	80/0	80/0	9.62	4.08
300	100	80	68/12	73/7	11.04	3.75
375	+25	80	0/80	0/80	24.41	6.12
450	+50	80	0/80	0/80	18.65	4.13
525	+75	80	0/80	0/80	46.66	8.89
600	+100	80	0/80	0/80	45.15	7.63

**Approximate concentrations*

Reproducibility:

Samples were prepared by spiking Nortriptyline into drug-free serum and drug-free urine at the cutoff as well as at 25%, 50%, 75%, and 100% above and below the cutoff. Spiked samples were tested as 1 run per day, 5 replicates per run for a total of 5 days in qualitative and semi-quantitative modes on 3 different instruments of the same model. The results of the reproducibility study are shown below:

Table #3 – Serum:

Spiked Concentration (ng/mL)*	% of Cutoff	Total Precision (n=75) - Serum				
		# of Determinants	Qualitative Immunoassay Results (Negative/ Positive)	Semi-quantitative Immunoassay Results (Negative/ Positive)	Semi-quantitative SD results	Semi-quantitative CV% results
0	-100	75	75/0	75/0	N/A	N/A
75	-75	75	75/0	75/0	5.26	6.66
150	-50	75	75/0	75/0	4.00	2.39
225	-25	75	75/0	75/0	4.36	1.76
300	100	75	30/45	29/46	19.24	6.11
375	+25	75	0/75	0/75	22.23	5.40
450	+50	75	0/75	0/75	21.06	4.41
525	+75	75	0/75	0/75	43.78	7.87
600	+100	75	0/75	0/75	43.77	6.54

**Approximate concentrations*

Table #4 – Urine:

Spiked Concentration (ng/mL)*	% of Cutoff	Total Precision (n=75) - Urine				
		# of Determinants	Qualitative Immunoassay Results (Negative/ Positive)	Semi-quantitative Immunoassay Results (Negative/ Positive)	Semi-quantitative SD results	Semi-quantitative CV% results
0	-100	75	75/0	75/0	N/A	N/A
75	-75	75	75/0	75/0	3.34	4.30
150	-50	75	75/0	75/0	4.60	2.82
225	-25	75	75/0	75/0	6.90	2.86
300	100	75	61/14	66/9	12.05	4.01
375	+25	75	0/75	0/75	23.21	5.85
450	+50	75	0/75	0/75	23.96	5.28
525	+75	75	0/75	0/75	39.74	7.73
600	+100	75	0/75	0/75	42.36	7.86

**Approximate concentrations*

2. Linearity:

Drug-free serum or drug-free urine was spiked with Nortriptyline to the concentration of the high calibrator level and diluted with drug-free serum or drug-free urine to generate 9 intermediate levels. Five (5) replicates of each sample using one (1) lot of reagents, calibrators, and controls were run in semi-quantitative mode and the average was used to determine percent recovery compared to the expected target value.

Table #5: Linearity Results Table

Expected Concentration (ng/mL)	Observed Mean Concentration for Serum (ng/mL)	Observed Mean Concentration for Urine (ng/mL)	Range of Recovery (%)	
			Serum	Urine
0	7	8	NA	NA
125	121	148	96-115*	94-118*
250	242	271		
375	385	383		
500	479	470		
625	720	620		
750	839	741		
875	913	838		
1000	1046	946		

**Excluding the observed mean concentration at the 1st Level (0 ng/mL).*

3. Analytical Specificity/Interference:

The cross-reactivity of tricyclic antidepressants as well as their metabolites was evaluated by adding known amounts of each compound to drug-free serum and urine. The specificity (cross-reactivity) study was performed using one lot of reagents, calibrators and controls in both qualitative and semi-quantitative modes. Two (2) replicates of each cross-reactant sample were run in qualitative and semi-quantitative modes on the Architect c4000 clinical chemistry analyzer. Percent cross-reactivity was calculated as (cut-off concentration / lowest concentration observed that provides a reliably positive result) x 100. Results are summarized in tables #6 and #7 below:

Table #6: Cross Reactivity of Tricyclic antidepressants and structurally related compounds - Serum

Tricyclic Antidepressants & Structurally related compounds	Concentration tested (ng/mL)	Cross-reactivity (%)
2 -Hydroxy Imipramine	1,300	23.1
7-Hydroxy Quetiapine	100,000	<0.3
7-Hydroxy Amoxapine solution	100,000	<0.3
8-Hydroxy Amoxapine solution	100,000	<0.3
10-Hydroxyamitriptyline	1,000	30.0
Alimemazine	12,000	2.5
Amitriptyline	300	85.7
Amoxapine	125,000	0.2
Blonanserin	100,000	<0.3
Chlorpromazine	525	57.1
Clomipramine	300	100.0
Clozapine	100,000	<0.3
Cyclobenzaprine	450	66.7

Tricyclic Antidepressants & Structurally related compounds	Concentration tested (ng/mL)	Cross-reactivity (%)
Desipramine	250	120.0
Desloratadine	100,000	<0.3
Diphenhydramine	60,000	0.5
Dosulepin	475	63.2
Doxepin	600	50.0
Fluoxentine	100,000	<0.3
Fluphenazine	2,000	15.0
Haloperidol	100,000	<0.3
Imipramine	190	157.9
Loratadine	100,000	<0.3
Lofepramine	430	69.8
Loxapine Succinate	100,000	<0.3
Maprotiline	100,000	0.3
Mianserin	100,000	<0.3
Mirtazapine	100,000	<0.3
N-Desmethylclozapine	100,000	<0.3
N-Desmethyltrimpramine	350	85.7
NefazodoneN-Desmethylmirtazapine	100,000	<0.3
Nefazodone N-Desmethylmirtazapine	100,000	<0.3
Norclomipramine Hydrochloride	375	80.0
Nordoxepin Hydrochloride	1,750	17.1
Normaprotiline	100,000	0.3
Nortriptyline	300	100.0
Olanzapine	100,000	<0.3
Opipramol HCL	400	85.7
Praoxetine	100,000	<0.3
Perphenazine	450	66.7
Phenoxybenzanmine	100,000	<0.3
Promazine	400	75.0
Promethazine	20,000	1.5
Protriptyline	450	66.7
Quetiapine Fumarate	50,000	0.6
Risperidone	100,000	<0.3
Sertraline	100,000	<0.3
Thioridazine	6,000	5.0
Thiothixene	100,000	<0.3
Tianeptine	100,000	<0.3
Trazodone	100,000	0.3
Trimipramine	390	76.9
Ziprasidone	100,000	<0.3

Table #7: Cross Reactivity of Tricyclic antidepressants and structurally related compounds - Urine

Tricyclic Antidepressants & Structurally related compounds	Concentration tested (ng/mL)	Cross-reactivity (%)
2 -Hydroxy Imipramine	1,000	30.0
7-Hydroxy Quetiapine	100,000	<0.3
7-Hydroxy Amoxapine solution	100,000	<0.3
8-Hydroxy Amoxapine solution	100,000	<0.3
10-Hydroxyamitriptyline	1,000	30.0
Alimemazine	12,000	2.5
Amitriptyline	300	100
Amoxapine	100,000	0.2
Blonanserin	100,000	<0.3
Chlorpromazine	600	50.0
Clomipramine	350	85.7
Clozapine	100,000	<0.3
Cyclobenzaprine	500	60.0
Desipramine	250	120
Desloratadine	100,000	<0.3
Diphenhydramine	30,000	1.0
Dosulepin	550	54.5
Doxepin	600	50.0
Fluoxentine	100,000	<0.3
Fluphenazine	2,000	15.0
Haloperidol	100,000	<0.3
Imipramine	250	120.0
Loratadine	100,000	<0.3
Lofepramine	460	65.2
Loxapine Succinate	100,000	0.3
Maprotiline	100,000	0.3
Mianserin	100,000	<0.3
Mirtazapine	100,000	<0.3
N-Desmethylclozapine	100,000	<0.3
N-Desmethyltrimpramine	325	92.3
N-Desmethylmirtazapine	100,000	<0.3
Nefazodone	100,000	<0.3
Norclomipramine Hydrochloride	450	66.7
Nordoxepin Hydrochloride	1,750	17.1
Normaprotiline	100,000	0.3
Nortriptyline	300	100.0
Olanzapine	100,000	<0.3
Opipramol HCL	350	85.7
Praoxetine	100,000	<0.3
Perphenazine	650	46.2
Phenoxybenzanmine	100,000	<0.3
Promazine	410	73.2
Promethazine	15,000	2.0

Tricyclic Antidepressants & Structurally related compounds	Concentration tested (ng/mL)	Cross-reactivity (%)
Protriptyline	550	54.6
Quetiapine Fumarate	45,000	0.7
Risperidone	100,000	<0.3
Sertraline	100,000	<0.3
Thioridazine	4,000	7.5
Thiothixene	100,000	<0.3
Tianeptine	90,000	0.33
Trazodone	100,000	<0.3
Trimipramine	400	75
Ziprasidone	100,000	<0.3

A specificity study of structurally unrelated compounds/or concurrently used drugs was evaluated by adding known amounts of each compound to low and high controls (225 and 375 ng/mL) in serum and urine. The study was performed using one lot of reagents, calibrators and controls in both qualitative and semi-quantitative modes. Two (2) replicates of each cross-reactant sample were run in qualitative and semi-quantitative modes on the Architect c4000 clinical chemistry analyzer. Results are summarized in tables #8 and #9 below:

Table #8: Structurally unrelated compounds – Serum

Structurally unrelated compounds	Serum		
	Concentration tested (ng/mL)	Low Control - 25% of cutoff (225 ng/mL)	High Control +25% of cutoff (375 ng/mL)
11-nor-Δ9-THC-COOH (11-Nor-9-carboxy-THC)	100,000	Negative	Positive
6-Acetyl morphine	75,000	Negative	Positive
Acetaminophen	100,000	Negative	Positive
Acetylsalicylic acid	100,000	Negative	Positive
Amisulpride	100,000	Negative	Positive
Amoxicillin	100,000	Negative	Positive
Amphetamine	100,000	Negative	Positive
Benzotropine Methane Sulfonate	3,000	Negative	Positive
Benzoylecgonine	100,000	Negative	Positive
Brompheniramine	3,000	Negative	Positive
Caffeine	100,000	Negative	Positive
Carbamazepine	3,000	Negative	Positive
Carbamazepine Epoxide	10,000	Negative	Positive
Chloroquine Phosphate	100,000	Negative	Positive
Cimetidine	100,000	Negative	Positive
Cocaine	75,000	Negative	Positive
Codeine	100,000	Negative	Positive
Dextromethorphan	100,000	Negative	Positive
Diacetylmorphine (Heroin)	100,000	Negative	Positive

Structurally unrelated compounds	Serum		
	Concentration tested (ng/mL)	Low Control - 25% of cutoff (225 ng/mL)	High Control +25% of cutoff (375 ng/mL)
Diazepam	100,000	Negative	Positive
Digoxin	100,000	Negative	Positive
Dihydrocodeine	100,000	Negative	Positive
EDDP Perchlorate	100,000	Negative	Positive
EMDP-HCL	100,000	Negative	Positive
Fentanyl	25,000	Negative	Positive
Glutethimide	100,000	Negative	Positive
Hydrocodone	100,000	Negative	Positive
Hydrocortisone	100,000	Negative	Positive
Hydromorphone	100,000	Negative	Positive
Hydroxyzine	3,000	Negative	Positive
Ibuprofen	100,000	Negative	Positive
Levorphanol-D3	100,000	Negative	Positive
Meperidine	100,000	Negative	Positive
Methadone	3,000	Negative	Positive
Methamphetamine	100,000	Negative	Positive
Methaqualone	500	Negative	Positive
Methsuximide	75,000	Negative	Positive
Methylphenidate	100,000	Negative	Positive
Morphine	100,000	Negative	Positive
Morphine-3β-glucuronide	100,000	Negative	Positive
Morphine-6β-glucuronide	100,000	Negative	Positive
Nalbuphine	100,000	Negative	Positive
Nalorphine	100,000	Negative	Positive
Naloxone	100,000	Negative	Positive
Naltrexone	100,000	Negative	Positive
Naproxen	100,000	Negative	Positive
Norcodeine	100,000	Negative	Positive
Nordiazepam	100,000	Negative	Positive
Norethindrone	100,000	Negative	Positive
Norhydrocone	100,000	Negative	Positive
Noroxycodone	100,000	Negative	Positive
Noroxymorphone	100,000	Negative	Positive
Norpropoxyphene	75,000	Negative	Positive
Oxaprozin	100,000	Negative	Positive
Oxazepam	100,000	Negative	Positive
Oxycodone	100,000	Negative	Positive
Oxymorphone	100,000	Negative	Positive
PCP	50,000	Negative	Positive
Phenobarbital	100,000	Negative	Positive
Phenytoin	100,000	Negative	Positive
Primidone	100,000	Negative	Positive
Procyclidine	100,000	Negative	Positive

Structurally unrelated compounds	Serum		
	Concentration tested (ng/mL)	Low Control - 25% of cutoff (225 ng/mL)	High Control +25% of cutoff (375 ng/mL)
Propoxyphene	100,000	Negative	Positive
Secobarbital	100,000	Negative	Positive
Tapentadol	100,000	Negative	Positive
Temazepam	100,000	Negative	Positive
Triprolidine	100,000	Negative	Positive
Valproic Acid	100,000	Negative	Positive
Venlafaxine	100,000	Negative	Positive
Verapamil	100,000	Negative	Positive

Table #9: Structurally unrelated compounds – Urine:

Structurally unrelated compounds	Urine		
	Concentration tested (ng/mL)	Low Control - 25% of cutoff (225 ng/mL)	High Control +25% of cutoff (375 ng/mL)
11-nor-Δ9-THC-COOH (11-Nor-9-carboxy-THC)	100,000	Negative	Positive
6-Acetyl morphine	100,000	Negative	Positive
Acetaminophen	100,000	Negative	Positive
Acetylsalicylic acid	100,000	Negative	Positive
Amisulpride	100,000	Negative	Positive
Amoxicillin	100,000	Negative	Positive
Amphetamine	100,000	Negative	Positive
Benzotropine Methane Sulfonate	7,000	Negative	Positive
Benzoylecgonine	100,000	Negative	Positive
Brompheniramine	5,000	Negative	Positive
Caffeine	100,000	Negative	Positive
Carbamazepine	5,000	Negative	Positive
Carbamazepine Epoxide	30,000	Negative	Positive
Chloroquine Phosphate	100,000	Negative	Positive
Cimetidine	100,000	Negative	Positive
Cocaine	100,000	Negative	Positive
Codeine	100,000	Negative	Positive
Dextromethorphan	100,000	Negative	Positive
Diacetylmorphine (Heroin)	100,000	Negative	Positive
Diazepam	100,000	Negative	Positive
Digoxin	100,000	Negative	Positive
Dihydrocodeine	100,000	Negative	Positive
EDDP Perchlorate	100,000	Negative	Positive
EMDP-HCL	100,000	Negative	Positive
Fentanyl	25,000	Negative	Positive
Glutethimide	100,000	Negative	Positive
Hydrocodone	100,000	Negative	Positive
Hydrocortisone	100,000	Negative	Positive

Structurally unrelated compounds	Urine		
	Concentration tested (ng/mL)	Low Control - 25% of cutoff (225 ng/mL)	High Control +25% of cutoff (375 ng/mL)
Hydromorphone	100,000	Negative	Positive
Hydroxyzine	5,000	Negative	Positive
Ibuprofen	100,000	Negative	Positive
Levorphanol-D3	100,000	Negative	Positive
Levothyroxine	100,000	Negative	Positive
Meperidine	25,000	Negative	Positive
Methadone	75,000	Negative	Positive
Methamphetamine	100,000	Negative	Positive
Methaqualone	1,000	Negative	Positive
Methsuximide	75,000	Negative	Positive
Methylphenidate	100,000	Negative	Positive
Morphine	100,000	Negative	Positive
Morphine-3β-glucuronide	100,000	Negative	Positive
Morphine-6β-glucuronide	100,000	Negative	Positive
Nalbuphine	100,000	Negative	Positive
Nalorphine	100,000	Negative	Positive
Naloxone	100,000	Negative	Positive
Naltrexone	100,000	Negative	Positive
Naproxen	100,000	Negative	Positive
Norcodeine	100,000	Negative	Positive
Nordiazepam	100,000	Negative	Positive
Norethindrone	100,000	Negative	Positive
Norhydrocone	75,000	Negative	Positive
Noroxycodone	100,000	Negative	Positive
Noroxymorphone	100,000	Negative	Positive
Norpropoxyphene	75,000	Negative	Positive
Oxaprozin	100,000	Negative	Positive
Oxazepam	100,000	Negative	Positive
Oxycodone	100,000	Negative	Positive
Oxymorphone	100,000	Negative	Positive
PCP	75,000	Negative	Positive
Phenobarbital	100,000	Negative	Positive
Phenytoin	100,000	Negative	Positive
Primidone	100,000	Negative	Positive
Procyclidine	100,000	Negative	Positive
Propoxyphene	100,000	Negative	Positive
Secobarbital	100,000	Negative	Positive
Tapentadol	100,000	Negative	Positive
Temazepam	100,000	Negative	Positive
Triprolidine	100,000	Negative	Positive
Valproic Acid	100,000	Negative	Positive
Venlafaxine	100,000	Negative	Positive
Verapamil	100,000	Negative	Positive

When Carbamazepine was added to near cutoff negative (225 ng/mL) samples at concentrations of 4,000 ng/mL in serum, positive results were observed. Device labeling includes the following limitation: "Patient samples containing tricyclic antidepressants in the presence of carbamazepine may yield falsely elevated results in the TCA immunoassay. Results should always be assessed in conjunction with the patient's medical history, clinical examinations, and other clinicopathological findings."

Interference Testing of exogenous and endogenous compounds

Interference from various compounds was evaluated by adding known amounts of each compound to drug free serum and urine samples containing near cutoff negative (225 ng/mL) and near cutoff positive (375 ng/mL) concentrations of Nortriptyline. Testing was performed in both qualitative and semiquantitative modes. The compounds listed in the table below did not cause any positive or negative interference at the concentrations shown:

Table #10: Interference Test of structurally unrelated compounds - Serum

Compounds	Tested Concentration (mg/dL)
Bilirubin (Conjugated)	40
Bilirubin (Unconjugated)	40
Hemoglobin	1000
Albumin	7500
γ-globulin	5000
Rh Factor	1300 IU
Triglycerides	1500
Cholesterol	1400

Table #11: Interference Test of structurally unrelated compounds – Urine

Compounds	Test Concentration (mg/dL)
Ascorbic Acid	150
Caffeine	5
Creatinine	400
Ethanol	1000
Galactose	5
Glucose	1000
Hemoglobin	150
Human Serum Albumin	200
Ibuprofen	10
Oxalic acid	50
Riboflavin	3
Sodium Chloride	1000
Urea	1000

Interference Testing of Specific Gravity and pH (Urine):

Drug free urine samples with specific gravity ranging in value from 1.004 to 1.030 were split and spiked with Nortriptyline to near cutoff negative (225 ng/mL) and near cutoff positive (375 ng/mL) concentrations. Samples were evaluated in qualitative and semi-quantitative modes. The following specific gravities did not cause any positive or negative interference:

1.004, 1.006, 1.008, 1.010, 1.011, 1.012, 1.013, 1.016, 1.022 and 1.030.

Interference from pH was evaluated by adjusting the pH of urine samples containing near cutoff negative (225 ng/mL) and near cutoff positive (375 ng/mL) concentrations of Nortriptyline. The following pH values did not cause any positive or negative interference: 3, 4, 5, 6, 7, 8, 9, 10 and 11.

4. Assay Reportable Range:

   Not applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Traceability: The primary calibrators are traceable to the certified reference material Nortriptyline purchased from a commercial source. The concentration of the primary calibrator stocks is confirmed by LC-MS/MS from independent laboratories.

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Characterization of how the device performs analytically around the claimed cutoff concentration is described in the precision section, VII.A.1. above.

B Comparison Studies:

1. Method Comparison with Predicate Device:
   One hundred seventeen serum clinical specimens and one hundred urine clinical specimens were tested using the DRI™ Tricyclics Serum Tox Assay on the Architect c4000 clinical chemistry analyzer and confirmed by LC-MS/MS. The results are presented below:

Table #12: Qualitative Accuracy Study with LC-MS/MS as Reference Method – Serum

Candidate Device Results	Negative by LC-MS/MS	< 50% of Cutoff concentration by LC-MS/MS (< 150 ng/mL)	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration as determined by LC-MS/MS) (150-299 ng/mL)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration as determined by LC-MS/MS) (300-450 ng/mL)	High Positives (Greater than 50% above cutoff concentration) (> 450 ng/mL)
Positive	0	1[1]	0	31	25
Negative	1	35	24	0	0

Table #13: Qualitative Accuracy Study with LC-MS/MS as Reference Method - Urine

Candidate Device Results	Negative by LC-MS/MS	< 50% of Cutoff concentration by LC-MS/MS (< 150 ng/mL)	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration as determined by LC-MS/MS) (150-299 ng/mL)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration as determined by LC-MS/MS) (300-450 ng/mL)	High Positives (Greater than 50% above cutoff concentration) (> 450 ng/mL)
Positive	0	0	2	7	42
Negative	22	11	15	1	0

Table #14: Semi-quantitative Accuracy Study with LC-MS/MS as Reference Method - Serum

Candidate Device Results	Negative by LC-MS/MS	< 50% of Cutoff concentration by LC-MS/MS (< 150 ng/mL)	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration as determined by LC-MS/MS) (150-299 ng/mL)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration as determined by LC-MS/MS) (300-450 ng/mL)	High Positives (Greater than 50% above cutoff concentration) (> 450 ng/mL)
Positive	0	2[2]	0	31	25
Negative	1	34	24	0	0

Table #15: Semi-quantitative Accuracy Study with LC-MS/MS as Reference Method - Urine

Candidate Device Results	Negative by LC-MS/MS	< 50% of Cutoff concentration by LC-MS/MS (< 150 ng/mL)	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration as determined by LC-MS/MS) (150-299 ng/mL)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration as determined by LC-MS/MS) (300-450 ng/mL)	High Positives (Greater than 50% above cutoff concentration) (> 450 ng/mL)
Positive	0	0	2	7	42
Negative	22	11	15	1	0

Table #16: Discordant Samples:

Sample ID	Sample Type	EIA		LC-MS/MS value (ng/ml)
		Qualitative	Semi-Quantitative	
APP9489-2[2]	Serum	Negative	Positive	110
APP9474-2[1,2]	Serum	Positive	Positive	120

Sample APP9489-2 contains the following parent Tricyclic antidepressants: Amitriptyline at 8.08 ng/mL, Imipramine at 18.35 ng/mL, Desipramine at 46.35 ng/mL, and Nortriptyline at 17 ng/mL by LC-MS/MS which cross-react at 100%, 158% 120% and 100% respectively by immunoassay. In addition to the tricyclic antidepressants identified, another cross-reacting drug compound was detected in the sample, as below:

Drug Class	Drug Name	LC-MS/MS value (ng/mL)
Antiepileptic drugs	Carbamazepine	4275

Sample APP9474-2 contains Amitriptyline at 9.08 ng/mL, Imipramine at 19.9 ng/mL and Desipramine at 49.8 ng/mL, and Nortriptyline at 19.65 ng/mL by LC-MS/MS and cross-reacts at 100%, 158% 120%, and 100% by immunoassay accordingly. In addition to the tricyclic antidepressants identified, another cross-reacting drug compound was detected in the sample, as below:

Drug Class	Drug Name	LC-MS/MS value (ng/mL)
Antiepileptic drugs	Carbamazepine	5285

2. Matrix Comparison:

50 Patient specimens were run in both qualitative and semi-quantitative modes. The testing specimens consisted of matched sets of; Serum, K2-EDTA, K3-EDTA, Lithium Heparin, Sodium Citrate, Potassium Oxalate samples; as well as 45 secondary matched sets of Serum and Sodium Heparin samples. The Nortriptyline concentrations of the samples tested spanned from approximately 135 ng/mL to approximately 930 ng/mL. The study demonstrates Nortriptyline concentrations obtained in different test plasma matrices with different anticoagulants are equivalent to those measured in the primary or control matrix, serum across the assay's measuring range.

Table #17: Matrix Equivalency results in qualitative and semi-quantitative mode

Serum Matrix		Qualitative		Semi- Quantitative	
		Positive	Negative	Positive	Negative
K2 EDTA Plasma	Positive	25	0	25	0
	Negative	0	25	0	25
K3 EDTA plasma	Positive	25	0	25	0
	Negative	0	25	0	25
Lithium Heparin Plasma	Positive	25	0	25	0
	Negative	0	25	0	25
Sodium Citrate Plasma	Positive	25	0	30	0
	Negative	0	25	0	25
Potassium Oxalate Plasma	Positive	25	0	25	0
	Negative	0	25	0	25
Sodium Heparin Plasma	Positive	25	0	25	0
	Negative	0	20	0	20

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

Qualitative results
A sample that exhibits a change in absorbance (ΔA) value equal to or greater than the cutoff calibrator is considered positive. A sample that exhibits a change in absorbance (ΔA) value lower than the cutoff calibrator is considered negative.

Semiquantitative results
A rough estimate of drug concentration in the samples can be obtained by running a standard curve with all calibrators and measuring samples off the standard curve.

Immunoassays that produce only a single result in the presence of a class of drugs such as Tricyclic Antidepressants (TCAs) cannot accurately measure the concentration of each individual component. For a qualitative application, a positive result indicates only the presence of TCAs. For a semiquantitative application, the assay gives an approximate, cumulative concentration of TCAs.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.