

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

A. 510(k) Number:

K041142

B. Purpose of the Submission: New 510(k)

C. Analyte:

Cannabinoids

D. Type of Test:

Qualitative immunoassay and associated calibrators

E. Applicant:

Randox Laboratories, Ltd.

F. Proprietary and Established Names:

Randox Cannabinoids Assay

Randox Drugs of Abuse Calibrators

G. Regulatory Information:

1. Regulation section:

862.3870, Enzyme Immunoassay, Cannabinoids

862.3200, Calibrator, Drug Mixture

2. Classification:

Both products are class II

3. Product Code:

LDJ and DKB, respectively

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

Refer to Indications for use.

2. Indication(s) for use:

The evidence cannabinoid test has been designed for use only on the evidence analyser for qualitative detection of cannabinoid in urine, using a cutoff concentration of 50 ng/mL. Qualitative results obtained can be utilized in the diagnosis and treatment of cannabinoids use or overdose.

The evidence Drugs of Abuse Calibrators (Catalog No.EV3550)are liquid Calibrators containing 11-nor-delta 9 carboxy-THC. There are nine levels of

calibrator. They have been developed for use in calibration of the evidence system.

Both products must only be used by suitably qualified laboratory personnel under appropriate laboratory conditions.

3. Special condition for use statement(s):

The assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. Gas chromatography/Mass spectrometry is the preferred confirmatory method. Other chemical confirmation methods are available. Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.

The assay is for Rx use.

The assay was not evaluated in point-of-care settings.

4. Special instrument Requirements:

The assay is for use only on the automated Evidence Analyser, cleared under k030360. The originally cleared version of this calibrator was also included in k030360.

I. Device Description:

The evidence analyser is a fully automated Biochip Array System. It performs simultaneous detection of multiple analytes from a single patient sample. The core technology is the Randox Biochip, a solid-state device containing an array of discrete test regions containing immobilized antibodies specific to different DOA compound classes.

Calibrator EV3550 is a phosphate buffer based material with THC added. It is a 9 level calibrator set ranging in concentration from 0 to approximately 150 ng/mL THC. Calibrations are run daily.

J. Substantial Equivalence Information:

1. Predicate device name(s):

CEDIA DAU Cannabinoids Assay, Microgenics

2. Predicate K number(s):

k935591

3. Comparison with predicate:

Both devices are for the qualitative determination of the same analyte(s) in the same matrix, and utilize the same cutoff concentration. Both are analyzed on instruments. The candidate device utilized chemiluminescent technology utilizing biochip array technology whereas the predicate is analyzed on a spectrophotometric analyzer.

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

The sponsor referenced the NCCLS EP5-T2 Precision document and the NCCLS Interference document, EP7-A.

L. Test Principle:

A competitive chemiluminescent immunoassay is employed for the assay with the drug in the specimen and drug labelled with horseradish peroxidase (HRP) being in direct competition for the antibody binding sites. Increased levels of drug in a specimen will lead to reduced binding of drug labelled with HRP and thus a reduction in chemiluminescence being emitted. The light signal generated from each of the test regions on the biochip is detected using digital imaging technology and compared to that from a stored calibration curve. A normalized value is calculated as a percentage of the signal intensity emitted from the cut-off point on the calibration curve relative to the signal intensity emitted from the sample test region. Samples producing a response value greater than, or equal to, the response value of the calibrator cut-off are considered positive (normalized result ≥ 100). Samples producing a response value less than the response value of the calibrator cut-off are considered negative (normalized result < 100).

Description of the test antibody: monoclonal sheep antibody against THC.

M. Performance Characteristics (if/when applicable):1. Analytical performance:a. *Precision/Reproducibility:*

Total imprecision data was determined at two different locations by assaying four calibrators for 20 days, 2 runs per day in replicates of 2 (n=80) according to National Committee of Clinical Laboratory Standards (NCCLS) EP5-T2.

Specimen description: calibrator

Number of days: twenty

Replicates per day: Duplicates run twice a day

Lots of product used: one

Operator: manufacturer staff and hospital staff member

Testing Facility: manufacturers facility and a hospital

Results of the study are presented below:

Total Imprecision

Concentration (ng/mL)	33	43	54	60
Site 1: Mean	83	88	99	114
Site 1: SD	7.3	10.6	11.2	13.5
Site 1: CV (%)	8.9	12.1	11.4	11.8
Site 2: Mean	79	91	102	113
Site 2: SD	5.1	7.5	7.9	9.8
Site 2: CV (%)	6.5	8.3	7.7	8.6

Results are expressed as normalized values.

b. Linearity/assay reportable range:

Not applicable. The assay is for qualitative use. It does, however, include a series of 9 calibrators. A representative calibration curve appears in the Operator's Manual.

c. Traceability (controls, calibrators, or method)

Nine levels of Calibrators are provided separately.

Representative concentrations of 11-nor- Δ^9 -THC-9 carboxylic acid in the calibrators are 0, 9.1, 21.5, 33.2, 43.1, 53.7, 59.5, 81.8, and 164.3 ng/mL.

The sponsor recommends daily calibrations of the test system.

Value Assignment:

According to the sponsor a Master Lot of calibrators has been quantified for the component drugs of abuse in all 9 levels by assaying 4 replicates for each component on GC/MS. The values assigned to each lot are the mean of those measurements. The laboratory performing the analysis is certified by the College of American Pathologists. The Master Lot is stored at -80°C and is used to assign concentrations to subsequent calibrator lots.

A minimum of 20 replicates from each subsequent lot are assayed and quantified by direct comparison to the mean values of a minimum of 20 replicate standard curves from the Master Lot of calibrators. Results are assigned to the calibrators by applying mean readings read from the standard curves.

Table 13 of the original information received from the sponsor displays a calibration curve. It appears adequate, i.e., the curve is not flat.

Stability:

Stability studies are summarized for the calibrators. Aliquots of the calibrators were stored at -80°C for reference purposes (the baseline) while the remainder were stored at $2-8^{\circ}\text{C}$. At 26, 52, and 104 weeks the calibrator values are compared to the values of calibrators stored at -80°C .

Accelerated studies are conducted in the same manner, but involve comparing samples stored at 37°C to those stored at $2-8^{\circ}\text{C}$.

For both the real time and accelerated stability study, the following acceptance criteria for the studies are used:

The Relative Light Units curve shape (B/B_0 , where B is the rlu for an individual calibrator level and B_0 is the rlu for the level 1 calibrator) and normalized values are examined. A stability of 1 year (at 2-8 °C) is assigned when the % difference in either % B/B_0 or normalized values between the -80 °C and the 2-8 °C is less than 10%.

Open vial stability was also assessed for 14 days, using an acceptance criteria of 10% when compared to the baseline.

Another manufacturer's control materials are identified for use in the package insert, e.g., Biorad Urine Liquichek Toxicology Controls.

d. Detection limit:

The sensitivity of the assay was established by analyzing 20 repeat determinations of a GC/MS verified negative urine sample. The mean normalized value was calculated and 2 standard deviations added.

The normalized value of 37 represents the lowest concentration of morphine which can be distinguished from the zero calibrator with a confidence level of 95%.

e. Analytical specificity:

Specificity and cross-reactivity of the Randox Cannabinoids assay was assessed by comparing the standard curves from selected compounds to the standard curve of 11-nor- Δ^9 -THC-9-carboxylic acid. Each compound was diluted in GC/MS verified negative urine.

The concentration of the compound rendering a signal equivalent to 11-nor- Δ^9 -THC-9-carboxylic acid at the cut-off concentration of the assay was determined. The percentage cross reactivities of those compounds are presented in Table 1.

Table 1. Cross reactivity of Cannabinoid compounds at the cut-off concentration.

Compound	% Cross reactivity
11-nor- Δ^9 -THC-9-carboxylic acid	100
11-nor- Δ^8 -THC-9-carboxylic acid	49
11-hydroxy- Δ^9 -THC	3
11-hydroxy- Δ^8 -THC	<5
Cannabinol	<0.5
Cannabidiol	<0.5

Compounds failing to generate a positive response (normalized result <100) appear in Table 2. Compounds were evaluated up to the concentration listed.

Table 2. Concentrations of compounds failing to produce a positive result.

Compound	Concentration (µg/mL)
Oxazepam	500
Lorazepam	500
Temazepam	500
Nordazepam	500
Nitrazepam	500
Flunitrazepam	500
6-Monoacetylmorphine	500
Amobarbital	500
Barbital	500
Benzoylecgonine	100
Butalbital	100
Codeine	500
MDA	500
MDEA	500
MDMA	500
Methadone	500
Methamphetamine	500
Morphine	500
Morphine-3-glucuronide	500
Pentobarbital	500
Phencyclidine	500
Phenobarbital	500
Secobarbital	500

This assay was also evaluated for interference in accordance with methods outlined in National Committee of Clinical Laboratory Standards (NCCLS) EP7-A. Various concentrations of interferants were added to urine containing 50 ng/mL 11-nor- Δ^9 -THC-9-carboxylic acid. Concentrations of these test materials (as read from a standard curve) were compared to the concentrations of the control. The control consisted of urine containing 50 ng/mL 11-nor- Δ^9 -THC-9-carboxylic acid, but no interferant. The percentage of change in concentration between the test and control material is presented in Table 3. A negative percent bias equates to a decrease in normalized value and thus may lead to a false negative result. A positive percentage bias equates to an increase in normalized value and thus may lead to a false positive result.

Table 3. Degree of interference caused by various compounds

Compound	Concentration (mg/dL)	% Bias
Acetaminophen	1 mg/mL	-7.6
Acetone	1000	4.1
Acetylsalicylic acid	1 mg/mL	-6.4
Ascorbic acid ^a	34	-10.0
Caffeine	1 mg/mL	7.9
Creatinine	500	2.3
Ethanol	1000	6.2
Galactose	10	9.6
K globulin	500	-4.0
Glucose	3000	-6.7
Haemoglobin ^b	175	10.0
Human serum albumin ^c	0.19 g/dL	10.0
Ibuprofen	1 mg/mL	7.8
Oxalic acid ^d	5	-10.0
Ranitidine	0.9 mg/mL	1.7
Riboflavin	7.5	1.4
Sodium chloride	6000	5.2
Urea	3500	0.2

Notes:

a-Ascorbic acid gave a bias of 34.0% at 1.5 g/dL.

b-Haemoglobin gave a bias of 23.0% at 300 mg/dL.

c-Human serum albumin gave a bias of 33.0% at 0.5 g/dL.

d-Oxalic acid gave a bias of -74.0% at 100 mg/dL

To evaluate the effects from specific gravity and pH, a series of urine samples were prepared. All urine samples contained 50 ng/mL 11-nor- Δ^9 -THC-9-carboxylic acid. Specific gravity and pH conditions were varied by adding HCl, NaOH, and NaCl. The concentrations of 11-nor- Δ^9 -THC-9-carboxylic acid observed in all urine samples (as determined from a standard curve) were within 10% of the 11-nor- Δ^9 -THC-9-carboxylic acid concentration seen in the urine with a pH of 7 and a specific gravity of 1.002. Conditions evaluated in the study are presented in Table 4.

Table 4. Acceptable pH and specific gravity conditions.

Chemistry	Acceptable range
pH	5.0 – 9.0
Specific gravity	1.002 – 1.04 g/mL

Notes:

- pH of 3 gave a bias of -22%, pH 11 gave a bias of 22%.
- Samples with specific gravity or pH values outside the quoted ranges may result in a bias of >10%.

f. Assay cut-off:

The identified cutoff concentration of the assay is standard for the industry.

Characterization of how the device performs analytically around the claimed cutoff concentration was performed: Ten GC/MS verified urine-based commercially available controls at 25% below the cut-off, at the cut-off (50 ng/mL) and 25% above the cut-off were analyzed. A 100% agreement with GC/MS was recorded for all control replicates tested.

Normalized Results
Characterizing Performance Around Cut-off

	-25% of C/O	C/O Concentration	+25% C/O
Mean	74	98	119
SD	4.2	8.7	9.4
%CV	5.8	8.9	7.9

2. Comparison studies:*a. Method comparison with predicate device:*

1335 urine samples were selected because they had been previously analyzed by the predicate device. The samples were assayed with the Randox Cannabinoids assay on the evidence analyser. GC/MS was performed on all positive samples, borderline samples or where discrepancies were observed. GC/MS concentrations were determined according to the concentration of 11-nor-delta 9-THC-carboxylic acid.

Comparison with competitor EIA

		Comparative EIA 50 ng/mL cut-off	
		+	-
Candidate Device	+	210	0
	-	28*	1097

*All 28 samples tested by GC/MS contained less than 50 ng/mL Cannabinoids

Comparison to Stratified GC/MS Measurements

New device	Negative by GC/MS or Predicate	Near Cutoff Negative (between -25% and cutoff)	Near Cutoff Positive (between cutoff and +25%)	GC/MS Positive (greater than +25%)
Positive	8	6	12	154
Negative	45	6	0	0

The study included an adequate number of samples that contained drugs near to the cutoff concentration of the assay, i.e., at least 10% of the study samples are evenly distributed between plus and minus 25% of the claimed cutoff concentration. This information was presented in table 12 of the originally received information.

b. Matrix comparison:

Not applicable. The assay is intended for only one sample matrix.

3. Clinical studies:

a. Clinical sensitivity:

Not applicable. Clinical studies are not typically submitted for this device type.

b. Clinical specificity:

Not applicable. Clinical studies are not typically submitted for this device type.

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

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Not applicable.

N. Conclusion:

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