

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

A. 510(k) Number:

K041144

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

C. Analyte:

Opiates

D. Type of Test:

Qualitative immunoassay and associated calibrators

E. Applicant:

Randox Laboratories, Ltd.

F. Proprietary and Established Names:

evidence Opiates Assay

evidence Drugs of Abuse Calibrators

G. Regulatory Information:

1. Regulation section:

862.3650, Enzyme Immunoassay, Opiates

862.3200, Calibrator, Drug Mixture

2. Classification:

Both products are class II

3. Product Code:

DJG 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 opiates test has been designed for use only on the evidence analyser for qualitative detection of opiates in urine, using a cutoff concentration of 300 ng/mL. Qualitative results obtained can be utilized in the diagnosis and treatment of opiates use or overdose.

The evidence Drugs of Abuse Calibrators (Catalog No.EV3550) are liquid Calibrators containing morphine sulphate pentahydrate. There are nine levels of calibrator. They have been developed for use in calibration of the evidence test 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 drugs of abuse compound classes.

Calibrator EV3550 is a phosphate buffer based material with opiates added. It is a 9 level calibrator set ranging in concentration from 0 to approximately 3000 ng/mL morphine. Calibrations are run daily.

J. Substantial Equivalence Information:

1. Predicate device name(s):

CEDIA DAU Opiates Assay, Microgenics

2. Predicate K number(s):

k954227

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: polyclonal sheep antibody against morphine.

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) based on a cut-off of 300 ng/mL according to the NCCLS Laboratory Standard 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)	195	262	328	1286
Site 1: Mean	79	90	97	212
Site 1: SD	9.8	8.5	9.8	24.8
Site 1: CV (%)	12.4	9.4	10.1	11.7
Site 2: Mean	87	91	100	197
Site 2: SD	7.1	6.4	7.6	16.4
Site 2: CV (%)	8.2	7.1	7.6	8.4

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 morphine sulphate penta-hydrate in the calibrators are presented in the package insert as 0, 96.8, 195.4, 262.5, 328.2, 1286.3, 1718.6, 2078.6, and 3217.5 ng/mL.

The sponsor recommends daily calibrations.

The sponsor indicates that 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 to 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 by applying mean readings to these 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 °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.

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 resultant normalized value of 20.3 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 assay was assessed by comparing the standard curves from selected compounds to the standard curve of morphine. Each compound was diluted in GC/MS verified negative urine to the concentrations specified. Compounds listed were tested in duplicate to a maximum of 0.5mg/mL. Concentrations of the cross-reactants, which produce a response equal to that of the target compound at the cut-off, were calculated. Percentage cross reactivities of opiates and opiates metabolites, as determined by the assay, are shown in Table 1. Compounds that demonstrate less than a 10% difference in their normalized response as compared to the control sample (no drug) are shown in Table 2.

No interference was observed for the assay from the compounds shown in Table 3 when added to urine. This study was run in accordance with methods outlined in the NCCLS interference document, EP7-A. Specific gravity and pH ranges were assessed using a dose-response series. Sodium chloride and hydrochloric acid

/ sodium hydroxide were used to vary specific gravity and pH ranges respectively. Result differences of <10% between test and control were deemed acceptable.

Table 1. Cross reactivity of opiates compounds:

Compound	% Cross Reactivity
Morphine	100
Codeine	115
Morphine-3-glucoronide	67
Hydropmorphone	27
Hydropcodone	17
Dihydrocodeine	13
6-Monoacetylmorphine	1500

Table 2. Concentrations of compounds showing no interference:

Compound	Concentration ($\mu\text{g/mL}$)
Oxazepam	500
Lorazepam	500
Temazepam	500
Nordiazepam	500
Nitrazepam	500
Flunitrazepam	500
11-nor-9-THC-COOH	10
Barbital	500
Benzoylecgonine	100
Butalbital	100
d-Amphetamine	300
MDA	500
MDEA	500
MDMA	500
Methamphetamine	500
Pentobarbital	500
Phencyclidine	500
Phenobarbital	500
Secobarbital	100

Table 3. Interfering compounds eliciting no interference:

Compound	Concentration tested (mg/dL)
Acetaminophen	1 mg/mL
Acetone	1000
Acetylsalicylic acid	1 mg/mL
Ascorbic acid	1500
Caffeine	1 mg/mL
Creatinine	500
Ethanol	1000

Compound	Concentration tested (mg/dL)
Galactose	10
globulin	500
Glucose	3000
Haemoglobin	300
Human serum albumin	500
Ibuprofen	1
Oxalic acid	100
Ranitidine	180 µg/mL
Riboflavin	7.5
Sodium chloride	6000
Urea	3500
pH	Acceptable range 3.0 – 11.0
Specific gravity	Acceptable range 1.002 – 1.04 g/mL

f. Assay cut-off:

The identified cutoff concentration of the assay is standard for the industry, although 2000 ng/mL is more commonly found in the U.S.

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 (200 ng/mL) and 25% above the cut-off were analyzed. A 100% agreement with GC/MS was recorded for all control replicates tested.

Normalised Results Characterizing Performance Around Cut-off

	-25% of C/O	C/O Concentration	+25% C/O
Mean	85	93	108
SD	2.4	3.3	3.0
%CV	2.8	3.6	2.8

2. Comparison studies:

a. Method comparison with predicate device:

1336 urine samples were selected because they had been initially assayed with the predicate device and by GC/MS for the presence of morphine, codeine, and hydromorphone. The samples were then analyzed by the Randox test system. GC/MS was performed on all positive samples, borderline samples or where discrepancies were observed. Total GC/MS concentrations were determined by adding together in an unweighted fashion morphine, codeine, and hydromorphone. 97 of the samples, were analyzed for and found to contain no 6-mam.

Comparison with competitor EIA

		Comparative EIA 300 ng/mL cut-off	
		+	-
Candidate Device	+	226	3*
	-	97**	1010

*All samples tested by GC/MS and found to contain Opiates >150 ng/mL

**Ninety six samples were found to contain opiates below the 300 ng/mL cutoff by GC/MS

Comparison to GC/MS

		GC/MS 300 ng/mL cut-off	
		+	-
Candidate Device	+	178	34*
	-	1**	109

* Twenty nine samples found to contain opiates by GC/MS

** Sample contained 313 ng/mL hydromorphone

Comparison of evidence Results to Stratified GC/MS Results

	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%)
New device Positive	21	13	14	164
Negative	94	15	1	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.

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.