

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

**A. 510(k) Number:**

K040570

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

**C. Analyte:**

Methadone

**D. Type of Test:**

Qualitative immunoassay and associated calibrators

**E. Applicant:**

Randox Laboratories, Ltd.

**F. Proprietary and Established Names:**

Randox Methadone Assay

**G. Regulatory Information:**

1. Regulation section:

862.3620, Enzyme Immunoassay, Methadone

862.3200, Calibrator, Drug Mixture

2. Classification:

II

3. Product Code:

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

Evidence Drugs of Abuse Calibrators are liquid Calibrators containing Methadone. There are nine levels of calibrator. They have been developed for the system.

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 Analyzer, cleared under k030360. The originally cleared version of this calibrator was also included in k030360.

**I. Device Description:**

The evidence analyzer 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 methadone added. It is a 9 level calibrator set which includes concentrations of 0, 25, 50, 100, 150, 225, 300, 375 and 600 ng/mL methadone. Calibrations are run daily.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

CEDIA Dau Methadone 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  $\geq 100$ ). 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 methadone.

**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 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

Testing Facility: manufacturers facility

Results of the study are presented below:

| Precision             |       |       |       |       |
|-----------------------|-------|-------|-------|-------|
| Total imprecision     |       |       |       |       |
| Concentration (ng/mL) | 143.8 | 237.2 | 315.6 | 383.3 |
| Site 1                | 72.4  | 83.2  | 100.7 | 109.0 |
| Site 1 SD             | 11.3  | 12.8  | 15.9  | 14.0  |
| Site 1 % CV           | 15.6  | 15.4  | 15.8  | 12.9  |
| Site 2                | 72.5  | 83.7  | 99.5  | 110.0 |
| Site 2 SD             | 6.3   | 7.6   | 8.6   | 10.8  |
| Site 2 % CV           | 8.7   | 9.1   | 8.6   | 9.8   |

Results for Site 1 and Site 2 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 8 calibrators.

*c. Traceability (controls, calibrators, or method):*

Nine levels of Calibrators are provided separately.

Calibrators are traceable to a master lot, GC/MS qualified by a College of American Pathologists approved laboratory. The master lot is stored at  $-80^{\circ}\text{C}$ . Test lots are read as unknown from a calibration curve constructed from a master lot of calibrators. Assignment of values is carried out on the Evidence analyzer.

The calibration curve provided by the sponsor appears adequate, i.e., the curve is not flat.

The sponsor indicates they have data on file to demonstrate that calibrations between cards are stable, thereby supporting their recommendation to run calibrators and QC materials on each card.

Stability studies are summarized for the calibrators. Aliquots of the calibrators were stored at  $-80^{\circ}\text{C}$  for reference purposes while the remainder were stored at  $2-8^{\circ}\text{C}$ . After 1 year the calibrators values were compared to the values of calibrators stored at  $-80^{\circ}\text{C}$ .

The Relative Light Units (RLU), 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 were examined. A stability of 1 year (at  $2-8^{\circ}\text{C}$ ) was assigned when the % difference in either  $\%B/B_0$  or normalized values between the  $-80^{\circ}\text{C}$  and the  $2-8^{\circ}\text{C}$  was 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 32 represents the lowest concentration of methadone 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 using a dose-response series based on a 300 ng/mL cut-off. Each compound was diluted in GC/MS verified negative urine to the ranges specified. Compounds listed were tested in duplicate to a maximum of 0.5 mg/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 methadone and methadone metabolites, as determined by the assay, are shown in Table 1. Compounds that elicit a negative response by the assay 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 based on a 300 ng/mL methadone cut-off in GC/MS verified negative urine. 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 methadone compounds at a 300 ng/mL cut-off.

| Compound  | % Cross Reactivity |
|-----------|--------------------|
| Methadone | 100                |
| EDDP      | <0.1               |
| EMDP      | <0.1               |
| LAAM      | <0.1               |

Table 2. Concentrations of compounds showing a negative response.

| Compound             | Concentration (□g/mL) |
|----------------------|-----------------------|
| Oxazepam             | 500                   |
| Lorazepam            | 500                   |
| Temazepam            | 500                   |
| Nordiazepam          | 500                   |
| Nitrazepam           | 500                   |
| Flunitrazepam        | 500                   |
| 11-nor-9-THC-COOH    | 10                    |
| 6-Monoacetylmorphine | 500                   |
| Amobarbital          | 500                   |
| Benzoyllecgonine     | 100                   |
| Butalbital           | 100                   |

|                        |     |
|------------------------|-----|
| Codeine                | 500 |
| d-Amphetamine          | 500 |
| MDA                    | 500 |
| MDEA                   | 500 |
| MDMA                   | 500 |
| Methamphetamine        | 500 |
| Morphine               | 500 |
| Morphine-3-glucuronide | 500 |
| Pentobarbital          | 500 |
| Phencyclidine          | 500 |
| Phenobarbital          | 500 |
| Secobarbital           | 100 |

Table 3. Interfering compounds eliciting a negative response using a 300 ng/mL cut-off.

| 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                               |
| Galactose            | 10                                 |
| globulin             | 500                                |
| Glucose              | 3000                               |
| Haemoglobin          | 300                                |
| Human serum albumin  | 500                                |
| Ibuprofen            | 40                                 |
| Oxalic acid          | 100                                |
| Ranitidine           | 90                                 |
| 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.

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.

## 2. Comparison studies:

### a. *Method comparison with predicate device:*

1351 urine samples were randomly collected and assayed with the Methadone assay on the analyzer by an independent laboratory using a comparative enzyme immunoassay method. Study included 15 samples diluted in GC/MS verified negative urine in order to obtain samples close to the cut-off value. This was followed by GC/MS confirmation of methadone, where required.

#### **Comparison with competitor EIA**

|                  |   | Comparative EIA<br>300 ng/mL cut-off |      |
|------------------|---|--------------------------------------|------|
|                  |   | +                                    | -    |
| Candidate Device | + | 179                                  | 0    |
|                  | - | 5 <sup>a</sup>                       | 1167 |

<sup>a</sup>All samples tested by GC/MS and found to contain Methadone below 300 mg/mL (140 – 296 ng/mL).

#### **Comparison to GC/MS**

|                  |   | GC/MS<br>300 ng/mL cut-off |                |
|------------------|---|----------------------------|----------------|
|                  |   | +                          | -              |
| Candidate Device | + | 129                        | 9 <sup>b</sup> |
|                  | - | 0                          | 24             |

<sup>b</sup>All samples tested by GC/MS and found to contain Methadone (one at 61 ng/mL methadone and >20,000 ng/mL EDDP, the rest ranging between 187 – 299 ng/mL methadone).

The study included an adequate number of samples that contained drugs near to the cutoff concentration of the assay. Approximately 10% of the study samples are evenly distributed between plus and minus 25% of the claimed cutoff concentration (12 below the cutoff and 9 above the 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.