Homogeneous Enzyme Immunoassay for Semi-Quantitative Determination of Buprenorphine (Reference – 2013.02.001)

Notice of Assessment

December 2013
1 GENERAL INFORMATION

1.1 Requestor: Hôpital Saint-Luc, CHUM

1.2 Application Submitted to MSSS: August 28, 2012

1.3 Application Received by INESSS: July 1, 2013

1.4 Notice Issued: October 31, 2013

Note
This notice is based on the scientific and commercial information (submitted by the requestor) and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE

2.1 Name of the Technology
Homogeneous enzyme immunoassay, semi-quantitative

2.2 Brief Description of the Technology, and Technical and Clinical Specifications
Buprenorphine is a semi-synthetic opioid analgesic derived from the baine, a component of opium. It can be used in chronic pain management and as substitution treatment for opioid addiction.

The CEDIA® Buprenorphine Assay (Microgenics Corporation) is a homogeneous enzyme immunoassay for qualitative or semi-quantitative determination of buprenorphine in human urine. The assay is based on the bacterial enzyme beta-galactosidase, which has been genetically engineered into two inactive fragments. These fragments spontaneously re-associate to form fully active enzymes that cleave a substrate, generating a colour change that can be measured spectrophotometrically.

Buprenorphine (the analyte) in the sample competes with analyte conjugated with one inactive fragment of beta-galactosidase for a limited number of antibody binding sites. If buprenorphine is present in the sample, it binds to the antibody, allowing the inactive enzyme fragments to re-associate spontaneously and form active enzymes. If buprenorphine is not present in the sample, the antibodies bind to the analyte conjugated on the inactive fragment, inhibiting the re-association of inactive beta-galactosidase fragments. Consequently, no active enzymes are formed. The quantity of active enzymes formed and the resulting absorbance change increase in direct proportion to the amount of buprenorphine present in the sample [Microgenics Corporation, 2012].

The Buprenorphine Enzyme Immunoassay, marketed by Lin-Zhi International, determines the presence of norbuprenorphine (buprenorphine metabolite) in urine. The assay is based on the competition between buprenorphine (the analyte) in the sample and the labelled analyte conjugated to the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for a fixed number of antibody binding sites. If buprenorphine is present in the sample, the antibody binds to it and the analyte conjugated to G6PDH exhibits maximal enzyme activity. In the absence of buprenorphine, the conjugated analyte binds to the

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1. Opioids are synthetic opiates with effects similar to those of opium, but without necessarily having the same chemical structures [Demalare and Garnier, 2002; Quevauvilliers, 2007].

2. CEDIA: cloned enzyme donor immunoassay.
antibody, and enzyme activity is inhibited. The absorbance change increases in direct proportion to the quantity of buprenorphine present in the sample [Lin-Zhi International, 2013].

2.3 **Company or Developer:** Not applicable.

2.4 **Licence:** Not applicable.

2.5 **Patent, If Any:** Not applicable.

2.6 **Approval Status (Health Canada, FDA)**

CEDIA® Buprenorphine Assay (Microgenics Corporation) is licensed by Health Canada (licence number 68551) and by the FDA (licence number K040316), as is Buprenorphine Enzyme Immunoassay (Lin-Zhi International) (Health Canada 91762, and FDA K081008). Health Canada has licensed eight other kits manufactured by other companies for the same purpose but by with different formats (strips, cassettes, cartridges).

2.7 **Weighted Value: 13.51**

3 **CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES**

3.1 **Targeted Patient Group**

According to the information provided by the requestor, the test is for monitoring patients being treated with buprenorphine for an addiction to opiates, to monitor treatment compliance [CMQ-OPQ, 2009; Simpson et al., 1997].

3.2 **Targeted Disease**

**Addiction to Opioids**

Substance abuse is a growing, devastating and costly problem throughout the world [Yokell et al., 2011]. It is associated with high morbidity and mortality rates and generates significant social costs. Untreated opiate addicts can become exposed to various health (blood-borne infections, mental health problems and behavioural problems) or social problems (marginalization, poverty, homelessness, incarceration) [CRAN, 2011]. On a yearly basis, an untreated substance abuser costs society at least ten times more than a treated substance abuser.\(^4\)

In 2007, the United Nations Office on Drugs and Crime (UNODC) estimated that 15.6 million people were addicted to opioids [Yokell et al., 2011]. In Quebec, about 12,000 people (a very conservative estimate) take or have previously taken heroin or other non-prescribed opiates [MSSS, 2006]. It is estimated that about 20% of these people have developed an addiction. The incidence of the risk of addiction to illicit drugs in Quebec is estimated at 8% [MSSS, 2006]. In 2008, in Quebec, 157 people died from opioid poisoning, either intentional, accidental or suicidal [CRAN, 2011].

**Treatment of Opioid Dependence**

Buprenorphine was introduced in 1980 for treating opioid addiction [Yokell et al., 2011; Kleber, 2007]. In the United States, it was adopted for that purpose in 2002 [Wu et al., 2009]. In 2005 in the United States, out of 1.2 million opioid addicts, only about 100,000 were treated with buprenorphine. The number of people treated with buprenorphine was estimated to be 400,000 worldwide in 2008 [Bryson et al., 2010].

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4. An untreated substance abuser costs society $44,600 per year, while the same user on methadone maintenance would cost $4,000 per year [CRAN, 2011].
About 20% of individuals addicted to opioids in Quebec are in a medical, social and psychological management program that includes methadone maintenance [CRAN, 2011; INESSS, 2012b]. This program aims at patient maintenance and, in the longer term, total detoxification or opioid abstinence. It should be noted that the majority of opioid addicts are not being treated because of a lack of medical and psychosocial resources [INESSS, 2012b].

In Quebec, buprenorphine in combination with naloxone⁵ (Suboxone™) has been on the list of medications covered by the basic prescription drug insurance plan since June 2008⁶ as an exceptional medication “for replacement therapy of opioid addiction: when methadone has failed, is not tolerated or is contraindicated; or when a methadone maintenance program is not available or not accessible” [CMQ-OPQ, 2009; INESSS, 2012b]. The terms of administering this treatment impose constraints during the stabilization phase.⁷

**Pharmacology and Adverse Effects**

Suboxone™ is administered sublingually.⁶ Buprenorphine is a partial mu-opioid receptor agonist and a kappa-opioid receptor antagonist [APhC, 2013].

Because of its high affinity for mu receptors, this agent prevents the molecules of other opioids from binding with the receptors and acting on the central nervous system [CSAT, 2004]. The effects of buprenorphine are qualitatively similar to those of morphine, but buprenorphine is 25 to 30 times more potent and has a longer duration of action [Simpson et al., 1997]. Because of its relatively low toxicity and pharmacological properties, and especially because of its plateau effect, confirmed cases of buprenorphine poisoning are rare [CMQ-OPQ, 2009].

Approximately 70% of buprenorphine is eliminated in feces and 30% in urine [APC, 2013]. The mean terminal elimination half-life for plasma buprenorphine is 37 hours, although its actual half-life could be shorter [APC, 2013].

The most frequently observed adverse effects linked to using Suboxone™ are consistent with the withdrawal effects of opioids or the effects of opioid agonists. Adverse effects include: headache, pain, sweating, insomnia and digestive symptoms (constipation, nausea, vomiting, diarrhea) [APC, 2013]. In addition, prolonged administration of buprenorphine can create a dependency similar to opiate addiction [APC, 2013].

**Treatment Success and Test Relevance**

The success rates of buprenorphine detoxification or maintenance programs are not documented. One of the objectives of such programs is to maintain compliance with buprenorphine treatment. The optimal duration of a buprenorphine maintenance program is uncertain [Kleber, 2007].

Detection of buprenorphine is often performed concomitantly with detection of other illicit substances⁹ [CMQ-OPQ, 2009; CSAT, 2004]. This test informs about consumption of these substances, and may prove useful for authorizing unsupervised doses and for confirming abstinence from or use of other substances that can interact with buprenorphine, among other benefits [CMQ-OPQ, 2009].

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5. Naloxone is a mu-opioid receptor antagonist. When administered intravenously, it triggers withdrawal symptoms, whereas, if administered sublingually or orally, it has no detectable pharmacological effect because of its low bioavailability [APhC, 2013]. Its inclusion in Suboxone™ serves to deter intravenous administration of Suboxone™.

6. In February and October 2012, INESSS published a notice of refusal to transfer Suboxone™ to the regular section of the formulary. This product therefore remains on the list of exceptional medications [INESSS, 2012ab].

7. The medication must be taken under the daily supervision (on business days) of a health care professional for a minimum of two months until the patient is clinically stable and able to store the medication in a secure place [APhC, 2013].

8. Oral dosing of buprenorphine results in low bioavailability and it thus does not perform well when administered orally.

9. One US clinical guideline recommends administering toxicology tests for relevant illicit drugs at least monthly [CSAT, 2004].
3.3 Number of Patients Targeted

The requestor estimates an expected provincial volume of approximately 1,300 tests annually.

In 2008, Suboxone™ was added to the RAMQ’s\textsuperscript{10} list of exceptional medications; since then, the number of patients treated has grown from 148 in 2009 to 376 in 2012 [RAMQ data]. This number continues to grow: during the first five months of 2013, 326 patients received this treatment.

With 60% of all opioid addicts being treated in Montreal [CRAN, 2011], the expected annual provincial volume is realistic if the trend continues. It is also possible that this monitoring assay (for medication compliance) will increase with the growing number of patients receiving buprenorphine treatment. However, there are no guidelines on the frequency at which the test should be prescribed. The frequency of requested tests is therefore at the discretion of and dependent on the clinical judgment of the attending physician [CMQ-OPQ, 2009; Handford et al., 2011; CSAT, 2004; Kleber, 2007].

3.4 Medical Specialties and Other Professions Involved

Medical biochemistry, toxicology.

In managing substance abuse, the practitioners involved in the buprenorphine maintenance program (trained doctors, pharmacists, nurses).

3.5 Testing Procedure

The test requires a urine sample from the patient, collected in accordance with the usual procedures for this kind of sample.

The guidelines published by the Collège des médecins du Québec and the Ordre des pharmaciens du Québec stipulate that urine samples must be obtained under direct supervision or be checked using the heat strip, on a random basis, during the first two months of treatment [CMQ-OPQ, 2009]. However, such measures are not applied in practice because of their costs and their relevance in a harm-reduction strategy. This kind of supervision is very rare, even exceptional.\textsuperscript{11}

No particular recommendation has been made in the other clinical practice guidelines on the setting or prescribed procedure for collecting samples (e.g., close supervision of patient to avoid sample falsification through adulteration or substitution).

4 TECHNOLOGY BACKGROUND


4.2 Brief Description of the Current Technological Context

Buprenorphine or its metabolites can be detected using chromatographic or immunological techniques (heterogeneous\textsuperscript{12} or homogeneous). Heterogeneous immunological techniques include radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) [Cirimele et al., 2003; Cirimele et al., 2004; De Giovanni et al., 2005, Miller et al., 2006]. Of note among the homogeneous immunological techniques are cloned enzyme donor immunoassay (CEDIA), enzyme multiplied

\textsuperscript{10} Régie de l’assurance maladie du Québec (Quebec’s health insurance board).

\textsuperscript{11} According to interviews with CRAN practitioners.

\textsuperscript{12} In a competitive homogeneous enzyme immunoassay, the analytes in the sample compete with labelled analytes to bind to an antibody. The amount of labelled, unbound analytes is then measured. Similarly, in a competitive heterogeneous enzyme immunoassay, the analytes in the sample compete with the labeled analytes to bind to an antibody. However, the labelled, unbound analytes are separated or washed away and the remaining labelled, bound analytes are measured [Wild, 2005].
immunoassay technique (EMIT), fluoroimmunoassay [Wang et al., 2007] and the LUCIO assay [Alves et al., 2003].

Some of the licensed kits use the enzyme immunoassay in various formats (strips, cassettes or reagent cartridges) for detection of buprenorphine or its metabolites. The same kit can be used to simultaneously detect other substances (illicit drugs) [Health Canada, 2013].

In the literature, liquid or gas chromatography combined with mass spectrometry (LC-MS or GC-MS) is the gold standard [Bottcher and Beck, 2005; Hull et al., 2008; Kronstrand et al., 2008; Leino and Loo, 2007; Wu et al., 2009]. These methods are mentioned in the monograph for the Buprenorphine Enzyme Immunoassay [Lin-Zhi International, 2013], while the monograph for the CEDIA® Buprenorphine Assay recommends gas chromatography combined with mass spectrometry (GC-MS) as the confirmatory method [Microgenics Corporation, 2012].

4.3 Brief Description of the Advantages Cited for the New Technology

The homogeneous enzyme immunoassay, compared with the chromatography method, can produce results more quickly, is simple and inexpensive, and requires a small sample volume. In addition, it is more rapid and sensitive than the heterogeneous method as it does not require the washing and separation steps [Wang et al., 2007; Wild, 2005].

The limitations of the immunoassay include the determination of the threshold values (cut-offs) and possible cross-reactivity with substances in the sample other than the targeted analyte [George, 2004].

Moreover, the inherent limitations of buprenorphine detection, when monitoring detoxification, are adulteration and urine sample substitution [George, 2004]. However, regular assays for the detection of buprenorphine and one of its metabolites (norbuprenorphine, for example) could help to detect these problems by means of the physiological parameters obtained (for example, the expected values at which a pharmacological dose will plateau). The experts consulted do not consider this to be a major problem and they indicate that obtaining samples under direct supervision is limited to highly targeted cases.

4.4 Cost of Technology and Options: Not assessed.

5 EVIDENCE

5.1 Clinical Relevance

5.1.1 Other Tests Replaced: Not applicable.

5.1.2 Diagnostic or Prognostic Value

Treatment Availability

Buprenorphine testing serves to monitor the administration of replacement medication for treating opioid addiction.

Treatment Changes Based on Assay Results

Assay results can be used to verify compliance with treatment, adjust dosage or modify the pharmacological treatment plan to better adapt it to the patient’s needs.

Buprenorphine abuse and diversion have been reported. For this reason, it is recommended that practitioners exercise vigilance [APC, 2013; Yokell et al., 2011].
5.1.3 Therapeutic Value
Buprenorphine testing is used mainly to monitor compliance with pharmacological treatment as part of overall patient management. When used simultaneously for detection of other illicit substances, this test can be used to document the patient’s drug use.

5.2 Diagnostic Validity

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>PRESENCE</th>
<th>ABSENCE</th>
<th>NOT APPLICABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Specificity</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Positive predictive value (PPV)</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Negative predictive value (NPV)</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Likelihood ratio (LR)</td>
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<td>X</td>
<td></td>
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<tr>
<td>ROC curve</td>
<td></td>
<td>X</td>
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<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

This assessment targets two commercially available buprenorphine assay kits because there has been a change in the requestor’s laboratory after the application was filed. Both kits involve a homogeneous enzyme immunoassay. Data on diagnostic sensitivity and specificity and on accuracy are presented in Table 1. Overall, for both kits, the values of the parameters evaluated exceed 80%, except in the study by Melanson et al. [2012], which presents somewhat lower values.

Moreover, the manufacturers’ proposed thresholds for distinguishing positive from negative samples are 5 ng/mL for CEDIA and 10 ng/mL for EIA [Microgenics Corporation, 2012; Lin-Zhi International, 2013].

The study by Hull et al. [2008] is the only one to present positive and negative predictive values by comparing CEDIA against LC-MS/MS and to compare interpretation by a clinician of CEDIA results against results using the reference method (Table 2).
### Table 1: Diagnostic Sensitivity, Diagnostic Specificity and Accuracy

<table>
<thead>
<tr>
<th>STUDY (NUMBER OF SAMPLES)</th>
<th>REFERENCE METHOD</th>
<th>THRESHOLD (ng/mL)</th>
<th>SENSITIVITY (%)</th>
<th>SPECIFICITY (%)</th>
<th>ACCURACY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEDIA KIT</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hull et al., 2008 (n = 96)</td>
<td>LC-MS/MS</td>
<td>5 20</td>
<td>100 100</td>
<td>87.5 96.3</td>
<td>97.9 99</td>
</tr>
<tr>
<td></td>
<td>LC-MS/MS (clinical interpretation)</td>
<td>5 20</td>
<td>100 87.5</td>
<td>87.5 100</td>
<td>97.9 89.6</td>
</tr>
<tr>
<td>Leino and Loo, 2007 (n = 49)</td>
<td>LC-MS/MS</td>
<td>5</td>
<td>100</td>
<td>95</td>
<td>n.a.</td>
</tr>
<tr>
<td>Melanson et al., 2012 (n = 149)</td>
<td>LC-MS/MS</td>
<td>5</td>
<td>88</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td><strong>EIA KIT</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanson et al., 2012 (n = 149)</td>
<td>LC-MS/MS</td>
<td>5 10</td>
<td>81 67</td>
<td>100 100</td>
<td>95 91</td>
</tr>
</tbody>
</table>

Abbreviations: GC-MS = gas chromatography combined with mass spectrometry; LC-MS/MS = liquid chromatography combined with mass spectrometry in tandem; n.a. = not available; ng/mL = nanograms per millilitre

### Table 2: Positive Predictive Value and Negative Predictive Value of the CEDIA Kit

<table>
<thead>
<tr>
<th>REFERENCE METHOD</th>
<th>THRESHOLD (ng/mL)</th>
<th>POSITIVE PREDICTIVE VALUE (PPV)</th>
<th>NEGATIVE PREDICTIVE VALUE (NPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC-MS/MS</td>
<td>5</td>
<td>97.6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>98.6</td>
<td>100</td>
</tr>
<tr>
<td>LC-MS/MS (clinical interpretation)</td>
<td>5</td>
<td>97.6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>100</td>
<td>61.5</td>
</tr>
</tbody>
</table>

Abbreviation: ng/mL = nanograms per millilitre

PPV and NPV values are greater than 97%, except for the NPV when comparing the interpretation of a clinician at the 20 ng/mL threshold.

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13. CEDIA refers to the CEDIA® Buprenorphine Assay kit marketed by Microgenics Corporation.
14. EIA refers to the Buprenorphine Enzyme Immunoassay kit marketed by Lin-Zhi International.
5.3 Analytical (or Technical) Validity

The data on analytical validity are drawn from the results of the product monographs and from studies comparing various analytical parameters of the CEDIA or EIA kits with other kits, or with immunological or chromatographic methods.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PRESENCE</th>
<th>ABSENCE</th>
<th>NOT APPLICABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeatability</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Reproducibility</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Analytical sensitivity</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analytical specificity</td>
<td>X</td>
<td></td>
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<tr>
<td>Matrix effect</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Concordance</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation between test and comparator</td>
<td>X</td>
<td></td>
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</tbody>
</table>

Repeatability and Precision

The data on repeatability and precision are drawn from the monographs for the kits assessed [Microgenics Corporation, 2012; Lin-Zhi International, 2013] and are presented in Table 3. For the EIA kit, the data are taken from the results for the DxC600 analyzer, which most closely resembles the equipment used by the requestor.\(^\text{15}\)

For both kits, within-test and between-test precision increases as the concentration in the sample increases.

\(^\text{15}\) According to the *Manuel de procédures opérationnelles normalisées* published by Hôpital Saint-Luc, CHUM.
Table 3: Within-Test and Between-Test Coefficients of Variation Observed at Different Buprenorphine Concentrations (CEDIA and EIA kits)

<table>
<thead>
<tr>
<th>CONCENTRATION (ng/mL)</th>
<th>NUMBER OF SAMPLES</th>
<th>WITHIN-TEST</th>
<th>BETWEEN-TEST*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% CV</td>
<td>% CV</td>
</tr>
<tr>
<td><strong>CEDIA KIT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.4</td>
<td>120</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>6.8</td>
<td>120</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>36.5</td>
<td>120</td>
<td>2.6</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>EIA KIT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 / 20**</td>
<td>0.0</td>
<td>200.0</td>
</tr>
<tr>
<td>2.5</td>
<td>21 / 20**</td>
<td>15.6</td>
<td>9.4</td>
</tr>
<tr>
<td>5.0</td>
<td>21 / 20**</td>
<td>4.9</td>
<td>5.0</td>
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<tr>
<td>7.5</td>
<td>21 / 20**</td>
<td>2.5</td>
<td>3.9</td>
</tr>
<tr>
<td>10.0</td>
<td>21 / 20**</td>
<td>3.8</td>
<td>3.0</td>
</tr>
<tr>
<td>12.5</td>
<td>21 / 20**</td>
<td>3.2</td>
<td>2.5</td>
</tr>
<tr>
<td>15.0</td>
<td>21 / 20**</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>17.5</td>
<td>21 / 20**</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>20.0</td>
<td>21 / 20**</td>
<td>2.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Abbreviations: CV = coefficient of variation; ng/mL = nanograms per millilitre
*2-week interval; ** 21 samples for within-test assay and 20 samples for between-test assay

Analytical Sensitivity
The limit of buprenorphine detection is 1.25 ng/mL for the CEDIA kit and 3 ng/mL for the EIA kit.

Analytical Specificity
According to the manufacturer’s monograph, the CEDIA kit can detect the metabolite buprenorphine-3-beta-D-glucuronide (98% cross-reactivity). Low cross-reactivity (< 0.015%) was also observed in the presence of the metabolites norbuprenorphine and norbuprenorphine-3-beta-D-glucuronide [Microgenics Corporation, 2012].

One study confirms the observations, but with higher reactivity values [Wu et al., 2009].

As regards the EIA kit, which detects norbuprenorphine, buprenorphine presents a cross-reactivity of 94.3%, whereas the other metabolites, namely buprenorphine-glucuronide and norbuprenorphine-glucuronide, have a low cross-reactivity (< 1%) [Lin-Zhi International, 2013].

Some studies report cross-reactivity with various substances (opioids) that may be present in a sample, at various threshold concentrations. They include: codeine, dihydrocodeine, morphine, morphine-3-glucuronide, methadone, hydrocodone, nalorphine, naltrexone and norpropoxyphene [Melanson et al., 2012; Microgenics Corporation, 2012; Bottcher and Beck, 2005; Pavlic et al., 2005]. A more comprehensive list is available from the manufacturers.
Interference
The potential interference of endogenous physiological substances on recovery of buprenorphine was checked with a spiking test. These substances can interfere in the range of ± 10% of the buprenorphine value [Microgenics Corporation, 2012] or ± 12% of the norbuprenorphine value [Lin-Zhi International, 2013].

Concordance
The concordance (qualitative) between the results obtained using the CEDIA and EIA kits and the results obtained using the ELISA and GC-MS methods is shown in Table 4.

Table 4: Concordance Between the Kits and the Other Methods

<table>
<thead>
<tr>
<th>STUDY</th>
<th>COMPARATIVE METHOD</th>
<th>NUMBER OF SAMPLES</th>
<th>CONCORDANCE (%)</th>
<th>THRESHOLD (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEDIA KIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottcher and Beck, 2005</td>
<td>ELISA</td>
<td>221</td>
<td>96.8</td>
<td>5</td>
</tr>
<tr>
<td>Microgenics Corporation, 2012</td>
<td>GC-MS</td>
<td>96</td>
<td>99.0</td>
<td>5</td>
</tr>
<tr>
<td>EIA KIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin-Zhi International, 2013</td>
<td>GC-MS</td>
<td>82</td>
<td>97.4*</td>
<td>10</td>
</tr>
</tbody>
</table>

* Positive concordance. Negative concordance is 95.3%.

Correlation Between Test and Comparator
The agreement between the CEDIA kit and the GC-MS method was determined with linear regression analysis. The correlation coefficient is $r^2 = 0.968$ [Bottcher and Beck, 2005]. Both methods therefore give very similar results because the $r^2$ value is close to 1.

The correlation between the CEDIA kit and the GC-MS method was analyzed using a least squares regression. The correlation coefficient obtained is $r = 0.988$ [Microgenics Corporation, 2012]. This means that both methods give very similar results because the $r$ value is close to 1.

The linearity study performed on the EIA kit gives a correlation coefficient of $r^2 = 0.9941$ [Lin-Zhi International, 2013], which indicates that the results obtained with this kit are close to the expected target values.

5.4 Recommendations for Listing in Other Jurisdictions
Monitoring the use of replacement medication in the treatment of opioid addiction is a reality in various countries [Pergolizzi et al., 2010; AWMSG, 2008; CSAT, 2004], including the United States. A US clinical practice guideline and Quebec guidelines state that buprenorphine tests can be used to document a patient’s treatment compliance [CMQ-OPQ, 2009; CSAT, 2004]. However, the guides do not indicate whether documenting treatment compliance helps to improve it.

While monitoring buprenorphine compliance is indicated, most Ontario laboratories do not routinely test for buprenorphine in urine [Handford et al., 2011].
6  ANTICIPATED OUTCOMES OF INTRODUCING THE TEST

6.1  Impact on Material and Human Resources

The impact on staff would be minimal, since it is a matter of adding one test to the set of tests performed by an automated analyzer. From a material resources standpoint, this test would require purchasing and managing reagents and calibrators [Lin-Zhi International, 2013; Microgenics Corporation, 2012], and could be performed using an existing analyzer (used for other substance tests).

6.2  Economic Consequences of Introduction Into Quebec's Health Care and Social Services System

Without a clear protocol on test frequency (at the discretion of the attending physician), it is impossible to determine the annual volume of required tests in the future given the increasing number of patients treated and the uncertain optimal duration of the buprenorphine maintenance program [Kleber, 2007].

Current practice seems to be concomitant testing for buprenorphine and for illicit or potentially cross-reactive substances [according to interviews with CRAN practitioners]. It may be noted that there are kits that detect buprenorphine along with other substances (strip tests or cassettes).

6.3  Main Organizational, Ethical, and Other (Social, Legal, Political) Issues

Patients treated with buprenorphine must be closely monitored as part of a comprehensive detoxification program based on medical, social and psychological management of their opioid addiction [APC, 2013]. The buprenorphine test primarily serves to verify compliance with the replacement therapy for opioid addiction. This test may therefore help to ensure the most judicious use of this medication.

However, the results of this test can also have negative legal and social repercussions on the lives of individuals. For example, non-compliance could lead to a refusal to authorize unsupervised administration of buprenorphine; in exceptional cases, the worst-case scenario would be withdrawal from a detoxification program constituting a breach of a court-imposed condition in a child custody matter [Clément and Tourigny, 1999; Simpson et al., 1997].

The test’s diagnostic specificity is important in light of the stakes and the potential impact on keeping an individual in the program after a false-negative result, or on aftercare effectiveness (with a financial impact) after a false-positive result (for cross-reactivity with one or more illicit drugs). Moreover, preventing sample falsification through adulteration or substitution has not been addressed in the identified studies, despite the recommendations for urine sample collection [CMQ-OPQ 2009].

7  IN BRIEF

7.1  Clinical Relevance

The buprenorphine test is used mainly to verify compliance with the substitution treatment for opioid dependence.

7.2  Diagnostic Validity

The CEDIA kit features good diagnostic validity with parameters (sensitivity, specificity, PPV, NPV, accuracy) greater than 75%. For the EIA kit, only one study is available to document its diagnostic validity, which is relatively good (at least 67%).
7.3 Analytical Validity

The two commercial kits assessed feature good analytical validity despite the potential interference of endogenous physiological substances or cross-reactivity with opioids.

7.4 Recommendations From Other Organizations

According to an US clinical practice guideline and the CMQ-OPQ (Quebec) guidelines, the buprenorphine test may be used to document treatment compliance.
8 INESSS NOTICE IN BRIEF

Homogeneous Enzyme Immunoassay for Semi-Quantitative Determination of Buprenorphine

<table>
<thead>
<tr>
<th>Status of the Diagnostic Technology</th>
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<tr>
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<td>☒ Innovative</td>
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<td>☐ Experimental (for research purposes only)</td>
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<td>☐ Replacement for technology____________________ which becomes obsolete</td>
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<th>INESSS Recommendation</th>
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<tr>
<td>☐ Introduce test to Index</td>
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<tr>
<td>☒ Do not introduce test to Index</td>
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<tr>
<td><em>Clinical utility is not proven.</em></td>
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<td>☐ Reassess test</td>
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<th>Additional Recommendation</th>
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<tr>
<td>☐ Draw connection with listing of drugs, if companion test</td>
</tr>
<tr>
<td>☐ Production of an optimal use guide</td>
</tr>
<tr>
<td>☐ Production of indicators, when monitoring is required</td>
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REFERENCES


Centre de recherche et d'aide pour narcomanes (CRAN). La dépendance aux opioïdes : portrait des traitements de substitution au Québec. Montréal, Qc : CRAN; 2011.


Clément M-E and Tourigny M. Négligence envers les enfants et toxicomanie des parents : portrait d’une double problématique. Montréal, Qc : Comité permanent de lutte à la toxicomanie; 1999.

Collège des médecins du Québec (CMQ) and Ordre des pharmaciens du Québec (OPQ). La buprénorphine dans le traitement de la dépendance aux opioïdes. Lignes directrices. Montréal, Qc : OPQ; 2009.


