

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k101753

B. Purpose for Submission:

New Device

C. Measurand:

Methamphetamine in oral fluid

D. Type of Test:

Qualitative enzyme immunoassay

E. Applicant:

Microgenics Corporation

F. Proprietary and Established Names:

CEDIA® Methamphetamine OFT Assay

CEDIA® Methamphetamine OFT Calibrators

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LAF	Class II	21 CFR § 862.3100	Toxicology (91)
DLJ	Class II	21 CFR§ 862.3200	Toxicology (91)

H. Intended Use:

1. Intended use(s):

See indication(s) for use below.

2. Indication(s) for use:

The CEDIA® Methamphetamine OFT Assay is intended for use in the qualitative detection of methamphetamine at a cutoff concentration of 120.0 ng/mL in neat oral fluid. The specimen must be collected exclusively with the Oral-Eze™ Saliva Collection System. The assay is calibrated against d-methamphetamine and performed on the MGC 240. This in vitro diagnostic device is intended for clinical laboratory use only.

The CEDIA Methamphetamine OFT Calibrators are intended for use in the calibration of d- Methamphetamine when used with the CEDIA Methamphetamine OFT Assay for human oral fluid samples collected with the Oral-Eze™ Saliva Collection System. This in vitro diagnostic device is intended for clinical laboratory use only.

The CEDIA Methamphetamine OFT Assay provides only a preliminary analytical test result. A more specific alternative method must be used to obtain a confirmed analytical result. Gas Chromatography/Mass Spectrometry (GC/MS) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) are the preferred confirmatory methods. Clinical consideration and professional judgment should be applied to any drug of abuse test result particularly when preliminary positive results are used.

3. Special conditions for use statement(s):

For prescription use only in clinical chemistry laboratories.

It is not for use in Point of Care settings.

4. Special instrument requirements:

MGC 240 Analyzer

I. Device Description:

CEDIA® Methamphetamine OFT Assay

The CEDIA® Methamphetamine OFT Assay uses recombinant DNA technology to produce a unique homogeneous enzyme immunoassay system. The assay is based on the bacterial enzyme β -galactosidase, which has been genetically engineered into two inactive fragments i.e., enzyme acceptor (EA) and enzyme donor (ED). These fragments spontaneously re-associate to form fully active enzyme that, in the assay format, cleaves a substrate, generating a color change that can be measured spectrophotometrically. In the assay, analyte in the sample competes with analyte conjugated to one inactive fragment of β -galactosidase for antibody binding site. If

analyte is present in the sample, it binds to antibody, leaving the inactive enzyme fragments free to form active enzyme.

If analyte is not present in the sample, antibody binds to analyte conjugated on the inactive fragment, inhibiting the re-association of inactive β -galactosidase fragments, and no active enzyme is formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of drug present in the sample.

The CEDIA® Methamphetamine OFT Assay consists of separately packaged reagents (R1, R1a, R2, and R2a):

CEDIA® Methamphetamine OFT Reagents

R1	EA Reconstitution Buffer: Contains buffer salts, mouse monoclonal anti-methamphetamine antibody, stabilizer, and preservative
R1a	EA Reagent: Contains Enzyme Acceptor (microbial)
R2	ED Reconstitution Buffer: Contains buffer salts, stabilizers, and preservative
R2a	ED Reagent: Contains Enzyme Donor (microbial) conjugated to methamphetamine derivative, chlorophenol red- β -Dgalactopyranoside stabilizers, and preservative

Calibrators are provided separately, in liquid form, for storage at 2 - 8°C, and ready to use.

The CEDIA® OFT Methamphetamine Calibrators are supplied separately in individual kits with the following target concentrations:

Calibrator Level	Target Concentration (ng/mL)
Negative	0.0
Cutoff	40.0
High	200.0

The Oral-Eze Saliva Collection System consists of Oral-Eze saliva collector and collection tube with preservative buffer. Oral-Eze saliva collector consists of an absorbent pad attached to a plastic handle. The saliva collector is provided with a volume adequacy indicator. The plastic handle has a round window where blue color will appear when sufficient volume of oral fluid is collected. Samples are collected by placing the collector pad and plastic shield between lower cheek and gum with the plastic shield facing the cheek. Oral fluid collection is done when blue color appears

in the window of the handle. The pad is ejected in to the collection tube by placing thumb on the ridges on the handle and pushing the thumb forward. The collection tube is capped and sent to the laboratory for processing and testing.

J. Substantial Equivalence Information:

Predicate device name	Predicate 510(k) number
OTI Methamphetamine Intercept® MICRO-PLATE EIA	K993208

Comparison with predicate:

Similarities and Differences		
Comparison	Candidate Device	Predicate (k993208)
Intended Use	Same	For use in the qualitative determination of methamphetamine in oral fluid samples.
Analyte	Same	Methamphetamine
Detection method	Same	Qualitative
Cutoff value	120ng/mL in Neat Oral Fluid	40 ng/mL when oral fluid collected with the Oral Specimen Collection Device
Sample matrix	Same	Oral Fluid (Saliva)

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

CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods.

CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples.

L. Test Principle:

Principle of Methamphetamine OFT Assay

Enzyme fragment complementation assays are based on competition between Methamphetamine in the sample and labeled-methamphetamine for a fixed amount of

antibody in the reagent. The presence of Methamphetamine in saliva sample facilitates the association of two inactive β -galactosidase enzyme fragments into an active enzyme complex that hydrolyzes a substrate, generating a color change that can be measured spectrophotometrically.

Specifically, methamphetamine in the saliva sample competes with Methamphetamine conjugated to one inactive fragment of β -galactosidase for antibody binding site. If methamphetamine is present in the saliva sample, it binds to antibody, leaving the inactive enzyme fragments free to form active enzyme. If Methamphetamine is not present in the saliva sample, antibody binds to methamphetamine conjugated on the inactive fragment, inhibiting the re-association of inactive β -galactosidase fragments, and no active enzyme complex is formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of Methamphetamine present in the sample.

The calibrator is set at diluted levels so that sample absorbance values can be compared directly to the absorbance values of the calibration curve. The assay result is reported as a positive or negative result relative to the neat oral fluid cutoff of 120.0 ng/mL.

Principle of Oral-Eze Saliva Collection System

The Oral-Eze Saliva Collection System contains a preservative buffer that dilutes the neat oral fluid sample. The calibrator levels are set at diluted levels so that sample absorbance values can be compared directly to the absorbance values of the calibration curve. The assay result is reported as a positive or negative result relative to the neat oral fluid cutoff of 120 ng/mL.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

All analytical performance data was collected on neat human oral fluid samples and processed through the Oral-Eze Saliva Collection System and analyzed on the MGC 240 instrument. The Oral-Eze collection device includes a diluent that results in a dilution of approximately 1/3. The assay cannot be used to measure undiluted (neat) samples. Analyte concentrations refer to the neat oral fluid concentration, unless otherwise noted.

a. Precision and Reproducibility

Negative neat oral fluid samples were collected and then prepared by spiking methamphetamine at negative, -75%, -50%, -25%, below the cutoff, at the cutoff, and +25%, +50%, +75% and +100% above the cutoff. All spiked neat oral fluid sample concentrations were confirmed by LC-MS/MS. The neat oral fluid samples were processed using the Oral-Eze device to obtain diluted oral fluid samples. The diluted oral fluid samples were confirmed by LC-MS/MS

and tested in the CEDIA Methamphetamine OFT Assay in qualitative mode.

The randomized CLSI (EP5-A2) precision protocol was followed with five replicates of each sample for each run, 2 runs per day for five non-consecutive days, total N= 50/level.

The results are summarized in the table below.

Analyte	Tested Concentration	Number of determinants	Methamphetamine OFT Assay # Neg / # Pos
Methamphetamine	0	50	50 Neg / 0 Pos
Methamphetamine	-75%	50	50 Neg / 0 Pos
Methamphetamine	-50%	50	50 Neg / 0 Pos
Methamphetamine	-25%	50	50 Neg / 0 Pos
Methamphetamine	cutoff	50	13 Neg / 37 Pos
Methamphetamine	+25%	50	0 Neg / 50 Pos
Methamphetamine	+50%	50	0 Neg / 50 Pos
Methamphetamine	+75%	50	0 Neg / 50 Pos
Methamphetamine	+100%	50	0 Neg / 50 Pos

b. Linearity/assay reportable range:

Not applicable, this is a qualitative assay.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability

The sponsor provided the following traceability Information:

Traceability is two-fold: 1) to a LC-MS/MS method, and 2) to a 1 mg/mL commercially available Methanol Standard.

Calibrator value assignment:

The LC-MS/MS results of the development lot are summarized in table

Methamphetamine OFT Calibrator LC-MS/MS Results

Drug	Cutoff Calibrator (ng/mL)	High Calibrator (ng/mL)
d-methamphetamine	39.2	188

The above data satisfies the acceptance criteria claimed by the sponsor.

Stability

The sponsor provided experimental data for accelerated closed vial, open vial and closed real time vial stability studies

Open Vial Stability

Open-Vial Stability Studies were conducted on one lot of calibrators in qualitative mode at 2-8°C and time points were every two weeks for 50 days. Testing was done in replicates of three. The open vial stability of reconstituted reagents is 50 days (2-8°C).

Closed-Vial Real-Time (2-8°C) Calibrator Stability

Real-Time Stability Studies were conducted on three lots of calibrators in qualitative mode at 2-8°C. Testing was done in replicates of three time points for 0, 3, 6, 9, 12, 18 months.

The data provided by the sponsor satisfied the acceptance criteria of Methamphetamine OFT Calibrators real time stability claim at 2-8°C for 18 months.

Sample and reagent storage stability

Reagent:

Reagents were stored at 2-8°C and tested every 3 months for the first year and then every 6 months for the 2 years using Reference calibrators stored at -20°C.

Sample:

The stability of oral fluid samples in the preservative buffer was evaluated in real time. The stability protocol was reviewed and found acceptable. Oral fluid samples can be stored at 2-8°C or at room temperature (21-25°C) for 21 days.

Shipping stability studies

Sample shipment/travel stability:

Conditions simulating ground shipping, air shipping and various climate conditions (desert, tropical) were tested. Samples spiked at concentrations below the cutoff (-50%) recovered as negative for both the control and shipped samples. Samples spiked at concentrations above the cutoff (+50%) recovered as positive for both the control and shipped samples. The shipping temperature should not exceed >40°C.

d. Detection limit:

Analytical performance of the device around the cutoff is described in the precision section 1.a above.

e. Analytical specificity:

The sponsor performed analytical specificity studies on four categories of potential interferents: structurally related substances, structurally unrelated substances, substances endogenous to oral fluid, and food and dental substances.

Cross Reactivity to Structurally Related Compounds

Cross-reactivity was evaluated by spiking various concentrations (which could be found in a neat oral fluid sample) of structurally related compounds into drug-free neat oral fluid pool, than added to the oral fluid collection device. By analyzing various concentration of each compound the sponsor determined the concentration of the drug that produced a response approximately equal to the cutoff. Results of those studies appear in the table below.

Compounds	Tested Concentration in Neat Oral Fluid (ng/mL)	Response Equivalent to the cutoff
MDMA	120	Positive
MDEA (3,4-	420	Positive
MDA	5,250	Positive

For the following compounds the concentrations were the highest levels yielding negative results in the assay.

Compounds	Tested Concentration in Neat Oral Fluid (ng/mL)	Methamphetamine OFT Assay Negative/Positive
d-Amphetamine	2,700	Negative
d,l-Amphetamine	9,000	Negative
l-Amphetamine	13,500	Negative
Diphenhydramine	3,000,000	Negative
Doxylamine	3,000,000	Negative
d-Ephedrine	300,000	Negative
D,l-Ephedrine	66,000	Negative
l-Ephedrine	42,000	Negative
Fenfluramine	300	Negative
Isoxsuprine	3,000,000	Negative
d,l-Methamphetamine	210	Negative
l-Methamphetamine	1,050	Negative
PMA	4,500	Negative
PMMA	90	Negative
Mephentermine	4,500	Negative
Phenethylamine	36,000	Negative
Phentermine	75,000	Negative
Phenylephrine	30,000	Negative
Phenylpropanolamine	1,200,000	Negative
Procaine	7,500	Negative
d-Pseudoephedrine	18,000	Negative
l-Pseudoephedrine	42,000	Negative

Interference from Structurally Unrelated Compounds

Various common over-the-counter medications and structurally unrelated compounds were tested for cross-reactivity in the assay. The cross-reactant solutions were prepared by adding the compounds to neat oral fluid samples at the concentration listed in the table below. The neat oral fluid samples were processed using the Oral-Eze device to obtain diluted oral fluid samples which were tested in the CEDIA Methamphetamine OFT Assay. All the compounds tested negative and did not show any cross reactivity.

Compounds	Tested Concentration In Neat Oral Fluid (ng/mL)	Response Equivalent to the cutoff
Acetaminophen	60,000	Negative
Acetylsalicylic Acid	60,000	Negative
Alprazolam	30,000	Negative
Amobarbital	30,000	Negative
Amoxicillin	12,000	Negative
Ampicillin	30,000	Negative
Atropine	30,000	Negative
Benzoylcegonine	60,000	Negative
Butabarbital	30,000	Negative
Butalbital	30,000	Negative
Caffeine	60,000	Negative
Captopril	60,000	Negative
Chlorazepate	30,000	Negative
Chlordiazepoxide	60,000	Negative
Chlorpromazine	30,000	Negative
Cimetidine	60,000	Negative
Clonazepam	30,000	Negative
Cocaine	30,000	Negative
Codeine	12,000	Negative
Cotinine	30,000	Negative
Cyclizine	30,000	Negative
Dextromethorphan	30,000	Negative
Diazepam	60,000	Negative
Digoxin	12,000	Negative
Enalapril	60,000	Negative
Fluoxetine	60,000	Negative
Gentisic Acid	30,000	Negative
Hydrocodone	30,000	Negative
Hydromorphone	30,000	Negative
Ibuprofen	60,000	Negative
Imipramine	30,000	Negative
Levothyroxine	6,000	Negative
Lidocaine	30,000	Negative
Loperamide	30,000	Negative
Medazepam	30,000	Negative
Meperidine	30,000	Negative
Methadone	60,000	Negative
Metoprolol	30,000	Negative
Morphine	12,000	Negative
Nicotine	30,000	Negative
Nifedipine	60,000	Negative
Norchlordiazepoxide	30,000	Negative

Nordiazepam	30,000	Negative
Penicillin	30,000	Negative
Pentobarbital	30,000	Negative
Phencyclidine	60,000	Negative
Phenobarbital	60,000	Negative
Procainamide	6,000	Negative
Propoxyphene	60,000	Negative
Ranitidine	12,000	Negative
Salicylic Acid	60,000	Negative
Secobarbital	60,000	Negative
Temazepam	30,000	Negative
Theophylline	30,000	Negative
Tolmetin	30,000	Negative
Δ^9 -THC	30,000	Negative
11-nor- Δ^9 -THC-COOH	1,200	Negative
Verapamil	60,000	Negative
Zomepirac	30,000	Negative

Endogenous, Exogenous Substances and pH Interference

The potential interference from several endogenous and exogenous substances, and pH on the detection accuracy of samples containing methamphetamine at +/- 50% of the cutoff concentration were tested in the assay. The interfering substances were added to neat oral fluid at the concentrations listed in the table below. The neat oral fluid samples were then processed using the Oral-Eze collection device and tested in the CEDIA Methamphetamine OFT Assay. No interference was observed with the interfering substances and pH 5-9 samples at the +/- 50% cutoff concentrations.

Compounds	Tested Concentration In Neat Oral Fluid	Methamphetamine OFT Assay	
		-50% Methamphetamine	+50% Methamphetamine
Cotinine	0.03 mg/mL	Negative	Positive
Nicotine	0.03 mg/mL	Negative	Positive
Hemoglobin	0.6 mg/mL	Negative	Positive
Human serum albumin	30.0 mg/mL	Negative	Positive

Sodium Chloride	18.0 mg/mL	Negative	Positive
Cholesterol	0.45 mg/mL	Negative	Positive
Acetaminophen	1.8 mg/mL	Negative	Positive
Acetylsalicylic Acid	1.8 mg/mL	Negative	Positive
Caffeine	0.3 mg/mL	Negative	Positive
Ibuprofen	0.6 mg/mL	Negative	Positive
Coffee	6% v/v	Negative	Positive
Milk	6% v/v	Negative	Positive
Orange Juice	6% v/v	Negative	Positive
Cranberry Juice	6% v/v	Negative	Positive
Soft drink (Coke)	6% v/v	Negative	Positive
Toothpaste	6% v/v	Negative	Positive
Mouthwash	6% v/v	Negative	Positive
Tea	6% v/v	Negative	Positive
Alcohol	6% v/v	Negative	Positive
Baking Soda	6% v/v	Negative	Positive
Cough Syrup	6% v/v	Negative	Positive
Whole Blood	6% v/v	Negative	Positive
Hydrogen Peroxide	6% v/v	Negative	Positive
pH	5-9	Negative	Positive
Denture Adhesive	6% v/v	Negative	Positive
Denture Adhesive	6% v/v	Negative	Positive

Potential interference from additional food and dental compounds was tested by collecting neat oral fluid from volunteers after use of the following substances: hard candy, chewing gum, chewing tobacco, cigarettes and tooth whitening strips.

Compounds	Tested Concentration in Neat Oral Fluid	Methamphetamine OFT Assay Results	
		-50% Methamphetamine	+50% Methamphetamine
Water	n/a	Negative	Positive
Chewing Tobacco	n/a	Negative	Positive
Cigarettes	n/a	Negative	Positive
Gum	n/a	Negative	Positive
Hard Candy	n/a	Negative	Positive
Tooth Whitening Strips	n/a	Negative	Positive

f. Assay cut-off:

Characterization of how the device performs analytically around the claimed cutoff concentration appears in the precision above.

2. Comparison studies:

a. Method comparison:

Two separate studies were conducted. In the first study, MAMP was spiked in to samples that had already been collected through the intercept device. In the second study samples were spiked with MAMP prior to the collection step to reflect the operation of the entire system.

Study 1:

41 unaltered clinical samples were tested in the CEDIA Methamphetamine OFT Assay in qualitative mode. The results were compared to GC/MS results. All samples were confirmed by GC/MS.

Note: The values obtained in this study were collected from samples spiked with MAMP prior to the collection step. Therefore the results reflect the performance of the entire system including the collection step.

Candidate Device Results	Less than half the cutoff concentration by LC-MS/MS analysis	Near Cutoff Negative (Between 50% below the cutoff and the cutoff)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration)	High Positive (greater than 50% above the cutoff concentration)
Negative	18	2	0	0
Positive	0	0	2	19

% Agreement among positive and negative is 100%.

LC/MS/MS values used to categorize samples in this table are based on the concentration found in the neat oral fluid sample.

Study 2: Eighty one unaltered clinical samples were tested in the CEDIA Methamphetamine OFT Assay in qualitative mode. The results were compared to GC/MS results. All samples were confirmed by GC/MS.

Note: this study was performed on samples already collected with the Intercept collection device. Therefore the results below do not reflect any inaccuracy inherent in the collection process itself.

Stratified data Table

Candidate Device Results	Negative	Less than half the cutoff concentration by GC/MS analysis	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration)	High Positive (greater than 50% above the cutoff concentration)
Negative	32	4	4	1	0
Positive	0	0	0	4	36

Sample #	OFT Assay POS/NEG	Drug/Metabolite GC/MS value (ng/mL)
15	Negative	123 (Methamphetamine)

- b. Matrix comparison:
Not applicable.
- 3. Clinical studies:
 - a. Clinical Sensitivity:
Not applicable.
 - b. Clinical specificity:
Not applicable.
 - c. Other clinical supportive data (when a. and b. are not applicable):
Not applicable.
- 4. Clinical cut-off:
Not applicable.
- 5. Expected values/Reference range:
Not applicable.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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