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

A. 510(k) Number:
k053337

B. Purpose for Submission:
New Device

C. Measurand:
Methylenedioxymethamphetamine (MDMA)

D. Type of Test:
Qualitative and semi-quantitative immunoassay

E. Applicant:
Dade Behring, Inc.

F. Proprietary and Established Names:
Dade Behring Dimension® Urine Ecstasy Screen Flex® reagent cartridge

G. Regulatory Information:

1. Regulation section:
   21 CFR 862.3100 (Enzyme Immunoassay, Amphetamine)
2. Classification:
   Class II
3. Product Code:
   DKZ
4. Panel:
   Toxicology (91)

H. Intended Use:

1. Intended use(s):
   Refer to Indications for use.

2. Indication(s) for use:
   The EXTC Flex® reagent cartridge used on the Dimension® clinical chemistry system provides reagents for an *in vitro* diagnostic test intended for the qualitative and semi-quantitative determination of methylenedioxymethamphetamine (MDMA) and closely related drugs in human urine using a cutoff of either 300 or 500 ng/mL. Measurements obtained with the EXTC method are used in the diagnosis and treatment of ecstasy use or overdose.

The EXTC method provides only a preliminary analytical test result. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result. Gas chromatography/mass spectrometry (GC/MS) 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.

1. Special condition for use statement(s):

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Semi-quantitative results may be helpful in estimating the concentrations of drug(s) in samples. This can aid users when they are preparing dilutions of the samples for further analysis.

The assay is not designated for use in point-of-care settings.

Certain foods or medications may interfere with tests for methylenedioxymethamphetamine and cause false positive results.

For professional use only.

2. Special instrument Requirements:

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The device is for use on automated clinical chemistry analyzers. Instruments must be capable of maintaining a constant reaction temperature, pipetting samples and reagents, mixing reagents, timing reactions, and measuring enzyme rates precisely.

Performance was demonstrated in this submission on the Dimension® RxL and Xpand® clinical chemistry systems.

F. Device Description:

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The Dimension Urine Ecstasy Screen Flex reagent cartridge is an in vitro diagnostic device that consists of prepackaged reagents in a plastic eight-well cartridge for use on the Dade Behring Dimension clinical chemistry system. Wells 2 and 3 contain enzyme conjugate. Wells 5, 6, and 8 contain antibody substrate. Wells 1 and 7 are empty.

Syva®Emit®II Plus Ecstasy reagents are contained in the EXTC Flex® reagent cartridge. The EXTC cartridge is used on the Dimension® system to provide an automated application of this assay. It is based on the competition of antibody binding sites between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH).

Matched lots of polyclonal antibody reactive to MDMA and MDA-glucose-6-phosphate dehydrogenase conjugate are used in the Syva®Emit®II Plus methodology.

G. Substantial Equivalence Information:

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1. Predicate device name(s):
   Emit® II Plus Ecstasy Assay
2. Predicate K number(s):
   k043028
3. Comparison with predicate:
   Both devices are for measurement of the same analyte in the same matrix and utilize the same test methodology.

Item	New Device EXTC Flex® reagent cartridge	Predicate Emit® II Plus Ecstasy Assay
Intended Use	In vitro diagnostic use for the qualitative and semi-quantitative determination of methylenedioxymethamphetamine (MDMA) and closely related drugs in human urine using a cutoff of either 300 or 500 ng/mL.	In vitro diagnostic use for the qualitative and semi-quantitative determination of methylenedioxymethamphetamine (MDMA) and closely related drugs in human urine using a cutoff of either 300 or 500 ng/mL.
Principle	Homogeneous enzyme immunoassay	Homogeneous enzyme immunoassay
Antibody	Sheep polyclonal antibodies to methylenedioxymethamphetamine (MDMA).	Sheep polyclonal antibodies to methylenedioxymethamphetamine (MDMA).
Reagent Composition	***Antibody/Substrate:*** Sheep polyclonal antibodies to methylenedioxymethamphetamine (MDMA), bovine serum albumin, G6P, NAD, preservatives and stabilizers. ***Enzyme Conjugate:*** Methylenedioxyamphetamine (MDA) labeled with bacterial G6PDH, tris buffer, bovine serum albumin, preservatives and stabilizers.	***Antibody/Substrate Reagent A:*** Sheep polyclonal antibodies to methylenedioxymethamphetamine (MDMA), bovine serum albumin, G6P, NAD, preservatives and stabilizers. ***Enzyme Reagent B:*** Methylenedioxyamphetamine (MDA) labeled with bacterial G6PDH, tris buffer, bovine serum albumin, preservatives and stabilizers.
Cutoff	300 ng/mL and 500 ng/mL	300 ng/mL and 500 ng/mL
Semiquantitative Range	300 ng/mL cutoff: 25 – 450 ng/mL 500 ng/mL cutoff: 75 – 900 ng/mL	100–1000 ng/mL

Sensitivity	300 ng/mL cutoff: 25 ng/mL 500 ng/mL cutoff: 75 mg/mL	75 ng/mL
Specimen Type	Human urine	Human urine
Instrument	Dimension® clinical chemistry system	Chemistry analyzers

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

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Premarket Submission and Labeling Recommendations for Drugs of Abuse Screening Tests - Draft Guidance for Industry and FDA Staff, published December 2003

NCCLS EP5-A: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline

I. Test Principle:

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The test is an enzyme immunoassay for use on automated clinical chemistry analyzers. Syva® Emit® II Plus Ecstasy reagents are contained in the EXTC Flex® reagent cartridge. The EXTC cartridge is used on the Dimension® system to provide an automated application of this assay. It is based on the competition for antibody binding sites between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH).

The concentration of drug in the sample determines the amount of MDA-glucose-6-phosphate dehydrogenase conjugate that is bound to the antibody. The unbound conjugate catalyzes the oxidation of glucose-6-phosphate with the simultaneous reduction of NAD^+ to NADH, more rapidly than does the bound conjugate. The rate of increasing absorbance at 340 nm due to the increase in NADH is related to the concentration of drug in the sample by a mathematical function.

J. Performance Characteristics (if/when applicable):

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1. Analytical performance:
   a. *Precision/Reproducibility:*
   All performance was established on the Dimension® RxL and Xpand® clinical chemistry systems.

   Reproducibility was determined by assaying the cutoff calibrator and ± 25% controls for 20 days, 2 runs per day in duplicate (n = 80). The data were calculated according to the Clinical Laboratory Standard Institute (CLSI) Guideline EP5-A2. Results of the studies are presented below.

	Reproducibility at 300 ng/mL cutoffs				
Calibrator/Control[d]		**Repeatability**		**Within-Lab**	
	Mean	SD	CV	SD	CV
ng/mL	ng/mL	ng/mL	%	ng/mL	%
225	244	7.2	3.0	13.1	5.4
300	307	6.4	2.1	13.9	4.5
375	418	12.7	3.0	17.3	4.1

	Reproducibility at 500 ng/mL cutoffs				
Calibrator/Control[d]		**Repeatability**		**Within-Lab**	
	Mean	SD	CV	SD	CV
ng/mL	ng/mL	ng/mL	%	ng/mL	%
375	404	8.9	2.2	18.1	4.5
500	526	13.0	2.5	26.6	5.1
625	661	15.1	2.3	40.4	6.1

b. Linearity/assay reportable range:
Support for the lower limit of the reportable range is characterized by the sensitivity studies**.**

Recovery for the EXTC Flex® reagent cartridge was assessed both qualitatively and semi-quantitatively.

Qualitative Recovery
A qualitative recovery study was performed using negative human urine samples spiked with MDMA at the cutoff concentration and at -75%, -50%, -25%, +25%, +50%, +75% and +100% of the cutoff concentration. Samples were assayed in two separate runs, with an n=5 in each run (total of n=10). The mean rate was calculated and compared to the rate of the cutoff calibrator.

The EXTC Flex® reagent cartridge correctly identified each of the mean rates of spiked samples containing less than the cutoff as negative, and each of the mean rates of spiked samples containing greater than the cutoff as positive. Results are shown below.

Qualitative Recovery for the 300 ng/mL cutoff								
MDMA spike concentration	75	150	225	300	375	450	525*	600*
Mean Rate (maU)	191.6	211.9	232.5	249.5	259.2	267.6	274.5	280.4
Neg/Pos compared to the rate of the c/o calibrator	neg	neg	neg	pos	pos	pos	pos	pos
Rate of the cutoff calibrator = 242.0								
* outside the assay range								

Qualitative Recovery for the 500 ng/mL cutoff								
MDMA spike concentration	125	250	375	500	625	750	875	1000*
Mean Rate (maU)	187	209	228	246	258	267	273	280
Neg/Pos compared to the rate of the c/o calibrator	neg	neg	neg	pos	pos	pos	pos	pos
Rate of the cutoff calibrator = 243.2								
* outside the assay range								

Semiquantitative Recovery

A semi-quantitative recovery study was performed using negative human urine samples spiked with MDMA at the cutoff concentration and at -75%, -50%, -25%, +25%, +50%, +75% and +100% of the cutoff concentration. Samples were assayed in two separate runs, with an n=5 in each run (total of n=10). The mean was calculated and compared to the nominal spiked concentration. % recovery was calculated using the following equation.

$$\% \text{ recovery} = \frac{\text{Dim EXTC mean result}}{\text{Nominal MDMA spike concentration}} \times 100$$

The EXTC Flex® reagent cartridge recovered 80-120% of the nominal spiked concentration for concentrations within the assay range. For the 300 ng/mL cutoff, the

assay range is 25 – 450 ng/mL. For the 500 ng/mL cutoff, the assay range is 75 – 900 ng/mL. Results are shown below.

Semi-Quantitative Recovery for the 300 ng/mL cutoff							
MDMA spike concentration	75	150	225	300	375	450	525*
Mean (ng/mL)	82	178	257	340	409	506	662
% Recovery	109.29	118.76	114.32	113.48	109.06	112.43	126.05
* outside the assay range							

Semi-Quantitative Recovery for the 500 ng/mL cutoff									
MDMA Spike Concentration	125	250	375	500	625	750	875	950*	1000*
Mean (ng/mL)	135	278	398	528	647	784	916	1137	1273
% Recovery	107.96	111.30	106.22	105.57	103.45	104.51	104.73	119.72	127.26
* outside the assay range									

c. *Traceability (controls, calibrators, or method):*
The Emit II Plus Ecstasy Calibrators/Controls that are referenced in this submission were cleared under 510(k), k043028. Five levels of calibrator/control material, ranging in concentration from 0 to 1000 ng/mL, are specified in the labeling but are supplied separately. Calibrators/controls are drug free urine based materials spiked with known concentrations of MDMA.

Stability studies are summarized for the EXTC Flex® reagent cartridge.

d. *Detection limit:*
The analytical sensitivity of the EXTC method is 25 ng/mL for the 300 ng/mL cutoff (13 uL sample size) and it represents the lowest concentration of EXTC that can be distinguished from zero. The sensitivity of the EXTC method is 75 ng/mL for the 500 ng/mL cutoff (8 uL sample size). The sponsor defines analytical sensitivity

as the concentration at two standard deviations above the mean of measurements of the Emit® Calibrator Level 0 Calibrator (n=20) with a confidence of 95%.

e. Analytical specificity:
The tables below list the compounds and the levels at which the compounds have been found to give a response approximately equivalent to that of the selected cutoff (300 or 500 ng/mL methylenedioxymethamphetamine). Each concentration represents the reactivity level for the stated compound when it is added to a negative urine specimen. If a sample contains more than one compound detected by the assay, lower concentrations than those listed below may combine to produce a rate approximately equivalent to or greater than that of the cutoff calibrator.

Concentrations of Ecstasy Related Metabolites that Produce a Positive Result Equivalent to the selected cutoff (300 or 500 ng/mL MDMA)

Compound	Concentration (ng/mL) at the 300 ng/mL cutoff	Concentration (ng/mL) at the 500 ng/mL cutoff
MDA (Methylenedioxyamphetamine)	350	606
MDEA (Methylenedioxyethylamphetamine)	243	446
MBDB (N-methyl-1-(1,3-benzodioxol-5-yl)-2-aminobutane)	219	439
BDB (3,4-(methylenedioxyphenyl)-2-butanamine)	214	575
PMA (Para-methoxyamphetamine)	2326	39365
PMMA (Para-methoxymethamphetamine)	4360	5154
HMMA (4-hydroxy-3-methoxy-methamphetamine)	>40000	>40000

Concentrations of Structurally Related Compounds that Produce a Positive Result Equivalent to the 300 ng/mL and 500 ng/mL MDMA Cutoffs

Compound	Concentration (ug/mL) at the 300 ng/mL Cutoff	Concentration (ug/mL) at the 500 ng/mL Cutoff
D-Amphetamine	>154	>300
D-Methamphetamine	>62	>99
D,L-Methamphetamine	>13	>21
D,L-Amphetamine	>75	>169
L-Amphetamine	>97	>246
L-Methamphetamine	>13	>13
4-Chloramphetamine	>4	>10
Benzphetamine	>10	>10
Buproprion	>500	>500
Chloroquine	>1000	>1000
L-Ephedrine	>106	>234
Fenfluramine	>2	>4
Mephentermine	>15	>15
Methoxyphenamine	>1000	>1000
Nor-pseudoephedrine	>100	>100
Phenmetrazine	>300	>300
Phentermine	>150	>150
Phenylpropanolamine (PPA)	>200	>200
Propanolol	>15	>15
Pseudoephedrine	>208	>359
Quinacrine	>1000	>1000
Tranylcypromine	>100	>100
Tyramine	>100	>100

Concentrations of Structurally Unrelated Compounds that Produce a Positive Result Approximately Equivalent to the 300 ng/mL and 500 ng/mL MDMA Cutoff.

Compound	Concentration (ug/mL) at the 300 ng/mL Cutoff	Concentration (ug/mL) at the 500 ng/mL Cutoff
Haloperidol	>2	>7
Isoxsuprine	>8	>20
Labelatol	>7	>16
Nylidrin	>7	>15
Trazodone	>3	>7

Concentration of Compounds Showing a Negative Response

Each of the following compounds was added to drug free urine and gave negative EXTC results at the concentration listed for either 300 or 500 ng/mL cutoff :

Compound	**Concentration (µg/mL)**
Acetaminophen	1000
α-Acetyl- N, N-dinormethadol	25
L-α-Acetylmethadol (LAAM)	25
N-Acetylprocainamide (NAPA)	400
Acetylsalicylic Acid	1000
Albuterol	1000
p-Aminobenzoic Acid (PABA)	1000
Amitriptyline	10
Amoxicillin	100
Atenolol	1000
Benzoylecgonine	1000
Buprenorphine	100
Caffeine	1000
Carbamazepine	250
Carisoprodol	1000
Chlorpheniramine	100
Chlorpromazine	200
Cimetidine	1000
Clomipramine	2.5
Clonidine	1000
Codeine	500
L-Cotinine	100
Cyclobenzaprine	28
Desipramine	800
Dextromethorphan	1000
Dextrorphan	280
Diphenhydramine	1000
Doxepin	10
Doxylamine	500
L-Epinephrine	1000
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)	1000
Fenoprofen	1000
Fluoxetine	500
Furosemide	1000
Glutethimide	500
Ibuprofen	1000
Imipramine	750

Compound	Concentration (µg/mL)
Ketamine	100
Ketoprofen	1000
Ketorolac Tromethamine	350
Lidocaine	100
LSD	0.15
Meperidine HCl	1000
Mescaline	1500
Metaclopramide	1000
Methadone	1000
Methaqualone	1500
D,L-Methyldopa	1000
L-Methyldopa	1000
Monoethylglycinexylidide (MEGX)	1000
Morphine	1000
Nalmefene	20
Naloxone	500
Naproxen	1000
Nicotinic Acid	500
Nitroglycerin	1000
Noracetylmethadol	25
11-nor-Δ9-THC-9-COOH	100
Nortriptyline	300
Ofloxacin	100
Oxazepam	300
Paroxetine	5
Phencyclidine	1000
Phenelzine	100
L-Phenylcyclohexylamine (PCA)	50
Phenytoin	1000
Phthalic Acid	1000
L-Piperidinocyclohexane Carbonitrile	50
Procainamide	1000
Promethazine	1000
Propoxyphene	1000
Ranitidine	900
Sertraline	10
Scopolamine	500
Secobarbital	1000
Thioridazine	100
Tolmetin Sodium	2000
Tramadol	100

Compound	Concentration (µg/mL)
Trifluoperazine	100
Trimethobenzamide	500
Trimethoprim	500
Verapamil	1000
Zidovudine (AZT)	2000
Zolpidem	100
Sympathomimetic Amines	
Diethylpropion	1000
D,L-Isoproterenol	1000
Metaproterenol	10
Methylphenidate (Ritalin®)	1000
Phendimetrazine	400
Phenethylamine	20
Phenylephrine	20
Propylhexedrine	125
3-OH-Tyramine (dopamine)	300

Interference Testing

Each of the following compounds when added to urine containing methylenedioxymethamphetamine (MDMA) at +/- 25% concentration of the cutoff do not yield a false response relative to the 300 and 500 ng/mL cutoff levels:

Compound	Concentration
Acetone	1.0 g/dL
Ascorbic Acid	1.5 g/dL
Bilirubin	2.0 mg/dL
Creatinine	0.5 g/dL
Ethanol	1.0 g/dL
Gamma Globulin	0.5 g/dL
Glucose	2.0 g/dL
Hemoglobin	115 mg/dL
Human Serum Albumin	0.5 g/dL
Oxalic Acid	0.1 g/dL
Riboflavin	7.5 mg/dL
Sodium Chloride	6.0 g/dL
Urea	6.0 g/dL

f. Assay cut-off:

Characterization of how the device performs analytically around the claimed cutoff concentrations, 300 or 500 ng/mL, appears in the precision section, above.

2. Comparison studies:

a. Method comparison with predicate device:

300 ng/mL cutoff

138 urine specimens were tested with the EXTC Flex® cartridge on the Dimension® system (cutoff=300 ng/mL) and compared to results obtained by GC/MS and the 138 urine specimens were tested with the EXTC Flex® cartridge on the Dimension® system (cutoff=300 ng/mL) and compared to results obtained by GC/MS and the Syva® Emit® II Plus Ecstasy Assay (9X029UL) (on the SYVA®-30R Biochemical System - cutoff=300 ng/mL).

		GC/MS (cutoff 300 ng/mL MDMA, MDEA or MDA)	
		+	–
EXTC Flex® Reagent Cartridge on Dimension® clinical chemistry system (cutoff 300 ng/mL)	+	73	0
	–	4	61

Discrepants (ng/mL):

GC/MS MDMA	GC/MS MDA	GC/MS MDEA	Dimension® EXTC
310	0	0	60
350	68	0	132
349	0	0	245
313	30	0	278

		SYVA® -30R Biochemical system (cutoff 300 ng/mL)	
		+	–
EXTC Flex® Reagent Cartridge on Dimension® clinical chemistry system (cutoff 300 ng/mL)	+	70	3
	–	0	65

Discrepants (ng/mL):

GC/MS MDMA	GC/MS MDA	GC/MS MDEA	Dimension® EXTC	SYVA® 30R
529	0	0	381	279
503	0	0	342	249
302	0	0	311	221

Contingency table for Dimension® Urine Ecstasy Screen Flex® reagent cartridge 300 ng/mL cutoff

New Device	Negative by GC/MS or Predicate	Near cutoff Negative (between -50% and cutoff)	Near cutoff Positive (between cutoff and +50%)	GC/MS Positive (greater than +50%)	Percent Agreement with GC/MS
Positive	0	0	6	67	100%
Negative	51	10	4	0	94%

500 ng/mL cutoff

125 urine specimens were tested with the EXTC Flex® cartridge on the Dimension® system (cutoff=500 ng/mL) and compared to results obtained by GC/MS and the Syva® Emit® II Plus Ecstasy Assay (9X029UL) (on the SYVA®-30R Biochemical System - cutoff=500 ng/mL).

		GC/MS (cutoff 500 ng/mL MDMA, MDEA or MDA)	
		+	–
EXTC Flex® Reagent Cartridge on Dimension® clinical chemistry system (cutoff 500 ng/mL)	+	56	2
	–	4	63

Discrepants (ng/mL):

GC/MS MDMA	GC/MS MDA	GC/MS MDEA	Dimension® EXTC
503	0	0	316
503	0	0	365
529	0	0	369
545	0	0	407
451	0	0	532
464	0	0	600

		SYVA® -30R Biochemical system (cutoff 500 ng/mL)	
		+	–
EXTC Flex® Reagent Cartridge on Dimension® clinical chemistry system (cutoff 500 ng/mL)	+	55	3
	–	0	67

Discrepants (ng/mL):

GC/MS MDMA	GC/MS MDA	GC/MS MDEA	Dimension® EXTC	SYVA® 30R
451	0	0	532	464
813	0	0	502	435
464	0	0	600	442

Contingency table for Dimension® Urine Ecstasy Screen Flex® reagent cartridge 500 ng/mL cutoff

New Device	Negative by GC/MS or Predicate	Near cutoff Negative (between -50% and cutoff)	Near cutoff Positive (between cutoff and +50%)	GC/MS Positive (greater than +50%)	Percent Agreement with GC/MS
Positive	0	2	3	53	97%
Negative	55	8	4	0	94%

b. Matrix comparison:
Not applicable.

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.

K. Proposed Labeling:

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

L. Conclusion:

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