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

A. 510(k) Number:
k060791

B. Purpose for Submission:
The sponsor is adding a Methadone assay to a previously cleared device (k012745 and k043242) (see device description section).

C. Measurand:
Methadone in urine.

D. Type of Test:
Qualitative, Fluorescence Immunoassay

E. Applicant:
Biosite, Inc.

F. Proprietary and Established Names:
Triage® TOX Drug Screen (available in different configurations)

G. Regulatory Information:

1. Regulation section:
   862. 3620 – Methadone Test System

   2. Classification:
   II

3. Product code:
1 DJR

4. Panel:

   Toxicology (91)

H. Intended Use:

1. Intended use(s):
   See indications for use.

2. Indication(s) for use:
   The Triage TOX Drug Screen is a fluorescence immunoassay intended to be used

with the Triage Meters for the point-of-care qualitative determination of the presence of drug and/or the major metabolites above the threshold concentrations of up to 10 distinct drug classes, including assays for acetaminophen/paracetamol, amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, THC and tricyclic antidepressants in urine.

The acetaminophen/paracetamol assay will yield positive results when acetaminophen/paracetamol is ingested at or above therapeutic doses.

The threshold concentrations are provided below:

Acetaminophen/Paracetamol	APAP	5 µg/mL
Amphetamines	AMP	1000 ng/mL
Methamphetamines	mAMP	1000 ng/mL
Barbiturates	BAR	300 ng/mL
Benzodiazepines	BZO	300 ng/mL
Cocaine	COC	300 ng/mL
Methadone	MTD	300 ng/mL
Opiates	OPI	300 ng/mL
Phencyclidine	PCP	25 ng/mL
THC	THC	50 ng/mL
Tricyclic Antidepressants	TCA	1000 ng/mL

This test provides only preliminary test results. Clinical consideration and professional judgment must be applied to any drug of abuse test result, particularly in evaluating a preliminary positive result. In order to obtain a confirmed analytical result, a more specific alternate chemical method is needed. Gas Chromatography/Mass Spectroscopy (GC/MS) is the preferred confirmatory method.

A quantitative serum acetaminophen/paracetamol measurement is the common confirmatory method for preliminary positive acetaminophen/paracetamol results.

3. Special conditions for use statement(s):
   For prescription use.

4. Special instrument requirements:
   Triage® MeterPlus (cleared under k973547)

I. Device Description:

The Triage TOX Drug Screen is a single use test device and is used in conjunction with the Triage ® MeterPlus. The device contains murine monoclonal antibodies and drug substrates labeled with a fluorescent dye or immobilized on the solid phase and stabilizers. The testing device is inserted into and read by the Triage MeterPlus. Threshold concentrations are used to separate a negative result from a presumptive positive result.

No human source materials are used during the manufacturing of this product.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Triage® TOX Drug Screen

2. Predicate 510(k) number(s):
   k042342

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Principle	Fluorescence Immunoassay	Same
Antibody	Murine monoclonal fluorescent	Same
Instrument	Triage Tox Meter	Same

Differences		
Item	Device	Predicate
Analytes	Methadone, Acetaminophen, Amphetamines, Methamphetamines, Barbiturates, Cocaine, Opiates, PCP, THC, and TCA	Acetaminophen, Amphetamines, Methamphetamines, Barbiturates, Cocaine, Opiates, PCP, THC, and TCA

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

None referenced

L. Test Principle:

The Triage Tox Drug Screen is a competitive fluorescence immunoassay used for the qualitative determination of parent compound and major metabolites of drugs of abuse in urine specimens. A urine sample is added to the device and moves through a filter by capillary action into a reaction chamber. The sample is allowed to react with murine monoclonal fluorescent antibody conjugates in competition with fluorescent drug conjugates. After an incubation period, the reaction mixture flows through the device detection lane. The presence of drug or drug metabolite in the urine specimen prevents binding of the fluorescent conjugates to the solid phase on the detection zone. Unbound fluorescent conjugate is washed from the detection lane by excess urine. The concentration of the drug metabolite in the urine specimen is inversely related to the fluorescence bound to the detection zone. Cutoff concentrations are used to separate a negative result from a presumptive positive result.

M. Performance Characteristics (if/when applicable):

See k043242 for acetaminophen. See k012745 for amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates, phencyclidine, THC and tricyclic antidepressants.

1. Analytical performance:

a. Precision/Reproducibility:

The cutoff for methadone of 300 ng//mL was challenged by testing specimens containing the drug or drug metabolite spiked into drug-free urine at concentrations within 25% and 50% of the threshold. Each specimen was tested using the Triage Tox Drug Screen. The data paralleled the expected agreement based on the coefficient of variation of the assay. The results are presented in the table below:

	50% Below Cutoff	25% Below Cutoff	25% Above Cutoff	50% Above Cutoff
Concentration (ng/mL)	150	225	375	450
N	10	30	30	10
Positive	0	0	28	10
Negative	10	30	2	0
% Agreement	100%	100%	93%	100%

b. Linearity/assay reportable range:

Not applicable.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Users are instructed to run external controls with each new lot or shipment of test materials, or every 30 days, and as otherwise required by federal, state or local guidelines. Commercial control materials are required but are not specifically identified in the labeling.

Each device has internal process controls which run with every sample. The controls monitor various procedural and functional parameters such as sufficient sample added to the test device and that the unbound fluorescent label has been washed sufficiently from the detection zone. During testing if the results are within the limits the results are reported. If the results are not within the limits the results are not reported and an error message will be displayed.

Real time stability studies have been conducted. Protocols and acceptance criteria were described and found to be acceptable. The manufacturer claims the following expiration date:

When stored at 2-8˚C product is good until expiration date which is 3 months. Real time studies are ongoing and the sponsor will extend the shelf-life as appropriate. Once removed from refrigeration, the pouched test device is stable for up to 14 days.

d. *Detection limit:*
Cutoff validation and sensitivity were evaluated. Four contrived samples were prepared by adding methadone to drug-free urine at concentrations ±25% and ±50% of the 300 ng/mL cutoff concentration. Samples at ±25% were measured 30 times and samples at ±50% were measured 10 times using the Triage TOX Drug Screen. The results of the study are presented in the table below.

Methadone Cutoff Validation

	0.5x	0.75x	1.25x	1.5x
POS	0/10	0/30	28/30	10/10
NEG	10/10	30/30	2/30	0/10
% Agreement	100%	100%	93%	100%

e. *Analytical specificity:*
Potential interfering substances were added to samples containing methadone at 25% above and below the cutoff concentration. Potential cross-reacting substances were added to drug-free urine. Samples were measured in duplicate. The substances did not interfere or cross-react with the methadone assay at the concentrations listed below:

Interfering Substances

Substance	Concentration	Substance	Concentration
Acetone	5 mg/mL	Hemoglobin	1.2 mg/mL
Acetylsalicylic Acid	1 mg/mL	Human Serum Albumin	5 mg/mL
Ascorbic Acid	15 mg/ml	Ibuprofen	1 mg/mL
Bilirubin	2.5µg/mL	Ketamine	25 µg/mL
Caffeine	0.125 mg/mL	Oxalic Acid	10 mg/mL
Creatinine	2.5 mg/mL	Riboflavin	75µg/mL
Dextrose	20 mg/mL	Scopalamine	62.5 µg/mL
Ethanol	5 mg mL	Sodium Chloride	30 mg/mL
Fluoxetine	0.5 mg/mL	Urea	30 mg/mL
Gamma Globulin	5 mg/mL		

Cross-Reacting Substances

Substance	Concentration	Substance	Concentration
Acetopromazine	100 µg/mL	Methoxyphenamine	100 µg/mL
Benzphentamine	100 µg/mL	Methylphenidate	100 µg/mL
Benztropine Methane	100 µg/mL	Naloxone	80 µg/mL
Bupropin	100 µg/mL	Naproxen	100 µg/mL
Butyrophenine	100 µg/mL	Norpsuedoephedrine	100 µg/mL
Cimetidine	100 µg/mL	Phenethylamine	100 µg/mL
Clonidine	100 µg/mL	Phenmetrazine	100 µg/mL
Cotinine	100 µg/mL	Phenylephrine	100 µg/mL
Dextromethorphan	100 µg/mL	Phenylhydantoin, d/l-5(p-hydroxyphenyl)-5-	100 µg/mL
Dextrorphan	100 µg/mL	Phenylpropanolamine	100 µg/mL
Diphenhydramine	100 µg/mL	Promrthazine	100 µg/mL
Dopamine	100 µg/mL	Propanolol, d/l	100 µg/mL
Epinephrine, 1-	100 µg/mL	Propoxyphene	100 µg/mL
Fenfluramine	20 µg/mL	Pseudoephedrine, d-	100 µg/mL
Glutethimide	100 µg/mL	Quinacrine	100 µg/mL
KetorolacTromethane	100 µg/mL	Ranitidine	100 µg/mL
Levorphanol	50 µg/mL	Thioridazine	100 µg/mL
Meperidine	100 µg/mL	Tramadol	100 µg/mL
Mesoridazine	100 µg/mL	Tyamine	60 µg/mL
Methadone d/l	100 µg/mL	Tranylcypromine	100 µg/mL
Methaqualone	100 µg/mL	Zolpidem	100 µg/mL

Cross-reactivity was established by spiking various concentrations of similarly-structured drug compounds into drug-free urine. The concentration

of each compound was determined gravimetrically. Six replicates of each compound were evaluated. By analyzing various concentrations of similarly-structured drug compounds, the sponsor determined the concentration of the drug that produced a response equivalent to the cutoff concentration of the assay. The results of these studies appear in the table below..

Cross Reactivity with Related Compounds

Compounds	Conc. ng/mL	X-reactivity
I-Methadone	1.75	Positive
d-methadone	14,000	Positive
d/l-methadone	300	Positive

Methadone was added at 75% and 125% of the cutoff concentration to urine samples with specific gravities ranging from 1.006 – 1.025 and to urine samples with the pH ranging from 4.5 – 8.0. Twenty (20) replicates of each sample were measured using the Triage TOX Drug Screen. There was no effect of specimen specific gravity or pH on the methadone assay results.

f. Assay cut-off:

Characterization of the analytical performance around the claimed cutoff concentration appears in precision and sensitivity sections, above.

The cutoff concentration of this qualitative assay was arbitrarily chosen by the sponsor. There is no known clinical significance regarding the cutoff concentration. It indicates only that the analyte was or was not present at that level.

2. Comparison studies:

a. Method comparison with predicate device:

One hundred and two clinical urine (102) specimens were tested with the Methadone TOX Drug Screen and compared to a Gas Chromatography/Mass Spectrophotometer (GC/MS). Sixty one (61) of the 102 specimens were neat samples. Forty one (41) of the 102 were diluted once to obtain data around the cutoff. All of the Triage TOX Drug Screen positive, GC/MS negative samples contained measurable amounts of methadone (>100 ng/ml), and 8 of the 9 samples contained concentrations greater than the threshold value established for l-methadone of 175 ng/mL.

Results from the study are presented below. The table describes the agreement between the device and the GC/MS.

All Samples

Triage TOX Drug Screen + MTD Result	Low Negative by GC/MS (less than -50%	Near Cutoff Negative (between -50% and cutoff)	Near Cutoff Positive (between cutoff and +50%)	High Positive (greater than +50%)	Percent Agreement With GC/MS
Positive	0	9	14	31	
Negative	44	4	0	0	
Percent Agreement with GC/MS					**93/102 91.2%**

Neat Samples

Triage TOX Drug Screen + MTD Result	Low Negative by GC/MS (less than -50%	Near Cutoff Negative (between -50% and cutoff)	Near Cutoff Positive (between cutoff and +50%)	High Positive (greater than +50%)	Percent Agreement With GC/MS
Positive	0	2	7	30	
Negative	21	1	0	0	
Percent Agreement with GC/MS					**59/61 96.7%**

Diluted Samples

Triage TOX Drug Screen + MTD Result	Low Negative by GC/MS (less than -50%	Near Cutoff Negative (between -50% and cutoff)	Near Cutoff Positive (between cutoff and +50%)	High Positive (greater than +50%)	Percent Agreement With GC/MS
Positive	0	7	7	1	
Negative	23	3	0	0	
Percent Agreement with GC/MS*					**34/41 82.9%**

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:

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.