MEDTOX® BUPRENORPHINE

MEDTOX® Buprenorphine is a rapid qualitative screening test for buprenorphine and its metabolites in human urine.

1. INTENDED USE

The MEDTOX Buprenorphine Test uses immunochromatographic test strips for the rapid, qualitative detection of buprenorphine and its metabolites in human urine. It is intended for prescription use only. The MEDTOX Buprenorphine Test is not for over-the-counter sale. It is not intended for use in point-of-care settings.

MEDTOX Buprenorphine detects buprenorphine and its metabolites at the following cutoff concentrations:

BUP	Buprenorphine (Buprenorphine)	10 ng/mL

The MEDTOX Buprenorphine Test provides only a preliminary analytical test result. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result. Liquid chromatography/tandem mass spectrometry (LC/MS/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be applied to any test result.

2. SUMMARY AND EXPLANATION OF THE TEST

The qualitative MEDTOX Buprenorphine Test utilizes a solid phase immunoassay technology to provide a very rapid test requiring no instrumentation. This test may be used to screen human urine samples for the following drug class prior to confirmatory testing:

Buprenorphine (BUP) is a potent analgesic often used in the treatment of opiate abusers.

Many factors influence the length of time required for drugs to be metabolized and excreted in the urine. A variety of factors influence the time period during which drugs are detected; the rate of urine production, the volume of fluid consumption, the amount of drug taken, the urine pH, and the length of time over which drug was consumed. Drinking large volumes of liquid or using diuretics to increase urine volume lowers the drug concentration and decreases the detection period. Although the detection period for these drugs varies widely depending upon the compound taken, dose and route of administration and individual rates of metabolism, some general times have been established and are listed below.[1-3]

Drug	Detection Period
Buprenorphine	up to 3 days

3. PRINCIPLES OF THE PROCEDURE

The MEDTOX Buprenorphine Test contains a device with rapid, competitive, membrane-based immunochromatographic test strips. A single urine sample can be evaluated for the presence of buprenorphine in a single device. Each test strip contains antibody colloidal gold, a drug conjugate and a control line.

ANTIBODY-COLLOIDAL GOLD – Mouse monoclonal antibodies were developed specifically targeted to the drug buprenorphine. The antibody only binds buprenorphine and its metabolites. Antibody-colloidal gold solutions were prepared by absorbing the monoclonal antibodies to colloidal gold. The colloidal gold solution was applied to the sample well pads on the test strip.

DRUG-CONJUGATES – The drug buprenorphine is conjugated to protein and immobilized as a line on a membrane at the BUP location labeled on the device.

CONTROL LINE – Each test strip has anti-mouse immunoglobulin antibodies immobilized as a line on the membrane at the CTRL location labeled on the device. The anti-mouse immunoglobulin antibodies bind the mouse antibodies coated on the colloidal gold.

Drug in the urine and the drug conjugated to the protein compete to bind to the antibody-colloidal gold. When the urine sample is placed in the sample well(s), the dried antibody-colloidal gold on the sample pad dissolves and the urine wicks up the white test strips carrying the red antibody-colloidal gold with it.

Negative Samples
When no drug(s) is present in the urine sample, the red antibody-colloidal gold migrates up the test strip and binds to the drug conjugate immobilized on the membrane. The binding of the antibody-colloidal gold to the drug conjugate generates an easily visible reddish-purple line at the BUP location on the device. Negative results can be reported as soon as a test line and a control line are visible.

Non-Negative Samples
When a drug is present in the sample the antibody-colloidal gold binds the drug before it migrates up the test strip. However, when the antibody-colloidal gold binds the drug in the urine, the antibody-colloidal gold cannot bind to the drug conjugate immobilized on the test strip. When the drug concentration is at or above the cutoff concentration, the majority of the antibody colloidal gold is bound to the drug from the urine. Therefore, as drug bound antibody-colloidal gold migrates up the test strip, it is unable to bind to the drug conjugate immobilized on the membrane. Therefore, no line is generated at the BUP location on the device for a non-negative sample. Read non-negative results at 5 minutes. The control line should be present for the test to be valid.

Control Line
Each test strip has an internal procedural control. A line must form at the control (CTRL) location on the device to indicate that the reagents are migrating properly. If a control line does not form, the test is considered invalid. A control line forms when the antibody-colloidal gold binds to the anti-mouse immunoglobulin antibody immobilized on the membrane as a line at the CTRL location on the device.

4. MATERIALS PROVIDED/STORAGE CONDITIONS

Each MEDTOX Buprenorphine Test contains all the reagents necessary to test one urine sample for buprenorphine.

1. The test device contains one test strip composed of a membrane strip coated with drug conjugate and a pad coated with antibody dye complexes in a protein matrix.
2. One disposable 100 µl sample pipette.

Kit Contents
1. Twenty-five (25) test devices in individual foil packages containing a sample pipette
2. One instructional package insert

Materials Required but not provided
1. Urine collection container
2. Timer
3. External positive and negative controls

Storage Conditions
The kit, in its original packaging, should be stored at 2-25°C (36-77°F) until the expiration date on the label.

5. PRECAUTIONS

1. Urine specimens and all materials coming in contact with them should be handled and disposed of as if infectious and capable of transmitting infection. Never pipette by mouth and avoid contact with broken skin.
2. Avoid cross-contamination of urine samples by using a new urine specimen container and pipette for each urine sample.
3. The device should remain in its original sealed foil pouch until ready to use. If the pouch is damaged, do not use the test.
4. Do not store the test kit at temperatures above 25°C (77°F).
5. If devices have been stored refrigerated, bring to ambient temperature (18-25°C/ 64-77°F) prior to opening foil pouch.
6. Do not use tests after the expiration date printed on the package label.
7. The device is for in vitro diagnostic use only.
8. If any of the lines formed are outside the arrow indicated by the drug name, the test is invalid.

6. SAMPLE COLLECTION AND PREPARATION

The urine sample should be collected in a clean glass or plastic container. Approximately 100 µL is required for each sample well. Collection of 45 mL of urine is more than sufficient for initial and subsequent testing. No preservatives should be added. Urine may be tested immediately following collection. The specimen may be refrigerated if testing is going to be delayed for more than a day. Urine may be frozen for longer storage. Stored urine must be brought to ambient temperature (18 to 25°C/64 to 77°F) and mixed well to assure a homogeneous sample prior to testing.

7. TEST PROCEDURE

1. Open one pouch for each sample to be tested and label the device with the patient or sample identification (ID).
   (You may notice a reddish-purple color in the sample well. This is normal, do not discard the test).

2. Apply 100 µl of urine to sample well as follows:
   - Hold the 100 µl sample pipette by the upper bulb.
   - Lower the pipette stem into the urine sample.
   - Squeeze the upper bulb then release it. This motion will draw 100 µl of urine into the stem. The urine sample should reach the top of the stem, and a drop or two should overflow into the middle bulb, if not, repeat this process.
   - Dispense the urine into the sample well by squeezing the upper bulb. This will empty the stem delivering 100 µL of sample. Excess urine in the middle bulb should remain in the bulb.
3. Read the results at 5 minutes or within 15 minutes of the sample application.

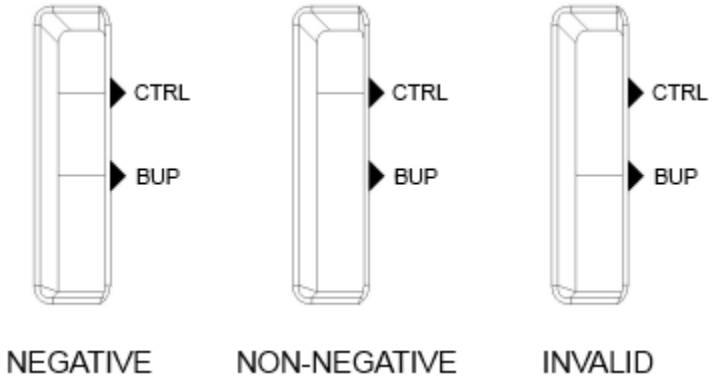
8. READING THE TEST RESULTS

Negative: The appearance of a reddish purple line at both the control area (CTRL) and test area (BUP) indicates a negative test result. The color intensities of the control line and test line may not be equal and may vary from test to test. The test line and control line positions may vary slightly from test strip to test strip. Any line of reddish-purple color, even of faint intensity, indicates a negative test result**.**

Non-Negative: The appearance of a control line and the absence of a test line indicate a preliminary positive test result for that drug.

Invalid: The control line must be present for the test to be valid. The absence of a control line indicates the test is invalid. The urine sample should be retested on a new device.

Examples of Negative, Non-Negative and Invalid results:



9. INTERPRETATION OF TEST RESULTS

A NEGATIVE test result for a specific drug indicates that the sample does not contain the drug/drug metabolite above the cutoff level.

A NON-NEGATIVE test result for a specific drug indicates that the sample may contain drug/drug metabolite near or above the cutoff level. It does not indicate the level of intoxication or the specific concentration of drug in the urine sample. Non-negative samples should be sent to a reference laboratory for more definitive testing.

10. QUALITY CONTROL

An internal procedural control is included on each test strip. A line must form at the control (CTRL) position on the test strip to indicate that adequate sample volume has been added, the reagents migrated properly, and the test strip is intact. If a control line does not form, the test is considered invalid. The control line consists of immobilized anti-mouse antibody that reacts with the antibody-colloidal gold as it passes this region of the membrane. Formation of a visible line verifies the control line antibody antigen reaction occurred. A visible control line should always be present regardless of whether drug is absent or present in the sample. Minimally, a QC program includes external negative and positive control material used to monitor the performance of each new lot of product, each new shipment of product and as otherwise required by your laboratory's standard quality control procedures.

For additional information concerning QC testing requirements, contact the appropriate regulatory authority. Users should follow federal, state, and local QC requirements.

11. LIMITATIONS OF THE PROCEDURE

1. The MEDTOX Buprenorphine Test is only for use with unadulterated human urine samples.
2. There is a possibility that other substances and/or factors, e.g. technical or procedural errors, may interfere with the test and cause false results.
3. A preliminary positive test result may only indicate presence of drug or metabolite. The cutoff concentration is not designed to distinguish between presence of the drug (at prescribed concentrations) and drug abuse or overdose.
4. There is a possibility that metabolites of other opiate drugs, or certain foods may interfere with this type of test.

12. EXPECTED VALUES

The MEDTOX Buprenorphine Test qualitatively detects buprenorphine and/or its metabolites in human urine at or above the specified cutoff levels. Buprenorphine is a legal drug and may appear in the urine for legitimate reasons.

13. PERFORMANCE CHARACTERISTICS

13A. Sensitivity, Accuracy, and Precision

Accuracy

The accuracy was evaluated by assaying a panel of blind coded clinical urine samples containing varying concentrations of buprenorphine and/or norbuprenorphine and comparing to LC/MS/MS results. The samples were obtained from MEDTOX Laboratories. Samples were screened with the CEDIA immunoassay system. Ten percent of samples with negative results by both the commercial immunoassay system and MEDTOX Buprenorphine were confirmed by LC/MS/MS. Samples with positive results by either the commercial immunoassay system or MEDTOX Buprenorphine were confirmed by LC/MS/MS. The five minute results are shown in the following tables, but identical results were obtained at fifteen minutes. The testing was performed by MEDTOX personnel.

ACCURACY COMPARED TO LC/MS/MS

5 Minute Test Result	Negative by immunoassay; if positive, no drug was detected above the limit of detection of the confirmatory method	Concentration range between -50% of the cutoff and the cutoff	Concentration range between the cutoff and 50% above the cutoff	Concentration range of greater than 50% above the cutoff
BUP Level		5 – 10 ng/mL	11 – 15 ng/mL	15 – 50042 ng/mL
Positive	0	3	8	72
Negative	70	4	0	0
Buprenorphine and norbuprenorphine were added together to determine the total buprenorphine concentration reported in the table.				
Overall agreement 98.1% (154/157). The three discrepant results had concentrations of total buprenorphine of 5, 7, and 9 ng/mL.				

Sensitivity/Precision
Performance around the cutoff for MEDTOX Buprenorphine was evaluated by testing standard drug solutions diluted in drug-free urine in triplicate on 5 different intervals by 3 in-house operators. Drug-free urine was also tested on each interval. The results were interpreted at five minutes.

Buprenorphine (Buprenorphine) Cutoff = 10 ng/mL			
Conc. (ng/mL)	Number Tested	Positive	Negative
0	45	0	45
2.5	45	0	45
5	45	0	45
7.5	45	17	28
12.5	45	41	4
15	45	45	0

13B. Non-Crossreactive Endogenous Compounds
The endogenous compounds were tested following the study of M.L. Smith, et. al.[4] Drug free urine samples were spiked with buprenorphine to the targeted concentrations of 5 ng/mL (50% of the cutoff) and 15 ng/mL (150% of the cutoff). Most of the compounds were evaluated for interference of the MEDTOX Buprenorphine Test at 100 µg/mL (albumin was evaluated at 20 mg/mL and bilirubin was evaluated at 200 µg/mL). Samples were evaluated in triplicate by in-house operators. None of the endogenous compounds listed below affected the expected results.

Acetaldehyde	Creatinine	Sodium Chloride
Acetone	Epinephrine	Tetrahydrocortisone
Albumin, Human	β-Estradiol	d,1-Thyroxine
Ascorbic acid	Estriol	Uric Acid
Bilirubin	Glucose Std. Solution	
Cholesterol	Hemoglobin, Human	

13C. Related and Reactive Compounds
The following metabolites and reacting compounds were evaluated in the MEDTOX Buprenorphine Test. Reference standards for the various metabolites and compounds were prepared in negative urine samples. Results are expressed as the minimum concentration expected to produce a positive result in the indicated assay. Compounds that reacted with the test are listed first, and related compounds that did not react with the highest concentration tested are listed second as Negative at 100,000 ng/mL (or highest level tested). The non-reacting opiate compounds were also tested following the study of M.L. Smith, et. al.[4] Drug free urine samples were spiked with buprenorphine to the targeted concentrations of 5 ng/mL (50% of the cutoff) and 15 ng/mL (150% of the cutoff). 100 µg/mL of the non-reactive opiate compounds were then added to the preparation and assayed by MEDTOX Buprenorphine Test. Samples were evaluated in triplicate by in-house operators. None of the non-reactive opiate listed in the following table affected the expected results.

Buprenorphine-(BUP) (Buprenorphine) 10ng/mL	**Result** Positive at 10 ng/mL	**% Cross-Reactive** 100%
Buprenorphine-glucuronide	Positive at 7.5 ng/mL	133%
Norbuprenorphine	Positive at 50 ng/mL	20%
Norbuprenorphine-glucuronide	Positive at 75 ng/mL	13%
Codeine	Negative at 100,000 ng/mL	None Detected
Diacetylmorphine	Negative at 100,000 ng/mL	None Detected
Hydrocodone	Negative at 100,000 ng/mL	None Detected
Hydromorphone	Negative at 100,000 ng/mL	None Detected
Levorphanol	Negative at 50,000 ng/mL	None Detected
6-Monoacetylmorphine	Negative at 100,000 ng/mL	None Detected
Morphine	Negative at 100,000 ng/mL	None Detected
Nalbuphine	Negative at 100,000 ng/mL	None Detected
Naloxone	Negative at 100,000 ng/mL	None Detected
Naltrexone	Negative at 100,000 ng/mL	None Detected
Norcodeine	Negative at 100,000 ng/mL	None Detected
Noroxycodone	Negative at 100,000 ng/mL	None Detected
Noroxymorphone	Negative at 100,000 ng/mL	None Detected
Oxycodone	Negative at 100,000 ng/mL	None Detected
Oxymorphone	Negative at 100,000 ng/mL	None Detected
Thebaine	Negative at 100,000 ng/mL	None Detected

13D. Interference

pH and Specific Gravity:
The MEDTOX Buprenorphine Test was assayed with four negative clinical samples with pH values of 5.0, 6.0, 7.0, and 8.0 ± 0.1. Each sample was assayed in triplicate. The pH samples were fortified with buprenorphine to the concentrations of 5 ng/mL and 15 ng/mL. All the pH levels gave negative results when fortified to 5 ng/mL, and all pH levels gave positive results when fortified to 15 ng/mL.

The MEDTOX Buprenorphine Test was assayed with three samples with specific gravity values of 1.003, 1.015, and 1.030 ± 0.001. Each sample was assayed in triplicate. The specific gravity samples were fortified with buprenorphine to the concentrations of 5 ng/mL and 15 ng/mL. All the specific gravity levels gave negative results when fortified to 5 ng/mL, and all specific gravity levels gave positive results when fortified to 15 ng/mL.

Common Drugs:
The common drugs were tested following the study of M.L. Smith, et. al.[4] Drug free urine samples were spiked with buprenorphine to the targeted concentrations of 5 ng/mL (50% of the cutoff) and 15 ng/mL (150% of the cutoff). 100 µg/mL of the common drugs were then added to the preparation and assayed by the MEDTOX Buprenorphine Test. Samples were evaluated in triplicate by in-house operators. None of the common drugs listed in the following table affected the expected results.

COMMON DRUGS EVALUATED WITH MEDTOX BUPRENORPHINE TEST

Acetylsalicylic Acid	Cocaine	Phenobarbital
Acetaminophen	Dextromethorphan	d-Pseudoephedrine
Amitriptyline	Diphenylhydantoin	Rifampin
Brompheniramine maleate	Doxylamine	Salicylic Acid
Caffeine	Fluoxetine	Vancomycin
Carbamazepine	Ibuprofen	
Chlorpheniramine	Morphine	

14. BIBLIOGRAPHY

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15. LIMITED EXPRESS WARRANTIES

The manufacturer makes no express warranty other than the diagnostic test kit will measure certain drugs and/or drug metabolites when used in accordance with the manufacturer's printed instructions. The use of the kit for any other purpose is outside the intended use of this product. The manufacturer gives no express warranty as to what the legal or clinical significance of the level of drug/drug metabolites detected by the MEDTOX test. The manufacturer disclaims any and all implied warranties of merchantability, fitness for use or implied utility for any other purposes. Any and all damages for failure of the kit to perform to its instructions are limited to the replacement value of the kit.

Covered by one or more patents.
U.S. Patent Nos. 6,566,051, 6,376,251, 6,653,139
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