

ARK™ Fentanyl II Assay

This ARK Diagnostics, Inc. package insert for the ARK Fentanyl II Assay must be read prior to use. Package insert instructions must be followed accordingly. The assay provides a simple and rapid analytical screening procedure for detecting Fentanyl in urine. Reliability of the assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

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KEY TO SYMBOLS USED

| | | | |
|--|------------------------------|---|---|
|  | Batch code |  YYYY-MM-DD | Use by/Expiration date |
|  | Catalog Number |  | Manufacturer |
|  | Authorized Representative |  | CE Mark |
|  | Consult Instructions for Use |  | Reagent 1/ Reagent 2 |
|  | Temperature limitation |  | <i>In Vitro</i> Diagnostic Medical Device |
| Rx Only | For Prescription Use Only | | |

1 NAME

ARK™ Fentanyl II Assay

2 INTENDED USE

The ARK Fentanyl II Assay is an immunoassay intended for the qualitative detection of fentanyl in human urine at a cutoff concentration of 1.0 ng/mL. The assay is intended for use in laboratories with automated clinical chemistry analyzers. This *in vitro* diagnostic device is for prescription use only.

The ARK Fentanyl II Assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used in order to obtain a confirmed positive analytical result. Gas Chromatography/Mass Spectrometry (GC/MS) or Liquid Chromatography/tandem Mass Spectrometry (LC-MS/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be exercised with any drug test result, particularly when the preliminary test result is positive.

3 SUMMARY AND EXPLANATION OF THE TEST

Fentanyl [N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylpropanamide] is a synthetic opioid narcotic analgesic similar to morphine.¹ Fentanyl is 50-100 times more potent than morphine. It is prescribed for patients with chronic pain and is used to manage pain after surgery or for treatment of breakthrough pain in cancer patients.² Fentanyl is prescribed in various forms: by injection (intravenous or intramuscular), transdermal patch³, and orally (transmucosal lozenge or film). Fentanyl such as the transdermal system can be abused in a manner similar to other opioid agonists, legal or illicit. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

Fentanyl has high potency and short duration of action, and it is abused for its intense euphoric effects. It is very dangerous when substituted illicitly for other opioids because of its potency and overdoses can lead to respiratory depression and death.^{4,5} It is a Schedule II substance under the U.S. Controlled Substances Act.



The ARK Fentanyl II Assay detects fentanyl in human urine. The test is not intended to differentiate between drugs of abuse and prescription use of fentanyl. There are no uniformly recognized drug levels for fentanyl in urine.

The primary metabolism of fentanyl leads to the time-dependent urinary excretion of fentanyl and norfentanyl.^{6,8} The half-life of fentanyl may range 3 - 12 hours. Fentanyl is exclusively metabolized by N-dealkylation and hydroxylation. More than 90% of the dose is eliminated as norfentanyl and hydroxylated metabolites. Less than 7% of the dose is excreted unchanged in the urine.

4 PRINCIPLES OF THE PROCEDURE

The ARK Fentanyl II Assay is a homogeneous enzyme immunoassay technique used for the analysis of a specific compound in human urine. The assay is based on competition between drug in the specimen and drug labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH) for antibody binding sites. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly related to the drug concentration. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH in the presence of glucose-6-phosphate (G6P), resulting in an absorbance change that is measured spectrophotometrically. Endogenous G6PDH does not interfere because the coenzyme NAD functions only with the bacterial enzyme used in the assay.

5 REAGENTS

| REF | Product Description | Quantity/Volume |
|--------------|--|-----------------|
| 5069-0001-00 | ARK Fentanyl II Assay Reagent  – Antibody/Substrate Rabbit monoclonal antibodies to fentanyl, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers | 1 X 28 mL |
| | Reagent  – Enzyme Fentanyl derivative labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH), bovine serum albumin, buffer, sodium azide and stabilizers | 1 X 28 mL |

Reagent Kit  5069-0001-00

Reagent Kit  5069-0001-01

Reagent Kit  5069-0001-02

| REF | Product Description | Quantity/Volume |
|--------------|---|-----------------|
| 5069-0001-01 | ARK Fentanyl II Assay Reagent [R1] – Antibody/Substrate Rabbit monoclonal antibodies to fentanyl, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers | 1 X 115 mL |
| | Reagent [R2] – Enzyme Fentanyl derivative labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH), bovine serum albumin, buffer, sodium azide and stabilizers | 1 X 115 mL |

| REF | Product Description | Quantity/Volume |
|--------------|---|-----------------|
| 5069-0001-02 | ARK Fentanyl II Assay Reagent [R1] – Antibody/Substrate Rabbit monoclonal antibodies to fentanyl, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers | 1 X 500 mL |
| | Reagent [R2] – Enzyme Fentanyl derivative labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH), bovine serum albumin, buffer, sodium azide and stabilizers | 1 X 500 mL |

Reagent Handling and Storage

ARK Fentanyl II Assay reagents are provided liquid, ready to use and may be used directly from the refrigerator. When not in use, reagents must be stored at 2–8°C (36–46°F), upright and with screw caps tightly closed. If stored as directed, reagents are stable until the expiration date printed on the label. Do not freeze reagents. Avoid prolonged exposure to temperatures above 32°C (90°F). **Improper storage of reagents can affect assay performance.**

ARK Fentanyl II products contain ≤0.09% sodium azide. As a precaution, affected plumbing including instrumentation should be flushed adequately with water to mitigate the potential accumulation of explosive metal azides. No special handling is required regarding other assay components.

6 WARNINGS AND PRECAUTIONS

- For *In Vitro* Diagnostic Use. For prescription use only. *Caution: Federal Law restricts this device to sale by or on the order of a licensed practitioner.*
- Reagents [R1] and [R2] are provided as a matched set and should not be interchanged with reagents from different lot numbers.
- Do not use reagents after the expiration date.
- Reagents contain ≤0.09% sodium azide.

7 SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

- Human urine is required. Treat as potentially infectious material.
- Collect urine using standard sampling cups and procedures. Care should be taken to preserve the chemical and physical integrity of the urine sample from the time it is collected until the time it is assayed, including during transport. Fresh urine specimens are suggested.
- Cap the urine sample immediately after collection, store refrigerated at 2–8°C (36–46°F) and assay within 7 days after collection. If the assay cannot be performed within 7 days, store the urine sample frozen at -20°C for up to 6 months prior to analysis.^{9,10,11,12}
- To protect the integrity of the sample, do not induce foaming and avoid repeated freezing and thawing.
- Frozen specimens must be thawed and mixed thoroughly prior to analysis.
- Centrifuge specimens with high turbidity or visible particulate matter before testing.
- The recommended pH range for urine specimens is 4.0 – 11.0¹³.
- Obtain another sample for testing if adulteration of the sample is suspected. Adulteration of urine specimens can affect the test result.

8 PROCEDURE

Materials Provided

ARK Fentanyl II Assay – [REF] 5069-0001-00, 5069-0001-01 or 5069-0001-02

Materials Required – Provided Separately

ARK Fentanyl Calibrator A (Negative) – [REF] 5031-0002-01

ARK Fentanyl Calibrator B (Cutoff) – [REF] 5031-0002-02

Quality Controls – ARK Fentanyl Control – [REF] 5031-0003-00

Instruments

Reagents [R1] and [R2] may need to be transferred to analyzer-specific reagent containers prior to use. Avoid cross-contamination of [R1] and [R2]. Refer to the instrument-specific operator's manual for daily maintenance. Consult the analyzer-specific application sheet for programming the fentanyl assay or contact Customer Support.

Assay Sequence

To run or calibrate the assay, see the instrument-specific operator's manual.

Qualitative Results

Use the 1.0 ng/mL Calibrator B as a Cutoff Calibrator to distinguish negative and positive samples. Run the Low and High Controls as Negative and Positive respectively. Report test results less than the rate (mA/min) value for the Cutoff Calibrator as Negative. Report results equal to or greater than the rate (mA/min) value for the Cutoff Calibrator as Positive.

When to Re-Calibrate

- Whenever a new lot number of reagents is used
- Whenever indicated by quality control results
- Whenever required by standard laboratory protocols

Quality Control (QC) and Calibration

Laboratories should establish QC procedures for the ARK Fentanyl II Assay. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or accreditation requirements.

Each laboratory should establish its own ranges for each new lot of controls. Control results should fall within established ranges as determined by laboratory procedures and guidelines. The ARK Fentanyl Control is intended for use in quality control of the ARK Fentanyl II Assay.

The Low Control should be Negative and the High Control should be Positive relative to the 1.0 ng/mL Cutoff Calibrator.

9 RESULTS AND EXPECTED VALUES

The actual fentanyl concentration cannot be determined. A confirmatory method is required.

Qualitative Analysis - Negative Results

A specimen that gives a rate (mA/min) value less than the ARK Fentanyl Calibrator B Cutoff rate (mA/min) value is interpreted as negative; either the specimen does not contain fentanyl or fentanyl is present in a concentration below the cutoff level of this assay.

Qualitative Analysis - Positive Results

A specimen that gives a rate (mA/min) value equal to or greater than the ARK Fentanyl Calibrator B Cutoff rate (mA/min) value is interpreted as positive, indicating that fentanyl is present.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

10 LIMITATIONS

- The assay is designated for use with human urine only.
- ARK Fentanyl II Assay reagents, and ARK Fentanyl calibrators and controls were developed as companion products. Performance with substituted products cannot be assured.
- A positive result using the ARK Fentanyl II Assay indicates only the presence of fentanyl and does not necessarily correlate with the extent of physiological and psychological effects.
- Do not use Boric Acid as a preservative.**
- Interpretation of results must take into account that urine concentrations can vary extensively with fluid intake and other biological variables.
- It is possible that substances other than those tested in the specificity study may interfere with the test and cause false results.

11 SPECIFIC PERFORMANCE CHARACTERISTICS

The following performance characteristics were collected on the Beckman Coulter AU680® automated clinical chemistry analyzer using the ARK Fentanyl II Assay.

Precision

Drug-free, negative human urine was supplemented with fentanyl (0.00 to 2.00 ng/mL). Each level was assayed in quadruplicate twice a day for 20 days (N=160). Results are summarized in the table below.

| Human Urine (ng/mL) | Relative % Cutoff | # of Results | Results |
|---------------------|-------------------|--------------|--------------------------|
| 0.00 | -100 | 160 | 160 Negative |
| 0.25 | -75 | 160 | 160 Negative |
| 0.50 | -50 | 160 | 160 Negative |
| 0.75 | -25 | 160 | 160 Negative |
| 1.00 | Cutoff | 160 | 84 Negative; 76 Positive |
| 1.25 | +25 | 160 | 160 Positive |
| 1.50 | +50 | 160 | 160 Positive |
| 1.75 | +75 | 160 | 160 Positive |
| 2.00 | +100 | 160 | 160 Positive |

Analytical Specificity

All compounds tested were added to drug-free, negative human urine.

The cross-reactivity of the following metabolites and structural analogs of fentanyl was evaluated by spiking these compounds into drug-free, negative human urine and evaluated by dose-response to determine the approximate equivalence to the 1.0 ng/mL fentanyl cutoff. These concentrations were used to determine the percent cross-reactivity according to the formula:

% Cross-reactivity = (Cutoff concentration / Concentration approximately equivalent to the 1.0 ng/mL cutoff) X 100

For the compounds Alfentanil and Remifentanil that did not produce a positive result, the highest concentration tested was used to calculate percent cross-reactivity.

Cross-reactivity

For the major metabolite, norfentanyl, the lowest concentration capable of producing a positive result is shown below.

Norfentanyl (Major Metabolite)

| Compound | Concentration Approximately Equivalent to the Cutoff (ng/mL) | Percent Cross-reactivity (%) |
|-------------|--|------------------------------|
| Norfentanyl | 15 | 7 |

Other Metabolites and Structural Analogs of Fentanyl

| Compound | Concentration Approximately Equivalent to the Cutoff (ng/mL) | Percent Cross-reactivity (%) |
|-----------------------------------|--|------------------------------|
| Acetyl fentanyl | 1.1 | 90.91 |
| Isobutyl fentanyl | 1.1 | 90.91 |
| ω-1-Hydroxyfentanyl | 1.2 | 83.33 |
| Acrylfentanyl | 1.3 | 76.92 |
| Butyl fentanyl | 1.4 | 71.43 |
| Furanyl fentanyl | 1.5 | 66.67 |
| Para-fluoro fentanyl | 1.5 | 66.67 |
| Ocfentanil | 1.6 | 62.50 |
| 4-Fluoro-isobutyl fentanyl | 1.9 | 52.63 |
| Para-fluorobutyl fentanyl (p-FBF) | 1.9 | 52.63 |
| Valeryl fentanyl | 2.3 | 43.48 |
| β-hydroxyfentanyl | 9.5 | 10.53 |
| Acetyl norfentanyl | 12.1 | 8.26 |
| (±) β-hydroxythiofentanyl | 32.7 | 3.06 |
| (±)-3-cis-methyl fentanyl | 144.1 | 0.69 |
| Carfentanil | 448.2 | 0.22 |
| Despropionyl fentanyl (4-ANPP) | 471.8 | 0.21 |
| Sufentanil | 2,362 | 0.04 |
| Remifentanil | 10,000 | <0.01 |
| Norcarfentanil | 2,418 | 0.04 |
| Alfentanil | 100,000 | <0.001 |

The following opioids, structurally similar compounds, and functional analogs were negative at the concentrations tested with the ARK Fentanyl II Assay.

| Compound | Concentration Tested (µg/mL) | Compound | Concentration Tested (µg/mL) |
|----------------------------------|------------------------------|----------------------|------------------------------|
| 6-Acetyl morphine | 100 | Naltrexone | 100 |
| Buprenorphine | 100 | Norbuprenorphine | 100 |
| Buprenorphine glucuronide | 100 | Norcodeine | 100 |
| Codeine | 100 | Normeperidine | 100 |
| Dextromethorphan | 100 | Normorphine | 100 |
| Dihydrocodeine | 100 | Noroxycodone | 100 |
| EDDP | 100 | Oxycodone | 100 |
| EMDP | 100 | Oxymorphone | 100 |
| Heroin | 100 | Pentazocine (Talwin) | 100 |
| Hydrocodone | 100 | Pipamperone | 90 |
| Hydromorphone | 100 | Quinine | 100 |
| 9-Hydroxyrisperidone | 100 | Quinidine | 100 |
| Labetalol | 100 | Risperidone | 100 |
| Levorphanol | 100 | Tapentadol | 100 |
| m-Chlorophenylpiperazine (m-CPP) | 100 | Thioridazine | 100 |
| Meperidine | 100 | Tiilidine | 100 |
| Methadone | 100 | Tramadol | 100 |
| Morphine | 100 | Tramadol-O-Desmethyl | 100 |
| Morphine-3-glucuronide | 100 | Tramadol-N-Desmethyl | 100 |
| Naloxone | 100 | Trazodone | 100 |

Interference – Structurally Unrelated Compounds

High concentrations of the following structurally unrelated compounds were added into fentanyl-spiked urine (± 50% of the cutoff concentration). The substances listed below did not yield a false result relative to the cutoff.

| Compound | Concentration Tested (µg/mL) | 0.5 ng/mL (-50% Cutoff) | 1.5 ng/mL (+50% Cutoff) |
|----------------------|------------------------------|-------------------------|-------------------------|
| Acetaminophen | 500 | Negative | Positive |
| Acetylsalicylic acid | 1000 | Negative | Positive |
| Albuterol | 100 | Negative | Positive |
| Amitriptyline | 100 | Negative | Positive |
| Amobarbital | 100 | Negative | Positive |
| Amphetamine | 100 | Negative | Positive |
| Benzoylcegonine | 100 | Negative | Positive |
| Bupropion | 100 | Negative | Positive |
| Caffeine | 100 | Negative | Positive |
| Carbamazepine | 100 | Negative | Positive |
| Chlorpromazine | 100 | Negative | Positive |
| Clomipramine | 100 | Negative | Positive |
| Cyclobenzaprine | 100 | Negative | Positive |
| Desipramine | 100 | Negative | Positive |
| Doxepin | 100 | Negative | Positive |
| Ecgonine | 100 | Negative | Positive |
| Ephedrine | 100 | Negative | Positive |
| Fluoxetine | 100 | Negative | Positive |
| Fluphenazine | 100 | Negative | Positive |
| Ibuprofen | 500 | Negative | Positive |
| Imipramine | 100 | Negative | Positive |
| Ketamine | 100 | Negative | Positive |
| Lidocaine | 100 | Negative | Positive |
| Maprotiline | 100 | Negative | Positive |
| Methapyrilene | 100 | Negative | Positive |
| Methaqualone | 100 | Negative | Positive |
| Metronidazole | 300 | Negative | Positive |
| Nicotine | 100 | Negative | Positive |
| Norketamine | 100 | Negative | Positive |
| Nortriptyline | 60 | Negative | Positive |
| Oxazepam | 100 | Negative | Positive |
| Phencyclidine | 100 | Negative | Positive |
| Phenobarbital | 100 | Negative | Positive |
| Propoxyphene | 100 | Negative | Positive |
| Ranitidine | 100 | Negative | Positive |
| Secobarbital | 100 | Negative | Positive |
| Valproic acid | 250 | Negative | Positive |
| Venlafaxine | 100 | Negative | Positive |

Interference – Endogenous Substances

High concentrations of the following endogenous substances were added into fentanyl-spiked urine (\pm 50% of the cutoff concentration). No interference was observed when tested with the ARK Fentanyl II Assay.

| Compound | Concentration Tested (mg/dL) | 0.5 ng/mL (-50% Cutoff) | 1.5 ng/mL (+50% Cutoff) |
|-----------------|------------------------------|-------------------------|-------------------------|
| Acetone | 1000 | Negative | Positive |
| Ascorbic Acid | 560 | Negative | Positive |
| Bilirubin | 2 | Negative | Positive |
| Creatinine | 500 | Negative | Positive |
| Ethanol | 1000 | Negative | Positive |
| Galactose | 10 | Negative | Positive |
| Gamma Globulin | 500 | Negative | Positive |
| Glucose | 3000 | Negative | Positive |
| Hemoglobin | 500 | Negative | Positive |
| Human Albumin | 500 | Negative | Positive |
| Oxalic Acid | 100 | Negative | Positive |
| Riboflavin | 7.5 | Negative | Positive |
| Sodium Chloride | 4000 | Negative | Positive |
| Urea | 2000 | Negative | Positive |

Interference – Boric Acid

One percent (1%) w/v of boric acid was added into fentanyl-spiked urine (\pm 50% of the cutoff concentration). Results are provided in the table below.

| Compound | Concentration Tested | 0.5 ng/mL (-50% Cutoff) | 1.5 ng/mL (+50% Cutoff) |
|------------|----------------------|-------------------------|-------------------------|
| Boric Acid | 1% w/v | Negative | Negative |

Interference – Specific Gravity and pH

Urine samples with specific gravity values from 1.002 to 1.030 and pH values ranging from 3.0 to 11.0 were tested in the presence of the two levels of fentanyl at \pm 50% of the cutoff concentration. No interference was observed when tested with the ARK Fentanyl II Assay.

Method Comparison

A total of one hundred forty seven (147) unaltered clinical urine specimens that are not individually identifiable were analyzed for fentanyl with the ARK Fentanyl II Assay and by LC-MS/MS. The LC-MS/MS confirmatory method was performed by a licensed reference laboratory and used a fentanyl cutoff of 0.2 ng/mL.

Specimens were tested with the ARK Fentanyl II Assay in singleton on a Beckman Coulter AU680 analyzer and compared to results obtained by LC-MS/MS. Groups of up to 31 specimens were assayed per run. Each run was verified by assaying the bi-level ARK Fentanyl Controls (0.5 ng/mL and 1.5 ng/mL) as quality control samples.

Results are summarized as follows:

| ARK Immunoassay Result | Low Negative Less than 50% below the Cutoff (< 0.5 ng/mL by LC-MS/MS) | Near Cutoff Negative Between 50% below the Cutoff and the Cutoff (0.5 – 0.9 ng/mL by LC-MS/MS) | Near Cutoff Positive Between the Cutoff and 50% above the Cutoff (1.0 – 1.5 ng/mL by LC-MS/MS) | High Positive Greater than 50% above the Cutoff (> 1.5 ng/mL by LC-MS/MS) |
|------------------------|--|---|---|--|
| Positive | 1* | 21 | 11 | 62 |
| Negative | 50 | 2 | 0 | 0 |

Discordant Results

*Norfentanyl was detected in this discordant sample (Sample ID #052) and contributed to the positive result obtained with the ARK Fentanyl II Assay for this sample.

| Sample ID Number | ARK Immunoassay Result | Fentanyl (ng/mL by LC-MS/MS) | Norfentanyl (ng/mL by LC-MS/MS) |
|------------------|------------------------|------------------------------|---------------------------------|
| 052* | Positive | 0.4 | 7.6 |
| 065 | Positive | 0.5 | 5.2 |
| 058 | Positive | 0.5 | 7.9 |
| 069 | Positive | 0.5 | 31.2 |
| 060 | Positive | 0.5 | 425.4 |
| 056 | Positive | 0.6 | 3.7 |
| 072 | Positive | 0.6 | 13.8 |
| 062 | Positive | 0.6 | 14.5 |
| 074 | Positive | 0.6 | 14.6 |
| 055 | Positive | 0.6 | 16.9 |
| 071 | Positive | 0.6 | 19.0 |
| 070 | Positive | 0.6 | 161.7 |
| 051 | Positive | 0.7 | 2.1 |
| 066 | Positive | 0.7 | 3.1 |
| 064 | Positive | 0.8 | 15.9 |
| 073 | Positive | 0.8 | 45.8 |
| 063 | Positive | 0.9 | 2.2 |
| 061 | Positive | 0.9 | 6.5 |
| 057 | Positive | 0.9 | 12.3 |
| 053 | Positive | 0.9 | 14.0 |
| 059 | Positive | 0.9 | 62.6 |
| 054 | Positive | 0.9 | 63.4 |

12 REFERENCES

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13 TRADEMARKS

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