EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR QUANTITATION OF ORGANOPHOSPHATE METABOLITES IN URINE BY LC/MS/MS

DECISION SUMMARY
Correction Date: March 10, 2017
This Decision Summary contains corrections to the August 8, 2013 Decision Summary

A. 510(k) Number: k122282

B. Purpose for Submission: De novo request for evaluation of automatic class III designation of the Quantitation of Organophosphate Metabolites in Urine by LC/MS/MS new assay

C. Measurand: Selected Organophosphate Metabolites

D. Type of Test: Quantitative LC/MS/MS

E. Applicant: Centers for Disease Control and Prevention (CDC).

F. Proprietary and Established Names:

Quantitation of Organophosphate Metabolites in Urine by LC/MS/MS

G. Regulatory Information:

FDA identifies this type of device as: Organophosphate test system

An organophosphate test system is a device intended to measure organophosphate metabolites quantitatively in human urine from individuals who have signs and symptoms consistent with cholinesterase poisoning. The data obtained by this device is intended to aid in the confirmation and investigation of organophosphate exposure.

1. New Regulation Number:

   21 CFR 862.3652

2. Classification:

   Class II (special controls)

3. Product code:

   PDY

4. Panel:

   Clinical Chemistry and Clinical Toxicology Devices

H. Intended Use:

1. Intended use(s):

   This device is intended for the quantitation of specific organophosphate metabolites by LC/MS/MS. The device system includes organophosphate metabolite calibrators to calibrate the system and organophosphate metabolite controls for quality control monitoring of the system. This device is intended for use in a single laboratory to detect and measure the concentration of specific organophosphate metabolites in human urine from individuals who have signs and symptoms consistent with cholinesterase poisoning. The data obtained by this device will be used following an exposure or suspected exposure event to confirm exposure, identify the causative agent, and distinguish exposed from the unexposed patients.

2. Indication(s) for use:

   Same as intended use.

3. Special conditions for use statement(s):

   For in vitro diagnostic use.

   For prescription use only, in a single laboratory.

4. Special instrument requirements:

   AB Sciex Qtrap 5500 – Serial number (S/N) AU23771008

   Agilent HPLC – (Degasser 1100 Series: S/N JP32750555; FC/ALS Therm Series: S/N DE60556845; HiP-ALS 1200 Series: S/N DE63055552; Bin Bump 1200 Series: S/N DE63057946; Degasser 1200 Series: S/N JP63705336)

   Caliper Life Sciences – (Sciclone i1000 Workstation: S/N SS0712N0548 and SS739N0661; Twister II Microplate Handler: S/N T20838N0168)

   Clearance of this assay is limited only to the instrument systems with the serial numbers as specified above. Any additional systems will require a validation panel to be reviewed and approved prior to use with the assay.

I. Device Description:

The device comprises internal standards which serve as the basis for the calibrators and quality control materials. A solid phase extraction cartridge is initially used to extract the metabolites for further separation and analysis on a tandem mass spectrometer and HPLC system.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   No predicate device exists

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

   Not applicable

3. Comparison with predicate:

   Not applicable

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

1. CLSI EP17-A, Protocol for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline, Vol. 24, No. 34, modified

2. CLSI EP6-A, Evaluation of the linearity of Quantitative Measurement Procedures: A Statistical approach; Approved Guideline, Vol. 23, No. 16

L. Test Principle:

This assay detects the presence of organophosphate metabolites in human urine. This is achieved through the separation, identification, and quantitation of the specific metabolites resulting from exposure to selected organophosphates by LC/MS/MS.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision and repeatability were both determined through analysis of quality control materials in synthetic urine at 15 and 75 ng/mL concentrations of five organophosphate metabolites (identified as OP-1, 2, 3, 4, 5). The samples were prepared, analyzed, and processed by three different operators over a

period of 14 days, with no more than 4 QC samples prepared and analyzed in one 24-hour period. Within-day and between-day studies were performed on a single instruments. The data are summarized in the tables below.

Instrument AU23771008

		Within Day, n=4, operators = 1			Between Day, n=20, days = 14, operators = 3		
Analyte	Concentration (ng/mL)	Mean	St. Dev.	%CV	Mean	St. Dev.	%CV
OP-1	15	15.2	0.8	5.4	14.9	0.6	4.2
	75	75.7	2.2	2.9	75.6	2.3	3.0
OP-2	15	15.0	0.4	2.4	15.0	0.5	3.4
	75	76.3	1.8	2.4	76.2	2.1	2.8
OP-3	15	15.4	0.4	2.7	15.0	0.6	4.1
	75	76.8	3.5	4.1	75.7	2.1	2.7
OP-4	15	15.5	0.9	5.8	15.0	0.6	4.0
	75	76.1	1.5	1.9	75.9	2.3	3.1
OP-5	15	14.9	0.5	3.1	14.8	0.6	4.2
	75	75.2	3.3	4.0	75.3	2.2	2.9

b. Linearity/assay reportable range:

The claimed measuring range is 2 – 200 ng/mL.

Recovery studies were conducted for each organophosphate metabolite. Spiked pooled urine samples at various concentrations were prepared and analyzed in triplicate.

Instrument AU23771008

Conc. ng/mL	**OP-3**		**OP-4**		**OP-5**	
	Mean, ng/mL	**% Recovery**	**Mean, ng/mL**	**% Recovery**	**Mean, ng/mL**	**% Recovery**
2	1.7	86.5	1.9	96.0	1.9	94.0
3	2.8	92.3	2.4	81.1	3.4	112.9
7	6.8	96.4	6.3	90.1	7.2	103.1
9	7.9	87.6	8.5	94.5	8.3	92.2
22	20.2	92.0	20.4	92.9	20.4	92.6
30	n/a	n/a	n/a	n/a	n/a	n/a
45	40.7	90.5	40.5	90.1	42.3	94.0
65	60.5	93.0	59.5	91.5	60.4	93.0
80	72.9	91.2	71.2	89.0	74.5	93.2
95	86.7	91.3	87.5	92.1	90.1	94.9
115	106.3	92.5	103.7	90.1	107.5	93.5
130	120.0	92.3	118.2	90.9	123.2	94.7
145	n/a	n/a	n/a	n/a	n/a	n/a

180	183.8	102.1	155.3	86.3	182.5	101.4
200	210.3	105.2	173.7	86.8	207.3	103.7

Conc. ng/mL	**OP-1**		**OP-2**	
	Mean, ng/mL	**% Recovery**	**Mean, ng/mL**	**% Recovery**
2	1.9	93.0	1.9	95.5
3	2.5	82.6	2.9	97.3
7	6.7	95.2	6.8	96.6
9	8.4	93.2	8.9	98.9
22	21.2	96.3	20.8	94.6
30	28.6	95.4	n/a	n/a
45	42.9	95.5	43.7	97.1
65	63.1	97.1	n/a	n/a
80	n/a	n/a	74.8	93.5
95	90.2	95.0	88.0	92.6
115	n/a	n/a	107.3	93.3
130	125.8	96.8	122.3	94.1
145	140.2	96.7	136.3	94.0
180	177.7	98.3	173.8	96.6
200	203.2	101.6	199.8	99.9

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

Traceability and Value assignment

Calibrators are prepared at the assigned levels by a vendor using a dilution scheme. Assigned values are verified according to precision, accuracy, and linear response.

Values assigned to the calibrators and quality control materials are traceable to the internal standards synthesized by a vendor. There are no certified reference materials available for these compounds.

Stability

Calibrator and quality control material storage stability was evaluated. All

data met the acceptance criteria and support the shelf life claim of 2 years at -70 C.

d. Detection limit:

The LoD for the five metabolites were determined by measuring piked synthetic urine samples at 1, 2, and 5 ng/mL, as well as a blank synthetic urine sample. The LoB, LoD, and LoQ are summarized below. The claimed measuring range is 2 – 200 ng/mL.

Instrument AU23771008

	OP-1	**OP-3**	**OP-2**	**OP-4**	**OP-5**
LoB	0.229	0.192	0.029	0.090	0.406
LoD	0.40	0.35	0.13	0.20	0.69
LoQ	2	2	2	2	2

e. Analytical specificity:

200 individual unexposed urine samples were extracted for the presence of any peaks that would contribute to false positive results (i.e. the presence of any positive peaks). No peaks were detected in the samples that were above the LoQ for all five metabolites. Six non-specific pesticide metabolites, known as dialkylphosphates, were spiked into samples and the samples were analyzed for the presence of any positive peaks associated with the organophosphates. No interfering peaks were detected.

f. Assay cut-off:

Not applicable

2. Comparison studies:
   a. Method comparison with predicate device:

   Not applicable

   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**:**

All values ≥ 2 ng/mL indicate exposure to an organophosphate metabolite. A value < 2 ng/mL will be reported as "non-detectable".

5. Expected values/Reference range:

The sponsor tested 200 individual unexposed urine samples for the presence of any positive peaks associated with the organophosphates and their metabolites. No peaks were detected. These organophosphate metabolites are not naturally occurring, and as such, 0 ng/mL is expected for an unexposed subject.

N. Instrument Name:

AB Sciex QTrap 5500

O. System Descriptions:

1. Modes of Operation:

Automated

2. Software:

The software used with this assay is off-the-shelf (OTS) software to manage the LC/MS/MS system and the liquid handling system for the solid-phase extraction. FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes ___x_____ or No _____

3. Specimen Identification:

Specimens are identified in a laboratory information management system and labeled/bar-coded with a traceable number. Final results are uploaded into the laboratory information management system to correspond with the label identified in the chain of custody form (refer to Section 4 below).

4. Specimen Sampling and Handling:

Specimens are collected, frozen, and sent to the laboratory. The sample is thawed and processed for analysis.

5. Calibration:
   Instruments are calibrated on-site by the instrument manufacturer.
   Calibration curves for the assay are prepared as specified by the procedure.

6. Quality Control:
   Quality Control is ensured through the analysis of two positive quality control samples and one negative quality control sample.

P. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10 and 21 CFR 801.109.

Q. Other Supportive Instrument Characteristics Data Not Covered In The "Performance Characteristics" Section above:

None

R. Identified Potential Risks and Required Mitigation Measures:

Identified Potential Risk	Required Mitigation Measure
False Positive	1) The distribution of these devices is limited to laboratories with experienced personnel who are trained to measure and evaluate organophosphate exposure and guide public health response. 2) Analytical testing must demonstrate the device has appropriate performance characteristics, including adequate precision and accuracy across the measuring range and near medical decision points.
False Negative	1) The distribution of these devices is limited to laboratories with experienced personnel who are trained to measure and evaluate organophosphate exposure and guide public health response. 2) Analytical testing must demonstrate the device has appropriate performance characteristics, including adequate precision and accuracy across the measuring range and near medical decision points.
Public Health Risk from Incorrect Test Results	1) The distribution of these devices is limited to laboratories with experienced personnel who are trained to measure and evaluate organophosphate exposure and guide public health response. 2) Analytical testing must demonstrate the device has appropriate performance characteristics, including adequate precision and accuracy across the measuring range and near medical decision

Identified Potential Risk	Required Mitigation Measure
	points.

S. Benefit/Risk Analysis:

Summary	
Summary of the Benefit(s)	• This is a public health tool whose primary utility is to identify exposure to selected organophosphate(s) and the metabolites to which the individual/individuals has/have been exposed. It would be highly valued for public health purposes in an effort to track and maintain epidemiologic data on exposures and potential exposures to organophosphate(s). • No other tests are available for identification of organophosphate metabolites

Summary of the Risk(s)	• Patients are subject to urine specimen collection, which is a standard procedure in clinical care and carries minimal risk. • Risk is related to inaccurate test results as follows: <u>False positive</u>: • The risks to the individual of a false positive result include unnecessary anxiety related to long term impact of such exposure and possible unnecessary medical work up, evaluation and follow-up for exposure-related complications. • Since no treatment decisions will be initiated based on test results, a false positive result will not lead to risk of inappropriate treatment. Treatment is initiated based on signs and symptoms of possible exposure in the immediate setting, prior to obtaining results of medical diagnostic tests. <u>False negative</u>: • The risk to the individual of a false negative result is missed identification of exposure to organophosphate(s). • Since no treatment decisions are expected to be initiated based on test results, a false negative result will not lead to missed opportunity to initiate appropriate treatment in the immediate setting. • A false negative result may lead to a missed opportunity for additional medical evaluation and follow-up for exposure-related complications. <u>Public Health Risk from Incorrect Test Results</u>: • The consequences to public health for both false positive and false negative results are similar and are related to inaccurate epidemiologic data leading to long term misconceptions and inaccurate conclusions related to exposure event. Missed opportunities for valuable information gathering that could lead to significant benefits to public health may occur.
Summary of Other Factors	Not applicable
Conclusions Do the probable benefits outweigh the probable risks?	
Given robust analytical performance characteristics and risk mitigation (i.e. proper labeling and use in the Public Health response sector), the probable benefits to both the individual and public health outweigh the probable risks of this device.	

T. Conclusion:

The information provided in this *de novo* submission is sufficient to classify this device into class II under regulation 21 CFR 862.3652. FDA believes that special controls, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type. This device, and similar devices, are classified under the following:

Product Code: PDY

Device Type: Organophosphate Test System

Class: II (special controls)

Regulation: 21 CFR 862.3652

(a) *Identification.* An organophosphate test system is a device intended to measure organophosphate metabolites quantitatively in human urine from individuals who have signs and symptoms consistent with cholinesterase poisoning. The data obtained by this device is intended to aid in the confirmation and investigation of organophosphate exposure.

(b) *Classification.* Class II (special controls). Organophosphate test systems must comply with the following special controls:

1) The distribution of these devices is limited to laboratories with experienced personnel who are trained to measure and evaluate organophosphate exposure and guide public health response.

2) Analytical testing must provide a reasonable assurance of safety and effectiveness demonstrate the device has appropriate performance characteristics, including adequate precision and accuracy across the measuring range and near medical decision points.