510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K202644

B Applicant

Sekisui Diagnostics P.E.I. INC.

C Proprietary and Established Names

Acetaminophen

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LDP	Class II	21 CFR 862.3030 - Acetaminophen Test System	TX - Clinical Toxicology

II Submission/Device Overview:

A Purpose for Submission:

New Device

B Measurand:

Acetaminophen

C Type of Test:

Quantitative enzymatic / colorimetric assay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Acetaminophen assay is used for the quantitative determination of acetaminophen in human serum or plasma on the ARCHITECT c Systems.

The Acetaminophen assay is to be used as an aid in the diagnosis and treatment of acetaminophen overdose toxicity.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

ARCHITECT c8000 analyzer

IV Device/System Characteristics:

A Device Description:

The assay consists of two reagents:

Reagent 1 (Enzyme Reagent) 8.6 mL
Active Ingredients: manganese (II) chloride (0.3 mmol/L), aryl acylamidase (0.9 KU/L).
Preservatives: gentamicin sulfate, p-hydroxybenzoic acid, sodium azide.

Reagent 2 (Color Reagent) 22.3 mL
Active ingredient: 2,5-dimethylphenol (31 mmol/L).

B Principle of Operation:

The Acetaminophen assay is an automated clinical chemistry assay. In the reaction, aryl acylamidase is the enzyme that hydrolyzes acetaminophen to p-aminophenol and acetate. Next, p-aminophenol reacts with 2,5-dimethylphenol in the presence of a manganese catalyst to create the chromophore, 4-(4-iminophenol)-2,5- dimethylcyclohexadiene-1-one. Generation of this reaction product is measured at 660 nm and its production is proportional to the concentration of acetaminophen in the patient sample.

V *Substantial Equivalence Information:*

A Predicate Device Name(s):
Acetaminophen L3K Assay

B Predicate 510(k) Number(s):
K081938

C Comparison with Predicate(s):

Device & Predicate Device(s):	Candidate K202644	Predicate K081938
Device Trade Name	Acetaminophen	Genzyme Diagnostics Acetaminophen L3K Assay
General Device Characteristic Similarities		
Intended Use/Indications For Use	Same	For the quantitative measurement of acetaminophen in serum and plasma. Measurement of acetaminophen is used in the diagnosis and treatment of acetaminophen overdose toxicity.
Methodology	Same	Enzymatic (Aryl acylamidase) and Spectrophotometric (2,5-dimethylphenol Chromophore)
General Device Characteristic Differences		
Analyzer platform	ARCHITECT c8000 System	Hitachi 717
Acceptable matrices	Serum Lithium heparin plasma Sodium heparin plasma	Serum Lithium heparin plasma
Measuring range	3 to 377 µg/mL	0.6 to 377.5 µg/mL

VI Standards/Guidance Documents Referenced:

- Clinical Laboratory and Standards Institute (CLSI) EP06 Evaluation of Linearity of Quantitative Measurement Procedures - 2nd Edition
- CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition
- CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition
- CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline
- CLSI EP34 Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking – First Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

The sponsor provided a within-laboratory precision study using one ARCHITECT c8000 analyzer, two reagent lots, two calibrator lots, and one control lot.

The samples included control materials, serum pools spiked with acetaminophen, and pooled serum samples. Samples were tested in a minimum of 2 replicates (target of 3 replicates, 2 times per day separated by a minimum of 2 hours), on at least 20 different days, for a minimum of 80 required measurements. Results are summarized in the table below.

				Within-Run		**Between-Run**		**Between-Day**		**Within-Lab**	
Sample	Rgt Lot	N	Mean (µg/mL)	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Level 1 (control)	1	127	15	0.2	1.2	0.2	1.5	0.0	0.0	0.3	1.9
	2	120	15	0.1	0.9	0.2	1.0	0.0	0.0	0.2	1.3
Level 2 (control)	1	125	72	0.4	0.5	0.3	0.4	0.4	0.6	0.7	0.9
	2	119	73	0.5	0.6	0.2	0.3	0.3	0.4	0.6	0.8
Level 3 (control)	1	127	226	0.8	0.4	0.8	0.4	1.4	0.6	1.8	0.8
	2	120	227	0.8	0.3	0.6	0.3	0.9	0.4	1.3	0.6
Panel A (spiked)	1	126	5	0.2	4.4	0.2	4.3	0.3	5.9	0.5	8.6
	2	120	5	0.3	5.6	0.4	6.6	0.1	2.7	0.5	9.1
Panel B (pooled)	1	126	51	0.3	0.7	0.2	0.5	0.2	0.4	0.5	0.9
	2	120	51	0.3	0.6	0.1	0.1	0.2	0.4	0.4	0.7
Panel C (pooled)	1	126	83	0.4	0.5	0.3	0.4	0.4	0.5	0.7	0.8
	2	120	84	0.4	0.4	0.2	0.3	0.3	0.4	0.6	0.7
Panel D (spiked)	1	138	277	1.0	0.4	0.8	0.3	1.2	0.4	1.7	0.6
	2	120	278	1.0	0.4	1.1	0.4	1.3	0.5	2.0	0.7
Panel E (spiked)	1	141	361	1.4	0.4	1.0	0.3	1.5	0.4	2.3	0.6
	2	120	362	1.6	0.4	1.1	0.3	1.7	0.5	2.6	0.7

2. Linearity:

The sponsor performed a study to evaluate the linearity of the candidate assay on the ARCHITECT c8000 by referencing the CLSI EP06-Ed2 guideline. A linearity series of 11 samples was prepared by making admixtures of a sample of known high concentration with an acetaminophen-free normal human serum. The evaluation samples had concentrations of 2, 5, 46, 91, 138, 182, 226, 276, 315, 364, and 394 µg/mL.

The maximum deviation from linearity was 1 µg/mL for samples with acetaminophen concentrations less than 20 µg/mL and the maximum % deviation from linearity ranged from -0.9% to 0.8% for samples with acetaminophen concentrations greater than or equal to 20 µg/mL

Linear regression of the data produced the following:

Slope	0.9916
Intercept	0.1964
Correlation Coefficient	0.999

The results of the linearity studies support the sponsor's claimed measuring interval of 3 – 377 µg/mL. Samples with a concentration greater than 377 µg/mL will be reported as > 377 µg/mL without dilution.

The sponsor also performed a study to evaluate the accuracy of the auto-dilute feature for samples with a concentration greater than 377 µg/mL. Five samples with acetaminophen concentrations within the range of 450 µg/mL to 3,000 µg/mL were prepared by spiking USP Reference Standard Acetaminophen Stock solution into five human serum specimens which had acetaminophen levels of 0 µg/mL as screened by a commercially available assay. The acetaminophen concentration of each sample was assigned using the mean concentration of ten replicates tested by a commercially available assay. Each sample was either manually or automatically diluted at a 1:10 dilution. The results of the study demonstrated that the dilution recoveries for the auto dilute feature were all within +/- 2% of the expected value. The dilution study results support the sponsor's labeling claims that samples with acetaminophen concentrations above 377 µg/mL may be diluted 1:10 either manually or on-onboard the analyzer to obtain results up to 3770 µg/mL.

3. Analytical Specificity/Interference:

The sponsor performed a study to evaluate potential interference from endogenous and exogenous compounds. The study used one ARCHITECT c8000 analyzer, one reagent lot, one calibrator lot, and one control lot.

Each potential interferent was tested at acetaminophen concentrations of approximately 5, 30, and 150 µg/mL.

The sponsor defined significant interference as ± ≤ 7.5% interference for acetaminophen samples ≥ 20 µg/mL or ± ≤ 1.50 µg/mL interference for acetaminophen samples < 20 µg/mL. By these criteria, no interference was observed at the following concentrations:

Potential Endogenous Interferents

Potential Interferent	Interferent Concentration
Bilirubin – conjugated	14 mg/dL
Bilirubin – unconjugated	28 mg/dL
Hemoglobin	570 mg/dL
Intralipid	2000 mg/dL

Potential Interferent	Interferent Concentration
Total Protein	10 g/dL
Triglycerides	933 mg/dL

Potential Exogenous Interferents

Potential Interferent	Interferent Concentration
Amitriptyline	0.048 mg/dL
Ampicillin	7.5 mg/dL
Benzocaine	560 mg/L
Cefoxitin	660 mg/dL
Codeine	0.141 mg/dL
Cyclosporine	0.18 mg/dL
Cysteamine	220 µmol/L
Dapsone	5.9 mg/L
2,5-Dihydroxybenzoic acid	117 µmol/L
Dipyrone/Metamizole	100 mg/L
Doxycycline	1.8 mg/dL
4-Ethoxyaniline	1.0 mmol/L
Ibuprofen	21.9 mg/dL
Imipramine	0.0315 mg/dL
L-Ascorbic acid	170 µmol/L
L-Cysteine	18 mg/dL
Levodopa	0.75 mg/dL
L-Methionine	500 µg/mL
Methyldopa	2.25 mg/dL
Metoclopramide	1.5 µmol/L
Metronidazole	12.3 mg/dL
N-Acetylcysteine	1663 mg/L
N-Acetylprocainamide	16 µg/mL
p-Aminosalicylic acid	5.3 mmol/L
Phenacetin	14 µg/mL
Phenylbutazone	32.1 mg/dL
Procainamide	102 µmol/L
Rifampicin	80 µmol/L
Salicylic acid	4.4 mmol/L
Tetracycline	34 µmol/L
Theophylline	6.0 mg/dL

4. Assay Reportable Range:

The reportable range of the assay is 3 – 377 µg/mL without dilution and 3 – 3770 µg/mL when the automatic x 10 dilution factor is applied. Samples with an acetaminophen concentration less than 3 µg/mL are reported as "< 3 µg/mL".

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

The Acetaminophen Calibrator is prepared gravimetrically from USP grade reference acetaminophen material to a concentration of 151 µg/mL (1000 µmol/L). The calibrator preparation is verified against the master calibrator (an internal reference standard).

6. Detection Limit:

The sponsor performed studies in accordance with CLSI EP17-A2 guideline to determine the limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) of the candidate device. Two lots of reagent were evaluated on the ARCHITECT c8000 analyzer.

The testing was performed using one zero-analyte sample (normal human serum) and ten low-level samples (2 samples at each of the 5 acetaminophen target concentrations of approximately 1, 2, 3, 4 and 5 µg/mL). The low-level samples were prepared by volumetrically spiking acetaminophen stock solution into normal human serum. A total of 60 replicates were collected per concentration per reagent lot.

The results of the studies supported the following detection limit claims:

	µg/mL
LoB	0.0
LoD	1.0
LoQ	3.0

7. Assay Cut-Off:

Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

The sponsor performed a method comparison study comparing results from the candidate device to those from the predicate device. A total of 119 human serum specimens were evaluated with the predicate and candidate devices. The concentration range evaluated was 3.5 – 356.3 µg/mL by the predicate device.

Contrived samples made up 4% of the total and were prepared by spiking serum specimens with a stock solution of acetaminophen material to the desired concentration range. The contrived samples were spiked to acetaminophen concentrations at the upper end of the measuring range where it is difficult to obtain unaltered clinical samples.

For the candidate method, one ARCHITECT c8000 analyzer, two reagent lots, two calibrator lots, and one control lot were used. For the predicate method, one ARCHITECT c8000 analyzer, two reagent lots, two calibrator lots, and one control lot were used.

A Passing-Bablok linear regression model was performed by comparing the first replicate result from the investigational method versus the mean result from the comparator method. Linear regression statistics from a representative lot were as follows:

Predicate Method vs Candidate Method

Correlation Coefficient	0.9993
Slope	1.042
Intercept	-0.034

2. Matrix Comparison:

The sponsor performed a matrix comparison study to verify which specimen tube types (matrices) may be used with the assay. A total of 78 samples were analyzed. Of those 78 samples, 45 native samples covered the claimed therapeutic range of 10-30 µg/mL and 18 samples were spiked to cover the assay reportable range.

The data was collected using Serum (with gel in plastic, Serum Separator Tube), Lithium heparin (with gel in plastic, Plasma Separator Tube), Lithium heparin (without gel in plastic), and Sodium heparin (without gel in plastic) vs serum (without gel in plastic) as the comparator matrix. All percent recoveries were within ± 10%.
Linear regression produced the following:

Matrix	Concentration Range	Slope - Deming	Slope - Passing-Bablok	Correlation Coefficient
Serum Separator Tube	3.52 – 342.51 µg/mL	1.004	1.005	0.999
Plasma Separator Tube	3.52 – 342.51 µg/mL	1.009	1.004	0.999
Lithium heparin (without gel in plastic)	3.52 – 342.51 µg/mL	1.017	1.009	0.999
Sodium heparin (without gel in plastic)	3.52 – 342.51 µg/mL	1.018	1.009	1.000

Therefore, the sponsor concluded that the following matrices are suitable for use with the assay and has claimed them as sample types in the labeling:

Plain serum
Serum separator tube
Plasma separator tube
Lithium heparin tube (without gel in plastic)
Sodium heparin tube (without gel in plastic)

C Clinical Studies:

1. Clinical Sensitivity:

   Not Applicable

2. Clinical Specificity:

   Not Applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not Applicable

D Clinical Cut-Off:

Not Applicable

E Expected Values/Reference Range:

The sponsor's labeling lists the following therapeutic and toxic acetaminophen concentrations:

[a]Therapeutic 10–30 µg/mL

[b]Toxic Levels
4 hours > 150 µg/mL
24 hours > 4.7 µg/mL

[a]Burtis CA, Ashwood ER, Bruns DE, editors. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. St. Louis, MO: Elsevier; 2012:2176.

[b]Rowden AK, Norvell J, Eldridge DL,et al. Acetaminophen poisoning. Clin Lab Med 2006;26(1):49-65.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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