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

A. 510(k) Number:
k110726

B. Purpose for Submission:
Modification of previously cleared Acetaminophen assays (k991598, k013757, and k060373); changed the low end of the measuring range claim to 15 µg/mL due to interference and updated Interference claims

C. Measurand:
Acetaminophen

D. Type of Test:
Quantitative colorimetric assay

E. Applicant:
Roche Diagnostics Corp

F. Proprietary and Established Names:
Roche Acetaminophen assay

G. Regulatory Information:

1. Regulation section:
   21 CFR 862.3030 – Acetaminophen test system
2. Classification:
   Class II
3. Product code:
   LDP
4. Panel:
   91 Toxicology

H. Intended Use:

1. Intended use(s):
   Refer to indications for use below.

2. Indication(s) for use:
   The Roche Acetaminophen assay is an in vitro test for the quantitative determination of toxic levels of acetaminophen in serum and plasma on Roche Cobas Integra, Roche/Hitachi and cobas c system analyzers.

3. Special conditions for use statement(s):
   For *in vitro* diagnostic use only.

For prescription use.

The sponsor includes the following warning in the labeling:

Warning: Bilirubin may cause erroneous acetaminophen results

Serum indices must be run on all acetaminophen samples and the acetaminophen results must be evaluated using the appropriate serum index for icteric samples.
All Acetaminophen results must be reviewed at the analyzer or at the host (LIS and Middleware) before being released. An acetaminophen result cannot be released if it is below the measuring range or has an associated bilirubin level above the I index specified in the following tables.

Cobas c501

Acetaminophen [µg/mL]	Interference occurs with an I index* greater than
15 - 30	8
> 30 - 50	8
> 50	8

* I Index value – corresponds approximately to mg/dL of bilirubin

Hitachi 917

Acetaminophen [µg/mL]	Interference occurs with an I index* greater than
15 - 30	4
> 30 - 50	9
> 50	9

* I Index value – corresponds approximately to mg/dL

Integra 800

Acetaminophen [µg/mL]	Interference occurs with an I index* greater than
15 - 30	4
> 30 - 50	9
> 50	12

* I Index value – corresponds approximately to mg/dL of bilirubin

4. Special instrument requirements:
Roche Cobas Integra 800, Hitachi 917 and cobas c501 system analyzers

I. Device Description:

The Roche Acetaminophen reagents under consideration in this submission are the same as previously cleared on the Cobas Integra in k991598, Hitachi 917 in k013757 and cobas c501s in k060373. The Roche Acetaminophen assay consists of the following reagents:

1. **R1** Sodium periodate 3.75 mmol/L
2. **R2** Arylacylamidase (microbial) ≥ 7000 U/L; o-cresol 3.75 mmol/L

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Roche Cobas Integra Acetaminophen
   Roche Acetaminophen Assay
   Cobas 6000 Series System

2. Predicate 510(k) number(s):
   k991598
   k013757
   k060373

3. Comparison with predicate:

Feature	Cobas c501 Acetaminophen (Candidate)	Cobas c501 Acetaminophen (Predicate k060373)
Indications for Use	In Vitro test for the quantitative determination of toxic levels of acetaminophen in serum and plasma on Roche/ Hitachi and cobas c systems	Same
Methodology	Enzymatic- end point	Same
Sample types	Serum and plasma	Same
Calibrators	COBAS Integra calibrators	Same
Reagents	R1: Sodium periodote 3.75 mmol/L R2: Arlyacylamidase (microbial) ≥7000U/L; o-cresol 3.75 mmol/L	Same
Measuring range	15-500 µg/ml	1.2-500 µg/ml

LoQ	15 µg/dL	1.2 µg/dL

Feature	**Hitachi 917 Acetaminophen (Candidate)**	**Hitachi 917 Acetaminophen (Predicate k013757))**
Indications for Use	The Roche Acetaminophen assay is for the quantitative determination of toxic levels of acetaminophen in human serum or plasma on automated clinical chemistry analyzers	Same
Methodology	Enzymatic- end point	Same
Sample types	Serum and plasma	Same
Calibrators	COBAS Integra calibrators	Same
Reagents	R1: Sodium periodote 3.75 mmol/L R2: Arlyacylamidase (microbial) ≥7000U/L; o-cresol 3.75 mmol/L	Same
Measuring range	15 - 500 µg/ml	1.2-500 µg/ml
LoQ	15 µg/dL	1.2 µg/dL

Feature	**COBAS Integra Acetaminophen (Candidate)**	**COBAS Integra Acetaminophen (Predicate k991598)**
Indications for Use	In Vitro test for the quantitative determination of toxic levels of acetaminophen in serum or heparinized plasma on COBAS INTEGRA systems	Same
Methodology	Enzymatic- end point	Same
Sample types	Serum and plasma	Same
Calibrators	COBAS Integra calibrators	Same

Reagents	R1: Arlyacylamidase (microbial) ≥7000U/L; o-cresol 3.75 mmol/L R2: Sodium periodote 3.75 mmol/L	Same
Measuring range	15-300 µg/ml	0.7-300 µg/ml
LoQ	15 µg/dL	0.7 µg/dL

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

None were referenced.

L. Test Principle:

The enzyme, arylacylamidase, cleaves the amide bond of the acetaminophen molecule, leaving p-aminophenol and acetate. Subsequently, the p-aminophenol is converted to an indophenol in the presence of o-cresol and a periodate catalyst. The production of indophenol is followed colorimetrically. The change in absorbance is directly proportional to the quantitative drug concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

Analytical performance of these devices was reviewed under k991598, k013757, k060373. Additional Interference study was included in this submission.

a. Precision/Reproducibility:

Established in original submissions (k991598, k013757, k060373)

b. Linearity/assay reportable range:

Established in original submissions (k991598, k013757, k060373)

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

Established in original submissions (k991598, k013757, k060373)

d. Detection limit:

Established in original submissions (k991598, k013757, k060373): For cobas c501 and Hitachi 917 the original LoQ was 1.2 µg/dL, while for the Integra assay the original LoQ was 0.7 mg/dL; however, due to the bilirubin interference, the claimed LoQ of the candidate acetaminophen assay is limited to 15 µg/dL for all three analyzers.

e. Analytical specificity:

Established in original submissions (k991598, k013757, k060373):
Additional studies were performed to evaluate the effects of endogenous

interferences such as 1. icterus (bilirubin), I index, 2. hemolysis (hemoglobin), H index, and 3. lipemia (intralipids), L index. Specifically, conjugated and unconjugated bilirubin, hemoglobin (erythrocyte lysates) and lipids (intralipids) were tested according to the CLSI EP7-A2 guideline. Normal human serum pools with very low serum indices for icterus, hemolysis and lipemia were spiked with acetaminophen and endogenous substances including conjugated and unconjugated bilirubin, erythrocyte lusate and intralipids (study #1). For each sample, acetaminophen recovery was measured with three replicates and the I/H/L index was determined. In addition, unaltered (native) patient samples with high bilirubin levels and spiked acetaminophen were tested in these studies as well (study #2). The sponsor defined insignificant interference as less than 10% difference between the control and test samples. The notes in the labeling state that acetaminophen assay results cannot be released to the users under conditions where interference is greater than 10%. Results are summarized below.

Cobas c501:

Bilirubin:

Study #1
Conjugated bilirubin:

I Index	% Difference for samples with acetaminophen ~ 14.86	I Index	% Difference for samples with acetaminophen of ~ 30.90	I Index	% Difference for samples with acetaminophen of ~ 50.90	I Index	% Difference for samples with acetaminophen of ~ 95.50
0	0.0	0	0.0	0	0.0	0	0.0
1	-3.7	9	6.1	13	6.7	7	0.1
2	1.5	12	7.4	24	9.2	14	0.7
4	2.2	14	9.1	29	9.4	20	1.5
6	8.9	22	11.7	n/a	n/a	27	1.0
8	8.1	29	12.9	n/a	n/a	34	-1.9
11	13.3	n/a	n/a	n/a	n/a	40	-2.7
13	17.8	n/a	n/a	n/a	n/a	46	-4.6
16	20.7	n/a	n/a	n/a	n/a	53	-5.4
21	23.0	n/a	n/a	n/a	n/a	58	-6.5
26	23.7	n/a	n/a	n/a	n/a	64	-5.6

I Index value – corresponds approximately to mg/dL of bilirubin (17 μmol/L).

Study #2:

I Index	% Difference for samples with acetaminophen of ~ 18.75	% Difference for samples with acetaminophen of ~ 35.35	% Difference for samples with acetaminophen of ~ 58.85	% Difference for samples with acetaminophen of ~ 113.05	% Difference for samples with acetaminophen of ~ 264.40

1	0.0	0.0	0.0	0.0	0.0
3	-4.0	-1.6	-1.9	-0.1	-1.1
5	-2.9	-2.3	-3.7	-1.5	-1.3
7	-2.7	-3.3	-6.5	-2.4	-1.7
8	-4.0	-5.0	-8.5	-3.0	-2.6
10	-2.1	-3.4	-10.2	-4.3	-2.9
12	-0.5	-5.0	-12.7	-5.1	-4.0
15	-1.3	-5.4	-15.9	-6.1	-4.1
23	4.0	-6.6	-25.1	-10.3	-9.6

Based on the study data summarized in the tables above and assuming the worst possible outcome/interference when either normal serum pool spiked with conjugated bilirubin or serum pool with high total bilirubin were tested, the sponsor stated in the black box warning statement that "an acetaminophen result cannot be released if it is below the measuring range or has an associated bilirubin level above the I index of 8"- see table below:

Acetaminophen [µg/mL]	Interference occurs with an I index* greater than
15 - 30	8
> 30 - 50	8
> 50	8

* I Index value – corresponds approximately to mg/dL of bilirubin

Hemolysis:

Acetaminophen [µg/mL]	Interference occurs with an H* Index greater than
15 - 30	40
> 30 - 50	250
> 50	500

* An H Index of 1 corresponds to an approximate 1 mg/dL of hemoglobin (0.625 µmol/L)

Based on the study data summarized in the table above, sponsor stated in the package insert the following: "Hemolysis causes a significant interference with the acetaminophen assay. Do not use hemolyzed samples. Acetaminophen results cannot be released if the associated H index is greater than 40".

Lipemia:

Acetaminophen [µg/mL]	Interference occurs with an L* Index greater than
15 - 30	1300
> 30 - 50	2000

> 50	2000

* An L index of 1000 is equivalent to a 1000 mg/dL Intralipid solution

Based on the study data summarized in the table above, sponsor stated in the package insert the following: "Lipemia may cause a significant interference with the acetaminophen assay. Acetaminophen results cannot be released if the associated L index is greater than 1300".

Hitachi917:

Bilirubin

Study #1
Unconjugated bilirubin:

I Index	% Difference for samples with acetaminophen of ~ 14.86	I Index	% Difference for samples with acetaminophen of ~ 32.90	I Index	% Difference for samples with acetaminophen of ~ 52.10	I Index	% Difference for samples with acetaminophen of ~ 90.20
0	0.0	0	0.0	0	0.0	0	0.0
1	-0.7	8	2.1	13	3.6	7	-1.4
2	3.0	10	3.3	24	3.3	14	-3.8
4	4.5	12	4.6	29	10.0	20	-4.4
7	13.4	20	13.4	n/a	n/a	27	-6.2
9	9.7	24	22.0	n/a	n/a	34	-1.6
11	12.7	n/a	n/a	n/a	n/a	40	6.1
13	13.4	n/a	n/a	n/a	n/a	46	18.5
16	16.4	n/a	n/a	n/a	n/a	53	28.9
21	15.7	n/a	n/a	n/a	n/a	58	34.0
25	14.2	n/a	n/a	n/a	n/a	64	32.8

Study #2:

I Index	% Difference for samples with acetaminophen of ~ 19.55	% Difference for samples with acetaminophen of ~ 34.90	% Difference for samples with acetaminophen of ~ 57.65	% Difference for samples with acetaminophen of ~ 109.25	% Difference for samples with acetaminophen of ~ 252.20
1	0.0	0.0	0.0	0.0	0.0
2	-2.3	-0.3	-1.6	-0.7	-0.2
4	-1.3	0.4	-3.6	-1.3	-1.1
5-6	2.3	0.4	-.5.5	-2.3	-1.4
7	2.3	1.1	-6.2	-2.7	-3.0
9	6.4	0.7	-8.5	-3.8	-3.3

10-11.5	10.2	1.1	-13.3	-4.3	-4.0
12-13	11.0	0.9	-21.8	-5.9	-5.1
19	14.3	-0.7	-21.8	-10.0	-7.9

Based on the study data summarized in the tables above for both the normal serum pool spiked with unconjugated bilirubin or the serum pool with high total bilirubin, the sponsor stated in the black box warning statement that "an acetaminophen result cannot be released if it is below the measuring range or has an associated bilirubin level above the I index " of 4 for acetaminophen samples ~ 15 µg/dL, and 9 for samples between 30-50 µg/dL and above 50 µg/dL of acetaminophen (please see section H.3. above) - see table below.

Acetaminophen [µg/mL]	Interference occurs with an I index* greater than
15 - 30	4
> 30 - 50	9
> 50	9

* I Index value – corresponds approximately to mg/dL

Hemolysis

Acetaminophen [µg/mL]	Interference occurs with an H* Index greater than
15 - 30	35
> 30 - 50	50
> 50	150

* An H Index of 1 corresponds to an approximate 1 mg/dL of hemoglobin (0.625 µmol/L)

Based on the study data summarized in the table above, sponsor stated in the product insert the following: "Hemolysis causes a significant interference with the acetaminophen assay. Do not use hemolyzed samples. Acetaminophen results cannot be released if the associated H index is greater than 35".

Lipemia:

Acetaminophen [µg/mL]	Interference occurs with an L* Index greater than
15 - 30	800
> 30 - 50	1800
> 50	2000

* An L index of 1000 is equivalent to a 1000 mg/dL Intralipid solution

Based on the study data summarized in the table above, sponsor stated in the package insert the following: “Lipemia may cause a significant interference with the acetaminophen assay. Acetaminophen results cannot be released if the associated L index is greater than 800”.

Integra 800:

Bilirubin

Study #1
Conjugated bilirubin:

I Index	% Difference for samples with acetaminophen of ~ 14.86	I Index	% Difference for samples with acetaminophen of ~ 33.90	I Index	% Difference for samples with acetaminophen of ~ 53.90	I Index	% Difference for samples with acetaminophen of ~ 90.20
0	0.0	0	0.0	0	0.0	0	0.0
1	0.5	9	-8.3	13	-8.6	7	-1.4
2	-1.5	12	-10.9	24	-13.3	14	-3.8
4	-5.8	14	-13.3	29	-14.6	20	-4.4
7	-14.2	14	-16.5	n/a	n/a	27	-6.2
9	-19.3	22	-19.8	n/a	n/a	34	-1.6
11	-18.8	29	-18.3	n/a	n/a	40	6.1
13	-24.1	n/a	n/a	n/a	n/a	46	18.5
16	-25.0	n/a	n/a	n/a	n/a	53	28.9
21	-30.2	n/a	n/a	n/a	n/a	58	34.0
25	-30.5	n/a	n/a	n/a	n/a	64	32.8

Study #2

I Index	% Difference for samples with acetaminophen of ~ 18.40	I Index	% Difference for samples with acetaminophen of ~ 35.00	% Difference for samples with acetaminophen of ~ 62.05	% Difference for samples with acetaminophen of ~ 117.45	% Difference for samples with acetaminophen of ~ 260.65
0	0.0	1	0.0	0.0	0.0	0.0
2	-0.8	3	-2.0	-1.9	-1.2	-1.1
4	-0.5	4-5	-3.0	-4.2	-2.6	-1.5
6	0.0	6	-4.1	-5.4	-3.4	-1.6
8	1.4	8	-4.0	-7.1	-5.1	-1.4
10	2.4	10	-4.1	-7.4	-6.0	-3.2
12	4.9	12	-4.0	-9.8	-7.8	-3.1
15	7.3	14-	-5.6	-11.0	-9.3	-4.1

		15				
21	12.8	21	-6.9	-17.5	-15.2	-6.4

Based on the study data summarized in the tables above and assuming the worst possible outcome/interference when either normal serum pool spiked with conjugated bilirubin or serum pool with high total bilirubin were tested, the sponsor stated in the black box warning statement that "an acetaminophen result cannot be released if it is below the measuring range or has an associated bilirubin level above the I index" of 4 for ~ 15 µg/dL acetaminophen, 9 for acetaminophen levels between 30-50 µg/dL and 12 for samples above 50 µg/dL of acetaminophen (please see section H.3. above))- see table below.

Acetaminophen [µg/mL]	Interference occurs with an I index* greater than
15 - 30	4
> 30 - 50	9
> 50	12

* I Index value – corresponds approximately to mg/dL of bilirubin

Hemolysis

Acetaminophen [µg/mL]	Interference occurs with an H* Index greater than
15 - 30	8
> 30 - 50	200
> 50	350

* An H Index of 1 corresponds to an approximate 1 mg/dL of hemoglobin (0.625 µmol/L)

Based on the study data summarized in the table above, sponsor stated in the package insert the following: "Hemolysis causes a significant interference with the acetaminophen assay. Do not use hemolyzed samples. Acetaminophen results cannot be released if the associated H index is greater than 8".

Lipemia

Acetaminophen [µg/mL]	Interference occurs with an L* Index greater than
15 - 30	1400
> 30 - 50	1800
> 50	2000

* An L index of 1000 is equivalent to a 1000 mg/dL Intralipid solution

Based on the study data summarized in the table above, sponsor stated in the package insert the following: "Lipemia may cause a significant interference with the acetaminophen assay. Acetaminophen results cannot be released if the associated L index is greater than 1400".

f. Assay cut-off:

2. Comparison studies:

   a. Method comparison with predicate device:
   Established in original submissions (k991598, k013757, k060373)

   b. Matrix comparison:
   Established in original submissions (k991598, k013757, k060373)

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:
   Existing literature reference was used:
   1. Tietz NW. In: Textbook of Clinical Chemistry. Philadephia, PA; 1986.
   2. Rumack BH. Acetaminophen overdose. Arch Intern Med 1981 ;141 :380. and the following was recommended in the product insert:
      "Toxic manifestations have been observed at serum concentrations> 100 μg/mL (> 662 μmol/L), however the toxic range is generally reported at >200 μg/mL (> 1324μmol/L). Toxic concentrations can be more effectively related to post dose interval; >200, > 100, and> 50 μg/mL (> 1324, >662, and >331 μmol/L) serum concentrations correspond to toxic concentrations at 4, 8, and 12 hours post dose, respectively. The therapeutic range varies and has been reported to be 10 to 30 μg/mL (66 to 199μmoVL). Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

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.