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

A. 510(k) Number: K031902

B. Analyte: Carbamazepine

C. Type of Test: Quantitative homogeneous microparticle agglutination immunoassay

D. Applicant: Roche Diagnostics Corporation

E. Proprietary and Established Names: ONLINE TDM Carbamazepine

F. Regulatory Information:
1. Regulation section: 21 CFR § 862.3645

2. Classification: Class II

3. Product Code: KLT

4. Panel: Toxicology (91)

G. Intended Use:
1. Intended use(s):
   The ONLINE TDM Carbamazepine assay is for the quantitative determination of carbamazepine in human serum or plasma on automated clinical chemistry analyzers.

2. Indication(s) for use:
   The ONLINE TDM Carbamazepine assay is for the quantitative determination of carbamazepine in human serum or plasma on automated clinical chemistry analyzers. This neuroleptic drug assay test system is a device intended to measure in serum or plasma the dopamine receptor blocking activity of carbamazepine.

   This device is for in vitro diagnostic use, and intended for prescription use.

3. Special condition for use statement(s):
   Not applicable.

4. Special instrument Requirements:
   The device is for use on automated clinical chemistry analyzers. Performance was demonstrated in this submission on the Roche Hitachi 917 analyzer and protocols for testing and minimum acceptance criteria were submitted for qualifying the assay on the Roche Hitachi 911, 912 and Modular P analyzers.

H. Device Description:
The ONLINE TDM Carbamazepine assay is for the quantitative determination of carbamazepine in human serum or plasma on automated clinical chemistry analyzers. It is a homogeneous microparticle agglutination immunoassay based on the kinetic interaction of microparticles (KIMS). Biotinylated drug hapten serves as the binding partner to anti-carbamazepine antibody and streptavidin coated latex beads. A competitive reaction to a limited amount of specific anti-carbamazepine antibody takes place between the hapten and free carbamazepine in the sample. A decrease in the apparent signal produced by the microparticle agglutination is proportional to the amount of drug present in the sample.

I. Substantial Equivalence Information:
1. Predicate device name(s): COBAS INTEGRA Carbamazepine assay

2. Predicate K number(s): K951595

3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended Use	Therapeutic Drug Monitoring of Carbamazepine	Therapeutic Drug Monitoring of Carbamazepine
Matrix	Human serum and plasma	Human serum and plasma
Calibrators and Controls	COBAS-FP Carbamazepine calibrators and TDM Multianalyte controls	COBAS-FP Carbamazepine calibrators and TDM Multianalyte controls
Differences		
Item	**Device**	**Predicate**
Methodology	Kinetic interaction of microparticles in a solution	Fluorescence Polarization Immunoassay
Chemistry Analyzers	Roche Hitachi analyzers	COBAS INTEGRA analyzers

J. Standard/Guidance Document Referenced (if applicable):
Not applicable.

K. Test Principle:
The ONLINE TDM Carbamazepine assay is for the quantitative determination of carbamazepine in human serum or plasma on automated clinical chemistry analyzers. It is a homogeneous microparticle agglutination immunoassay based on the kinetic interaction of microparticles (KIMS). Biotinylated drug hapten serves as the binding partner to anti-carbamazepine antibody and streptavidin coated latex beads. A competitive reaction to a limited amount of specific anti-carbamazepine antibody takes place between the hapten and free carbamazepine in the sample. A decrease in

the apparent signal produced by the microparticle agglutination is proportional to the amount of drug present in the sample.

L. Performance Characteristics (if/when applicable):
1. <u>Analytical performance:</u>
   a. *Precision/Reproducibility:*
      Reproducibility was determined in two different experiments using three levels of the COBAS-FP Multianalyte controls and a low and high human serum pool. Within-run imprecision was calculated from 21 determinations of each of the samples. Day to Day imprecision was calculated using one determination of the five samples in one run per day for 21 days. Total imprecision was calculation using three determinations of the five samples in one run per day for 21 days.

Sample	Within-run			Day-to-Day			Total		
	Mean	**SD**	**%CV**	**Mean**	**SD**	**%CV**	**Mean**	**SD**	**%CV**
Level I	2.9	0.05	1.6	2.8	0.15	5.4	2.8	0.15	5.6
Level II	8.4	0.14	1.6	8.3	0.32	3.8	8.3	0.36	4.3
Level III	14.4	0.29	2.1	14.1	0.49	3.5	14.1	0.55	3.9
Low	6.3	0.12	1.9	5.8	0.21	3.6	5.8	0.21	3.6
High	12.2	0.29	2.3	12.2	0.48	3.9	12.2	0.44	3.6

   b. *Linearity/assay reportable range:*
      To assess linearity a drug free pool of human serum was spiked to a high concentration and diluted with a pool of drug free serum. Results were evaluated by linear regression.

% High Sample	Theoretical Value (ug/mL)	Assayed Value (ug/mL)	% Recovery
100	27.3	31.0	113.3
90	24.6	27.0	109.6
80	21.8	23.5	107.7
70	19.1	19.1	100
60	16.3	15.7	96.0
50	13.6	13.6	100
40	10.8	10.8	100
30	8.1	7.8	96.4
20	5.3	5.2	97.2
10	2.6	2.6	100

   c. *Traceability (controls, calibrators, or method):*
      Not applicable.

d. *Detection limit:*
   The lower detection limit is 0.2 ug/mL as determined by the zero
   calibrator plus 2 standard deviations.

e. *Analytical specificity:*
   The following compounds were tested for cross-reactivity at two
   different levels of carbamazepine concentrations:

Compound	Concentration Tested ug/mL	% Cross-reactivity at ≈ 6 ug/mL drug	% Cross-reactivity at ≈ 13 ug/mL drug
10-Hydroxycarbamazepine	100	1.2	1.6
5-(p-Hydroxyphenyl)-5-phenyl	1000	ND	ND
Acetaminophen	200	0.3	0.6
Acetyl cysteine	150	0.7	2.2
Acetylsalicylic Acid	1000	1.0	1.9
Amitriptylene	100	0.2	0.3
Amobarbital	1000	ND	0
Ampicillin-Na	1000	1.7	0.1
Ascorbic Acid	300	0.3	0.6
Carbamazepine-10,11-epoxide	29.6	14.0	17.6
Cefoxitin	2500	9.3	5.8
Chlordiazepoxide	30	ND	ND
Clonazepam	12	ND	ND
Cyclosporine	5	2	0.6
Diazepam	25	ND	0.7
Doxycycline (Tetracycline)	50	2.7	2.2
Ethosuximide	1000	ND	ND
Ethotoin	1000	ND	ND
Glutethimide	1000	ND	0
Ibuprofen	500	0.8	0.8
Imipramine	200	0.1	0.2
K-Dobesilate	200	1.9	0.2
Levodopa	20	1.8	0.2
Mephenytoin	1000	0	ND
Methosuximide	100	ND	0.2
Methyldopa + 1,5	20	1.4	0.8
Metronidazole	200	1	1.1
Nortriptylene	50	0.5	0.8
Oxacarbazepine	100	1.0	1.4
Phenobarbital	1000	ND	ND
Phenothiazine	200	0.1	0.2
Phenylbutazone	400	2.2	3.4
Phenytoin	1000	0	0

Compound	Concentration Tested ug/mL	% Cross-reactivity at ≈ 6 ug/mL drug	% Cross-reactivity at ≈ 13 ug/mL drug
p-Hydroxyphenobarbital	100	ND	0.2
Primidone	1000	ND	0
Probenecid	500	ND	0.1
Promethazine	1000	0	0.1
Rifampicin	60	1	3.1
Secobarbital	1000	ND	0
Theophylline	100	1.4	1.6

      f. *Assay cut-off:*
         Not Applicable

2. Comparison studies:
      a. *Method comparison with predicate device:*
         A total of 102 non-pooled human serum samples were tested with the ONLINE TDM Carbamazepine assay on a Roche Hitachi 917 analyzer and with the COBAS-FP Carbamazepine assay on an Integra 700 analyzer. A comparison of the data from the two assays with Passing-Bablok regression and linear regression analyses gave best fits with slopes of 1.068 and 1.062, respectively, and y intercepts of -0.20 and -0.17, respectively ($r = 0.984$ for both). Sample concentrations were between 0.5 and 11.93 ug/mL.

      b. *Matrix comparison:*
         Comparison of results obtained with human serum and lithium heparin plasma, sodium heparin plasma, EDTA K2 plasma and EDTA K3 plasma were performed. All Passing-Bablok regression analyses have slopes between 0.9 and 1.1 and correlation coefficient $r \geq 0.95$.

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. <u>Expected values/Reference range:</u>
   Not Applicable

M. Conclusion:

Based upon the information provided, I recommend that the ONLINE TDM Carbamazepine assay be found substantially equivalent to predicate devices according to 21 CFR § 862.3645.