510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k182063

B. Purpose for Submission:

Adding previously cleared assays to a new instrument platform

C. Measurand:

Carbamazepine, Creatinine, and Total Bilirubin

D. Type of Test:

Carbamazepine assay: quantitative competitive immunoassay
Creatinine assay: quantitative colorimetric assay
Total Bilirubin assay: quantitative colorimetric assay

E. Applicant:

Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:

VITROS Chemistry Products CRBM Slides
VITROS Chemistry Products CREA Slides
VITROS Chemistry Products TBIL Slides
VITROS XT 7600 Integrated System

G. Regulatory Information:

Analyte	Product Code	Classification	Regulation Section	Panel
Creatinine	JFY	II	21 CFR 862.1225	Chemistry (75)
Total Bilirubin	CIG	II	21 CFR 862.1110	Chemistry (75)
Carbamazepine	KLT	II	21 CFR 862.3645	Toxicology (91)
Discrete photometric chemistry analyzer for clinical use	JJE	I	21 CFR 862.2160	Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indication(s) for use below.

2. Indication(s) for use:

   Carbamazepine: Rx Only. For *in vitro* diagnostic use only. VITROS Chemistry Products CRBM Slides quantitatively measure carbamazepine (CRBM) concentration in serum and plasma using VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600/ XT 7600 Integrated System. Measurements obtained are used in monitoring levels of carbamazepine to help ensure appropriate therapy.

   Creatinine: Rx Only. For *in vitro* diagnostic use only. VITROS Chemistry Product CREA Slides quantitatively measure creatinine (CREA) concentration in serum, plasma, and urine using VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600/ XT 7600 Integrated System. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.

   Total Bilirubin: Rx Only. For *in vitro* diagnostic use only. VITROS Chemistry Products TBIL Slides quantitatively measure total bilirubin (TBIL) concentration in serum and plasma using VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600/ XT 7600 Integrated System. Measurements of the levels of bilirubin are used in the diagnosis and treatment of liver, hemolytic hematological and metabolic disorders, including hepatitis and gall bladder block.

   VITROS XT 7600 Integrated System: Rx Only. For *in vitro* diagnostic use only. The VITROS XT 7600 Integrated System is intended for use in the measurement of a variety of analytes of clinical interest.

3. Special conditions for use statement(s):

   For prescription use only.
   Not for Point-of-Care use.

4. Special instrument requirements:

   VITROS XT 7600 Integrated System

I. Device Description:

VITROS Chemistry Products CRBM Slides
The VITROS CRBM Slide is a multilayered, analytical element coated on a polyester support. The reactive ingredients per cm^2 are immobilized mouse monoclonal anti-carbamazepine antibody 0.02 mg; carbamazepine-horseradish peroxidase conjugate 1.6 ng; and 2-(3,5- dimethoxy-4-hydroxyphenyl)-4,5-bis(4-dimethylaminophenyl) imidazole (leuco dye) 0.02 mg.

VITROS Chemistry Products CREA Slides

The VITROS CREA Slide is a multilayered, analytical element coated on a polyester support. The reactive ingredients per cm^2 are creatinine amidohydrolase (*Flavobacterium sp.*) 0.20 U; creatine amidinohydrolase (*Alcaligenes sp.*) 3.6 U; sarcosine oxidase (*Bacillus sp*.) 0.55 U; peroxidase (horseradish root) 1.6 U and 2- (3,5-dimethoxy-4-hydroxyphenyl)-4,5-bis(4- dimethylaminophenyl) imidazole (leuco dye) 32 µg.

VITROS Chemistry Products TBIL Slides

The VITROS TBIL Slide is a multilayered, analytical element coated on a polyester support. The reactive ingredients per cm^2 are dyphylline 0.5 mg and 4-(N-carboxymethylaminosulfonyl) benzene diazonium hexafluorophosphate 57 µg.

VITROS XT 7600 Integrated system:

The VITROS XT 7600 Integrated System is a fully automated, computer controlled, clinical chemistry and immunodiagnostic analyzer intended for the in vitro determination of a variety of analytes in biological fluids such as serum, plasma, urine and cerebral spinal fluid. The System operates in conjunction with reagents, calibrators and controls designed for use with the system in the MicroSlide format.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITROS CRBM Slides on the VITROS 5600 Integrated System
   VITROS CREA Slides on the VITROS 5600 Integrated System
   VITROS TBIL Slides on the VITROS 5600 Integrated System
   VITROS 5600 Integrated System

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

   k160495
   k063591
   k081543
   k840880

3. Comparison with predicate:

Carbamazepine:

Similarities and Differences		
Device Characteristic	**Candidate Device VITROS CRBM Slides k182063**	**Predicate Device VITROS CRBM Slides k160495**
Intended Use	For the quantitative measurement of carbamazepine (CRBM) concentration in serum and	Same
Measuring range	3.0–20.0 (µg/mL)	Same
Basic principle	Multiple-point Immuno-rate	Same
Wavelength	670 nm, 540 nm is also used for wash detection	Same
Sample type	Serum and plasma	Same
Sample volume	11 µL	Same
Instrumentation	VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600/ **XT 7600** Integrated System	VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600 Integrated System

Creatinine:

Similarities and Differences		
Device Characteristic	**Candidate Device VITROS CREA Slides k182063**	**Predicate Device VITROS CREA Slides k063591**
Intended Use	For the quantitative measurement of creatinine (CREA) concentration in serum, plasma, and urine.	Same
Measuring range	Serum/Plasma 0.15–14.0 (mg/dL), Urine 3.2–346.5 (mg/dL)	Same
Basic principle	Two-point rate	Same
Wavelength	670 nm	Same
Sample type	Serum, plasma, urine	Same
Sample volume	6 µL	Same
Instrumentation	VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600/ **XT 7600** Integrated System	VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600 Integrated System

Total Bilirubin:

Similarities and Differences		
Device Characteristic	**Candidate Device VITROS TBIL Slides k182063**	**Predicate Device VITROS TBIL Slides k840880**
Intended Use	For the quantitative measurement of total bilirubin (TBIL) concentration in serum and plasma.	Same
Measuring range	0.1–27.0 (mg/dL)	Same
Basic principle	Dual wavelength endpoint	Same
Wavelength	measured at 2 wavelengths, 460 and 540nm	Same
Sample type	Serum and plasma	Same
Sample volume	10 μL	Same
Instrumentation	VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600/ **XT 7600** Integrated System	VITROS 250/350/950/5,1 FS and 4600 Chemistry Systems and the VITROS 5600 Integrated System

VITROS XT 7600 Integrated System:

Similarities and Differences		
Device Characteristic	**Candidate Device VITROS XT 7600 Integrated System k182063**	**Predicate Device VITROS 5600 System k081543**
Intended use	For use in the measurement of a variety of analytes of clinical interest.	Same
Operating principle	Sample programming, sampling processing, result calculation, result reporting	Same
Modes of operation	Continuous, Random, STAT	Same
Throughput	845 tests per hour	Same

Similarities and Differences		
Device Characteristic	**Candidate Device VITROS XT 7600 Integrated System k182063**	**Predicate Device VITROS 5600 System k081543**
Fundamental scientific technology	The analyzer uses four main detection systems: 1. Reflection densitometry for colorimetric and Immunorate VITROS MicroSlides. 2. Transmission spectrophotometry for VITROS MicroTip assays. 3. Enhanced chemiluminescent detection for VITROS MicroWell assays. 4. Electrometer for VITROS MicroSlide ion-selective electrode (ISE) assays.	Same
User interface	Touch screen (17-inch monitor), keyboard, ADD	Same
Sample and reagent volume verification	Verification to ensure sufficient quantity of sample and reagent to run requested assays	Same
On-Board Dilution Range	Dilution factor of 1: 400	Same
Predictive alerts through eConnectivity	The predictive alerts are logged and are electronically sent to the equipment service group real time for monitoring.	Same
e-Connectivity	Yes	Same
The following subsystems of the VITROS 5600 Integrated System are modified	REFL – Reflectometer SLIN – Slide Incubator SLSU – Slide Supply SAIN – Sample Integrity SRME – Sample and Reagent Metering SWCT - System Control and Sample Processing Software SWIN – Software Infrastructure SWUI – Graphical User Interface Software ADDI – Assay Data Disk.	All modifications pertain solely to the MicroSlide processing center. There are no changes being made to the MicroTip and MicroWell processing centers.

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

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline -Third Edition

CLSI EP06-A, Evaluation of Linearity of Quantitative Measurement Procedures, Approved Guideline;1st Edition

CLSI EP07, Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition

CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition

IEC 61010-1:2010, Safety Requirement for Electrical Equipment for Measurement, Control, and Laboratory Use-Part 1: General Requirements

IEC 61010-2-010:2014, Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use-Part 2-010: Particular Requirements for Laboratory Equipment for the Heating of Materials

IEC 61010-2-101:2015, Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use-Part 2-101: Particular Requirements for In Vitro Diagnostic (IVD) Medical Equipment

IEC/EN 61326-1:2012- Electrical Equipment for Measurement, Control and Laboratory Use-EMC requirements-Part 1: General Requirements

IEC/EN 61326-2-6:2013- Electrical Equipment for Measurement, Control and Laboratory Use-EMC requirements-Part 2-6: Particular Requirements- In Vitro Diagnostic (IVD) Medical Equipment

L. Test Principle:

VITROS CRBM Slides (Multiple-point colorimetric/immuno-rate assay):

A drop of patient sample is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. Carbamazepine in the sample competes with the carbamazepine-peroxidase conjugate for a limited number of antibody binding sites during incubation. The subsequent addition of 12 µL of VITROS Immuno-Wash Fluid to the slide removes unbound carbamazepine-peroxidase conjugate from the read area, while also providing a substrate for the enzyme mediated oxidation of leuco dye. The rate of dye formation, as monitored by reflectance spectrophotometry during incubation, is inversely proportional to the carbamazepine concentration in the sample. To determine if an adequate wash has occurred, a wash detection dye is read at 540 nm during incubation.

VITROS CREA Slides (Colorimetric, two-point rate assay):

A drop of patient sample is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. Creatinine diffuses to the reagent layer, where it is hydrolyzed to creatine in the rate-determining step. The creatine is converted to sarcosine and urea by creatinine amidinohydrolase. The sarcosine, in the presence of sarcosine oxidase, is oxidized to glycine, formaldehyde, and hydrogen peroxide. The final reaction involves the peroxidase-catalyzed oxidation of a leuco dye to produce a colored product. Following addition of the sample, the slide is incubated. During the initial reaction phase, endogenous creatine in the sample is oxidized. The resulting change in reflection density is measured at 2-time points. The difference in reflection density is proportional to the concentration of creatinine present in the sample

VITROS TBIL Slides (Colorimetric, dual-wavelength endpoint):

A drop of patient sample is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. This layer provides a reflective background for measuring the diazo products of bilirubin and contains all reagents necessary to determine total bilirubin. The method uses dyphylline to dissociate unconjugated bilirubin from albumin. Unconjugated bilirubin, conjugated bilirubin, and albumin-linked bilirubin (delta) subsequently react with the diazonium salt 4-(N-carboxymethylsulfonyl) benzenediazonium hexafluorophosphate to produce azobilirubin chromophores that have similar molar absorptivity and absorbance maxima around 520 nm. The concentration of total bilirubin is determined by measuring the azobilirubin chromophores at two wavelengths through the transparent support. The reflectance measurement at 460 nm corrects for spectral interferences.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

      Precision studies were conducted following EP05-A3 guideline. The study was performed by testing a minimum of two quality control fluids and three human serum pools using the Carbamazepine (CRBM), Creatinine (CREA), and Total Bilirubin (TBIL) assays. Samples were analyzed using one VITROS XT 7600 Integrated System over 20 days, with 2 runs per day and 2 replicates per specimen (n=80). The results of the precision studies are shown in the tables below:

Carbamazepine Serum:

Sample	Mean (µg/mL)	Repeatability (Within Run)		Within Day		Within Lab (Total)	
		SD	%CV	SD	%CV	SD	%CV
Serum Pool 1	3.9	0.13	3.30	0.13	3.30	0.16	3.98
QC -1	4.7	0.14	2.97	0.14	3.02	0.16	3.32
QC -2	10.1	0.24	2.38	0.25	2.46	0.28	2.76
Serum Pool 3	11.6	0.30	2.57	0.35	2.98	0.39	3.37
QC -3	13.1	0.29	0.35	0.35	2.67	0.41	3.14
Serum Pool 5	17.6	0.33	0.37	0.37	2.10	0.42	2.41

Creatinine Serum:

Sample	Mean (mg/dL)	Repeatability (Within Run)		Within Day		Within Lab (Total)	
		SD	%CV	SD	%CV	SD	%CV
QC -1	0.82	0.006	0.713	0.009	1.050	0.013	1.579
Serum Pool 1	0.88	0.006	0.642	0.007	0.743	0.016	1.850
S Pool (native)	0.99	0.007	0.697	0.008	0.829	0.17	1.720
QC -2	5.39	0.039	0.716	0.049	0.914	0.088	1.624
Serum Pool 2	9.63	0.057	0.594	0.070	0.729	0.135	1.400
Serum Pool 5	12.65	0.109	0.865	0.109	0.071	0.169	1.337

Creatinine Urine:

Sample	Mean (mg/dL)	Repeatability (Within Run)		Within Day		Within Lab (Total)	
		SD	%CV	SD	%CV	SD	%CV
U QC -1	55.6	0.58	1.05	0.67	1.20	1.24	2.23
Urine Pool 1	78.4	1.10	1.40	1.13	1.44	1.36	1.73
U Pool (native)	88.0	0.69	0.79	0.98	1.11	1.41	1.60
U QC -2	131.2	1.67	1.27	1.89	1.44	2.71	2.06
Urine Pool 4	251.8	1.99	0.79	2.12	0.84	3.90	1.55
Urine Pool 5	320.9	2.99	0.93	3.49	1.09	5.51	1.72

Total Bilirubin serum:

Sample	Mean (mg/dL)	Repeatability (Within Run)		Within Day		Within Lab (Total)	
		SD	%CV	SD	%CV	SD	%CV
Serum Pool 1	0.3	0.01	4.57	0.02	5.20	0.02	6.72
QC-1	1.6	0.03	1.68	0.04	2.88	0.05	3.45
Serum Pool 3	6.5	0.03	0.52	0.06	0.87	0.09	1.40
QC -2	15.3	0.10	0.67	0.16	1.05	0.24	1.60
Serum Pool 5	21.6	0.17	0.77	0.20	0.92	0.34	1.58

b. *Linearity/assay reportable range:*

Linearity studies were performed according to CLSI EP06-A guideline. A series of eleven proportionally related admixtures of low and high levels samples were tested to verify linearity; each sample was tested in duplicate.

The results of the linearity studies support the following claimed measuring ranges for the VITROS CRBM, VITROS CREA, and VITROS TBIL assays:

Analyte	Slope	Intercept	Correlation Coefficient	Range Tested	Claimed Measuring range
Carbamazepine	1.00	0.27	1.00	2.1 - 22.9	3.0 - 20.0 µg/mL
Serum Creatinine	1.00	-0.04	1.00	0.08 - 15.8	0.15 - 14.0 mg/dL
Urine Creatinine	1.01	-0.16	1.00	1.6 - 384.7	3.2 - 346.5 mg/dL
Total bilirubin	1.00	0.29	1.00	0.00 - 27.26	0.10 - 27.00 mg/dL

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

VITROS Chemistry Products CRBM Slides: Values assigned to the VITROS Chemistry Products Calibrator Kit 9 for carbamazepine are traceable to the Certified NIST (National Institute of Standards and Technology) Reference Material, SRM (Standard Reference Material) 1599.

VITROS Chemistry Products CREA Slides: The values assigned to the VITROS Chemistry Products Calibrator Kit 1 for Creatinine are traceable to a Gas Chromatography Isotope Dilution Mass Spectrometry (GC/IDMS) method 8 and National Institute of Standards and Technology (NIST) SRM 914 creatinine standard reference material.

VITROS Chemistry Products TBIL Slides: Values assigned to the VITROS Chemistry Products Calibrator Kit 4 for total bilirubin are traceable to the Certified NIST (National Institute of Standards and Technology) Reference Material, SRM (Standard Reference Material) 916.

d. *Detection limit:*

Detection capability studies for each analyte were evaluated based upon CLSI EP17-A2 guideline.

Limit of blank (LoB) studies were performed by testing 4 blank samples. Samples were tested in replicates of 6 over 3 days, using 3 lots of reagents, 4 samples every day, for a total of 216 observations (72 results per reagent lot). The LoB value for each assay was defined as the highest value achieved using blank samples with the stated probability (i.e. $\alpha = 5\%$). Since the data for all assays were non-gaussian, a

non-parametric approach was applied that estimates the LoB using the calculated rank position corresponding to the 95th percentile of the distribution of blank values observed.

Limit of detection (LoD) studies were performed by testing 4 pools of human samples with analyte concentrations close to the expected detection limit for each analyte. Samples were tested in replicates of 6 over 3 days, using 3 lots of reagents, with the 4 human sample pools every day, for a total of 216 observations (72 results per reagent lot). The LoD was calculated using a pooled SD from the low level sample results and the input LoB value for the assay, determined as described above. The LoD value for the assay was defined as the highest resultant value achieved among the combinations of reagent lots and human pools evaluated, with the stated probability (i.e. β= 5%).

Limit of quantitation (LoQ) studies were performed using 4 pools of low level samples with analyte concentrations close to the expected LoQ of the corresponding assay. Samples were tested in replicates of 4 over 3 days, using 3 lots of reagents, 4 samples every day, for a total of 144 observations (48 results per reagent lot). Ortho defines LoQ as the lowest concentration with a percent total allowable error $\leq$ 19% for carbamazepine; percent total allowable error $\leq$ 30% for creatinine in serum and urine, and total allowable error $\leq$ 0.09 mg/dL for total bilirubin in serum.

The results of the detection capability studies for each assay are presented in the table below.

	CARB (µg/mL)	**TBIL (mg/dL)**	**Creatinine (mg/dL)**	
			Serum/plasma	**Urine**
LoB	0.6108	0.0378	0.0933	1.9973
LoD	0.6821	0.0722	0.0991	2.1986
LoQ	2.6860	0.0616	0.1119	2.0060
Claimed LoQ	3.0	0.10	0.15	3.2
Assay Claimed Range	3.0-20.0	0.10-27.00	0.15-14.0	3.2-346.5

e. *Analytical specificity:*

Interference studies were performed in accordance with CLSI EP07-A2 guideline, by using pool of human serum, plasma or urine (samples may have been spiked or diluted to achieve the appropriate target analyte concentration). Each representative assay was tested at a minimum of two analyte concentrations in 6 replicates on one lot of reagent or multiple lots if needed. Bias was evaluated between interferent test and control samples and compared to the Maximum Allowable Interference (MAI) for each analyte. The substances that were tested included known chemical interferents, common chemical substances identified with potential to interfere based upon risk assessment.

Carbamazepine:
The study was conducted using samples with carbamazepine concentrations of 3 and 12 µg/mL. The sponsor defined non-interference as a bias < 1.4 µg/mL (vs. control condition). The compounds and the highest concentration that don't interfere with the carbamazepine assay are listed in the table below:

Compound	Concentration
Acetaminophen	20 mg/dL
Amitriptyline	1 µg/mL
Amobarbital	100 µg/mL
Amoxicillin	1500 µg/mL
Ascorbic acid	6 mg/dL
Atenolol	20 µg/mL
Caffeine	10 mg/dL
Cephalexin	400 µg/mL
Chlordiazepoxide	2 mg/dL
Chlorpromazine	10 µg/mL
Cholesterol	450 mg/dL
Cimetidine	100 µg/mL
Ciprofloxacin	5 mg/dL
Clomipramine	3 µg/mL
Clonazepam	1 µg/mL
Clorazepate	7 µg/mL
Codeine	4 µg/mL
Creatinine	30 mg/dL
Desipramine	2.5 µg/mL
Dextromethorphan	3.8 µg/mL
Diazepam	20 µg/mL
Digoxin	30 ηg/mL
Diltiazem	5 µg/mL
Diphenhydramine	10 µg/mL
Doxepin	1.5 µg/mL
Enalapril	1.2 µg/mL
Ethanol	200 mg/dL
Ethosuximide	500 µg/mL
Felbatol	30 mg/dL
Fluoxetine	8 µg/mL
Furosemide	10 mg/dL
Gentamicin	120 µg/mL
Glucose	1200 mg/dL
Glutethimide	6 mg/dL

Compound	Concentration
HPPH	200 µg/mL
Hydrochlorothiazide	2 mg/dL
Ibuprofen	70 mg/dL
Imipramine	0.1 mg/dL
Intralipid	800 mg/dL
Lithium	15 mmol/L
Lorazepam	1 µg/mL
Mephobarbital	200 µg/mL
Methsuximide	40 mg/dL
Metoprolol	3.4 µg/mL
Naproxen	900 µg/mL
Nifedipine	2 µg/mL
Nortriptyline	5 mg/dL
PEMA	40 mg/dL
Pentobarbital	100 µg/mL
Phenobarbital	250 µg/mL
Phenytoin	100 µg/mL
Prednisone	1 µg/mL
Primidone	200 µg/mL
Promazine	0.09 mg/dL
Promethazine	10 µg/mL
Protriptyline	2.5 µg/mL
Pseudoephedrine	20 µg/mL
Ranitidine	20 µg/mL
Salicylate, Na salt	50 mg/dL
Secobarbital	100 µg/mL
Sodium bromide	120 mg/dL
Theophylline	25 mg/dL
Tobramycin	12 mg/dL
Total Protein	4.0–9.0 g/dL
Triglycerides	1100 mg/dL
Valproic acid	500 µg/mL
Vancomycin	300 µg/mL
Verapamil	90 µg/mL

Compound	Concentration
Glyburide	6.4 µg/mL
Guaifenesin	100 mg/dL

Compound	Concentration
Warfarin	100 µg/mL

Cross-Reactivity:
Carbamazepine 10,11-epoxide, the major active metabolite of carbamazepine, was tested for cross-reactivity at several concentrations as listed in the table.

Epoxide Conc.	Carbamazepine Concentration (µg/mL)	% Cross Reactivity
2.5	0.0	11.2
	5.2	10.5
	10.1	7.1
10.0	0.0	9.3
	5.2	8.1
	10.1	7.7

The substances that interfere with carbamazepine determinations in serum are summarized in the table below:

Interferent	The highest concentrations of known interfering substances
Ethamsylate	3.0 mg/dL
Gentisic acid	5.0 mg/dL
N-acetylcysteine	100.0 mg/dL
Bilirubin(conjugated)	20.0 mg/dL
Hemoglobin	200.0 mg/dL
Ethanol	394.0 mg/dL

The sponsor included in the labeling the following limitations for carbamazepine:

- Specimens with low total protein <4.0 g/dL (<40.0 g/L) may give a negative bias greater than -1.4 µg/mL (-5.9 µmol/L).
- Specimens with an elevated total protein >9.0 g/dL (>90.0 g/L) may give a positive bias greater than +1.4 µg/mL (+5.9 µmol/L).

Creatinine:
The study was conducted using a minimum of 2 samples with creatinine concentrations of approximately 1.50 and 5.00 mg/dL. The sponsor defined non-interference as a bias <0.13 mg/dL (vs. control condition). The compounds and the highest concentration that don't interfere with the creatinine assay are listed in the table below:

Compound	Concentration
Acetaminophen	400 µg/mL
Acetoacetate	30 mmol/L
Ampicillin	1.5 mg/dL
Amikacin	1.5 mg/dL
Ammonium Chloride	1 mmol/L
Amphotericin B	1.5 mg/dL
Ascorbic Acid	3 mg/dL
Bacitracin	1.5 mg/dL
Bicarbonate	40 mmol/L
Bilirubin	20 mg/dL
Bleomycin Sulfate	1.5 mg/dL
Carbenicillin	1.5 mg/dL
Cefazolin	1.5 mg/dL
Cephalothin	1.5 mg/dL
Cephaloridine	1.5 mg/dL
Cephaloglycin	1.5 mg/dL
Cephalexin	1.5 mg/dL
Cephardine	1.5 mg/dL
Cleocin	1.5 mg/dL
Cloxacillin	1.5 mg/dL
Demeclocycline	1.5 mg/dL
Dextran	1000 mg/dL
Dicloxacillin	1.5 mg/dL
Doxycycline	1.5 mg/dL
Di-cycloserine	1.5 mg/dL
Dilantin	2 mg/dL
Ethambutol	1.5 mg/dL
Ethanol	300 mg/dL
Furazolidone	1.5 mg/dL
5-Flurocytosine	5 mg/dL
Gentamicin	1.5 mg/dL
Glucose	600 mg/dL
Glutathione	1 mg/dL
Hypaque	500 mg/dL
Intralipid	800 mg/dL
Kanamycin	1.5 mg/dL

Compound	Concentration
Isoniazid	1.5 mg/dL
Limcomycin	1.5 mg/dL
Methicillin	1.5 mg/dL
6-Mercaptopurine	1.5 mg/dL
Minocycline	1.5 mg/dL
Nalidixic Acid	1.5 mg/dL
Nafcillin	1.5 mg/dL
Neomycin	1.5 mg/dL
Nitrofurantoin	1.5 mg/dL
Oxacillin	1.5 mg/dL
Oxytetracycline	1.5 mg/dL
Penicillin-g	1.5 mg/dL
Phenobarbital	3 mg/dL
Phenoxymethyl-penicillinic acid	1.5 mg/dL
pH	6.8
pH	8.8
Polymyxin B sulfate	1.5 mg/dL
Polymyxin E	1.5 mg/dL
Potassium	8 mEq/L
Rifampicin	1.5 mg/dL
Spectinomycin	1.5 mg/dL
Streptomycin sulfate	1.5 mg/dL
Sulfachloropyridazine	1.5 mg/dL
Sulfamethoxypyridazine	1.5 mg/dL
Sulfamethoxazole	1.5 mg/dL
Sulfisoxazole	1.5 mg/dL
Sulfadiazine	1.5 mg/dL
Sulfathiazole	6 mg/dL
Tetracycline	1.5 mg/dL
Ticarcillin	1.5 mg/dL
Tolbutamide	22 mg/dL
Triglycerides	800 mg/dL
Vancomycin	1.5 mg/dL
Urea Nitrogen	100 mg/dL
Uric Acid	15 mg/dL

The results of substances that interfere with creatinine determinations in serum and plasma are summarized in the table below:

Interferent	Interferent concentrations (mg/dL)	Comments	Creatinine concentrations tested(mg/dL)	Bias
Dipyrone (Metamizol)	18.0	3X IV Therapeutic (Based on 1000 mg intravenous dose)	1.2	-0.24
			4.2	-0.73
Tolazamides	4.5 mg/d	3X oral Therapeutic	3.5	-0.39

Urine Creatinine:

The following preservatives have been tested and demonstrated an effect of less than 2% on creatinine results:
• Thymol
• Toluene
• Boric acid
• Glacial acetic acid (0.5 to 1.0 v/v)
• 12N HCl
• NH4OH
• Bromide
• Iodide
• 5% NaOH

The sponsor included in the labeling the following limitations for creatinine determinations in serum:

- Creatine: At a creatinine concentration of 1.5 mg/dL (133 µmol/L), creatine greater than 8 mg/dL (707 µmol/L) will be flagged with a DP code (because highly elevated creatine concentrations may cause excessive background density). For unflagged samples, residual bias because of creatine will be less than 0.15 mg/dL (13 µmol/L). At a creatinine concentration of 14 mg/dL (1237 µmol/L), creatine greater than 1 mg/dL (88 µmol/L) will be flagged with a DP code.
- Proline: Patients receiving hyperalimentation fluids containing proline may show an increase of 0.2 mg/dL (18 µmol/L). Do not collect specimens from intravenous fluid lines contaminated with hyperalimentation fluid.
- Lidocaine: Patients on long-term lidocaine therapy may show an increase of up to 1.0 mg/dL (88 µmol/L) due to a metabolite of lidocaine, N-ethyl glycine (NEG).

Total Bilirubin:
The study was conducted using a minimum of 2 samples with total bilirubin concentrations of approximately 0.3 and 15 mg/dL. The sponsor defined non-interference as a bias <0.2 mg/dL (vs. control condition). The compounds and the highest concentration that don't interfere with the total bilirubin assay are listed in the table below:

Compound	Concentration
Acetaminophen	5 mg/dL
Acetylsalicylic acid	30 mg/dL
5-Aminosalicylic acid	40 µg/mL
Ascorbic acid	3 mg/dL
Beta-carotene	0.6 mg/dL
Bile acids	6 mg/dL
Calcium	4 mmol/L
Calcitrol	80 µg/mL
Cefamandole nafate	533 µg/mL
Cyclosporin-a	238 µg/mL
Chloride	120 meq/L
Dextran	1000 mg/dL
Doxycycline	9 µg/mL
Ethanol	300 mg/dL
Free fatty acids	3 mmol/L
Gentamicin	5 µg/mL
Gentisic acid	0.5 mg/dL
Glucose	600 mg/dL
Hypaque	500 mg/dL
Intralipid	800 mg/dL

Compound	Concentration
L-dopa	6 µg/mL
Liposyn	10%
Magnesium	1.85 mmol/L
Minoxidil	2 µg/mL
Nafcillin	30 µg/mL
Piroxicam	10 µg/mL
Propanolol	2 µg/mL
Rifampin	14 µg/mL
Sulfapyridine	40 µg/mL
Sulfasalazine	38 µg/mL
Sulfathiazole	60 µg/mL
Sulfobromophthalein	150 µg/mL
Sulfisoxazole	60 µg/mL
Tetracycline	30 µg/mL
Tobramycin	5 µg/mL
Total protein	10 g/dL
Triglycerides	800 mg/dL
Urea Nitrogen	100 mg/dL
Vitamin A	50 IU/mL
Vitamin K1	8.3 µg/mL

The substances listed below, when tested at the concentrations indicated, caused the bias shown.

Interferent	Interferent concentrations	Bilirubin concentrations tested (mg/dL)	Bias
Levodopa	300 µg/mL	0.3	+0.9
		17.1	-9.8
4-Aminosalicylic acid	8 mg/dL	0.3	-0.4
		16	+2.5
Phenazopyridine	8 mg/dL	2.5-6.3	+4.4
Biliverdin	4 mg/dL	15	+0.6
Hemoglobin	150.0 mg/dL	1.1	+0.3

The sponsor included in the labeling the following limitations for total bilirubin determinations:

- Cefotiam (Pansporin) has been reported to show very large positive biases on TBIL results. This drug is normally cleared through the kidney. Biases will be largest in specimens from patients with renal insufficiency and may be as large as 5 mg/dL (86 µmol/L). Because the VITROS BuBc Slide is not affected by Cefotiam, patients known to be receiving Cefotiam therapy should be monitored only with the BuBc Slide.
- Drugs and other compounds that are diazo-reactive or that absorb light in the vicinity of 540 and 460 nm may interfere.

- Certain drugs and clinical conditions are known to alter total bilirubin concentration in vivo.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were conducted by testing a minimum of 116 human serum samples with analyte concentrations across the analytical ranges of carbamazepine, creatinine and total bilirubin assays on the VITROS XT 7600 Integrated System and the VITROS 5600 Integrated System (predicate device). In addition, 125 human urine samples were tested for creatinine on the candidate and predicate test systems. The results of the regression analyses for each of the assays are summarized below:

Assay	N	Regression Analysis	Slope	Intercept	Correlation Coefficient	Tested range	Claimed Measuring Range
CRBM Serum (µg/mL)	118	Deming	1.00	0.12	1.00	3.1 - 17.8	3.0 - 20.0
CREA Serum (mg/dL)	116	Passing Bablok	0.99	0.00	1.00	0.25 - 13.4	0.15 - 14.0
CREA Urine (mg/dL)	122	Passing Bablok	0.99	-0.45	1.00	3.7 - 331.0	3.2 - 346.5
TBIL Serum (mg/dL)	125	Passing Bablok	0.99	0.01	1.00	0.14 - 23.65	0.10 - 27.00

b. Matrix comparison:

Based on the sponsor's risk assessment for adding the VITROS Chemistry Products CRBM Slides, VITROS Chemistry Products CREA Slides and VITROS Chemistry Products TBIL Slides to the VITROS 7600 System and the results of the analytical testing conducted that demonstrated there was no impact on the assays' performance characteristics, new matrix comparison studies were not conducted. FDA found this justification to be acceptable.

The VITROS Chemistry Products CRBM Slides can be used with serum and plasma

samples collected in lithium heparin, sodium heparin and sodium citrate.
The VITROS Chemistry Products CREA Slides can be used with serum, lithium heparin plasma, and urine.
The VITROS Chemistry Products TBIL Slides can be used with serum and lithium heparin plasma.

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:

Assay	Range
Carbamazepine[1]	4.0–12.0 (µg/mL)
Serum Creatinine[2]	Male 0.66–1.25 mg/dL
	Female 0.52–1.04 mg/dL
Urine Creatinine[3]	Male 1000–2000 mg/day[4]
	Female 800–1800 mg/day[4]
Total Bilirubin[5]	0.2-1.3 mg/dL

1. Tietz NW (ed). Fundamentals of Clinical Chemistry. ed. 5. Philadelphia: WB Saunders; 1019; 2001.
2. The serum reference intervals for creatinine were established as the central 95% of results from an external study of apparently healthy adults (serum: 180 males and 180 females).
3. McPherson R, Pincus M (eds.). Henry's Clinical Diagnostics and Management by Laboratory Methods, 21st edition. Philadelphia: Saunders Elsevier [ISBN-13: 978-1-4160-0287-1; 1410; 2006.
4. Urine Creatinine calculation: Creatinine concentration (mg/dL) x 24-hour volume (dL) = mg/day.

5. The reference interval for total bilirubin is the central 95% of results from a study of 110 apparently healthy adults with normal liver enzymes (85 females and 25 males).

N. Instrument Name:

VITROS XT 7600 Integrated System

O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___X___ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No ___X___

2. Software:

   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 that are labeled with a barcode will be scanned in automatically when placed into the Reagent and Sample Manager area or manually using the bar code scanner.

4. Specimen Sampling and Handling:

   The Sample Handler (SAHA) uses the universal sample tray to house patient sample containers. Once samples are loaded onto the System, they are advanced into a metering zone, where a bar code reader scans the bar code labels to identify tray and samples.

5. Calibration:

   Calibration is an automatic process: bar-coded calibrators or manually programmed trays are placed on the system for assay calibration, the calibrators are processed in a random-access format (bar-coded) or in the order they were defined (manual), and a new calibration curve is calculated. The new curve is saved on the system and used for

subsequent assays to determine the analyte concentrations in the patient and control samples.

6. Quality Control:

   To perform Quality Control, QC materials are run with either known, or unknown values along with patient samples to determine whether the system is functioning within the established ranges.

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

Not applicable.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable.

R. Conclusion:

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