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

A. 510(k) Number: k042643

B. Purpose For Submission:

Premarket Notification (510(k)) for Ortho-Clinical Diagnostics, Inc., of intention to manufacture and market the VITROS® Chemistry Product mALB Reagent, VITROS Chemistry Products Calibrator Kit 24, and the VITROS Chemistry Products mALB Performance Verifiers I and II.

C. Analyte: Microalbumin

D. Type of Test:

The VITROS Chemistry Products mALB Reagent is used for the quantitative in vitro diagnostic measurement of human urine albumin in conjunction with the VITROS Chemistry Products Calibrator Kit 24 on the VITROS 5, 1 FS Chemistry Systems. The basic test principle utilizes a turbidimetric inhibition immunoassay technology.

E. Applicant: Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:

VITROS Chemistry Products mALB Reagent
VITROS Chemistry Products Calibrator Kit 24
VITROS Chemistry Products mALB Performance Verifiers I and II

G. Regulatory Information:

1. Regulation section:

21 CFR §866.5040, Albumin immunological test system
21 CFR §862.1660, Single (Specified) Analyte Controls (Assayed and Unassayed)
21 CFR §862.1150, Calibrator, Secondary

2. Classification:

Class II (assay) - Subject to limitations of exemptions, 21 CFR 866.9 (c)(5)
Class I (controls)
Class II (calibrator)

3. Product Code:

DCF (assay)
JXX (controls)
JIT (calibrator)

4. Panel:

82 (Immunology)
75 (Chemistry)
75 (Chemistry)

H. Intended use(s):

1. Intended use(s)

VITROS Chemistry Products mALB Reagent: For in vitro diagnostic use only. VITROS Chemistry Products mALB Reagent is used to quantitatively measure albumin concentration in human urine (mALB).

VITROS Chemistry Products Calibrator Kit 24: For in vitro diagnostic use only. VITROS Chemistry Products Calibrator Kit 24 is used to calibrate VITROS 5, 1 FS Chemistry Systems for the quantitative measurement of albumin in urine (mALB).

VITROS Chemistry Products mALB Performance Verifiers I and II: For in vitro diagnostic use only. VITROS Chemistry Products mALB Performance Verifiers are assayed controls used to monitor the performance of mALB Reagent on VITROS 5, 1 FS Chemistry Systems.

2. Indication(s) for use:

VITROS Chemistry Products mALB Reagent: For in vitro diagnostic use only. VITROS Chemistry Products mALB Reagent is used to quantitatively measure albumin concentration in human urine (mALB). Measurement of urinary albumin aids in the diagnosis of diabetic nephropathy, hypertension and cardiovascular disease.

VITROS Chemistry Products Calibrator Kit 24: For in vitro diagnostic use only. VITROS Chemistry Products Calibrator Kit 24 is used to calibrate VITROS 5, 1 FS Chemistry Systems for the quantitative measurement of albumin in urine (mALB).

VITROS Chemistry Products mALB Performance Verifiers I and II: For in vitro diagnostic use only. VITROS Chemistry Products mALB Performance Verifiers are assayed controls used to monitor the performance of mALB Reagent on VITROS 5, 1 FS Chemistry Systems.

3. Special condition for use statement(s): For Prescription Use.

4. Special instrument Requirements: VITROS 5, 1 FS Chemistry Systems

I. Device Description:

The VITROS 5, 1 FS Chemistry System is a fully automated clinical chemistry analyzer intended for use in the in vitro determination of various analytes in human specimens (serum, plasma, urine, and cerebrospinal fluid). The VITROS 5, 1 FS Chemistry System is designed for use with VITROS Chemistry Products MicroTip and Thin Film assays.

The system is comprised of four main elements:

1. The VITROS 5, 1 FS Chemistry System-instrumentation, which provides automated use of chemistry reagents. The VITROS 5, 1 FS Chemistry System was cleared for market by a separate 510(k) premarket notification (k031924).

2. The VITROS Chemistry Products MicroTip range of liquid reagent products (in this case VITROS Chemistry Products mALB Reagent, VITROS Chemistry Products Calibrator Kit 24, and VITROS Chemistry Products mALB Performance Verifiers I and II), which are combined by the VITROS 5, 1 FS Chemistry System to perform the VITROS mALB assay.

3. The VITROS Chemistry Products Thin Film range of dry products, which are dry, multilayered, analytical elements, coated on polyester supports. The thin film products each have there own 510(k) clearance numbers and were cleared for market use on the VITROS 5, 1 FS Chemistry System though submission of information required by the ODE Guidance Document: "Data For Commercialization Of Original Equipment Manufacturer, Secondary and Generic Reagents for Automated Analyzers". The required information was provided in the VITROS 5, 1 FS Chemistry System premarket notification (k031924)

4. Common reagents used by multiple assays on the VITROS System (in this case, VITROS Chemistry Products FS Diluent Pack 2). The VITROS System and reagents are designed specifically for use with the VITROS Chemistry Products range of products.

J. Substantial Equivalence Information:

1. Predicate device name(s): Dade Behring N Antiserum to Human Albumin, Prealbumin and Retinol-binding Protein

2. Predicate K number(s): k972929

3. Comparison with Predicate:

The VITROS Chemistry Products mALB Reagent and VITROS Chemistry Products Calibrator Kit 24 are substantially equivalent to N Antiserum to Human Albumin assay on the Dade Behring BN ProSpec System (predicate device) which was 510(k) cleared in k972929 for IVD use.

The relationship between the VITROS mALB assay and the predicate device, determined by the Passing & Bablock linear regression is:

VITROS mALB assay = 0.93x + 0.03
with a correlation coefficient of 0.977,
where X is the result for the N Antiserum to Human Albumin assay on the Dade Behring BN ProSpec System.

In addition to the above mentioned correlation study, studies were performed to determine precision, analytical sensitivity, specificity and expected values of the VITROS mALB assay. The table below lists the characteristics of the VITROS mALB assay (new device) and the Dade N Antiserum to Human Albumin assay (predicate device).

Device Characteristics	**VITROS mALB assay (k402643) New Device**	**Dade Albumin assay (k972929) Predicate Device**
Intended Use	For in vitro diagnostic use only. VITROS Chemistry Products mALB Reagent is used to quantitatively measure albumin concentration in human urine (mALB)	In vitro diagnostic reagents for the quantitative determination of albumin in human urine using the BN Systems.
Method	Immunoturbidimetry	Rate Nephelometry
Reportable Range	0.6 to 19 mg/dL	0.0 to 34.0 mg/dL
Instrumentation	VITROS 5, 1 FS Chemistry Systems	Dade Behring BN ProSpec Systems
Sample Type	Urine	Urine
Reactive Ingredient	Goat anti-sera to human albumin	Rabbit antiserum to human albumin

The VITROS Chemistry Products mALB Performance Verifiers I and II are substantially equivalent to the VITROS Chemistry Products Performance Verifiers (predicate device) which were 510(k) cleared in k041720 for IVD use. The table below lists the similarities and differences of the device characteristics between the VITROS mALB Performance Verifiers and the predicate device, VITROS Performance Verifiers I and II.

Device Characteristics	Performance Verifiers I and II (k042643) New Device	Performance Verifiers I and II (k041720) Predicate Device
Intended Use	For in vitro diagnostic use only. VITROS Chemistry Products mALB Performance Verifiers are assayed controls used to monitor the performance of mALB Reagents on VITROS 5, 1 FS Chemistry Systems.	For in vitro diagnostic use only. VITROS Performance Verifier is an assayed control used to monitor performance on VITROS Chemistry Systems.
Fluid Matrix	A base matrix of processed human serum to which inorganic salt, buffers, protein, surfactant and preservatives have been added.	A base matrix of freeze-dried human serum to which enzymes, electrolytes Stabilizers, preservatives and other organic analytes have been added.
Analyte Levels	Low and High	Low and High

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

Values assigned to the VITROS Chemistry Products Calibrator Kit 24 for urine albumin are traceable to IRMM/IFCC (Institute for Reference Methods and Materials/ International Federation of Clinical Chemistry and Laboratory Medicine) CRM 470 (RPPHS – Reference Preparation for Proteins in Human Serum) Reference Material.

FDA Guidance Document: "Data For Commercialization Of Original Equipment Manufacturer, Secondary and Generic Reagents for Automated Analyzers"

NCCLS Protocol EP5-A (Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline)

NCCLS EP6-A (Evaluation of the Linearity of Quantitative Analytical Methods-Approved Guideline)

NCCLS C28 (How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline-Second Edition)

NCCLS protocol EP7-A (Interference Testing in Clinical Chemistry; Approved Guideline (2002))

L. Test Principle:

The quantitative measurement of urine albumin is performed using the VITROS Chemistry Products mALB Reagent in conjunction with the VITROS Chemistry Products Calibrator Kit 24 on VITROS 5, 1 FS Chemistry Systems. The VITROS Chemistry Products mALB Reagent is a dual chambered package containing ready-to-use liquid

reagents. Samples, calibrators and controls are mixed with Reagent 1 containing a polymer and surfactant. Addition of antisera specific for human albumin (Reagent 2) produces an immunochemical reaction yielding antibody/antigen complexes. The light scattering properties of the antibody/antigen complexes increase solution turbidity proportional to albumin concentration in the sample. The turbidity is measured spectrophotometrically at 340 nm. Once a calibration has been performed for each reagent lot, the urinary albumin concentration in each unknown sample can be determined using the stored calibration curve and the measured absorbance obtained in the assay of the sample.

Reaction Sequence

Step 1: Dilution of mALB Sample

Sample $\xrightarrow[\text{Surfactant/ Polymer}]{\text{R1}}$ Diluted Sample

Step 2: Formation of mALB/ Antibody Complexes

Diluted Sample $\xrightarrow[\text{Polyclonal antibodies}]{\text{R2}}$ Antigen/ Antibody Complexes

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision was evaluated with quality control materials on the VITROS 5, 1 FS Chemistry System following NCCLS Protocol EP5-A (Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline).

Two runs per day were performed on 22 different days, using three VITROS 5, 1 FS Chemistry Systems with three different reagent lots. Each run consisted of two control fluids to evaluate system precision and one human urine pool to simulate customer use. All fluids were run in duplicate. Runs within day were separated by at least two hours. The data were screened for outliers according to the statistical outlier test in NCCLS EP5-A. Two replicates were removed as a result of this analysis. The calibrator samples tested each week were used to generate a calibration for each week of the experiment, which was used to calibrate and predict all results from that week. This analysis introduces the variability inherent in the act of calibration.

The results of the test samples, for each matrix evaluated, were analyzed by ANOVA as detailed in NCCLS EP5-A. A nested ANOVA was performed to estimate within-run, run-to-run (within-day), day-to-day, week –to-week (cal-to-cal), and total within lab precision. Another nested ANOVA was performed to estimate within-day, day-to-day, week-to-week (cal-to-cal) and total within lab precision. The ANOVA results represent an approximation of the total, within-laboratory variability that would be observed using a single lot of reagents.

Testing was performed on three lots of reagent. Results from one lot were used to determine the product claim, since performance achieved with this lot defines the most conservative claim. See the table below:

VITROS Chemistry Products mALB Reagent Precision

	Conventional Units (mg/dL)			SI Units (mg/dL)					
System	Mean Conc.	Within Day SD*	Within Lab SD*	Mean Conc.	Within Day SD*	Within Lab SD*	Within Lab CV**	Number of Observation	Number of Day
VITROS 5, 1 FS Chemistry System	4.4	0.05	0.07	43.6	0.50	0.73	1.67	88	22
	7.9	0.11	0.07	78.7	1.09	2.58	3.28	88	22
	2.6	0.03	0.007	25.8	0.34	0.73	2.83	88	22

* Within Day precision was determined using two runs per day with two replicates per run.
** Within Lab precision was determined using a single lot of reagent with one analyzer and four calibrations.

b. Linearity/assay reportable range:

The linearity evaluation was performed based on NCCLS EP6-A (Evaluation of the Linearity of Quantitative Analytical Methods-Approved Guideline). A "high pool" was obtained by spiking a normal urine pool with human serum to an estimated albumin concentration of 190 mg/L. The low pool (normal urine pool) had an albumin concentration of 2.6 mg/L. Admixtures of the high pool and low pool were mixed to create 22 levels spanning the assay reportable range.

Four determinations of each of 22 pools were made together with 2 determinations each of VITROS Chemistry Products mALB Performance Verifiers I and II with each reagent lot on a VITROS 5, 1 FS Chemistry System. The VITROS Chemistry System operated within normal conditions.

The data were screened for outliers according to the statistical outlier test in NCCLS EP5-A. No data were rejected as statistical outliers. For each lot, the system responses were plotted against the percent high pool concentration to assess the degree to which the plotted curve conforms to a straight line.

The data presented define the linear range of the VITROS mALB Reagent assay when run on the VITROS 5, 1 FS Chemistry System. Based on the analysis of data from 21 fluids, the linear range of the assay was defined. Analysis by linear regression indicated that the assay is linear across the range of 0.6 – 19.0 mg/dL (6.0- 190.0 mg/L) for all three lots tested.

c. Traceability (controls, calibrators, or method):

Values assigned to the VITROS Chemistry Products Calibrator Kit 24 for urine albumin are traceable to IRMM/IFCC (Institute for Reference Methods and Materials/ International Federation of Clinical Chemistry and Laboratory Medicine) CRM 470 (RPPHS – Reference Preparation for Proteins in Human Serum) Reference Material.

d. Detection limit:

The lower end of the reportable range is set at the value of the lowest calibrator which is 0.6 mg/dL or 6.0 mg/L.

e. Analytical specificity:

To determine the effect of levels of exogenous and endogenous substances on the performance of the VITROS Chemistry Products mALB Reagent, NCCLS protocol EP7-A was used. A human urine pool spiked with human serum to obtain a target mALB of 25 mg/L and a simulated urine base spiked with human serum to a target mALB of 90 mg/L were used to test the following substances:

Test Substance	**Test Conc. Conv. Units**	**Test Conc SI Units**
Hemolysate	500 mg/dL 750 mg/dL 1000 mg/dL	5 g/L 7.5 g/L 10 g/L
Acetaminophen	140 mg/dL	9.3 mmol/L
Ammonia as Ammonium Sulfate	570 mg/dL	334.7 mmol/L
Amoxicillin	200 mg/dL	5.5 mmol/L
Ascorbic acid (L)	500 mg/dL	28.4 mmol/L
Ditaurobilirubin	10 mg/dL 20 mg/dL 26 mg/dL	0.17 mmol/L 0.34 mmol/L 0.44 mmol/L
Bovine Serum Albumin	10 mg/dL	0.1 g/L
Calcium as calcium chloride	30 mg/dL	7.5 mmol/L
Ceftriaxone, Na salt	550 mg/dL	9.91 mmol/L
Creatinine	300 mg/dL	26.5 mmol/L
Furosemide	60 mg/dL	1.8 mmol/L
Glucose	4000 mg/dL	222.0mmol/L
Hemolysate	500 mg/dL 750 mg/dL 1000 mg/dL	5 g/L 7.5 g/L 10 g/L
Human IgG	200 mg/dL	2 g/L
Ibuprofen	50 mg/dL	2.4 mmol/L
Magnesium As magnesium chloride	60 mg/dL	24.7 mmol/L
Propanol HCL	55 mg/dL	2.1 mmol/L
Salicylic Acid As sodium salicylate	100 mg/dL	7.3 mmol/L
Sulfamethoxazole	120 mg/dL	4.7 mmol/L
Trimethoprim	2 mg/dL	69 µmol/L
Urea	3000 mg/dL	499.5 mmol/L

Uric Acid as sodium salt	120 mg/dL	7.14 mmol/L
Thymol	5 mL of 10% thymol per 1500 mL urine	
Boric Acid/Sodium Formate	2g Boric Acid + 1g Sodium Formate per 100 mL urine	
Conc. HCL	10 mL HCL per 1 L urine	
Glacial Acetic Acid	10 mL glacial acetic acid per 1 L urine	

Testing for endogenous and exogenous interferents followed the protocol outlined in EP7-A for paired-difference method.

Four to six determinations of each test substance and three determinations of the control fluids were carried out with two reagent lots on one VITROS 5, 1 FS Chemistry System.

For each substance tested, the "control" pool and the test substance pool replicate VITROS mALB assay results were calculated. The mean VITROS mALB assay results SD and CV (%) were calculated for each "control" pool and test substance pool. The bias was calculated as shown below:

Bias = (Mean conc. of interfering substance pool) – (Mean conc. of "control" pool).

Known Interferences

The substances listed in the table, when tested at the concentrations indicated, cause the bias shown.

Known Interfering Substances for mALB

Interferent	Interferent Concentration	mALB Concentration		Bias**	
		Conv. (mg/dL)	SI (mg/L)	Conv. (mg/dL)	SI (mg/L)
Furosemide	60 mg/dL 1.8 mmol/L	2.4	23.8	-0.5	-4.7
Sulfamethoxazole	120 mg/dL 4.7 mmol/L	2.3	23.3	0.5	5.0

****** The bias is an estimate of the maximum difference observed.

A literature search was conducted to determine whether interferences from therapeutic drugs and their metabolites have been observed while

using immunoturbidimetric assay methods to quantify urinary albumin in human samples. No therapeutic drugs or metabolites were identified as causing analytical interference in urinary albumin assays.

The substances listed in the table below, at the concentrations shown, were tested according to NCCLS Protocol EP7-A. Bilirubin and hemoglobin were tested at urinary albumin concentrations of approximately 2.5 mg/dL (25 mg/L) and 10.0 mg/dL (100 mg/L) and found not to interfere, bias < 0.38 mg/dL (3.8 mg/L) and bias < 1.5 mg/dL (15 mg/L) respectively. The remaining compounds listed in the table were tested at a urinary albumin concentration of approximately 2.5 mg/dL (25 mg/L) and found not to interfere, bias < 0.38 mg/dL (3.8 mg/L).

Substances that do not interfere

Compound	**Concentration**	
Acetaminophen	140 mg/dL	9.3 mmol/L
Ammonia	570 mg/dL	334.7 mmol/L
Amoxicillin	200 mg/dL	5.5 mmol/L
Ascorbic acid (L)	500 mg/dL	28.4 mmol/L
Bilirubin	26 mg/dL	0.44 mmol/L
Bovine Serum Albumin (BSA)	10 mg/dL	0.1 g/L
Calcium	30 mg/dL	7.5 mmol/L
Ceftriaxone	550 mg/dL	9.9 mmol/L
Creatinine	300 mg/dL	26.5 mmol/L
Glucose	4000 mg/dL	222.0 mmol/L
Hemoglobin	500 mg/dL	5 g/L
Human IgG	200 mg/dL	2 g/L
Ibuprofen	50 mg/dL	2.4 mmol/L
Magnesium	60 mg/dL	24.7 mmol/L
Propanol	55 mg/dL	2.1 mmol/L
Salicylic acid	100 mg/dL	7.3 mmol/L
Trimethoprim	2 mg/dL	69µmol/L
Urea	3000 mg/dL	499.5 mmol/L
Uric acid	120 mg/dL	7.1 mmol/L

Urine preservatives were tested with the VITROS Chemistry Products mALB Reagent at nominal concentrations of urinary albumin of approximately 2.5 mg/dL (25 mg/L) and found not to interfere, bias < 0.38 mg/dL (3.8 mg/L), at the concentrations shown.

f. Assay cut-off: Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A total of 179 human urine samples were assayed using the VIIROS Chemistry Products mALB assay and the Dade Behring albumin assay (predicate device). Samples were analyzed by both methods on the same day. All samples were analyzed in triplicate on the VITROS 5, 1 FS Chemistry System analyzers and in duplicate on the ProSpec (predicate device). Testing was performed on two VITROS analyzers. Two different reagent lots were tested on both VITROS Systems.

For the quantitative comparison of methods, only those data within the reportable range of both the VITROS 5, 1 FS System (0.6 to 19.0 mg/dL) and the Dade Behring ProSpec (0.0 to 34.0 mg/L) were analyzed. One hundred and fifteen samples were removed from the regression analysis because they were out of the range on one of the assays tested.

The data were screened for outliers according to NCCLS Protocol EP5-A. A single replicate from one sample was excluded from the regression as a result of this analysis. The mean of the triplicates from the VITROS Chemistry Products mALB assay and the mean of the duplicates from the Dade Behring N Antiserum to Human Albumin assay were used in the analysis.

The relationship between the two methods, determined by Passing & Bablock linear regression, using 61 samples, the relationship between the two methods was as follows:

VITROS mALB assay = 0.93 x (Dade Behring) + 0.03 (mg/dL)
Correlation coefficient(r) = 0.977

b. Matrix Comparison: Not applicable

3. Clinical studies:

a. Clinical sensitivity: Clinical studies are not typically submitted for this device type.

b. Clinical specificity: Clinical studies are not typically submitted for this device type.

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:

A total of 129 random urine specimens from apparently healthy adult subjects were assayed on two VITROS 5, 1 FS Chemistry System Analyzers. Two different reagent lots were used.

The evaluation of the results was performed according to NCCLS C28 (How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline-Second Edition.)

Histograms were created for each analyzer and reagent lot combination as well as the grand mean. The data were analyzed for outliers using box plots. Ten outliers were removed and the remaining data stored in ascending order of magnitude. Rank order numbers were assigned such that the lowest value has a rank of 1, and the highest number has a rank of n. The rank number of the 97.5^{th} percentile was computed as 0.975 (n+1). The upper reference limit is equal to the value corresponding to the rank of the 0.975 fractile. The 90% confidence interval around the upper reference limit was determined. The same data analysis was applied to compute the lower reference limit (2.5^{th} percentile) with sample values predicted using an offline software analysis tool.

Results - The 97.5^{th} percentile value of the distribution and corresponding 90% confidence interval was calculated for each analyzer and reagent lot as well as the grand mean across both analyzers and reagent lots. The combined results are summarized in the table below:

Conventional Units (mg/dL	**SI Units (mg/L)**
< 1.7	< 16.7 (15.0 – 18.7)

The results of this study are in the product labeling. In addition, a reference will be made to the following guidelines recommended by the American Diabetes Association[5].

Category	24-h collection (mg/24h)	Timed collection (µg/min.)	Spot collection (µg/mg creatinine)
Normal	<30	<20	<30
Microalbuminuria	30-300	20-200	30-300
Clinical albuminuria	>300	>200	>300

[5.] American Diabetes Association. "Standards of Medical Care for Patients with Diabetes Mellitus" Diabetes Care, 23: Suppl. 1, S32-42, (2000).

N. Conclusion:

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