

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

A. 510(k) Number:

k052867

B. Purpose for Submission:

Obtain clearance to market a reagent pack on the VITROS Chemistry Systems platform. The reagent pack is used to measure the unsaturated iron-binding capacity in human serum.

C. Measurand:

Iron

D. Type of Test:

Quantitative spectrophotometric

E. Applicant:

Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:

VITROS Chemistry Products dTIBC Reagent

VITROS Chemistry Products Calibrator Kit 29

VITROS Chemistry Products Performance Verifiers I & II

G. Regulatory Information:

1. Regulation section:

CFR 862.1415: Iron-binding capacity test system

CFR 862.1150: Calibrator

CFR 862.1660: Quality control material

2. Classification:

Class I (reserved): VITROS Chemistry Products dTIBC Reagent

Class II: VITROS Chemistry Products Calibrator Kit 29

Class I (reserved): VITROS Chemistry Products Performance Verifiers I & II

3. Product code:
JMO: VITROS Chemistry Products dTIBC Reagent;
JIS: VITROS Chemistry Products Calibrator Kit 29
JJY: VITROS Chemistry Products Performance Verifiers I & II

4. Panel:

Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

For in vitro diagnostic use only. VITROS Chemistry Products dTIBC Reagent is used to quantitatively measure total iron-binding capacity (TIBC) in human serum. The iron binding capacity is useful in the differential diagnosis of anemia, iron deficiency anemia, thalassemia, sideroblastic anemia, and iron poisoning.

For in vitro diagnostic use only. VITROS Chemistry Products Calibrator Kit 29 is used to calibrate VITROS 5,1 FS Chemistry Systems for the quantitative measurement of total iron-binding capacity (TIBC) using VITROS Chemistry Products dTIBC Reagent.

For in vitro diagnostic use only. VITROS Chemistry Products Performance Verifiers are assayed controls intended for use in monitoring performance on VITROS Chemistry Systems.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

The VITROS 5,1 FS Chemistry System

I. Device Description:

The VITROS Chemistry Products dTIBC Reagent is a dual chambered package containing two ready-to-use liquid reagents. Reagent 1, an acidic buffer containing ferric ions bound to chromazurol B (iron-binding dye) is added to the sample. The acidic pH releases iron from the carrier protein transferrin. The released iron binds to chromazurol B, a complexing chromophore present in excess. Reagent 2, a neutral buffer is added, shifting the pH, which results in increased affinity of transferrin for iron. Serum transferrin rapidly extracts iron from the dye- iron complex. The decrease in absorbance of the colored dye-iron complex is directly proportional to the total iron-binding capacity of the sample and is measured spectrophotometrically at 660 nm.

The VITROS Chemistry Products Calibrator Kit 29 is a two level standard used to calibrate VITROS FS Chemistry Systems for the quantitative measurement of total iron binding capacity (TIBC). VITROS Calibrator Kit 29 level 1 is an aqueous solution containing processed bovine serum albumin and preservatives. VITROS Calibrator Kit 29 level 2 is a lyophilized powder based on human serum, a powder containing proteins, enzymes, organic compounds, electrolytes, immunoglobulins, inorganic compounds, hormones, and metals. The VITROS Chemistry Products FS Reconstitution Diluent is processed water used to reconstitute the VITROS Calibrator Kit 29 level 2.

The VITROS Chemistry Products Performance Verifiers I and II are lyophilized materials prepared from processed human serum to which enzymes, electrolytes, stabilizers, preservatives, and other organic analytes have been added. The powder is reconstituted using diluent manufactured from processed water to which inorganic salts have been added. These are assayed quality control materials are used to monitor the performance of the VITROS dTIBC assay on the VITROS System.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Dade Behring Total Iron Binding Capacity (IBCT) Flex® assay

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

K994115

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	For in vitro diagnostic use only. Used to quantitatively measure total iron-binding capacity (TIBC) in human samples. The iron binding capacity is useful in the differential diagnosis of anemia, iron deficiency anemia, thalassemia, sideroblastic anemia, and iron poisoning.	Same
Sample Pretreatment	None (Human Serum)	Same
Instrumentation	Automated clinical chemistry Analyzer	Same
Calibration	Traceable to NIST SRM 937	Same
Differences		
Item	Device	Predicate
Sample Type	Human Serum	Human serum or plasma
Reportable Range	60 – 650 mg/dL	0 - 1000 mg/dL
Calibrators	Two concentration (levels)	Three concentration (levels)

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

CLSI EP05-A2: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline-Second Edition

CLSI EP06-A: Evaluation of the Linearity of Quantitative Analytical Methods; Approved Guideline

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition

CLSI EP09-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition

L. Test Principle:

The quantitative measurement of TIBC is performed using the Vitros Chemistry products dTIBC reagent in conjunction with the Vitros Chemistry products calibrator Kit 29 on Vitros 5,1 FS Chemistry Systems. Serum is added to an acidic buffer containing ferric ions bound to chromazural B (iron-binding dye). The acidic pH releases iron from transferrin, and the released iron binds to the excess chromazural B. A neutral buffer, is added shifting the pH which results in increased affinity of transferrin for iron. Serum transferrin rapidly extracts iron from the dye-iron complex. The decrease in absorbance of the colored dye-iron complex is directly proportional to the total iron-binding capacity of the sample and measured spectrophotometrically at 660 nm. After a calibration has been performed, the TIBC concentration in each unknown sample can be determined using the stored calibration curve and the measured absorbance obtained in the assay of the sample.

M. Performance Characteristics (if/when applicable):**1. Analytical performance:*****a. Precision/Reproducibility:***

The company followed CLSI EP05-A2: "Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline-Second Edition" in determining their precision.

Four different concentrations spanning the range were studied. For each concentration, the company made 4 precision measurements per day for 23 days for a total of 92 measurements per concentration, 368 measurements in total. Three test samples were discarded when accompanying quality control samples tested out-of-range.

The within-day precision was determined as the mean standard deviation of 23 sets of measurements. Each member of this set consisted of 4 points acquired as 2 runs/day and 2 measurements/run for a total of 4 points – a day's measurements. The mean of the set of the 4-point standard deviations was used to determine the within-day standard deviation and within-day %CV.

Within-Lab precision was determined using a single lot of reagents on a single analyzer. Four measurements were made per day. The machine was calibrated once per week. The same reagent lot was used throughout the study.

Conventional Units (mg/dL)			SI Units (mmol/L)						
Mean Conc.	Within- Day SD*	Within- Lab SD**	Mean Conc.	Within- Day SD*	Within- Lab SD**	Within- Day %CV**	Within- Lab %CV**	No. Observations	No. of Days
250	6.0	9.1	44.8	1.06	1.62	2.4	3.6	91	23
412	5.6	9.5	73.7	1.00	1.69	1.36	2.3	90	23
232	3.6	5.2	41.6	0.64	0.64	1.55	2.2	92	23
303	2.8	6.5	54.3	0.49	0.49	0.92	2.1	92	23

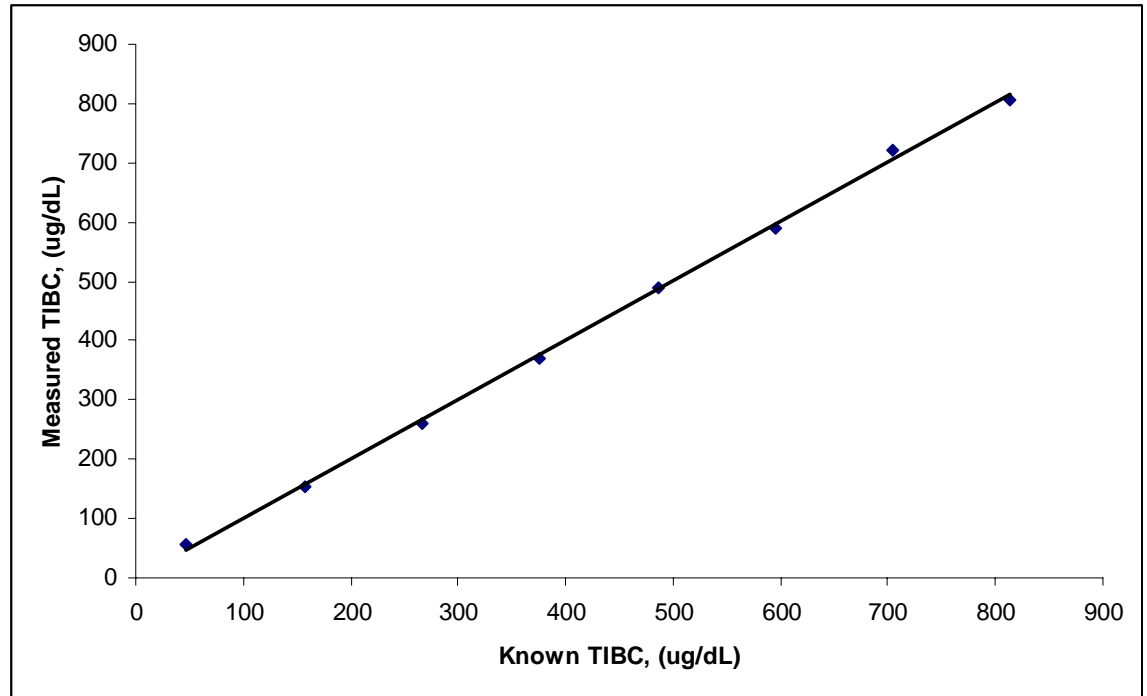
*Within Day precision was determined using the two-runs/day with two replicates per run. The mean of the set of 4-point standard deviations was used to determine the within-day standard deviation and within-day %CV.

** Within Lab precision was determined using a single lot of reagents on a single analyzer, calibrated once a week.

b. Linearity/assay reportable range:

The company followed CLSI EP06-A: “Evaluation of the Linearity of Quantitative Analytical Methods; Approved Guideline” in determining the linear range of their device.

Linearity was evaluated using three assay reagent lots and comparing the measured results against the expected results from 8 pooled samples. The concentration of these samples ranged from 47 to 805 µg/dL. A linear regression was performed and the results demonstrated a linear fit with an R-square value of 0.9988, a slope of 0.9988, and an intercept of 0.52914. The range of the assay is 60 – 650 µg/dL TIBC.



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

Concentration values for the calibrators are determined on a lot-to-lot basis by comparison to NIST SRM 937 reference material. The company follows CLSI H17-A: “The Determination of Serum Iron and Total Iron-Binding Capacity; Approved Standard.” in determining this concentration.

The long-term and in-use stability of the VITROS Chemistry Products dTIBC reagents was evaluated using real-time data. The company periodically removed samples from three lots of dTIBC reagents from storage for testing. The performance of each lot was sampled 7 times over 6 months. On each sampling, the company made 6 repeated measurements on each lot.

There was no change in performance for at least 6 months when stored at 2-8°C as indicated in the product labeling. Using real-time data, the company demonstrated that the stability of opened reagent packs stored on the analyzer is 28 days

The company demonstrated the “on-board” stability of their calibrator using real-time data. The company made 6 replicate measurements per vial, 2 vials per lot, on 3 lots over 14 days. Variations in concentrations over this time were less than 2%. The data supplied by the company supports the “in use stability” claim of 14 days for opened calibrator vials when stored at 2° - 8°C (36° - 46°F).

The shelf life of the calibrator was demonstrated using data from real-time storage experiments on 3 lots of calibrator. Sampling, done with 6 replicate measurements per time point, demonstrated performance in the properly stored calibrator for at least 6 months.

The VITROS Chemistry Products dTIBC Performance Verifiers are stable for up to 6 months when stored at or below -18°C . The in use stability is up to 14 days when stored at $2-8^{\circ}\text{C}$ when tightly closed.

Stability testing for the Performance Verifiers paralleled that used for the reagent pack and calibrator. Real-time stability data was used to assess both the “in-use” (opened) and properly stored material. To demonstrate the product shelf life, the company periodically sampled 3 stored lots of materials. At each sampling, the company made 6 replicate measurements per lot. The performance showed stability over the 4 months tested when stored at or below -18°C . The “in use” involved periodic testing across 3 lots, testing each lot a total of 9 times per time point. The data supports a stability claim of up to 14 days when stored at $2-8^{\circ}\text{C}$.

d. Detection limit:

The detection limit was determined by the use of the “limit of blank”, “limit of detection” and “limit of quantitation” on three different lots of reagent and on two instrument platforms. The company used the highest “limit of quantitation” of the three lots to determine the lower limit. The claimed lower limit for VITROS dTIBC is $60\text{ }\mu\text{g/dL}$.

e. Analytical specificity:

The company conducted extensive interference studies following CLSI EP07-A2. The substances listed in this table below were determined to introduce less than a 10% bias in the two TIBC concentrations tested, 250 and 450 $\mu\text{g/dL}$, up to the concentrations shown:

Compound	Concentration	
	mg/dL	SI
Acetaminophen	20 mg/dL	1.32 mmol/L
Amoxicillin	20 $\mu\text{g/mL}$	55 $\mu\text{mol/L}$
Ampicillin	5 mg/dL	143 $\mu\text{mol/L}$
Ascorbic Acid (L)	3 mg/dL	1.14 mmol/L
Acetylsalicylic acid	50 mg/dL	2.78 mmol/L
Bilirubin	27 mg/dL	461 $\mu\text{mol/L}$
Caffeine	10 mg/dL	515 $\mu\text{mol/L}$
Carbamazepine	120 $\mu\text{g/mL}$	508 $\mu\text{mol/L}$
Chromium	5 $\mu\text{g/dL}$	0.96 $\mu\text{mol/L}$

Copper (cupric chloride)	3 mg/dL	472 µmol/L
Creatinine	30 mg/dL	2.62 mmol/L
Diazepam	2 mg/dL	70 µmol/L
Doxycyclin	5 mg/dL	104 µmol/L
D-penicillamine	8 µg/mL	54 µmol/L
Gentamycin Sulfate	120 µg/mL	256 µmol/L
Hemoglobin	1000 mg/dL	10 g/L
Heparin	8 U/mL	8 U/mL
Ibuprofen	40 mg/dL	1.94 mmol/L
Imferon (Iron Dextran)	1400 µg/dL	-
Magnesium	15 mg/dL	738 µmol/L
Methotrexate	10 mmol/L	10 mmol/L
Nickel	500 µg/dL	85 µmol/L
Nicotine	2 mg/dL	123 µmol/L
Ranitidine	20 mg/dL	638 µmol/L
Rheumatoid Factor	300 IU/mL	300 IU/mL
Theophylline	250 µg/mL	1.39 mmol/L
Urea	500 mg/dL	83.25 mmol/L
Valproic Acid	500 µg/mL	13.28 mmol/L
Zinc	250 µg/dL	38 µmol/L
Sodium Azide	100 mg/dL	15.38 mmol/L
ProClin 300	15 ppm	-

In addition, the company determined that high levels of protein (up to 11 g/dL) and triglycerides (up to 1241 mg/dL) did not interfere with this assay.

The company noted that patient samples containing Desferal (Deferoxamine), a therapeutic chelating agent used to remove excess iron from patients suffering from iron overloading, showed significant positive interference (50% - 80%) with this assay.

In addition, the company determined that serum samples containing ferrous sulfate gave results with a negative bias ranging between 8% and 18%.

f. Assay cut-off:

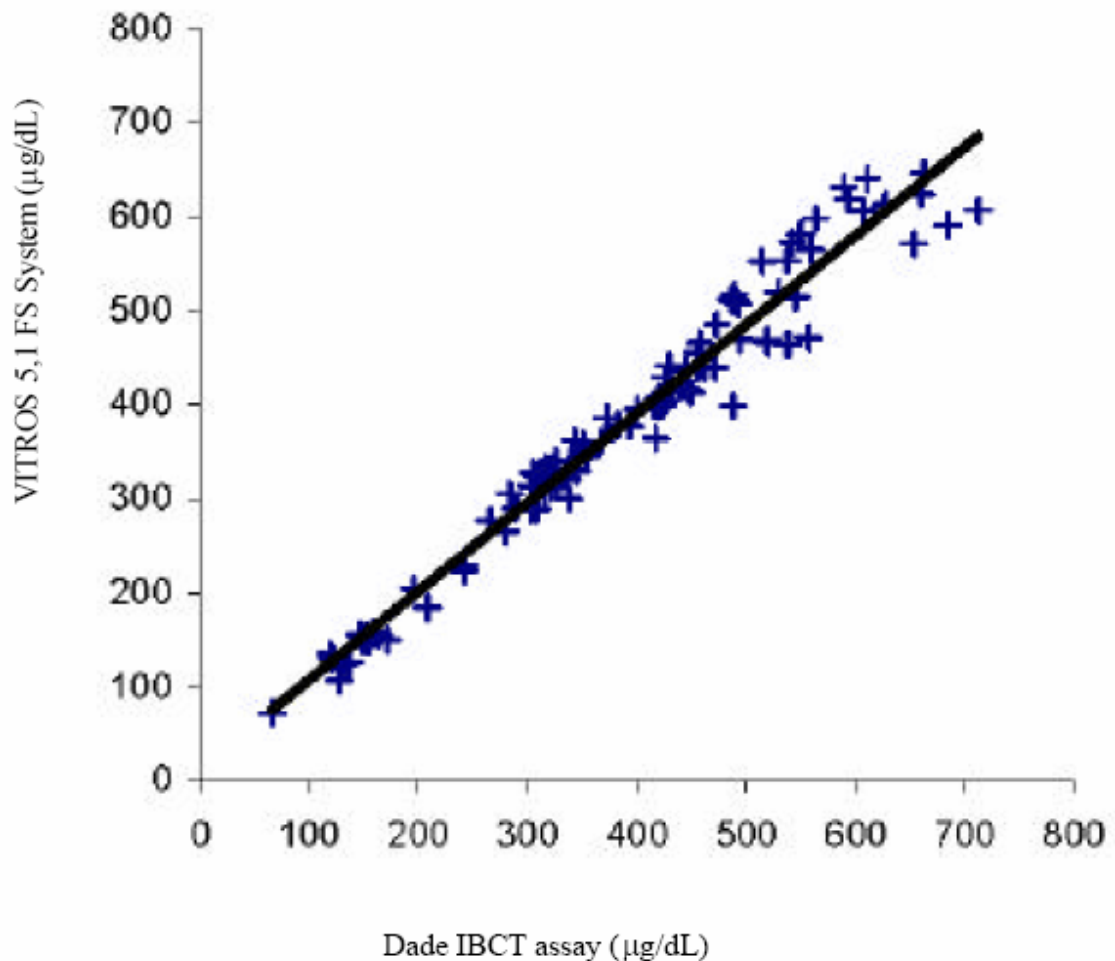
Not applicable for devices of this type.

2. Comparison studies:

a. *Method comparison with predicate device:*

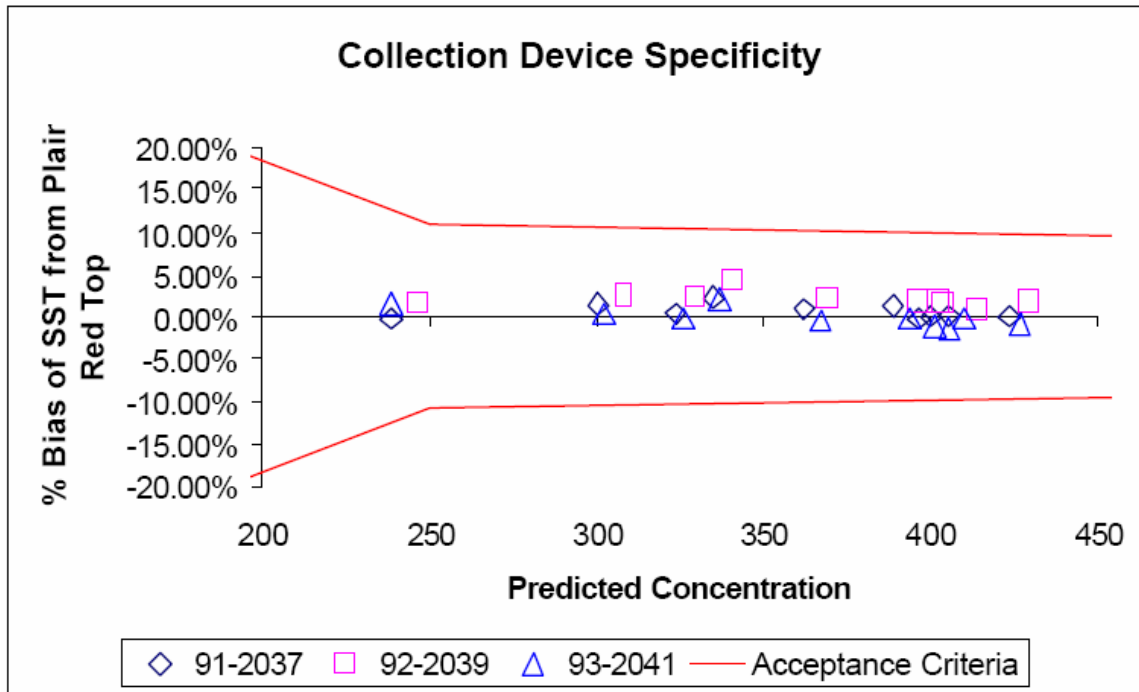
The company followed CLSI guideline EP09-A2 “Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition” in comparing their device to its predicate.

One hundred samples ranging in concentrations from 72 µg/dL to 647 µg/dL TIBC were analyzed on the Vitros 5,1 System and the predicate., The correlation is $y = 0.944x + 12.99$, $r = 0.981$. The following graph illustrates the linear relationship between the proposed device and its predicate:



b. *Matrix comparison:*

The company investigated the impact of sample collection and preparation on their device. The performance of paired sera drawn into plain glass tubes was compared to 20% filled serum separator tubes (SST). Performance of both specimen types was within acceptance criteria. The following figure is a bias plot showing the comparison of results generated using specimens collected in plain glass tubes to those collected in serum separator tubes for 3 different lots of reagents:



This graph shows that the impact of the matrix material – either glass or serum separators - used in specimen collection has a clinically insignificant impact on the results of the device.

The performance of stored specimens drawn into plain glass tubes was evaluated using three VITROS dTIBC Reagent lots. 10 patient serum specimens stored for up to three days at room temperature (18-28°C), up to 14 days refrigerated (2-8°C) and up to 14 days frozen (at or below -20°C) did not generate clinically different results compared to initial measurements using VITROS dTIBC Reagents.

3. Clinical studies:

a. *Clinical Sensitivity:*

Not applicable for devices of this type.

b. Clinical specificity:

Not applicable for devices of this type.

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable for devices of this type.

4. Clinical cut-off:

Not applicable for devices of this type.

5. Expected values/Reference range[†]:

Population	Conventional Units (µg/dL)	SI Units (µmol/L)	Alternate Units (mg/L)
Males	261 - 462	46.8 - 82.7	2.6 - 4.6
Females	265 - 497	47.4 - 89.0	2.7 - 5.0

[†]Hollowell, JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C. Hematological and Iron-Related Analytes - Reference Data for Persons Aged 1 year and Over: United States, 1988 - 1994. Vital and Health Statistics, Series 11, Number 247, Center for Disease Control, Atlanta, USA; March 2005.

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.