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

A. 510(k) Number:

k132058

B. Purpose for Submission:

New device

C. Measurand:

Free Thyroxine (FT4)

D. Type of Test:

Quantitative chemiluminescent immunoassay

E. Applicant:

bioMerieux SA

F. Proprietary and Established Names:

VIDAS FT4

G. Regulatory Information:

Device Name	Product Code	Classification	Regulation Section	Panel
VIDAS FT4	CEC	II	21 CFR § 862.1695 Free Thyroxine Test System	Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

   VIDAS FT4 is an automated quantitative enzyme immunoassay for use on the instruments of the VIDAS family, for the determination of free thyroxine (FT4) in human serum or plasma (lithium heparin), using the ELFA technique (Enzyme Linked Fluorescent Assay). Measurement of free thyroxine is intended for use as an aid in the

diagnosis and treatment monitoring of thyroid disorders.

3. Special conditions for use statement(s):

   For prescription use only

   For in vitro diagnostic use

   Not for use in point-of-care settings

4. Special instrument requirements:

   VIDAS and miniVIDAS analyzers

I. Device Description:

Each VIDAS FT4 kit contains 60 tests. The kit is comprised of: 60 FT4 Reagent Strips, 60 Solid Phase Receptacles (SPR), FT4 control, FT4 calibrator, and one Master Lot Entry (MLE) Card.

The FT4 Reagent Strips consist of 10 wells covered with a labeled foil seal. Five of the wells contain conjugate (alkaline phosphatase-labeled monoclonal mouse anti-T4 antibody and preservative), wash buffer, or a cuvette with substrate (4-Methyl-umberlliferyl phosphate, dietholamine, and preservative). One well is designated for the sample and the remaining wells are empty.

The interior of the Solid Phase Receptacles (SPR) are coated with T4 antigen.

The FT4 control (C1) is supplied with the kit as a 2 mL vial of liquid human serum, L-thyroxine, and preservative.

The FT4 calibrator (S1) is supplied with the kit as a 2 mL vial of liquid human serum, and preservative.

This product has been tested and shown to be negative for HBs antigen, antibodies to HIV1, HIV2 and HCV by FDA approved test method or equivalent method.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Roche Elecsys FT4 assay

2. Predicate 510(k) number(s):
   k961489

3. Comparison with predicate:

Similarities and Differences		
Item	VIDAS FT4 (Candidate Device)	Elecsys FT4 (Predicate Device, k961489)
Intended Use	For the quantitative determination of FT4 levels in human serum/plasma	Same
Assay Methodology	Enzyme linked Immunofluorescent Assay	Electrochemiluminescence Immunoassay
Measuring Range	0.13 to 6.61 ng/dL	0.023 to 7.77 ng/dL
Calibrators	One level in human serum matrix included in kit	Two levels in bovine serum albumin matrix sold separately
Control Level	One level in human serum matrix included in kit	One level in human serum matrix sold separately
Sample type	Serum and Plasma	Same
Antibody	Monoclonal mouse anti-T4	Polyclonal sheep anti-T4 antibodies

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

CLSI EP05-A2: *Evaluation of Precision Performance of Quantitative Measurement Methods*

CLSI EP07-A2: *Interference Testing in Clinical Chemistry*

CLSI EP17-A: *Protocols for Determination of Limits of Detection and Limits of Quantitation*

CLSI EP09-A2: *Method Comparison and Bias Estimation Using Patient Samples*

CLSI EP25-A: *Evaluation of Stability of In Vitro Diagnostic Reagents*

L. Test Principle:

The assay principle combines a one-step enzyme immunoassay competition method with a final fluorescent detection (ELFA). The Solid Phase Receptacle (SPR) serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips. All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR several times. The sample is collected and transferred into the well containing an alkaline phosphatase-labeled anti-T4 antibody (conjugate). The antigen present in the sample and the T4 antigen coated on the interior of the SPR compete for the available sites on the specific anti-T4 antibody conjugated to alkaline phosphatase. During the final detection step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured at 450 nm.

The intensity of the fluorescence is inversely proportional to the concentration of free thyroxine present in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The sponsor performed two precision studies for VIDAS FT4 assay in accordance with CLSI EP05-A2.

A panel of human serum samples was tested on three VIDAS (6 samples) and three miniVIDAS (5 samples) analyzers with two lots of reagents. Each sample was tested in duplicate, in 2 runs per day, for 10 days with each lot, for a total of 20 testing days, for a total of 240 results per sample.

The precision data for the miniVIDAS are summarized below:

Sample ID	N	Mean (ng/dL)	Within-run		Total	
			SD	%CV	SD	%CV
Serum 1	240	0.24	0.03	11.2	0.04	15.4
Serum 2	240	0.78	0.03	3.7	0.04	5.6
Serum 3	240	1.45	0.05	3.3	0.07	4.9
Serum 4	240	3.04	0.07	2.3	0.10	3.4
Serum 5	240	5.64	0.11	2.0	0.16	2.8

The precision data for the VIDAS analyzer are summarized below:

Sample ID	N	Mean (ng/dL)	Within-run		Total	
			SD	%CV	SD	%CV
Serum 1	240	0.31	0.02	6.3	0.04	13.4
Serum 2	240	0.79	0.03	3.6	0.07	8.3
Serum 3	240	1.54	0.05	3.1	0.11	7.4
Serum 4	240	2.57	0.06	2.5	0.13	5.1
Serum 5	240	4.00	0.09	2.3	0.24	5.9
Serum 6	240	5.78	0.17	3.0	0.36	6.5

b. Linearity/assay reportable range:

To establish the linearity of the assay, a study design was used based on CLSI protocol EP6-A. A high concentration serum sample was diluted with a low concentration serum sample to generate 12 concentrations that spanned the range 0.130 ng/dL to 8.077 ng/dL. The samples were analyzed in triplicates within a single run using one lot of reagent, on VIDAS and mini-VIDAS analyzers.

The results were plotted and the slope, intercept, and correlation coefficient values were calculated using weighted regression. The degree of nonlinearity was assessed

by analysis of second and third order polynomial regression. Results of the linearity analyses demonstrated that from 0.13 to 6.6 ng/dL there was a maximum deviation from linearity of ≤ 5-7%.

The weighted regression results for the VIDAS instrument are summarized in the following table:

Sample	Observed Mean result (ng/dL)	Predicted 1st order Polynomial (ng/dL)	Deviation from Linearity
1	0.130	0.125	4.4%
2	0.200	0.204	-1.9%
3	0.547	0.560	-2.5%
4	1.183	1.155	2.5%
5	2.313	2.343	-1.3%
6	4.773	4.721	1.1%
7	5.937	5.909	0.5%
8	7.793	7.891	-1.2%

The weighted regression results for the miniVIDAS instrument are summarized in the following table:

Sample	Expected Mean result (ng/dL)	Predicted 1st order Polynomial (ng/dL)	Deviation from Linearity
1	0.127	0.122	3.9%
2	0.187	0.199	-6.3%
3	0.533	0.547	-2.5%
4	1.193	1.126	5.9%
5	2.260	2.285	-1.1%
8	4.683	4.603	1.7%
9	5.823	5.762	1.1%
10	7.357	7.694	-4.4%

Linearity data support sponsor's claimed measuring range from 0.13 to 6.6 ng/dL.

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

Currently there is no reference method for FT4 assay. The VIDAS FT4 assay is traceable to the Roche Elecsys FT4 assay (k961489).

The VIDAS FT4 assay kit calibrators were prepared in house with a pool of human sera diluted with T4 stripped human sera. The values for the internal reference calibrators are assigned using the VIDAS FT4 kit in comparison with the predicate device. The VIDAS FT4 Calibrator is a liquid human serum matrix and is traceable to internal reference calibrators. The target value of the calibrator can range from 0.46-1.70 ng/dL, and the value is lot specific.

The VIDAS FT4 Control is a liquid human serum matrix spiked with synthetic T4

and is traceable to internal materials. The target value of the control is between 1.00-1.70 ng/dL, and the value is lot-specific. Multiple measurements were obtained from the VIDAS FT4 assay to calculate the control mean. The control range is calculated as mean ± 3SD.

Sponsor has the following recommendation for their Quality Control section in the labeling, "User should test at least 2 levels of quality control materials, one normal and one abnormal. Since Biomereiux FT4 assay kit only have one level of quality control material, additional quality control level should be used. Additional quality control may be purchased from commercially available source."

Stability of calibrator and control:

The calibrators and controls are ready to use liquid human serum matrix and are stable for 12 months unopened when stored at 2-8°C. Once open, they are stable up to 3 months when stored at 2-8°C. The stability study protocol and the acceptance criteria were provided, and found to be adequate.

d. *Detection limit:*

The Limit of the Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) for the VIDAS FT4 assay was determined in accordance with the CLSI guideline EP17-A.

LoB Test Protocol
One blank sample was tested on one VIDAS analyzer with 2 reagent lots in 12 replicates per day for 5 days yielding 120 results. For the miniVIDAS analyzer, the blank sample was tested with one reagent lot in 6 replicates in two runs per day for five days for a total of 60 results. The LoB is calculated as the mean of the 57th and 58th highest values for the blanks.

LoD Test Protocol
A total of 9 low level human serum samples were tested on one VIDAS analyzer with 2 reagent lots in 4 replicates per run, and 5 runs yielding 180 results. For the miniVIDAS analyzer, a total of 4 low level samples were with one reagent lot in 4 replicates per run for five days. LoD= LoB +1.650 x pooled SD of low level samples.

LoQ Test Protocol
A total of 9 low level human serum samples were tested on one VIDAS and one miniVIDAS analyzer with 2 reagent lots in 4 replicates per run, and 5 runs yielding 180 results. Sponsor defines the LoQ as the concentration at which inter-assay precision is ≤ 20% CV.

The detection limits results are summarized in the table below:

	VIDAS	miniVIDAS
LoB	0.013 ng/dL	0.005 ng/dL
LoD	0.055 ng/dL	0.063 ng/dL
LoQ	0.13 ng/dL	0.10 ng/dL

The sponsor claimed that the VIDAS FT4 assay has a measuring range of 0.13 to 6.61 ng/dL on the VIDAS and miniVIDAS analyzers.

e. *Analytical specificity:*

i. Interference from endogenous substances

The sponsor performed studies to evaluate the effects of potential interferents on the performance of the VIDAS FT4 assay, following CLSI EP7-A2. Two levels of serum samples containing approximately 0.93 to 1.24 ng/dL and 2.48 to 2.71 ng/dL FT4 were spiked with different concentrations of the listed interferents. Each level of FT4 was tested with each interferent in 5 replicates. The level of interference was considered not significant if there was no more than 10% difference between the result in the presence of the interferent and the unspiked control result. The table below lists the substances tested and the concentrations at which no significant interference was observed:

Interferent	Highest concentration tested at which no significant interference was observed.
Lipids	750 mg/dL
Hemoglobin	500 mg/dL
Bilirubin	22.5 mg/dL
HAMA	0.2 mg/dL
Albumin	6300 mg/dL

The sponsor states the following in the labeling regarding potentially interfering substances:

"It is not recommended to use clearly hemolyzed, lipemic, or icteric samples, and if possible to collect a new sample."

"Samples containing abnormal TBG levels (very high or very low) should be not used with this assay."[1]

"No interference was observed with samples containing HAMA up to 0.2 mg/dL when tested with VIDAS FT4 assay. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interferes with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

[1] SOLDIN O.P. – Thyroid function testing in pregnancy and thyroid disease: trimester-specific reference intervals. Ther. Drug Monit., 2006, 28(1), 8-11.
FANTZ, C. R., DAGOGO-JACK S., LADENSON J.H., GRONOWSKI A.M. - Thyroid function during pregnancy. Clin.Chem, 1999, 45(12), 2250-2258.

ii. Interference from common drugs

The effect of 18 common drugs was evaluated on the VIDAS analyzer. For each drug, a low FT4 concentration and a high FT4 concentration containing human serum samples were tested. At each FT4 level, the drug-free pool and drug-containing pool were tested in 5 replicates. For all substances tested, no significant interference was defined as recovery ± 10% of initial value. The drugs and the highest concentration tested which did not cause significant interference are listed below.

Drug	Highest concentration at which no interference was observed
Acetylsalicylic Acid	32.61 mg/dL
Amiodarone	0.58 mg/dL
Carbamazepine	1.5 mg/dL
Danazol	24 mg/dL
Diclofenac	0.315 mg/dL
Diphenyldantoin	2.5 mg/dL
Dipyrone	580.08 mg/dL
Furosemide	0.075 mg/dL
Isotretinonine	1.20 mg/dL
Lithium	13.56 mg/dL
Mefenamic Acid	0.5625 mg/dL
Mestranol	0.002 mg/dL
Methimazole	2.40 mg/dL
Norethindrone	0.001 mg/dL
Phenylbutazone	5 mg/dL
Propanolol	0.20 mg/dL
Propylthiouracil	3.08 mg/dL
Sodium Salicylate	17.37 mg/dL

iii. Cross reactivity study:

The cross-reactivity study was carried out by adding known amounts of potential cross reactants to a low and a high FT4 serum and measuring the FT4 concentrations. The cross reactivity results for the VIDAS analyzer are shown below:

Cross reactant	**Concentration Tested**	**% Cross reactivity**
3,5,-diiodothyrosine	167.70 µg/L	0.00095 %
3,5-diiodothyronine	273.10 µg/L	0.00040 %
L-Triiodothyronine	6.78 µg/L	0.02655 %

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The sponsor performed two method comparison studies for VIDAS FT4 assay in accordance with CLSI EP09-A2.

54 human serum samples ranging in concentration from 0.41 ng/dL to 6.42 ng/dL were measured with 1 lot of the VIDAS FT4 assay on each VIDAS (53 native samples and 1 one spiked sample) and miniVIDAS analyzers (54 native samples) and compared to the predicate device on the cobas 8000 instrument. Results of the Passing-Bablok regression analysis are presented below:

For VIDAS:

	Passing-Bablok
Slope (95% CI)	1.0268 [95% CI: 0.9914, 1.0345]
Intercept (95% CI)	-0.0836 [95% CI:-0.1059, -0.0613]
Correlation Coefficient	0.9884

For miniVIDAS:

	Passing-Bablok
Slope (95% CI)	1.0425 [95% CI: 1.0026, 1.0785]
Intercept (95% CI)	-0.1061 [95% CI: -0.1930, -0.0126]
Correlation Coefficient	0.9868

b. Matrix comparison:

A matrix comparison study was conducted on the VIDAS analyzer using 31 blood samples collected in 5 different types of tubes. The serum glass tube with silicone coated stoppers was set as the reference and all other tube types (listed below) were compared against the reference tube type using the VIDAS FT4 assay. Plasma samples result range tested was 0.15 to 6.24 ng/dL. The Passing Bablok regression correlation for each sample type is summarized in the table below:
(y = reference tube, x = tested tube)

Tube type	Passing Bablok Regression	Correlation Coefficient (R)

Serum PET tube with coagulation activator	y = 0.9867 x + 0.0252	0.999
Serum PET tube with separator gel	y = 1.0368 x + 0.0058	0.999
Plasma PET tube with lithium heparin	y = 0.9708 x- 0.0074	0.997
Plasma PET tube with lithium heparin and separator	y = 0.9854 x - 0.0309	0.999

The results of the study support the sponsor's claim that serum and lithium-heparin plasma sample types may be used with the assay:

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:

   To determine the reference range for the VIDAS FT4 assay, a total of 544 serum samples from apparently healthy adults were measured at 3 testing sites using the VIDAS analyzer. The reference range is determined to be 0.77-1.51 ng/dL based on the central 95% observed values. The sponsor recommends that each laboratory should establish its own reference range.

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.