510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k103676

B. Purpose for Submission:
Device modification to k072939 by replacing the HE4 EIA kit control supplied as part of k072939 with the separately marketed multi-analyte Tumor Marker Control cleared in k101809.

C. Measurand:
Control material, **HE4 (Human Epididymis Protein 4)**, (Kit also contains control materials for AFP (Alpha Fetoprotein), CEA (carcinoembryonic antigen) 15-3, CA 19-9, CA 125, CEA (Carcinoembryonic Antigen), Ferritin, PSA (Prostate Specific Antigen) and Free PSA)

D. Type of Test:
Assayed Quality control material for use in Quantitative, Enzymatic Immunoassay (EIA)

E. Applicant:
Fujirebio Diagnostics, Inc.

F. Proprietary and Established Names:
HE4 EIA Kit
Fujirebio Diagnostics Tumor Marker Control

G. Regulatory Information:

1. Regulation section:
   21 CFR §866.6010, Tumor-associated Antigen Immunological Test System.
   21 CFR §862.1660, Quality Systems Material (assayed and unassayed)
2. Classification:
   Class II HE4 assay
   Class I, reserved - Control
3. Product code:
   OIU, Epithelial ovarian tumor associated antigen test (HE4)
   JJY, Multi-analyte controls, ally kinds, (assayed)
4. Panel:
   Immunology (82) (HE4)
   Clinical Chemistry (75) (Control)

H. Intended Use:

1. Intended use(s):
   No change to the Intended use of the HE4 EIA kit which states:
   The HE4 EIA is an enzyme immunometric assay for the quantitative determination of HE4 in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

Intended use of the Fujirebio multi-analyte Tumor Marker Control is the same as in k101809:
For In Vitro Diagnostic Use Only.
Fujirebio Diagnostics Tumor Marker Control is intended for use as an assayed control serum to monitor the precision of laboratory testing procedures for the analytes listed in the lot specific assigned values sheet.

2. Indication(s) for use:
   Same as intended use
3. Special conditions for use statement(s):
   For Prescription Use Only.
4. Special instrument requirements:
   Microplate reader capable of measuring optical density (OD) at 620 nm or 405 nm.

I. Device Description:

Replacement of the HE4 EIA kit control supplied as part of k072939 with the separately marketed multi-analyte Tumor Marker Control cleared in k101809.

The Fujirebio Diagnostics Tumor Marker Control (k101809) consists of a Low and High Control. The kit includes six bottles of lyophilized material (three of each level). The control is prepared from human serum, purified biochemical materials, and chemicals. The control contains a preservative (MIT (2-Methylisothiazolin) at a concentration of 0.1 g/L) and stabilizers (Methylamine at 7.5 g/L and Sucrose at 60g/L).

The table below shows an example of typical target ranges for the two control levels:

Analyte	Typical Range Level 1	Typical Range Level 2	Assay unit	SI Unit
AFP	15.4-28.6	196-344	ng/mL	µg/L
CA 15-3	11.9-22.1	105-195	U/mL	kU/L
CA 19-9	39.2-72.8	431-800**	U/mL	kU/L
CA 125	17.5-32.5	280-520	U/mL	kU/L
CEA	3.5-6.5	42.0-78.0	ng/mL	µg/L
HE4	**50.0-100.0**	**450-850**	**pM**	**µg/L**
Ferritin	31.5-75.0	280-250	ng/mL	pmol/L
Free PSA	≥1.0	7.0-19.0	ng/mL	µg/L
PSA	2.3-4.2	21.0-39.0	ng/mL	µg/L

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) number(s):
   HE4 EIA (HE4 kit controls only), k072939

2. Comparison with predicate HE4 control:

Similarities		
Item	Device	Predicate
Name	Fujirebio Diagnostics Tumor Marker Control (k101809)	HE4 EIA kit controls (k072939)
Supplier	Manufactured by Fujirebio Diagnostics	Same
Matrix	Human Serum	Same
Form	Lyophilized	Same
HE4 Analyte control	Purified, recombinant antigen	Same
Number of Control Levels	2	Same
Stability (unopened)	18 months at 2–8°C.	Same
Differences		
Controls Supplied	Sold Separately	Sold with HE4 EIA kit
Analyte (s)	Multiple analytes: AFP, CA 15-3, CA 19-9, CA 125, CEA, Ferritin, **HE4,** PSA and Free PSA	**HE4 (Human Epididymis Protein 4)**
Target HE4 Control Concentrations	75 and 500 pM*	50 and 400 pM*
Target HE4 Control Ranges	Ranges of expected results indicated on the Assigned Value Sheet provided with the Fujirebio Diagnostics Tumor Marker Controls.	Ranges of expected results are indicated on the vial labels.
Reconstitution Volume	3.0 mL distilled or deionized water	1.0 mL distilled or deionized water
Stability after Reconstitution	14 days at 2–8°C; 60 days at -20°C or below	4 weeks at 2–8°C 4 months at -20°C or below

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

CEN standard, 13640 – Stability Testing of *In Vitro* Diagnostic Reagents.
Guidance for Industry and FDA Staff – Assayed and Unassayed Quality Control Material.

L. Test Principle:

Not applicable

M. Performance Characteristics (if/when applicable):

Performance data are for validation of the Fujirebio muti-analyte Tumor Marker Control for the 510k cleared manual HE4 EIA kit, k072939.

1. Analytical performance:
   a. Precision/Reproducibility:

Two each of the low and high levels Fujirebio multi-analyte Tumor Marker Controls were analyzed with 1 HE4 test kit in 2 replicates, 2 runs per day for 10 days (two hours between runs) and 2 operators performed 10 assays each.

Sample		Total mean	Intermediate precision		Between-Day precision		Between-Run precision		Repeatability precision	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%
1	27221	76.6	3.7	4.8	0.0	0.0	3.4	4.5	1.4	1.8
2	27222	715.6	20.5	2.9	13.7	1.9	9.0	1.3	12.4	1.7
3	29033	75.9	2.7	3.5	0.0	0.0	2.4	3.1	1.2	1.5
4	29034	620.7	19.6	3.2	0.0	0.0	17.8	2.9	8.3	1.3

b. *Linearity/assay reportable range:*
Not applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Traceability:
No claims for traceability. There is no standard or reference material for the HE4 protein.

Expected/assigned Values:
Value assignments for the HE4 analyte for each lot are performed by Fujirebio Diagnostics, AB. Mean values for each level of each analyte are performed by running a minimum of 24 replicates using different HE4 EIA kit reagent combinations. It is recommended that each laboratory establish its own means and acceptable ranges and use the printed ranges as guidance only. Values and ranges are lot specific. Acceptance ranges for the target-setting reference system, EIA from Fujirebio Diagnostics are summarized in the table below:

Analyte	Design Goal Target Mean Level 1	Level 1 Mean Acceptance Range	Design Goal Target Mean Level 2	Level 2 Mean Acceptance Range
HE4 pM	75.0	45 – 105	500	300-700

Stability:
The stability studies were performed in compliance to the CEN standard, 13640 – Stability Testing of *In Vitro* Diagnostic Reagents. Stability data was submitted in k101809.

Accelerated Stability and real time (closed/shelf life) stability:
Two lots of lyophilized Fujirebio Diagnostics Tumor Marker Controls were tested. The lyophilized Fujirebio Diagnostics Tumor Marker Control vials were stored at 2-8°C (reference), ambient temperature (test) and 37°C (test). The Fujirebio Diagnostics Tumor Marker Controls (test and reference) were run in duplicate after reconstitution per product insert instructions. Real time

stability studies are currently ongoing. The shelf life stability is based on the accelerated stability study. The claimed shelf life stability is 18 months lyophilized at 2-8°C

Open vial stability/Reconstituted Stability:
Two lots of Fujirebio Diagnostics Tumor Marker Controls were tested. Lyophilized Fujirebio Diagnostics Tumor Marker Control vials (reference) were stored at 2-8˚C. Reconstituted vials were stored at 2-8°C (test) or ≤ 20°C (test). The tests and reference (after reconstitution) were run in duplicate at various time points. The claimed open vial stability once the control is reconstituted for HE4 is 14 days when stored tightly capped at 2-8°C or 60 days when stored at ≤ 20°C after reconstitution.

Freeze/Thaw Stability:
Two lots of lyophilized Fujirebio Diagnostics Tumor Marker Controls are used for the study. The test vials were reconstituted at the start of the study and then frozen and thawed for multiple cycles and compared to lyophilized Fujirebio Diagnostics Tumor Marker Control vials (reference) that were stored at 2-8˚C before reconstitution. The sponsor claims that controls may be frozen and thawed repeatedly for up to 9 cycles.

Transport stability:
Two lots of lyophilized Fujirebio Diagnostics Tumor Marker Controls are used for the study. The lyophilized Fujirebio Diagnostics Tumor Marker Control vials were stressed under varying conditions and then stored at the recommended storage condition of 2-8°C. Transport stability for the Fujirebio Diagnostics Tumor Marker Controls is currently ongoing.

d. Detection limit:
Not applicable

e. Analytical specificity:
Not applicable

f. Assay cut-off:
Not applicable

2. Comparison studies:
   a. Method comparison with predicate device:
   Not applicable
   b. Matrix comparison:
   Not applicable
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:
   Not applicable

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.