510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k071597

B. Purpose for Submission:
New device

C. Measurand:
Alpha-Fetoprotein (AFP)

D. Type of Test:
Quantitative, Chemiluminescence

E. Applicant:
Seimens Healthcare Diagnostics Inc. (formerly Dade Behring Inc.)

F. Proprietary and Established Names:
Dimension Vista® Alpha-Fetoprotein (AFP) reagent cartridge
Dimension Vista® LOCI 5 Calibrator

G. Regulatory Information:
1. Regulation section:
   866.6010   Tumor-associated antigen immunological test system
   862.1150   Calibrator
2. Classification:
   Class II
3. Product code:
   LOJ   Kit, Test, Alpha-fetoprotein for testicular cancer
   JIX   Calibrator, Multi-analyte mixture
4. Panel:
   Immunology (82)

H. Intended Use:
1. Intended use(s):
   Dimension Vista® AFP Method: The AFP method is an in vitro diagnostic test for the quantitative measurement of alpha-fetoprotein in human serum on the Dimension Vista® system. Measurements of alpha-fetoprotein are used as an aid in managing non-seminomatous testicular cancer when used in conjunction with physical examination, histology/pathology and other clinical evaluation procedures.
   Dimension Vista® LOCI 5 Calibrator: For the calibration of the Alpha-Fetoprotein (AFP) method on the Dimension Vista® System.
2. Indication(s) for use:
   Same as above
3. Special conditions for use statement(s):
   Prescription use only
4. Special instrument requirements:
   Dimension Vista® System

I. Device Description:
The AFP method consists of two synthetic bead reagents and a biotinylated murine-

anti-AFP antibody. The first bead reagent (Chemibeads) is coated with an anti-AFP monoclonal antibody and contains a chemiluminescent dye. The second bead reagent (Sensibeads) is coated with streptavidin and contains a photosensitizer dye. All are supplied in liquid format in a reagent cartridge.

The LOCI™ 5 Calibrator is a liquid multi-analyte product containing AFP from human cord serum. The kit consists of 10 vials, 2 each of 5 levels containing 2 mL per vial.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Abbott AxSYM® AFP Method
   Beckman Access AFP Calibrators on the Access® Immunoassay System

2. Predicate 510(k) number(s):
   P820060/S019
   k981354

3. Comparison with predicate:

AFP Method

Similarities		
Item	Device	Predicate
Intended Use	The AFP method is an in vitro diagnostic test for the quantitative measurement of alpha-fetoprotein in human serum on the Dimension Vista® System.	AxSYM AFP is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of alpha-fetoprotein (AFP) in human serum or plasma to aid in the management of patients with non-seminomatous testicular cancer.
Indications for Use	Measurements of alpha-fetoprotein are used as an aid in managing non-seminomatous testicular cancer when used in conjunction with physical examination, histology/pathology, and other clinical evaluation procedures	Same
Standardization	WHO 72/225	Same
Capture antibody	Mouse monoclonal	Same
Storage	Store at 2 to 8°C	Same

Differences		
Item	Device	Predicate
Indications for Use	Not applicable	For the quantitative determination of alpha-fetoprotein (AFP) in amniotic fluid at 15 to 21 weeks gestation to aid in the detection of fetal open neural tube defects (NTD).
Methodology	Chemiluminescent immunoassay	Microparticle enzyme immunoassay
Measuring range	0.5 to 1000 ng/mL	0.4 to 350 ng/mL
Sample types	Serum	Serum, plasma and amniotic fluid
Sample size	2 μL	58 μL
Stability: Open	7 days	112 cumulative hours

Calibrator

Similarities		
Item	Device	Predicate
Intended Use	For the calibration of Alpha-Fetoprotein (AFP) method on the Dimension Vista® system.	The Access AFP Calibrators are intended to calibrate the Access AFP assay for the quantitative determination of AFP levels in human serum, using the Access Immunoassay System.
Traceability	WHO reference preparation for human AFP (72/225)	Same
Composition	BSA-based matrix	Same
Preparation	Liquid, ready-to-use	Same
Storage	Store at 2 to 8°C	Store at 2 to 10°C

Differences		
Item	Device	Predicate
Calibrator Levels	5 target concentrations: 0, 8, 100, 500 and 1050 ng/mL	6 target concentrations: 0, 2.5, 5, 25, 500 and 3000 ng/mL
Instrument	Dimension Vista system	Access Immunoassay systems

K. Standard/Guidance Documents referenced (if applicable):
Guidance documents: "Bundling Multiple Devices of Multiple Indications in a Single

Submission," "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable- Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff." CLSI EP9-A2 Approved Guideline Method Comparison and Bias Estimation Using Patient Samples. CLSI EP17-A, Approved Guideline Protocols for Determination of Limits of Detection and Limits of Quantitation.

L. Test Principle:

The AFP method is a homogeneous, sandwich chemiluminescent immunoassay based in LOCI™ technology. The LOCI™ reagents include two synthetic bead reagents and a biotinylated anti-AFP monoclonal antibody fragment. The first bead reagent (Chemibeads) is coated with an anti-AFP monoclonal antibody and contains chemiluminescent dye. The second bead reagent (Sensibeads) is coated with streptavidin and contains a photosensitizer dye. Sample is incubated with biotinylated antibody and Chemibeads to form bead-AFP-biotinylated antibody sandwiches. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffused into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the AFP concentration in the sample.

The LOCI™ 5 Calibrator is a liquid multi-analyte product containing AFP from human cord serum.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   The reproducibility testing was conducted in accordance with the CLSI/NCCLS Approved Guideline for User Evaluation of Precision Performance of Clinical Chemistry Devices EP5-A2. Samples (pooled serum, pooled plasma, and controls) were measured in duplicate, two times per day over 20 days. Repeatability, between-run, between day, and within-lab were determined by the analysis of variance method. The repeatability and within-lab data are presented below. Imprecision was less than 2.3% CV.

Sample	Mean (ng/mL)	Repeatability		Within Lab	
		SD (ng/mL)	%CV	SD (ng/mL)	%CV
Serum Pool*	0.92	0.01	1.3	0.02	1.9
Liquimmune ® Control					
Level 1	12.8	0.1	1.1	0.2	1.8
Level 2	75.6	0.7	0.9	1.2	1.6
Level 3	139.3	1.7	1.2	2.6	1.8
Plasma Pool	249	2.9	1.2	5.1	2.0
Serum Poo1	496.2	7.0	1.4	10.9	2.2
Serum Pool	772.5	9.4	1.2	17.9	2.3
Serum Pool	832.5	12.7	1.5	16.4	2.0

*5-day protocol was employed for this sample.

Between-Lot reproducibility was also evaluated using 4 different samples (2

sera and 2 quality control materials) representing the range of the assay 12 ng/mL to 891 ng/mL) on two different AFP Flex® reagent lots (with two different calibrator lots). The %CV was less than 2.0%

b. *Linearity/assay reportable range:*
   Linearity of the reportable range (1.7 to 1014 ng/mL) and for the low end of the assay range (1.6 to 178.2 ng/mL) was evaluated by comparing observed vs. expected values using a series of equally spaced sample pools that were prepared by a sequential mixing of a high spiked serum equivalent and low serum equivalent of known concentrations. Linear regression analysis demonstrated the following results:

Range (ng/mL)	Slope (95% CI)	Intercept ng/mL (95% CI)	Correlation Coefficient	n
1.7 to 1014	1.00 (0.98-1.01)	3.24 (-5.98 to 12.46)	1.000	7
1.6 to 178.2	1.00 (0.99-1.01)	-0.24 (1.74 – 1.25)	1.000	5

Spiking recovery: A spiking recovery study was performed by adding known amounts of AFP (WHO 72/225) to a human serum pool with baseline AFP values of 1.5 ng/mL. The sample concentrations were measured and the percent recovery ranged from 97.8% to 101.7% with a mean recovery of 100%.

Dilution recovery: A dilution recovery study was performed by diluting 2 plasma and 3 serum samples with AFP values from 93.2 ng/mL to 761.9 ng/mL with Reagent grade water. The samples were diluted 1:2, 1:5, 1:10 and 1:20 and assayed for recovery. The recoveries ranged from 98.0% to 112.3% with a mean of 104.2%.

Sample	Dilution	Observed (ng/mL)	Expected (ng/mL)	Observed (IU/mL)	Expected (IU/mL)	Recovery %
Plasma 1	-	93.2		77.0		
	1:2	45.8	46.6	37.8	38.5	98.2
	1:5	18.3	18.6	15.1	15.4	98.3
	1:10	9.3	9.3	7.7	7.7	99.4
	1:20	4.6	4.7	3.8	3.8	98.0
	Mean					98.5
Plasma 2	-	270.2		223.2		
	1:2	137.6	135.1	113.7	111.6	101.8
	1:5	57.0	54.0	47.1	44.6	105.5
	1:10	28.2	27.0	23.3	22.3	104.4
	1:20	13.7	13.5	11.3	11.2	101.3
	Mean					103.3
Serum 1	-	464.8		383.9		
	1:2	243.7	232.4	201.3	192.0	104.9
	1:5	101.8	93.0	84.1	76.8	109.5
	1:10	50.2	46.5	41.5	38.4	108.0
	1:20	25.1	23.2	20.7	19.2	107.8
	Mean					107.5
Serum 2	-	373.7		308.7		
	1:2	187.1	186.9	154.5	154.4	100.1
	1:5	78.0	74.7	64.4	61.7	104.4
	1:10	38.0	37.4	31.4	30.9	101.6
	1:20	19.2	18.7	15.8	15.4	102.6
	Mean					102.2
Serum 3	-	761.9	761.9	629.4		
	1:2	398.0	381.0	328.8	314.7	104.5
	1:5	168.5	152.4	139.2	125.9	110.6
	1:10	84.6	76.2	69.9	62.9	111.1
	1:20	42.8	38.1	35.3	31.5	112.3
	Mean					109.6

All Samples Mean Recovery (%)   104.2

Antigen Excess (Hook Effect): The effect of antigen excess was evaluated using a serum sample above the assay range. No effect was seen up to 2877 IU/mL. Samples above this level are reported as exceeding assay range (>600 IU/mL).

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The AFP calibrators are traceable to WHO reference preparation for human AFP (72/225).
Stability claims in the IFU were supported by stability protocols and data. Specimen stability claims were supported by protocols employing freeze-thaw and stress testing up to 7 days or stored at -20°C for 30 days.

d. *Detection limit:*
The Limit of Blank (LoB) and the Limit of Detection (LoD) were evaluated according to CLSI EP17-A "Protocols for Determination of Limits of Detection and Limits of Quantitation." The data supports the claim of 0.5 ng/mL.

e. *Analytical specificity:*
   i. <u>Interference Studies</u>: Interference testing was performed according to CLSI Approved Guideline for Interference Testing in Clinical Chemistry EP7-A2, to determine the effect of various substances on the Dimension Vista® AFP assay at two concentrations of AFP (~9.0 ng/mL and ~230 ng/mL). The following interferents were tested for their effect on test samples and compared to a control sample without interferent; bias exceeding 10% is considered interference: bilirubin (conjugated and unconjugated, 60 mg/dL), hemoglobin (1000 mg/dL), Intralipid 3000 mg/dL, total protein (12 g/dL) and rheumatoid factor (500 IU/mL). Acceptance criteria were met. Additionally, 41 potentially interfering drugs were also assayed on serum samples containing 10 ng/mL AFP and shown to exhibit minimal interference (<10%).
   ii. <u>Interference by chemotherapeutic reagents</u>: Interference by common chemotherapeutic reagents was evaluated on two AFP concentrations (10 ng/mL and 250 ng/mL). The results are shown below. The acceptance criteria (bias <10%) were met.

Substance	Test Concentration	Bias (%) at 10 ng/mL	Bias (%) at 250 ng/mL
Bleomycin	3.3 mg/dL	-0.3	-0.6
Cisplatin	8.8 mg/dL	0.6	0.6
Cyclophosphamide	327.9 mg/dL	-2.3	-3.1
Doxorubicin	16.5 mg/dL	-1.2	-2.3
Etopside	22.0 mg/dL	0.1	0.1
5-Fluorouracil	130.9 mg/dL	0.1	0.9
Ifosfamide	261.8 mg/dL	-2.3	-3.4
Mesna	84.0 mg/dL	-5.0	-6.0
Methotrexate	450.5 mg/dL	2.5	5.5
Mitomycin C	6.0 mg/dL	-0.4	-0.9
Paclitaxel	38.2 mg/dL	1.2	0.0
Vinblastine	4.0 mg/dL	0.4	-0.9
Vincristine	0.44 mg/dL	0.7	-2.7

   iii. <u>HAMA</u>: Interference by human anti-murine antibodies was evaluated using three heterophilic human plasma samples containing HAMA and two AFP concentrations (10 and 250 ng/mL). The percent bias was calculated and shown to be less than -4.8%.
   iv. <u>Cross Reactivity</u>: The following substances were evaluated for cross-reactivity with the AFP method when present in serum in the amounts indicated. Systematic inaccuracies (bias) due to these substances are less than 10 % at an AFP concentration of 10 ng/mL and 240 ng/mL.

Substance	**Concentration**
α_1-glycoprotein	2.0 mg/mL [2.0 g/L]
α- globulin	32 mg/mL [32 g/L]
Chorionic gonadotropin	1000 mIU/mL [IU/L]

f. *Assay cut-off:*
Not applicable.
2. Comparison studies:
   a. *Method comparison with predicate device:*
A split sample method comparison study was performed according to CLSI document EP9-A2; "Guideline for Method Comparison and Bias Estimation using Patient Samples." A total of 317 serum samples spanning the assay range (0.97 to 881 ng/mL) were evaluated on both the Dimension® Vista and the Abbott AxSYM® AFP methods. A similar comparison using 84 samples (range 1.6 – 842.9 ng/mL) was performed between the Dimension Vista® AFP Method and the ADVIA Centaur® AFP method. Passing-Bablok non-parametric linear regression of singlicate measurements yielded the following statistics:

Comparative Method	Slope (95% CI)	Intercept ng/mL (95% CI)	Correlation Coefficient	n
AxSYM® AFP	0.93 (0.912-0.938)	0.093 (0.042-0.146)	0.995	317
ADVIA Centaur® AFP	0.97	-0.6	0.997	84

   b. *Matrix comparison:*
Serum is the sample type used.
3. Clinical studies:
   a. *Clinical Sensitivity and Specificity:*
Not applicable.
   b. *Other clinical supportive data (when a .is not applicable)*:
A clinical evaluation was performed to assess the Dimension Vista® AFP method for the purpose of obtaining FDA premarket clearance for monitoring patients with non-seminomatous testicular cancer. Seventy (74) retrospective serial serum sample sets (with a minimum of 3 blood draws for each patient) with clinical data from men with testicular cancer were tested. Inclusion and exclusion criteria for the samples were provided. Four patients were excluded from statistical analysis when it was determined they did not meet the inclusion criteria for non-seminomatous testicular cancer. Samples were selected for age (range 1.1 year old to 53.7 years old; average age 30.8 years old), ethnicity (specimens from African Americans were not evaluated in this study), and stage of disease (stage I through IV).

A longitudinal analysis of serial draws from 70 patients was performed. All patients were categorized as Active/Progressive, Responding, Stable, or No Evidence of Disease (NED). Disease progression was determined by the patient physician based on either or all of the following:
- Physical examination of clinical signs and symptoms, including results of laboratory tests.

- Radiographic findings used in the assessment of cancer status (CAT Scans, MRI, X-rays, or ultrasound images.
- Surgical procedures including needle aspirations and Orchiectomy.

The Reference Change Value (RCV) was used to determine if a significant change in AFP occurred. For this calculation, the RCV for each assay (the Dimension Vista AFP method and predicate) was derived by taking into account the published biological variation for AFP and the total imprecision of the assay. The formula for this calculation is $RCV = 2^{1/2} * Z * (CV_A^2 + CV_I^2)^{1/2}$, where Z is the z-score, CV_A is the analytical variation, and CV_I is the biological variation (Fraser, Callum G. Biological Variation: From Principles to Practice, Washington, DC: AACC Press, 2001). The within-subject biological variation (12%) was obtained from the literature (Trapé J, Botarges JM, Porta F, Ricós C, Badal JM, Salinas R, Sala M, Roca A. Reference change value for alpha-fetoprotein and its application in early detection of hepatocellular carcinoma in patients with hepatic disease. Clin Chem 2003;49:1209-1211). The RCV for the Vista AFP method was calculated to be 33.7% and that of the predicate to be 37.7%.

Per Visit analysis:
Changes in AFP concentrations and in disease status were analyzed on a per visit basis. Patients were categorized as Active/Progressive, Responding, Stable or No Evidence of Disease (NED) by the attending physician based on the clinical information. All 70 patients were analyzed to determine the change of disease status per sequential pair (n=244). The table below shows the distribution of results when compared to the disease status:

Change in AFP	Change in Disease State				
	Responding n (%)	Stable n (%)	No Evidence of Disease n (%)	Progression n(%)	Total
>33.7% increase	5 (2.1%)	10 (4.1%)	9 (3.7%)	16 (6.6%)	40 (16.5%)
No significant Change	4 (1.6%)	13 (5.3%)	94 (38.5%)	22 (9.0%)	133 (54.4%)
>33.7% decrease	16 (6.6%)	24 (9.8%)	10 (4.1%)	21 (8.6%)	71 (29.1%)
Total	25 (10.3%)	47 (19.2%)	113 (46.3%)	59 (24.2%)	244 (100.0%)

The following two tables show per visit clinical performance results for the Dimension Vista AFP test and predicate device analyzed as "Progression" and "No Progression" with "No Progression" consisting of responding, stable, and no evidence of disease:

Vista AFP Value vs. Disease Progression

	Progression	No-Progression	Total
>33.7% increase	**16**	24	40
≤33.7% increase	43	**161**	204
Total	59	185	244

	Estimate	Exact 95% Confidence Interval
Accuracy	72.5%	(66.5% - 77.8%)
Sensitivity	27.1%	(16.4% - 40.3%)
Specificity	87.0%	(81.3% - 91.5%)

Predicate AFP Value vs. Disease Progression

	Progression	No-Progression	Total
>37.7% increase	16	18	34
≤37.7% increase	43	167	210
Total	59	185	244

	Estimate	Exact 95% Confidence Interval
Accuracy	75.0%	(69.2% - 80.0%)
Sensitivity	27.1%	(16.4% - 40.3%)
Specificity	90.3%	(85.1% - 94.1%)

Per Patient analysis:

Within each patient's series, disease status was classified as "Progression" and "No Progression" with "No Progression" consisting of responding, stable, and no evidence of disease, and computed on a per patient basis according to the theory presented in, "Analysis of repeated markers used to predict progression of cancer", by B. Emir, S. Wieand, John Q.S., and S. Cha, Statistics in Medicine, 17, 2563-2578 (1998).

Efficacy is demonstrated when the sum of sensitivity and specificity is greater than one. Non-parametric estimates for the 95% confidence intervals were derived using a bootstrap resampling technique with 2000 iterations. For the Dimension Vista AFP method, the bootstrap 95% CI was between 1.0062 and 1.2861 for the sum of Sensitivity and Specificity, and for the comparative method the bootstrap 95% CI for the sum of Sensitivity and Specificity was between 1.0444 and 1.3166.

Concordance between Dimension Vista AFP and predicate:

All specimens were analyzed for percent agreement between the two assays using their RCVs. Results are shown below:

Vista AFP Concordance to Comparative Method (on a per visit basis)

	>37.7% increase	≤37.7% increase	Total
>33.7% increase	34	6	40
≤33.7% increase	0	204	204
Total	34	210	244

		95% Confidence Interval
% Overall agreement	97.5%	(94.7% - (99.1%)
% Positive agreement	100%	(89.7% – 100%)
% Negative agreement	97.1%	(93.9% - 98.9%)

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The distribution of AFP values determined in 803 specimens from normal individuals and patients with nonmalignant or malignant disease was evaluated. In this study 97.4% of the healthy subjects had AFP levels less than 8.0 ng/mL.

	Number of Subjects	0-8.0 ng/mL [0-6.6 IU/mL]	8.1-20.0 ng/mL [6.7-16.5 IU/mL]	20.1-500 ng/mL [16.6-413 IU/mL]	500.1-1000 ng/mL [413-826 IU/mL]	> 1000 ng/mL > 826 IU/mL]
Distribution of AFP values (%)						
Healthy Subjects						
Males 18 -61 years	231	97.4	2.6	0	0	0
Carcinoma						
Testicular						
Seminoma	10	100	0	0	0	0
Hepatocellular	123	44.7	7.3	20.3	7.3	20.3
Pancreatic	35	91.4	8.6	0	0	0
Other GI Cancers[2]	164	91.5	6.1	1.8	0	0.6
Nonmalignant Disease						
Liver Cirrhosis	122	50.8	16.4	27.0	2.5	3.3
Hepatitis	118	90.7	8.5	0.8	0	0

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.