510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K251630

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

Atellica IM total PSA II (tPSAII)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LTJ	Class II	21 CFR 866.6010 - Tumor-Associated Antigen Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

Addition of intended use/indication for use of the device as aid in monitoring of patients with prostate cancer

B Measurand:

Total Prostate Specific Antigen (tPSA)

C Type of Test:

Quantitative, Chemiluminescent Immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Atellica IM total PSA II (tPSAII) assay is for in vitro diagnostic use in the quantitative measurement of total prostate-specific antigen (PSA) in human serum and plasma (EDTA and lithium-heparin) using the Atellica IM Analyzer.

This assay is indicated as an aid in the detection of prostate cancer in conjunction with a digital rectal exam (DRE) in men aged 50 years and older. Prostate biopsy is required for diagnosis of prostate cancer. This assay is further indicated as an aid in the management (monitoring) of patients with prostate cancer.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The Instructions for Use of the device contains the following warning statement:

The concentration of total PSA in a given specimen, as determined by assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay for total PSA used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining serial levels of total PSA is changed, the laboratory must perform additional testing to confirm baseline values.

D Special Instrument Requirements:

Atellica IM Analyzer

IV Device/System Characteristics:

A Device Description:

Materials provided:

The Atellica IM total PSA II (tPSAII) is available in a 1-pack (100 tests) kit and in a 5-pack (500 tests) kit. Both versions of the assay include:

- tPSAII ReadyPack primary reagent pack consisting of:
    - Lite Reagent: 10.0 mL/reagent pack; Unlabeled monoclonal mouse anti-free-PSA (fPSA) antibody (~250 ng/mL); monoclonal mouse anti-PSA antibody

(~180 ng/mL) labeled with acridinium ester; buffer; bovine serum albumin (BSA); preservative

- Solid Phase: 20.0 mL/reagent pack; Monoclonal mouse anti-PSA antibody (~3.5 µg/mL) labeled with biotin and bound to streptavidin paramagnetic particles; buffer; BSA, bovine gamma globulin (BGG); sodium azide (< 0.1%); preservative

- Atellica IM tPSAII master calibration curve
- tPSAII CAL low calibrator: 2.0 mL/vial; Purified PSA from human seminal fluid in buffer; BSA; sodium azide (< 0.1%)
- tPSAII CAL high calibrator: 2.0 mL/vial; Purified PSA from human seminal fluid in buffer; BSA; sodium azide (< 0.1%)
- Atellica IM tPSAII CAL calibrator assigned value sheet

Materials needed but not provided:

Atellica IM Analyzer – with additional system fluids to operate the system including Atellica IM Wash, Atellica IM Acid, Atellica IM Base, and Atellica IM Cleaner

Optional materials may be used but not provided:

Atellica IM Multi-Diluent 2
Atellica IM tPSAII MCM (master curve material)

B Principle of Operation:

The Atellica IM total PSA II (tPSAII) assay is a fully automated sandwich immunoassay using acridinium ester chemiluminescent technology. The assay uses three monoclonal mouse antibodies in the tPSAII ReadyPack primary reagent pack. The Lite Reagent contains a monoclonal anti-PSA antibody labeled with acridinium ester, and an unlabeled free-PSA-specific monoclonal mouse anti-PSA antibody. The Solid Phase contains a monoclonal mouse anti-PSA antibody labeled with biotin and bound to streptavidin paramagnetic latex particles. The sample is incubated with the Lite Reagent and Solid Phase simultaneously, and then the immune complex is washed. A direct relationship exists between the amount of analyte present in the patient sample and the amount of relative light units (RLUs) detected by the system.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Atellica IM PSA assay

B Predicate 510(k) Number(s):

P950021/S015

C Comparison with Predicate(s):

Device & Predicate Device(s):	K251630	P950021/S015
Device Trade Name	Atellica IM tPSAII	Atellica IM PSA
General Device Characteristic Similarities		
Intended Use/ Indications For Use	Atellica IM total PSA II (tPSAII) assay is for in vitro diagnostic use in the quantitative measurement of total prostate-specific antigen (PSA) in human serum and plasma (EDTA and lithium-heparin) using the Atellica IM Analyzer. This assay is indicated as an aid in the detection of prostate cancer in conjunction with a digital rectal exam (DRE) in men aged 50 years and older. Prostate biopsy is required for diagnosis of prostate cancer. This assay is further indicated as an aid in the management (monitoring) of patients with prostate cancer	The Atellica IM Prostate Specific Antigen (PSA) assay is for in vitro diagnostic use in the quantitative measurement of prostate specific antigen (PSA) in human serum using the Atellica IM Analyzer. This assay is indicated for the measurement of serum PSA in conjunction with a digital rectal exam (DRE) as an aid in the detection of prostate cancer in men aged 50 years and older. This assay is further indicated as an aid in the management (monitoring) of patients with prostate cancer.
Analyzer	Atellica IM	Same
Measurement	Quantitative	Same
Technology	Chemiluminescence	Same
Principle	Sandwich Immunoassay	Same
Calibration Levels	Two (low and high)	Same
General Device Characteristic Differences		
Specimen	Serum and Plasma	Serum
Sample Volume	30 µL	35 µL
Analytical Measuring Interval	0.009 – 50.00 ng/mL	0.04–100.00 ng/mL
Detection Antibody	Unlabeled monoclonal mouse anti-fPSA antibody; monoclonal mouse anti-PSA antibody labeled with acridinium ester	Polyclonal goat anti-PSA antibody labeled with acridinium ester
Capture Antibody	Biotinylated mouse monoclonal anti-PSA antibody bound to streptavidin paramagnetic particles	Mouse monoclonal anti-PSA antibody covalently coupled to paramagnetic particles

VI Standards/Guidance Documents Referenced:

The following Clinical and Laboratory Standards Institute (CLSI) guidelines were used:

- CLSI EP34 1st Edition, Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

Analytical performance of the Atellica IM tPSAII has been established in P240021.

1. Precision/Reproducibility:

   Refer to P240021

2. Linearity:

   a. Linearity:

      Refer to P240021

   b. Dilution:

      The Atellica IM tPSAII has automated dilution function when the patient sample results in the value exceed the upper limit of the AMI of the assay (result is ">50 ng/mL"). A study was performed according to CLSI EP34-Ed1 to evaluate the effect of auto-dilution to the assay performance with Atellica IM Multi-Diluent 2. A high PSA stock was prepared by spiking high concentration PSA (Scripps PSA-ACT) into normal female serum above the upper limits of AMI and few concentrations inside of the AMI. Data of the study verified the function of auto-dilutions 1:5, 1:10, 1:50, 1:100 and 1:500 with diluent Atellica IM Multi-Diluent 2.

3. Analytical Specificity/Interference:

   Refer to P240021

4. Assay Reportable Range:

   The Atellica IM tPSAII assay reportable range without dilution is 0.009–50.00 ng/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Refer to P240021

6. Detection Capability:

   For LoB, LoD and LoQ values, refer to P240021

7. Assay Cut-Off:

   Refer to Clinical Cut-off

B Comparison Studies:

1. Method Comparison with Predicate Device:

   See Section C below

2. Matrix Comparison:

   Refer to P240021

C Clinical Studies:

1. Clinical Sensitivity and Specificity:

   A prospective clinical study was conducted by enrolling subjects from six different collection sites to evaluate the clinical performance of the Atellica IM tPSAII as an aid in monitoring patients diagnosed with prostate cancer. A total of 88 male subjects that met the following inclusion and exclusion criteria are used in the study analysis:

   Inclusion Criteria:
   - The subject must be a male above 50 years of age with a confirmed diagnosis of prostate cancer
   - The specimen collected must be serum
   - The subject must be monitored using local, standard of care PSA testing
   - Specimens were collected at minimum of three visits per patient, with collections occurring within ±28 days of standard-of-care PSA draws.

   Exclusion Criteria:
   - Subject previously diagnosed with a malignancy (non-melanoma skin cancer excluded) other than prostate cancer within five years prior to the study blood draw

   Among 88 subjects, majority were Caucasian (n=73, 83.0%), with the remaining subjects being African Americans (n=15, 17.0%).

   In the study, 13 subjects (14.8%) were from group 54-59 years old, 39 subjects (44.3%) were from age group 60-69 years old, 32 (36.4%) subjects were from age group 70-79 years old, and 4 (4.5%) subjects were from age group 80-86 years old. The mean age was 67.7 years ranging from 54 to 86 years.

The length of time (in days) over which the subjects were monitored ranged from 121 to 1014 days (median of 768 days). The median interval (in days) between successive visits was 182, ranging from 61 to 465 days.

Results:

In this study, a total of 323 samples (including 88 baseline and 235 follow-up measurements) were obtained and measured using both the candidate tPSAII and predicate total PSA assays using the Atellica IM Analyzer platform. At each follow-up visit, the percentage change of the total PSA was calculated by comparing the test result to the results obtained from the previous visit. The performance of the tPSAII assay as an aid in the management of patients with prostate cancer subjects was evaluated by assessing the changes in PSA levels correlated to the clinical assessment at the time of assay. The reference change value (RCV) of 50.0% of the visit compared to previous visit is used to determine the disease progression for both tPSAII and the predicate device. The change in the PSA concentration was compared to the change in the clinical status of the patients as determined by the physician based upon an examination of the subject for clinical signs and symptoms, including Digital Rectal Exam (DRE), medical notes and records, radiographic findings, and subject interviews. The following definition was used to categorize the patient's disease status:

- No Evidence of Disease (NED) – Based on one or more of the following diagnostic tools (total PSA, DRE, Biopsy, Ultrasound, MRI, CT, PET, bone scan) the physician determines that there is no tumor present.
- Stable/Persistent – Based on one or more of the following diagnostic tools (total PSA, DRE, Biopsy, Ultrasound, MRI, CT, PET, bone scan) the physician determines that tumor burden remains constant.
- Responding – Based on one or more of the following diagnostic tools (total PSA, DRE, Biopsy, Ultrasound, MRI, CT, PET, bone scan) the physician determines that tumor burden is decreasing.
- Progression – Based on one or more of the following diagnostic tools (total PSA, DRE, Biopsy, Ultrasound, MRI, CT, PET, bone scan) the physician determines that tumor burden is increasing and/or metastasis may be present.

The following table represents the summary of all follow-ups (n=323) for subjects at which a clinical evaluation occurred for the tPSA II assay. A positive percentage change of the subjects at these clinical evaluations was defined by increase in 50% RCV of the visit compared to previous visit.

		Clinical Status				
		Progression	**NED**	**Stable**	**Responding**	**Total**
Change in Atellica IM tPSAII	**Progression**	18	13	23	0	54
	No Progression	15	52	143	59	269
	Total	33	65	166	59	323

To evaluate clinical sensitivity and specific of the Atellica IM tPSAII, the clinical disease status was condensed into two categories: Progression and No-progression. Subjects with progression contained those monitoring events defined as progressive disease. Subjects with no-progression contained those monitoring events defined as NED, stable disease and

responding disease. The clinical performances of the Atellica IM tPSAII are summarized in the tables below:

		Clinical Status		
		Progression	**No-Progression**	**Total**
Change in Atellica IM tPSAII	**Progression**	18	36	54
	No Progression	15	254	269
	Total	33	290	323

	Point Estimate	**95% CI***
Sensitivity	54.5% (18/33)	36.4%–71.9%
Specificity	87.6% (254/290)	83.3%–91.2%
Positive Predictive Value (PPV)	33.3% (18/54)	21.1%–47.5%
Negative Predictive Value (NPV)	94.4% (254/269)	91.0%–96.9%
Positive Likelihood Ratio	4.39	2.95–6.56
Negative Likelihood Ratio	0.52	0.34–0.79
Prevalence	10.22% (33/323)	

*95% CI were calculate using bootstrap method

2. Comparison of the tPSAII and Predicate total PSA

All 323 follow-ups for 88 subjects were also tested with the predicate device, Atellica IM PSA assay. For the predicate device, a positive percentage change of the subjects at these clinical evaluations was also defined by increase in 50% RCV of the visit compared to previous visit. The following tables summarized the performance estimates of the predicate device.

		Clinical Status				
		Progression	**No Progression**			**Total**
			NED	**Stable**	**Responding**	
Change in Atellica IM PSA	**Progression**	18	10	21	0	49
	No Progression	15	55	145	59	274
	Total	33	65	166	59	323

	Point Estimate	**95% CI***
Sensitivity	54.5% (18/33)	36.4%–71.9%
Specificity	89.3% (259/290)	85.3%–92.6%
Positive Predictive Value (PPV)	36.7% (18/49)	23.4%–51.7%
Negative Predictive Value (NPV)	94.5% (259/274)	91.2%–97.0%
Positive Likelihood Ratio	5.10	3.32–7.81
Negative Likelihood Ratio	0.51	0.33–0.78

*95% CI were calculate using bootstrap method

Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) were evaluated between Atellica IM tPSAII and predicate total PSA and summarized in the table below:

		Atellica IM PSA (Predicate)		
		Progression	**No Progression**	**Total**
Atellica IM tPSAII	**Progression**	45	9	54
	No Progression	4	265	269
	Total	49	274	323

PPA : 91.8% (45/49), (95% CI : 80.4%-97.7%)
NPA : 96.7% (265/274), (95% CI : 93.9%-98.6%)

The overall results demonstrate substantial equivalence between Atellica IM tPSAII and predicate device for monitoring disease progression. Both assays exhibited identical sensitivity (54.5%) when compared against clinical progression status, with comparable specificity values (87.6% for the Atellica IM tPSAII vs. 89.3% for predicate total PSA). The direct comparison between the two assays with a positive percent agreement of 91.8% and negative percent agreement of 96.7%.

D Clinical Cut-Off:

Refer to P240021

E Expected Values/Reference Range:

Refer to P240021

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete.