510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K221801

B Applicant

Siemens Healthcare Diagnostics Inc.

C Proprietary and Established Names

ADVIA Centaur® Anti-Müllerian Hormone (AMH)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
PQO	Class II	21 CFR 862.1092 - Anti-Mullerian Hormone Test System	TX - Clinical Toxicology

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

AMH (Anti-Müllerian [Mullerian] Hormone)

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:

The ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay is for in vitro diagnostic use in the quantitative determination of anti-Müllerian hormone (AMH) in human serum and plasma (lithium heparin) using the ADVIA Centaur® XP system.

The measurement of AMH is used as an aid in the assessment of the ovarian reserve in women presenting to fertility clinics. This assay is intended to distinguish between women with AFC (antral follicle count) values > 15 (high ovarian reserve) and women with AFC values ≤ 15 (normal or diminished ovarian reserve).

This assay is intended to be used in conjunction with other clinical and laboratory findings, such as AFC, before starting fertility therapy. This assay is not intended to be used for monitoring women undergoing controlled ovarian stimulation in an Assisted Reproduction Technology program.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Specimens for AMH levels should be drawn on days 2-4 of the menstrual cycle.

This assay is intended to be used for assessing the ovarian reserve in conjunction with other clinical and laboratory findings before starting any fertility therapy and should be used in conjunction with the AFC. This assay is not intended to be used for monitoring women undergoing controlled ovarian stimulation in an Assisted Reproduction Technology program.

D Special Instrument Requirements:

ADVIA Centaur® XP system

IV Device/System Characteristics:

A Device Description:

The ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay consists of the following components:

- ADVIA Centaur AMH ReadyPack® primary reagent pack (Solid Phase): 22.0 mL/reagent pack. Streptavidin-coated paramagnetic microparticles (~0.15 mg/mL) with biotinylated mouse monoclonal anti-human AMH antibody (~2 µg/mL) in buffer; sodium azide (< 0.1%); blocker (bovine); surfactant; preservatives.

- ADVIA Centaur AMH ReadyPack® ancillary reagent pack (Ancillary Reagent): 10.0 mL/reagent pack. Mouse monoclonal anti-human AMH antibody labeled with acridinium ester in buffer (~0.6 µg/mL); sodium azide (< 0.1%); blocker (bovine, murine); stabilizers; surfactant; preservatives.

- AMH CAL: 2.0 mL/vial (1 vial of Low and High AMH CAL). After reconstitution, low and high levels of AMH antigen (bovine) in defibrinated human plasma; sodium azide (< 0.1%); preservatives.

B Principle of Operation:

The ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay is a fully automated 1-step sandwich immunoassay using acridinium ester chemiluminescent technology. The assay employs two anti-AMH antibodies. The first antibody, in the Ancillary Reagent, is a mouse monoclonal anti-AMH antibody labeled with acridinium ester. The second antibody is a biotinylated mouse monoclonal anti-AMH antibody that is bound to streptavidin-coated paramagnetic microparticles in the Solid Phase. A patient sample is first incubated with Ancillary Reagent followed by addition of and incubation with Solid Phase. A wash step is conducted and then ADVIA Centaur Acid Reagent and ADVIA Centaur Base Reagent (sold separately) are added to initiate the chemiluminescent reaction. A direct relationship exists between the amount of AMH present in the patient sample and the amount of relative light units (RLUs) detected by the system. AMH concentration results (ng/mL) are calculated based on a 2-point calibration from a pre-defined master curve.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Access AMH

B Predicate 510(k) Number(s):

K170524

C Comparison with Predicate(s):

Device & Predicate Device(s):	K221801	K170524
Device Trade Name	ADVIA Centaur® Anti-Müllerian Hormone (AMH)	Access AMH
General Device Characteristic Similarities		
Intended Use	Intended for the quantitative determination of AMH levels to aid in the assessment of ovarian	Same

	reserve in women presenting to fertility clinics, before starting fertility therapy.	
Sample Type / Matrix	Human serum, lithium heparin plasma	Same
Methodology	Quantitative chemiluminescent immunoassay	Same
Clinical cut-off	1.77 ng/mL	Same
General Device Characteristic Differences		
Capture antibody	Mouse monoclonal anti-AMH antibody labeled with biotin bound to streptavidin paramagnetic particles	Mouse monoclonal anti-AMH antibody bound to paramagnetic particles
Detection antibody	Mouse monoclonal anti-AMH antibody labeled with acridinium ester	Mouse monoclonal anti-AMH antibody conjugated to alkaline phosphatase
Calibration	2 levels	6 levels
Assay range	0.043 – 24 ng/mL	0.08 – 24 ng/mL
Sample volume	100 µL	20 µL

VI Standards/Guidance Documents Referenced:

- CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition.
- CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition.
- CLSI EP07 3rd Edition: Interference Testing in Clinical Chemistry.
- CLSI EP37 1st Edition: Supplemental Tables for Interference Testing in Clinical Chemistry.
- CLSI EP09c 3rd Edition: Measurement Procedure Comparison and Bias Estimation Using Patient Samples.
- CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition.
- CLSI EP25-A: Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.
- CLSI EP12-A2: User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline – Second Edition.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision

A precision study for the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay was performed based on CLSI EP05-A3. Six native human female serum pools (Serum 1-4, 6, 7), two human female serum pools spiked with AMH (Serum 5 and 8), and three levels of ADVIA Centaur AMH quality controls (Control 1-3) were tested using three reagent lots and two ADVIA Centaur® XP systems over two replicates per run, two runs per day, and twenty days for a total of 480 replicates per sample (160 replicates per sample per lot). The results of the study for a representative individual lot and combined lots are shown below.

Representative individual lot:

			Between system		Between day		Between run		Repeatability		Total imprecision	
Sample	N	Mean (ng/mL)	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Serum 1	160	0.1	0.00	1.2	0.00	0.6	0.00	2.7	0.00	2.3	0.00	3.8
Serum 2	160	0.2	0.00	1.1	0.00	1.4	0.00	1.5	0.00	1.9	0.01	3.0
Serum 3	160	1.0	0.01	1.0	0.01	0.9	0.01	1.3	0.01	1.5	0.02	2.4
Serum 4	160	3.7	0.02	0.4	0.02	0.5	0.06	1.6	0.07	1.8	0.09	2.5
Serum 5	160	6.8	0.14	2.0	0.10	1.4	0.06	0.9	0.11	1.6	0.21	3.1
Serum 6	160	7.0	0.06	0.8	0.10	1.4	0.07	1.0	0.13	1.9	0.19	2.7
Serum 7	160	16.6	0.04	0.2	0.13	0.8	0.24	1.4	0.26	1.6	0.38	2.3
Serum 8	160	16.6	0.22	1.3	0.15	0.9	0.27	1.6	0.28	1.7	0.47	2.8
Control 1	160	0.9	0.02	1.7	0.00	0.0	0.02	2.0	0.02	1.7	0.03	3.1
Control 2	160	4.8	0.08	1.6	0.03	0.6	0.07	1.5	0.08	1.7	0.14	2.9
Control 3	160	14.3	0.19	1.3	0.00	0.0	0.27	1.9	0.25	1.7	0.41	2.9

Combined lots:

			Between lot		Between system		Between day		Between run	
Sample	N	Mean (ng/mL)	SD (ng/mL)	% CV	SD (ng/mL)	% CV	SD (ng/mL)	% CV	SD (ng/mL)	% CV
Serum 1	480	0.1	0.00	2.9	0.00	0.5	0.00	1.2	0.00	0.9
Serum 2	480	0.2	0.00	2.0	0.00	0.1	0.00	1.2	0.00	0.7
Serum 3	480	1.0	0.00	0.4	0.00	0.2	0.01	1.1	0.01	0.6
Serum 4	480	3.6	0.04	1.2	0.01	0.2	0.03	0.9	0.05	1.3
Serum 5	480	6.7	0.09	1.4	0.05	0.7	0.09	1.3	0.08	1.3
Serum 6	480	6.9	0.11	1.5	0.00	0.0	0.08	1.1	0.02	0.2
Serum 7	480	16.2	0.33	2.0	0.07	0.4	0.15	0.9	0.13	0.8
Serum 8	480	16.4	0.22	1.3	0.02	0.1	0.10	0.6	0.16	1.0
Control 1	480	1.0	0.01	1.1	0.01	0.9	0.00	0.4	0.01	1.3
Control 2	480	4.8	0.03	0.6	0.02	0.5	0.00	0.0	0.06	1.3
Control 3	480	14.1	0.18	1.3	0.05	0.4	0.06	0.4	0.14	1.0

			Repeatability		Total imprecision	
Sample	N	Mean (ng/mL)	SD (ng/mL)	% CV	SD (ng/mL)	% CV
Serum 1	480	0.1	0.00	2.9	0.00	4.4
Serum 2	480	0.2	0.00	2.4	0.01	3.4
Serum 3	480	1.0	0.02	2.1	0.02	2.5
Serum 4	480	3.6	0.09	2.6	0.12	3.2
Serum 5	480	6.7	0.16	2.3	0.22	3.3
Serum 6	480	6.9	0.16	2.3	0.21	3.0
Serum 7	480	16.2	0.34	2.1	0.52	3.2
Serum 8	480	16.4	0.37	2.3	0.47	2.9
Control 1	480	1.0	0.03	2.6	0.03	3.3
Control 2	480	4.8	0.12	2.5	0.14	2.9
Control 3	480	14.1	0.33	2.3	0.41	2.9

Reproducibility

Reproducibility of the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay was evaluated across three clinical sites (1 internal, 2 external) and is based on CLSI EP05-A3. Three native human female serum pools (Serum 1-3), two human female serum pools spiked with AMH (Serum 4 and 5), and three levels of ADVIA Centaur AMH controls (Control 1-3) were tested using one reagent lot on three ADVIA Centaur® XP systems with three replicates per run and two runs per day over five days for a total of 90 replicates per sample across the three sites. The results of the study are shown below.

			Between Site		Between Day		Between Run		Repeatability		Reproducibility	
Sample	N	Mean (ng/mL)	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum 1	90	0.2	0.00	1.3	0.00	0.0	0.00	1.4	0.00	2.1	0.01	2.8
Serum 2	90	1.0	0.01	0.7	0.02	1.6	0.00	0.0	0.03	2.5	0.03	3.1
Serum 3	90	3.7	0.03	0.9	0.00	0.0	0.04	1.0	0.06	1.6	0.08	2.1
Serum 4	90	7.0	0.07	1.0	0.00	0.0	0.16	2.3	0.11	1.5	0.20	2.9
Serum 5	90	17.0	0.06	0.4	0.00	0.0	0.31	1.8	0.31	1.8	0.44	2.6
Control 1	90	1.0	0.01	0.8	0.01	0.5	0.02	1.7	0.02	2.2	0.03	2.9
Control 2	90	4.9	0.03	0.7	0.09	1.8	0.05	0.9	0.08	1.6	0.13	2.8
Control 3	90	14.4	0.00	0.0	0.17	1.2	0.17	1.2	0.30	2.1	0.38	2.6

2. Linearity:

Linearity of the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay was evaluated with one reagent lot on the ADVIA Centaur® XP system. Samples were prepared by combining a high native human female serum pool with a low native human female serum pool for a total of 12 levels (0.021 – 26.9 ng/mL) spanning the assay reportable range. Samples were tested in replicates of five with their observed mean concentration assessed relative to the expected sample concentrations using a weighted linear regression analysis. Results of the weighted linear regression are shown below.

$y = 1.03x + 0.0009$, $r = 1.000$

The device is linear over the claimed reportable range of 0.043 to 24 ng/mL AMH.

3. Analytical Specificity/Interference:

Endogenous and exogenous interference

Endogenous and exogenous interference was evaluated for the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay according to CLSI EP07 3rd Edition and CLSI EP37 1st Edition. Two native human female serum sample base pools containing ~1 ng/mL or ~7 ng/mL AMH were spiked with potential interferents (test samples) or the corresponding diluent without potential interferent (control samples). All samples were tested in replicates of five (except for rheumatoid factor (RF) testing, which included 2-5 replicates depending on the RF-containing spiker sample used) with one reagent lot on the ADVIA Centaur® XP system. The percentage bias between the mean AMH concentration of the test sample relative to the mean AMH concentration of the control sample was determined. Significant interference was defined as greater than 10% bias between the test sample mean and the control sample mean. The highest concentrations of endogenous substances tested that showed non-significant interference are summarized in the table below.

Substance	Highest concentration tested with no significant interference (mg/dL unless otherwise indicated)
Acetaminophen	20
Acetylcysteine	15
Acetylsalicylic acid	65
Ampicillin sodium	100
L-Ascorbic acid	3
Bilirubin, conjugated	66
Bilirubin, unconjugated	39
Biotin	0.35
Cefoxitin Sodium Salt	250
Cholesterol	500
Cyclosporine	0.5
Doxycycline Hyclate	5
Folic acid	0.04
Gonapeptyl (Triptorelin acetate)	0.01
Hemoglobin	1000
Heparin	500 U/dL
Human immunoglobulin A (IgA)	18 g/L
Human immunoglobulin G (IgG)	25 g/L
Human immunoglobulin M (IgM)	5 g/L
Ibuprofen	50
Levodopa	2
Levothyroxine	0.02
Lipemia (intralipid)	2000
Metformin hydrochloride	200

Substance	Highest concentration tested with no significant interference (mg/dL unless otherwise indicated)
Methyldopa	2
Metronidazole	20
Phenylbutazone	40
Rheumatoid factor (RF)	1000 IU/mL
Rifampicin	6
Theophylline	10
Total Protein (human serum albumin)	12,000
Uric Acid	25

The labeling contains the following limitations:

"The following drugs may interfere with this test: Cetrotide, Ovitrelle, Endometrin, and Follistatin: do not use this test to analyze samples from patients who have received one or more of these products within one to two weeks of testing."

"Unconjugated bilirubin concentrations of ≥ 40.0 mg/dL may lead to falsely elevated results for patient samples."

The performance section of the labeling states:

"At concentrations ≥ 40.0 mg/dL, there is significant interference (>10% bias) for unconjugated bilirubin. At 40.0 mg/dL, the following biases were observed: 10.6% at 6.79 ng/mL AMH and 11.4% at 0.936 ng/mL AMH."

HAMA/Heterophile interference

HAMA/heterophile interference has not been evaluated for this device. The labeling contains the following limitation:

"Patients routinely exposed to animals or to animal serum products may develop heterophilic antibodies and be prone to interference with *in vitro* immunoassays. Specimens from patients who have received mouse monoclonal antibodies or other immunoglobulins or immunoglobulin fragments for diagnosis or therapy may contain human anti-mouse antibodies (HAMA) or other heterophilic antibodies that can interfere in the assay.[16,17] Assays employing antibodies may have erroneous results caused by rheumatoid factor antibodies with variable affinities.[17,18] Interference from HAMA/ heterophilic antibodies may cause falsely elevated or depressed results. Additional information, such as the patient's medical history and clinical presentation should be considered in conjunction with the test result for patients suspected of having heterophilic antibodies."

References 16 through 18 are provided in the *References* section of the labeling.

Cross-reactivity

The cross-reactivity of the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay was evaluated according to CLSI EP07 3rd Edition. Testing was performed with an AMH-negative serum (0 ng/mL) and a native human female serum sample containing AMH (~1 ng/mL) on the ADVIA Centaur® XP system. For each sample, five replicates with potential cross-reactant (test) or without potential cross-reactant (control) were tested. Percent cross-reactivity was calculated by taking the difference between the AMH concentration for test sample and the AMH concentration for the control sample, dividing it by the concentration of the cross-reactant and multiplying by 100. Less than 0.1% cross-reactivity was observed for 100 ng/mL inhibin A, 100 ng/mL inhibin B, 100 ng/mL activin A, 50 ng/mL activin B, 50 ng/mL activin AB, and 65 ng/mL TGF-β1.

Since luteinizing hormone (LH) and follicule-stimulating hormone (FSH) were expressed in biological activity units (mIU/mL) and did not have direct concentration results to calculate percent cross-reactivity, the percent bias was calculated instead. Percent bias was calculated by taking the difference between the AMH concentration for test sample and the AMH concentration for the control sample, dividing it by the AMH concentration of the control sample and multiplying by 100. At a concentration of 1 ng/mL AMH, 2.9% bias was observed with 500 mIU/mL LH and 0.2% bias was observed with 500 mIU/mL FSH.

High dose hook effect

A study was conducted to evaluate the potential for a high dose hook effect in the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay. AMH-negative native female human serum was spiked with AMH to a level of 1151 ng/mL and diluted into eight dilutions down to 15.4 ng/mL AMH. The dilution series and a control sample at 27.5 ng/mL (close to the upper limit of the assay reportable range) were tested in replicates of six on one ADVIA Centaur® XP system using two reagent lots. The mean system response in relative light units (RLUs) was plotted against the expected AMH concentration of the samples. No hook effect was observed in samples with concentrations up to 1151 ng/mL AMH.

4. Assay Reportable Range:

The claimed assay reportable range is from 0.043 ng/mL to 24.0 ng/mL.

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

Traceability

The ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay is traceable to internal standards manufactured using highly purified material. The sponsor submitted a detailed traceability assurance plan that was reviewed and found to be acceptable.

Sample stability

Sample stability studies were performed and demonstrated that serum (collected in tubes without gel or serum separator tubes) and lithium heparin plasma are stable under the following conditions:

- After centrifugation, in the primary collection device, for up to 4 days at 2-8°C.
- After separation, in a secondary container, for up to 16 hours at room temperature (20-25°C), up to 6 days at 2-8°C, and up to 24 months at ≤ -20°C.
- After separation, for up to 8 hours at room temperature (20-25°C) on board the system.
- Up to three freeze-thaw cycles.

Sample stability studies were also performed to demonstrate that unprocessed specimens prior to separation are stable in the primary collection tubes for up to 24 hours at 2-8°C.

6. Detection Limit:

The Limit of Blank, Limit of Detection, and Limit of Quantitation of the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay were determined in accordance with CLSI EP17-A2.

The Limit of Blank (LoB) was determined by testing six blank native female human serum samples free of AMH analyte. Each sample was measured in two replicates per run and two runs per day over five days with three reagent lots on two ADVIA Centaur® XP systems for 240 replicates per lot. The LoB was calculated non-parametrically at the 95th percentile of all measurements of the blank samples. The highest LoB among the reagent lots was taken as the LoB value. The claimed LoB is 0.010 ng/mL.

The Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined by testing nine native human female serum samples and two pools of native human female serum samples with low AMH values. Each sample was measured in four replicates per run and two runs per day over five days with three reagent lots on two ADVIA Centaur® XP systems for 880 replicates per lot. The LoD was calculated based on the LoB and within-lab standard deviation for the samples. The highest LoD among the reagent lots was taken as the LoD value. The claimed LoD is 0.020 ng/mL. The LoQ was determined based on analytical and clinical performance data. The claimed LoQ is 0.043 ng/mL. At an AMH concentration of 0.043 ng/mL, the within-lab CV is ≤ 15%.

7. Assay Cut-Off:

The AMH cut-off, intended to predict an antral follicle count (AFC) > 15, is 1.77 ng/mL.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison study was conducted with the candidate device, ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay, and the predicate device, Beckman Coulter Access AMH assay (k170524), according to CLSI EP09c Edition 3. One hundred and twenty (120) native female human serum samples with AMH concentrations ranging from 0.080 ng/mL to 22 ng/mL were tested using one reagent lot on the candidate and predicate devices. Passing-Bablok regression analysis was conducted for AMH results from the candidate device versus AMH results from the predicate device. The results of this regression analysis are shown below.

$y = 1.04x – 0.032$, $r = 0.994$

2. Matrix Comparison:

A matrix comparison study was conducted, according to CLSI EP09c, 3rd Edition, to compare samples drawn into serum without gel tubes, serum separator tubes (SST), and lithium heparin plasma tubes. Eighty eight (88) matched native human female samples were tested in duplicate using one reagent lot on one ADVIA Centaur® XP system. Weighted Deming regression analyses were performed using the first replicate and results are summarized below.

Comparison	N	Sample range (ng/mL)	Slope	y-intercept	r
SST vs. serum without gel tube	88	0.110 to 19.7	1.00	0.003	0.997
Lithium heparin plasma tube vs. serum without gel tube	88	0.110 to 19.7	1.08	-0.004	0.997

C Clinical Studies:

1. Clinical Sensitivity:

See section VII.C.3. below.

2. Clinical Specificity:

See section VII.C.3. below.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

A prospective clinical study was conducted at 11 fertility clinics in the United States with 533 women ranging in age from 22 to 45 years (with a mean age of 34 years). Between days two and four of the same menstrual cycle, serum samples were collected for testing and transvaginal ultrasound was used to determine the antral follicle count (AFC) for each subject. Serum AMH levels were tested using the ADVIA Centaur® Anti-Müllerian Hormone (AMH) assay and the AMH levels were correlated to the AFC of the subjects.

Of the 533 subjects, 76.0% were Caucasian, 12.4% were Black or African American, 7.7% were Asian, 0.2% were Native Hawaiian or Other Pacific Islander, 0.8% were American Indian or Alaska Native, 1.1% were reported as Other, and 1.9% did not report race. Of the 533 subjects, 81.1% were not Hispanic or Latino, 18.0% were Hispanic or Latino, and 0.9% did not report ethnicity.

Subject Body Mass Index (BMI) ranged from 16.0 to 39.9 kg/m2, with a mean BMI of 26.8 kg/m^2, and was distributed amongst subjects as shown below:

BMI (kg/m^2)	Number of subjects
< 18.5	13
18.5 – 24.9	205
25 – 29.9	167
30 – 39.9	148

The table below shows the number of subjects presenting with AFC values > 15 (high ovarian reserve) and AFC values ≤ 15 (normal or diminished ovarian reserve) relative to the serum AMH levels of these subjects using an AMH cutoff of 1.77 ng/mL (where AMH > 1.77 ng/mL represents high ovarian reserve).

	AFC > 15	AFC ≤ 15	Total
AMH > 1.77 ng/mL	256	120	376
AMH ≤ 1.77 ng/mL	27	130	157
Total	283	250	533

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the overall study population. These performance estimates and 95% confidence intervals (CI) are shown in the table below.

Parameter	Estimate	95% CI
Sensitivity	90.5% (256/283)	(86.5%, 93.4%)
Specificity	52.0% (130/250)	(45.8%, 58.1%)
PPV	68.1% (256/376)	(63.2%, 72.6%)
NPV	82.8% (130/157)	(76.1%, 87.9%)

Sensitivity, specificity, PPV, and NPV with 95% CI were also calculated for subjects < 35 years of age and ≥ 35 years of age because differences in clinical performance were observed between these subjects. The results are shown in the table below along with the prevalence for each group.

Parameter	< 35 years old	≥ 35 years old
Prevalence (AFC > 15)	67.4%	38.4%
Sensitivity with 95% CI	91.8% (86.9%, 94.9%)	88.1% (80.4%, 93.1%)
Specificity with 95% CI	31.8% (22.3%, 42.6%)	63.0% (55.0%, 70.4%)
PPV with 95% CI	73.6% (67.5%, 78.9%)	59.7% (51.7%, 67.3%)
NPV with 95% CI	65.1% (50.2%, 77.6%)	89.5% (82.5%, 93.9%)

The labeling contains the following information:

"Differences in clinical performance were observed between subjects < 35 years of age and ≥ 35 years of age. The number of subjects with a result > 1.77 ng/mL having high ovarian reserve was higher in subjects < 35 years of age (73.6% of subjects <35 years of age compared to 59.7% of subjects ≥ 35 years of age) and the number of subjects with a result ≤ 1.77 ng/mL having normal/diminished ovarian reserve was higher in subjects ≥ 35 years of age (89.5% of subjects ≥ 35 years of age compared to 65.1% of subjects < 35 years of age)."

D Clinical Cut-Off:

The AMH cutoff, intended to predict an antral follicle count (AFC) > 15, is 1.77 ng/mL.

E Expected Values/Reference Range:

A reference range study was conducted in accordance with CLSI EP28-A3c to establish age-dependent reference ranges for AMH in 992 apparently healthy, non-pregnant females. Serum samples obtained from subjects were tested using one reagent lot and one ADVIA Centaur® XP system.

Age Range (years)	N	Median (ng/mL)	90% Reference Interval (ng/mL)	95% Reference Interval (ng/mL)
18 to 25	209	4.70	1.28 to 11.8	1.02 to 15.6
26 to 30	122	3.80	0.843 to 8.81	0.520 to 10.0
31 to 35	123	2.70	0.772 to 8.07	0.676 to 10.2
36 to 40	126	1.59	0.156 to 6.13	0.079 to 8.66
41 to 45	152	0.493	<0.043 to 3.47	<0.043 to 4.46
46 to 50	121	0.083	<0.043 to 1.33	<0.043 to 1.89
≥ 51	139	< 0.043	<0.043 to 0.134	<0.043 to 0.277

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 and supports a substantial equivalence decision.