510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number: K181213

B. Purpose for Submission: To obtain a substantial equivalence determination and FDA clearance for a new device.

C. Measurand: Anti-CMV IgG antibodies

D. Type of Test: Enzyme Immunoassay

E. Applicant: Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names: ADVIA Centaur CMV lgG
ADVIA Centaur CMV IgG Quality Control

G. Regulatory Information:

1. Regulation section:

   21 CFR §866.3175; Cytomegalovirus serological reagents

2. Classification:

   Class II

3. Product code:

   LFZ

4. Panel:

   Microbiology (83)

H. Intended Use:

1. Intended use(s):
   ADVIA Centaur CMV lgG
   The ADVIA Centaur CMV IgG (CMV IgG) assay is for *in vitro* diagnostic use in the qualitative detection of IgG antibodies to cytomegalovirus (CMV) in human pediatric and adult serum and plasma (dipotassium EDTA, lithium heparin) using the ADVIA Centaur XP system. This assay is used to determine CMV IgG serological status and as an aid in the diagnosis of CMV infection in individuals for whom a CMV IgG test was ordered, including pregnant women.

The ADVIA Centaur CMV IgG assay is not intended for blood and tissue donor screening.

ADVIA Centaur CMV IgG Quality Control
The ADVIA Centaur CMV IgG (CMV IgG) Quality Control material is for *in vitro* diagnostic use for monitoring the performance of the ADVIA Centaur CMV IgG (CMV IgG) assay on ADVIA Centaur systems.

2. Indication(s) for use: Same as Intended Use

3. Special conditions for use statement(s): N/A

4. Special instrument requirements: ADVIA Centaur XP system

I. Device Description: The ADVIA Centaur CMV IgG Assay is a fully automated, 2-step sandwich immunoassay using indirect chemiluminometric technology. The patient specimen is diluted with ADVIA Centaur CMV IgG Diluent and incubated with the Solid Phase reagent. The Solid Phase reagent contains a heterogeneous mixture of biotinylated CMV viral lysate antigens, preformed to streptavidin-coated magnetic particles. The antigen coated particles subsequently capture CMV specific antibodies in the specimen. The antibody-antigen complex is washed and detection reagent is added. The detection reagent consists of an acridinium-ester (AE)-labeled anti-human IgG mouse monoclonal antibody. The entire complex is washed and the signal is generated in the presence of Lite Reagent bound to the Solid Phase via the CMV IgG-CMV antigen complex. The system reports results according to the selected option, as described in the system operating Instructions.

J. Substantial Equivalence Information:

1. Predicate device name(s): bioMerieux VIDAS CMV IgG (CMVG) Assay

2. Predicate 510(k) number(s): k920661

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The ADVIA Centaur CMV IgG (CMV IgG) assay is for *in vitro* diagnostic use in the qualitative detection of IgG antibodies to cytomegalovirus (CMV) in human pediatric and adult serum and plasma (dipotassium EDTA, lithium heparin) using the ADVIA Centaur XP system. This assay is used to determine CMV IgG serological status and as an aid in the diagnosis of CMV infection in individuals for whom a CMV IgG test was ordered, including pregnant women. The ADVIA Centaur CMV IgG assay is not intended for blood and tissue donor screening. The assay is not intended for use in neonatal screening or for use at point-of-care facilities.	The VIDAS CMV IgG (CMVG) Assay is intended for use on the instruments of the VIDAS family (Vitek ImmunoDiagnostic Assay System) as a semi-quantitative automated enzyme-linked fluorescent immunoassay (ELFA). It is intended for use in determination of CMV immunological experience from a single serum sample, or as an aid in the diagnosis of current CMV infection through evaluation of paired sera for a significant increase in CMV-specific IgG. It is not intended for use in testing (screening) blood or plasma donors.
Assay Protocol	sandwich immunoassay	sandwich immunoassay
Controls	Negative and Positive	Negative and Positive
Calibrator fill volume	Liquid, 2 mL	Liquid, 2 mL

Differences		
Item	Device	Predicate
Instrument	ADVIA Centaur	VIDAS/mini-VIDAS
Measurement	Qualitative	Semi-Quantitative
Technology	Chemiluminescense	enzyme-linked fluorescent immunoassay
Sample type	Serum, Plasma	Serum
Cut-Offs	< 1.0 (Index) - nonreactive ≥ 1.0 (Index) - reactive	< 4 AU/mL - negative ≥4 to < 6 AU/mL - equivocal ≥ 6 AU/mL - positive
Sample Volume	20 µL	100 µL
Calibrators matrix	Human plasma	Human serum
Calibrator fill volume	Liquid, 2 mL	Liquid, 2 mL

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

N/A

L. Test Principle:

Indirect chemiluminometric technology

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:

Precision: Precision was evaluated according to CLSI document EP05-A3. Repeatability and Within-Lab imprecision were evaluated by testing 5 serum-based samples (serum sample pools), and 2 plasma-based samples (negative and positive controls). The samples were assayed in duplicate over 20 days, 2 runs per day, for a total of 40 runs and 80 replicates. The results are shown below.

Table 1: Precision Study

Sample Type	N	Mean	Repeatability		Between-Run		Between-Day		Within-Lab	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control 1 (negative)	80	0.08	0.00	NA[a]	0.00	0.0	0.00	0.0	0.01	NA
Control 2 (positive)	80	4.54	0.09	2.0	0.12	2.6	0.09	2.0	0.18	3.9
Serum Pool 1	80	0.07	0.00	NA	0.00	0.6	0.00	NA	0.01	NA
Serum Pool 2	80	0.90	0.02	2.1	0.01	1.3	0.02	2.3	0.03	3.4
Serum Pool 3	80	1.36	0.03	2.5	0.02	1.1	0.02	2.1	0.05	3.5
Serum Pool 4	80	2.70	0.06	2.2	0.07	2.5	0.07	1.7	0.10	3.7
Serum Pool 5	80	9.68	0.20	2.1	0.12	1.3	0.12	1.8	0.29	3.0

[a] NA = not applicable.

Reproducibility: Reproducibility was evaluated according to CLSI document EP05-A3. A reproducibility study was conducted at 3 external sites using two reagent lots. The protocol was run over 5 days, 2 runs per day. There were 3 replicates per run for the serum pools and 6 replicates per run for the negative and positive control materials. Reproducibility data was pooled across 3 sites. Data are presented for 1 representative reagent lot.

Table 2: Reproducibility Study

Sample Type	N	Mean	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Control 1 (negative)	180	0.10	0.01	NA[a]	0.00	NA	0.00	NA	0.02	NA	0.02	NA
Control 2 (positive)	180	4.55	0.12	2.7	0.07	1.5	0.02	0.3	0.15	3.4	0.21	4.6
Serum Pool 1	90	0.10	0.01	NA	0.00	NA	0.00	NA	0.01	NA	0.01	NA
Serum Pool 2	89[b]	0.80	0.01	1.8	0.02	1.9	0.01	1.1	0.05	6.1	0.05	6.7
Serum Pool 3	90	1.23	0.02	1.9	0.02	2.0	0.00	0.0	0.07	5.4	0.07	6.0
Serum Pool 4	90	2.98	0.06	1.9	0.06	1.9	0.05	1.7	0.13	4.2	0.16	5.3
Serum Pool 5	90	25.25	0.45	1.8	0.40	1.6	0.26	1.0	1.64	6.5	1.77	7.0

[a] NA = not applicable.
[b] One run had 2 replicates instead of 3.

b. Linearity/assay reportable range:

N/A

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

N/A

d. Detection limit:

N/A

e. Analytical specificity:

Cross-Reactivity: The ADVIA Centaur CMV IgG assay was evaluated for potential cross-reactivity in specimens with other viral and microbial antibodies and disease states. The CMV IgG status of each sample was compared using the comparator assay and the true nature of the reactive samples shown below is not determined.

Table 3: Cross-Reactivity Study

Clinical Category	Number Tested	ADVIA Centaur CMV IgG Reactive	Comparator CMV IgG Reactive
Chlamydia IgG	11	4	4
CMV IgM	10	6	6
Epstein-Barr virus (EBV) IgG	13	0	0
Epstein-Barr virus (EBV) IgM	10	4	4
Graves' disease	3*	0	0
Hepatitis A infection (HAV) IgG	10	3	3
Hepatitis B Core (HBc) IgG	10	3	4
Hepatitis C infection (HCV) IgG	10	1	1
Herpes simplex virus 1 (HSV1)	13	3	3
Herpes simplex virus 2 (HSV2)	12	0	0
Human anti-mouse antibody (HAMA)	14	7	6
Human chorionic gonadotropin (hCG)	11	0	0
Human herpes virus (HHV6) IgG	11	0	0
Human immunodeficiency virus (HIV) Antibodies	16	9	9
Influenza Antibodies	11	7	7
Measles IgG	11	0	0
Multiparity	20	18	18
Multiple myeloma	23	11	11
Parvovirus B19 IgG	11	3	3
Rheumatoid factor (RF)	10	1	1
Rubella IgG	13	0	0
Sjogren's Syndrome	4*	0	0
Systemic lupus erythematosus (SLE)*	3*	0	0
Syphilis IgG	11	4	4
Toxoplasma IgG	10	4	4
Varicella zoster virus (VZV) IgG	16	0	0
Total	**297**	**88**	**88**

* Results may not be conclusive due to low number of samples tested.

Interferences: Interference by endogenous substances in the ADVIA Centaur CMV IgG assay was evaluated at four CMV IgG levels (low negative, high negative, low positive,

and high positive). Interfering substances at the levels indicated were tested as described in CLSI Document EP07-A2. There was no change in clinical interpretation throughout the assay range at the levels indicated.

Table 4: Endogenous Interfering Substances Study

Interferent	Concentration
Hemoglobin (hemolyzed)	500 mg/dL
Conjugated bilirubin (Icteric)	20 mg/dL
Unconjugated bilirubin (Icteric)	20 mg/dL
Triglycerides (Lipemic)	3000 mg/dL (Intralipids)
Total protein*	9g/dL of protein
Immunoglobulins*	3g/dL of immunoglobulin
Biotin	4500 ng/mL of biotin
Cholesterol	400 mg/dL of cholesterol

* Total protein and immunoglobulins were tested using clinical samples with high serum protein and samples from multiple myeloma patients respectively.

f. Assay cut-off:

Cutoff Determination: A comparison study between the ADVIA Centaur CMV IgG assay and a comparator CMV IgG assay was performed to determine the placement of the cutoff value at a 1.00 Index by testing 389 remnant clinical samples. Of these, 196 samples were negative, 186 samples were positive, and the rest were equivocal by the comparator device. The cutoff value was set at ≥ 95% positive agreement and ≥ 95% negative agreement to the comparator device.

2. Comparison studies:

a. Method comparison with predicate device:

Method Comparison: Percent agreement was determined by comparing the performance of the ADVIA Centaur CMV IgG assay to a comparator CMV IgG assay. A total of 1842 samples that were sent for CMV IgG testing were analyzed, including:

- 1699 prospectively collected specimens
    - 684 subjects sent for CMV IgG testing
    - 348 pregnant subjects
    - 229 pediatric subjects (2–21 years old)
    - 44 HIV-positive subjects
    - 394 transplant-patient subjects
- 143 retrospective HIV-positive specimens

Prospective Study: A total of 1699 clinical routine specimens (from people aged 6 months – 91 years, both male and female) were obtained from 6 collection sites in the

United States. The specimens were from subjects sent for CMV IgG testing, pediatric subjects (aged 2–21 years), pregnant women, HIV-positive subjects, and transplant patients. The following results were obtained:

Table 5: Prospective Study - Combined Population

ADVIA Centaur CMV IgG Assay	**Comparator CMV IgG Assay**			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	1037	11	10	**1058**
Nonreactive	1	3	637	**641**
Total	**1038**	**14**	**647**	**1699**
ADVIA Centaur CMV IgG Assay	**Agreement (%)**		**95% Confidence Interval**	
Positive agreement	99.6% (1037/1041)		99.0%–99.9%	
Negative agreement	96.8% (637/658)		95.2%–98.0%	

Note: Fourteen samples that tested equivocal on the comparator assay were further tested on two other CMV IgG assays. Of these 14 samples, 10 remained equivocal, and 3 agreed and 1 did not agree with the ADVIA Centaur CMV lgG assay when compared to the two out of three consensus result.

The results obtained with the different subgroup prospective populations are presented in the sections that follow.

Subjects Sent for CMV IgG Testing: A total of 684 other prospective serum samples sent for CMV IgG testing were analyzed. The following results were obtained:

Table 6: Subjects Sent for CMV IgG Testing

ADVIA Centaur CMV IgG Assay	**Comparator CMV IgG Assay**			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	375	6	7	**388**
Nonreactive	1	1	294	**296**
Total	**376**	**7**	**301**	**684**
ADVIA Centaur CMV IgG Assay	**Agreement (%)**		**95% Confidence Interval**	
Positive agreement	99.5% (375/377)		98.1%–99.9%	
Negative agreement	95.8% (294/307)		92.9%–97.7%	

Note: Seven samples that tested equivocal on the comparator assay were further tested on two other CMV IgG assays. Of these 7 samples, 5 remained equivocal and 2 agreed with the ADVIA Centaur CMV lgG assay when compared to the two out of three consensus result.

Pregnant Women Subgroup: Serum samples sent for CMV IgG testing from 348 pregnant women prospectively collected from 4 sites were tested. The following results were obtained:

Table 7: Pregnant Women Subgroup

ADVIA Centaur CMV IgG Assay	Comparator CMV IgG Assay			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	287	0	1	**288**
Nonreactive	0	0	60	**60**
Total	**287**	**0**	**61**	**348**
ADVIA Centaur CMV IgG Assay	**Agreement (%)**		**95% Confidence Interval**	
Positive agreement	100.0% (287/287)		98.7%–100.0%	
Negative agreement	98.4% (60/61)		91.2%–9.9%	

Pediatric Subgroup: A total of 229 pediatric prospective serum samples were tested at 3 sites. Specimens were obtained from 4 sites, from males and from females who were not pregnant. The subjects' ages ranged from 2–21 years. The following results were obtained:

Table 8: Pediatric Subgroup

ADVIA Centaur CMV IgG Assay	Comparator CMV IgG Assay			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	80	1	1	**82**
Nonreactive	0	1	146	**147**
Total	**80**	**2**	**147**	**229**
ADVIA Centaur CMV IgG Assay	**Agreement (%)**		**95% Confidence Interval**	
Positive agreement	98.8% (80/81)		93.3%–99.9%	
Negative agreement	98.6% (146/148)		95.2%–99.8%	

Note: Two samples that tested equivocal on the comparator assay were further tested on 2 other CMV IgG assays and remained equivocal.

Human Immunodeficiency Virus (HIV) Patient Subgroup: Serum specimens sent for CMV IgG testing were prospectively collected at 5 sites, from 44 HIV-positive patients and were tested. The following results were obtained:

Table 9: HIV-Positive Patient Subgroup

ADVIA Centaur CMV IgG Assay	Comparator CMV IgG Assay			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	43	0	0	**43**
Nonreactive	0	0	1	**1**
Total	**43**	**0**	**1**	**44**
ADVIA Centaur CMV IgG Assay	**Agreement (%)**		**95% Confidence Interval**	
Positive agreement	100.0% (43/43)		91.8%–100.0%	
Negative agreement	100.0% (1/1)		2.5%–100.0%	

Transplant Patient Subgroup: Serum samples from 238 preoperative transplant patients from 3 sites were tested. The following results were obtained:

Table 10: Transplant Patient Subgroup - Preoperative

ADVIA Centaur CMV IgG Assay	Comparator CMV IgG Assay			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	151	0	0	**151**
Nonreactive	0	0	87	**87**
Total	**151**	**0**	**87**	**238**
ADVIA Centaur CMV IgG Assay	**Agreement (%)**		**95% Confidence Interval**	
Positive agreement	100.0% (151/151)		97.6%–100.0%	
Negative agreement	100.0% (87/87)		95.8%–100.0%	

Post Transplant: Serum samples from 156 transplant patients were collected from 3 sites that perform kidney, pancreas, bone and marrow stem cell, liver, face and limb, heart, and lung transplants. After testing the following results were obtained:

Table 11: Transplant Patient Subgroup - Postoperative

ADVIA Centaur CMV IgG Assay	Comparator CMV IgG Assay			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	101	4	1	**106**
Nonreactive	0	1	49	**50**
Total	**101**	**5**	**50**	**156**

ADVIA Centaur CMV IgG Assay	**Agreement (%)**	**95% Confidence Interval**
Positive agreement	99.0% (101/102)	94.7%–99.9%
Negative agreement	90.7% (49/54)	79.7%–96.9%

Note: Five samples that tested equivocal by the comparator assay were further tested on two other CMV IgG assays. Of these 5 samples, 3 remained equivocal, and 1 agreed and 1 did not agree with the ADVIA Centaur CMV lgG assay when compared to the two out of three consensus result.

Retrospective Study

HIV-Positive Patient Subgroup: A total of 143 retrospective remnant samples from the HIV-positive patient subgroup collected at 1 site were tested. The following results were obtained:

Table 12: Retrospective HIV-Positive Patient Subgroup

ADVIA Centaur CMV IgG Assay	Comparator CMV IgG Assay			
	Positive	**Equivocal**	**Negative**	**Total**
Reactive	135	0	0	**135**
Nonreactive	0	0	8	**8**
Total	**135**	**0**	**8**	**143**

ADVIA Centaur CMV IgG Assay	**Agreement (%)**	**95% Confidence Interval**
Positive agreement	100.0% (135/135)	97.3%–100.0%
Negative agreement	100.0% (8/8)	63.1%–100.0%

b. Matrix comparison:

Specimen Collection Tube Comparison: The ADVIA Centaur CMV IgG assay was evaluated using different specimen matrices. ADVIA Centaur CMV IgG results that ranged from 0.74–28.55 Index were analyzed using orthogonal regression. The following results were obtained:

Table 13: Matrix Comparison

Serum (x) vs.	N	Mean (Index)	Slope	Intercept (Index)	Correlation Coefficient (r)
Dipotassium EDTA plasma (y)	38	10.76	1.01	-0.08	0.99
Lithium heparin plasma (y)	38	10.76	1.01	-0.07	0.96

3. Clinical studies:

a. Clinical Sensitivity:

Centers for Disease Control (CDC) Panel: A panel of 80 previously characterized serum samples was obtained from the CDC and evaluated with the ADVIA Centaur CMV IgG assay to determine the performance of the assay. There was 100% agreement with the serological status provided by the CDC.

Table 14: CDC Panel Testing

ADVIA Centaur CMV IgG Assay	Expected CDC Panel Results		
	Positive	Negative	Total
Reactive	39	0	39
Nonreactive	0	41	41
Total	**39**	**41**	**80**

Note: The results are presented as a means to convey further information on the performance of this assay with a characterized serum panel from the CDC. This does not imply an endorsement of the assay by the CDC.

b. Clinical specificity: N/A

c. Other clinical supportive data (when a. and b. are not applicable): N/A

4. Clinical cut-off**:** N/A

5. Expected values/Reference range:

CMV is a universally dispersed pathogen with approximately 40%–100% of the world's population having CMV antibody present in blood. Age, socioeconomic status, and geographic location have all been suggested to play a role in the overall incidence of CMV IgG. A population of 1842 male and female subjects (1827 subjects from the US), were tested in the clinical studies described above using the ADVIA Centaur CMV lgG assay. The values obtained and the demographic information are shown in the table below.

Table 15: Expected Values

Population	N	Reactive	Nonreactive
Subjects sent for CMV IgG testing (6 months–85 years) (45.9% male and 54.1% female)	684	388 (56.7%)	296 (43.3%)
Pregnant women (20–45 years)	348	288 (82.8%)	60 (17.2%)
HIV-positive patients (prospective: 25–73 years) (68.2% male and 31.8% female)	44	43 (97.7%)	1 (2.3%)
HIV-positive patients (retrospective: 18–70 years) (69.9% male and 30.1% female)	143	135 (94.4%)	8 (5.6%)
Transplant patients (20–45 years) (60.4% male and 39.6% female)	394	257 (65.2%)	137 (34.8%)
Pediatric subjects (2–<12 years) (53.6% male and 46.3% female)	69	25 (36.2%)	44 (63.7%)
Pediatric subjects (12-21 years) (35.0% male and 65.0% female)	160	57 (35.6%)	103 (64.4%)
Total	**1842**	**1193 (64.8%)**	**649 (35.2%)**

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.