Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number

K191578

B Applicant

Siemens Healthcare Diagnostics Inc.

C Proprietary and Established Names

ADVIA Centaur Zika test, ADVIA Centaur Zika Ab (100 tests), ADVIA Centaur Zika IgM (50 tests), ADVIA Centaur Zika Ab Quality Control, ADVIA Centaur Zika IgM Quality Control

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QFO	Class II	21 CFR 866.3935 - Zika Virus Serological Reagents	MI - Microbiology
QCH	Class II	21 CFR 866.3920 - Assayed quality control material for clinical microbiology assays	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

New 510(k) application for the ADVIA Centaur Zika Test.

B Measurand:

Human IgM antibodies to the Zika virus.

C Type of Test:

A dual-assay antibody capture immunoassay.

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
The ADVIA Centaur Zika test is for in vitro diagnostic use in the qualitative detection of IgM antibodies to the Zika virus in human serum and plasma (potassium EDTA or lithium heparin) specimens using the ADVIA Centaur XP and ADVIA Centaur XPT systems.

The ADVIA Centaur Zika test is intended for the presumptive clinical laboratory diagnosis of Zika virus infection. The test is intended for use only in individuals (children, adolescents and adults, including pregnant women) with clinical signs and symptoms consistent with Zika virus infection, and/or meeting the CDC Zika virus epidemiological criteria (history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated). Positive results must be confirmed by following the latest CDC guidelines for the diagnosis of Zika virus infection.

Results of this test are intended to be used in conjunction with clinical observations, patient history, epidemiological information, and other laboratory evidence to make patient management decisions. Zika IgM levels are variable over the course of the infection, and may be detectable near day 4 post onset of symptoms and persist up to approximately 12 weeks following initial infection.

Negative results may be seen in specimens collected before day four post onset of symptoms or after the window of detectable IgM closes, and therefore do not preclude the possibility of Zika virus infection, past or present.

This ADVIA Centaur Zika test is not indicated for testing blood or plasma donors.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:
ADVIA Centaur XP
ADVIA Centaur XPT

IV Device/System Characteristics:

A Device Description:

The ADVIA Centaur Zika test is an automated *in vitro* diagnostic test for the qualitative detection of IgM antibodies to the Zika virus. The test can be performed on either the ADVIA Centaur XP or the ADVIA Centaur XPT instrument systems. For both the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays, the system automatically performs the following actions:

1. Dispenses 15 µL of sample into a cuvette.
2. Dispenses 250 µL of Solid Phase, and incubates for 18.25 minutes at 37°C.
3. Separates, aspirates, and washes the cuvettes with ADVIA Centaur Wash 1.
4. Dispenses 50 µL each of Ancillary Well Reagent and Lite Reagent and incubates for 18 minutes at 37°C.
5. Separates, aspirates, and washes the cuvettes with ADVIA Centaur Wash 1.
6. Dispenses 300 µL of ADVIA Centaur Acid Reagent and 300 µL of ADVIA Centaur Base Reagent to initiate the chemiluminescent reaction.
7. Reports results according to the selected option, as described in the system operating instructions.

The systems consist of an instrument, computer, and preloaded software for running the tests and viewing the results. The instrument software manages the algorithm reflex testing, repeat testing, and results interpretation.

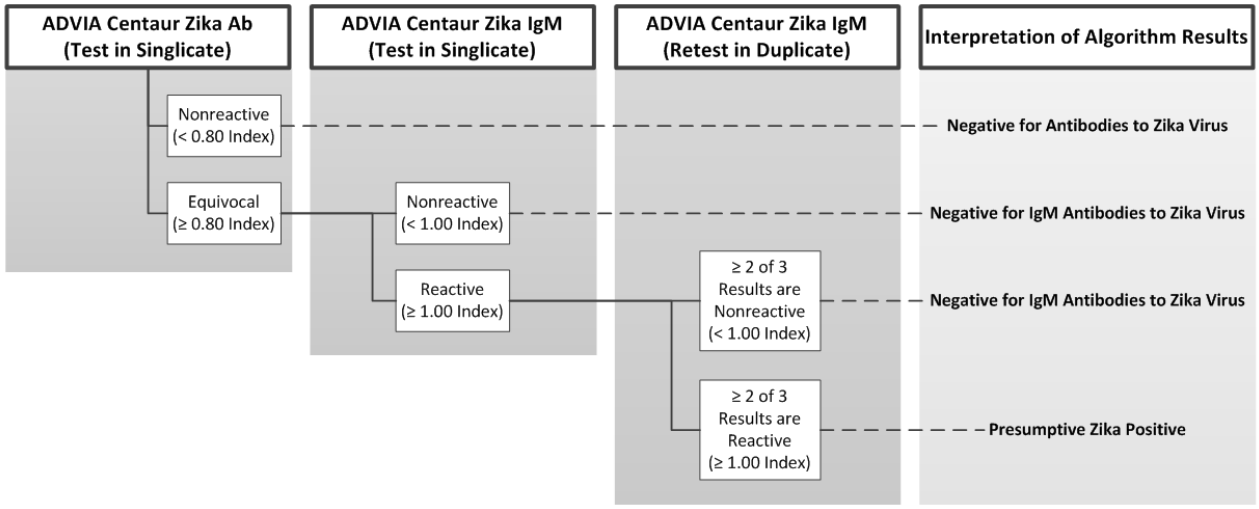
B Principle of Operation:

The ADVIA Centaur Zika test detects IgM antibodies to the Zika virus by combining in a 2-assay algorithm the measurements of the ADVIA Centaur Ab assay and, as applicable, the ADVIA Centaur IgM assay. All patient samples are initially tested with the ADVIA Centaur Zika Ab assay. All ADVIA Centaur Zika Ab equivocal samples are then tested with the ADVIA Centaur Zika IgM assay.

The ADVIA Centaur Zika Ab assay is an antibody capture immunoassay using a 2-pass format. In the first pass, coated microparticles (Solid Phase) are added to the cuvette, binding antibodies from the patient sample. The captured antibodies are washed and resuspended. In the second pass, the anti-Zika antibodies captured on the Solid Phase are detected by the addition of NS1 antigen labeled with acridinium ester (Lite Reagent) for chemiluminescent detection.

The ADVIA Centaur Zika IgM assay is an IgM capture immunoassay using a 2-pass format. In the first pass the microparticles, coated with anti-human IgM monoclonal antibody (Solid Phase), are added to the cuvette, binding IgM from the patient sample. The captured IgM antibodies are washed and resuspended. In the second pass the anti-Zika IgM captured on the Solid Phase is detected by the addition of NS1 antigen labeled with acridinium ester (Lite Reagent) for chemiluminescent detection.

Interpretation of results:



C Instrument Description Information:

Modes of Operation	Yes	No
Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?	☒	☐
Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?	☐	☒
Software		
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types.	☒	☐

1. Instrument Name:

   ADVIA Centaur XP
   ADVIA Centaur XPT

2. Specimen Identification:

   Sample identification is either manually entered or barcode scanned into the system computer.

3. Specimen Sampling and Handling:

   Managed by system software.

4. Calibration:

   The instrument is calibrated with assay-specific calibrators provided in each assay kit. Calibration interval is 14 days or when reagent lot number is replaced, when system components are replaced, or when quality control results are repeatedly out of range.

5. Quality Control:

The assay manufacturer recommends use of ADVIA Centaur Zika Ab Quality Control with the ADVIA Centaur Zika Ab assay and ADVIA Centaur Zika IgM Quality Control with the ADVIA Centaur Zika IgM assay. Quality control samples should be assayed at least once on each day that samples are analyzed to monitor system performance and chart trends.

V Substantial Equivalence Information:

A Predicate Device Name(s):
ZIKV Detect 2.0 IgM Capture ELISA

B Predicate 510(k) Number(s):
DEN180069

C Comparison with Predicate:

Device & Predicate Device:	K191578	DEN180069
Device Trade Name	ADVIA Centaur Zika Test	ZIKV Detect 2.0 IgM Capture ELISA
General Device Characteristic Similarities		
Analyte	Zika virus IgM antibodies	Same
Assay Results	Qualitative	Same
Methodology	Immunoassay using chemiluminescence detection	ELISA
Intended Use/Indications For Use	The ADVIA Centaur Zika test is for *in vitro* diagnostic use in the qualitative detection of IgM antibodies to the Zika virus in human serum and plasma (potassium EDTA or lithium heparin) specimens using the ADVIA Centaur XP and ADVIA Centaur XPT systems. The ADVIA Centaur Zika test is intended for the presumptive clinical laboratory diagnosis of Zika virus infection. The test is intended for use only in individuals (children, adolescents and adults, including pregnant women) with clinical signs and symptoms consistent with Zika virus infection, and/or meeting the CDC Zika virus epidemiological criteria (history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated). Positive results must be confirmed by following the	The ZIKV Detect 2.0 IgM Capture ELISA is intended for the qualitative detection of Zika virus IgM antibodies in human sera for the presumptive clinical laboratory diagnosis of Zika virus infection. The assay is intended for use only in patients with clinical signs and symptoms consistent with Zika virus infection, and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated). Assay results are for the presumptive detection of IgM antibodies to Zika virus (ZIKV). Positive results must be confirmed by following the latest CDC guidelines for the diagnosis of Zika virus infection. Results of this test are intended to be used in conjunction with clinical observations, patient history,

	latest CDC guidelines for the diagnosis of Zika virus infection. Results of this test are intended to be used in conjunction with clinical observations, patient history, epidemiological information, and other laboratory evidence to make patient management decisions. Zika IgM levels are variable over the course of the infection, and may be detectable near day 4 post onset of symptoms and persist up to approximately 12 weeks following initial infection. Negative results may be seen in specimens collected before day 4 post onset of symptoms or after the window of detectable IgM closes, and therefore do not preclude the possibility of Zika virus infection, past or present. The ADVIA Centaur Zika test is not indicated for testing blood or plasma donors.	epidemiological information, and other laboratory evidence to make patient management decisions. Zika IgM levels are variable over the course of the infection, and may be detectable near day four post onset of symptoms and persist up to approximately 12 weeks following initial infection. Negative results may be seen in specimens collected before day four post onset of symptoms or after the window of detectable IgM closes, and therefore do not preclude the possibility of Zika virus infection, past or present. This assay is not indicated for testing blood or plasma donors.
General Device Characteristic Differences		
Automation	Fully automated	Manual
Detection Label	Acridinum ester	Horseradish peroxidase
Specimen Type	Serum & Plasma (EDTA, LiHep)	Serum
Interpretation of Results	ADVIA Centaur ZikaAb < 0.80 Index: Negative for Antibodies to Zika Virus ADVIA Centaur ZikaAb ≥ 0.80 Index: Reflex to ADVIA Centaur ZikaM: ADVIA Centaur ZikaM Rep 1 < 1.00 Index: Negative for IgM Antibodies to Zika Virus ADVIA Centaur ZikaM Rep 1 ≥ 1.00 Index: Repeat ADVIA Centaur ZikaM in duplicate ADVIA Centaur ZikaM Rep 2&3 < 1.00 Index: Negative for IgM Antibodies to Zika Virus ADVIA Centaur ZikaM Rep 2or3 ≥ 1.00 Index: Presumptive Zika Positive	Zika Ag OD450 ≥ Threshold Zika Ag OD450 AND Zika ISR value > 1.90: Presumptive Zika Positive Initial: Zika Ag OD450 ≥ Threshold Zika Ag OD450 AND 1.50 ≤ Zika ISR ≤ 1.90: Retest in duplicate Retest: Zika Ag OD450 ≥ Threshold Zika Ag OD450 AND Zika ISR value ≥ 1.70 Presumptive Zika Positive Not Presumptive Zika Positive & CCA / NCA ratio ≥ 5.00: Presumptive Other Flavivirus Positive Not Presumptive Zika Positive & CCA / NCA ratio < 5.00: Negative

VI Standards/Guidance Documents Referenced:

Standard Title	*Document Number*	*Publication Date*	*Recognition Number*
Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Third Edition	CLSI EP05-A3	2014	7-251
Interference Testing in Clinical Chemistry. 3rd Edition	CLSI EP07-3rd Ed.	2018	7-275
Supplemental Tables For Interference Testing In Clinical Chemistry	CLSI EP37	2018	7-284
Medical devices – Application of risk management to medical devices	ANSI/AAMI/ISO 14971:2007/(R)2010	2007/2010	5-40
Special controls under 866.3935, Zika virus serological reagents	Code of Federal Regulation	2019	

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

a. Precision (single site):

Within-laboratory precision was evaluated for the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays. The study was performed over twenty (20) days, with two (2) replicates taken in each of two (2) runs per day. Each completed run was evaluated with a single replicate from two separate aliquots of 2 levels of controls (Negative Control, Positive Control) and 2 of negative basepools spiked at various levels with a patient pool positive for Zika Virus IgM (Medical Decision Pools; MDPs). Dose values were calculated using a 2-point calibration curve stored from Day 0. The data were analyzed for the Repeatability %CV and Within-Lab %CV.

20-day Precision Results for ADVIA Centaur Zika Ab (Lot 1)

Sample	Replicates	Mean	Repeatability		Within-Run	
			SD	CV (%)	SD	CV (%)
Negative Control	80	0.01	0.01	---	0.02	---
Positive Control	80	3.18	0.07	2.2	0.11	3.5
MDP 1	80	0.58	0.02	4.2	0.03	5.3
MDP 2	80	1.91	0.03	1.8	0.06	3.2

20-day Precision Results for ADVIA Centaur Zika Ab (Lot 2)

Sample	Replicates	Mean	Repeatability		Within-Run	
			SD	CV (%)	SD	CV (%)
Negative Control	80	0.05	0.03	---	0.04	---
Positive Control	80	3.26	0.06	2.0	0.13	3.9
MDP 1	80	0.63	0.03	4.0	0.03	5.0
MDP 2	80	1.98	0.05	2.6	0.08	4.3

20-day Precision Results for ADVIA Centaur Zika IgM (Lot 1)

Sample	Replicates	Mean	Repeatability		Within-Lab	
			SD	CV (%)	SD	CV (%)
Negative Control	80	0.05	0.06	---	0.07	---
Positive Control	80	3.15	0.04	1.3	0.09	2.8
MDP 1	80	0.88	0.03	3.5	0.05	5.3
MDP 2	80	2.12	0.05	2.2	0.07	3.1

20-day Precision Results for ADVIA Centaur Zika IgM (Lot 2)

Sample	Replicates	Mean	Repeatability		Within-Lab	
			SD	CV (%)	SD	CV (%)
Negative Control	80	0.00	0.02	---	0.02	---
Positive Control	80	2.92	0.06	1.9	0.13	4.6
MDP 1	80	0.82	0.04	4.4	0.06	7.9
MDP 2	80	2.11	0.05	2.5	0.10	4.6

b. Reproducibility (multi-site):

Assay reproducibility was evaluated for the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays at three US sites. Five (5) panel membered pools spanning the non-reactive to reactive region of assay range were used for three (3) lots each of ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays. Testing was performed at three sites, over five days, with two runs per day and three replicates per run (3 x 5 x 2 x 3 design).

Precision estimates were derived for repeatability, within-lab precision and reproducibility.

Reproducibility Results for ADVIA Centaur Zika Ab

Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Lot		Between-Site		Reproducibility	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
ZikAR1	270	0.05	0.03	---	0.02	---	0.03	---	0.00	---	0.00	---	0.05	---
ZikAR2	270	0.58	0.03	5.1	0.01	2.0	0.02	2.9	0.00	0.0	0.02	4.3	0.04	7.6
ZikAR3	270	1.00	0.04	4.2	0.04	3.8	0.00	0.0	0.00	0.0	0.01	1.4	0.06	5.9
ZikAR4	270	2.15	0.06	2.7	0.04	1.8	0.04	2.0	0.02	0.8	0.06	2.6	0.10	4.7

ZikAR5	270	3.08	0.08	2.7	0.09	2.8	0.06	1.9	0.04	1.3	0.08	2.6	0.16	5.2

Reproducibility Results for ADVIA Centaur Zika IgM

Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Lot		Between-Site		Reproducibility	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
ZikMR1	270	0.09	0.07	---	0.04	---	0.02	---	0.04	---	0.04	---	0.10	---
ZikMR2	270	0.67	0.05	7.3	0.00	0.0	0.00	0.0	0.01	1.0	0.05	6.9	0.07	10.1
ZikMR3	270	1.08	0.04	3.8	0.02	1.9	0.00	0.0	0.00	0.0	0.05	4.4	0.07	6.1
ZikMR4	270	2.40	0.05	2.2	0.04	1.5	0.03	1.3	0.04	1.8	0.09	3.9	0.13	5.2
ZikMR5	270	3.53	0.08	2.3	0.02	0.7	0.06	1.6	0.06	1.8	0.14	4.0	0.19	5.3

2. Linearity:

   Not applicable

3. Analytical Specificity/Interference:

   a. Cross-Reactivity:

   The performance of the ADVIA Centaur Zika test algorithm, incorporating the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM, was evaluated in the presence of potentially cross-reacting substances. Potentially cross-reactive samples previously characterized as positive, per the supplier's Certificate of Analysis for various disease states were tested. Except for specimens with HCV, ANA, RF, HAMA, Malaria, and Yellow Fever Virus Post-Immunization, only specimens confirmed positive for IgM of the respective disease state were included in the analysis.

Summary ADVIA Centaur Zika Test Cross-Reactivity

Disease State	Number of Samples Tested	ADVIA Centaur Zika Test Nonreactive Samples	ADVIA Centaur Zika Test Reactive Samples	Cross-Reactivity
Anti-Adenovirus	1	1	0	0.00%
Anti-*Borrelia sp.* (Lyme)	11	11	0	0.00%
Anti-Chikungunya Virus	21	21	0	0.00%
Anti-CMV	12	12	0	0.00%
Anti-Dengue Virus	41	39	2	4.88%
Anti-EBV	11	11	0	0.00%
Anti-HBV	11	11	0	0.00%
Anti-HCV	15	15	0	0.00%
Anti-HSV-1/2	21	21	0	0.00%
Anti-HSV-1	2	2	0	0.00%
Anti-HSV-2	3	3	0	0.00%
Anti-*Leptospira*	16	16	0	0.00%
Malaria	10	8	2	20.00%

ANA	19	19	0	0.00%
Anti-Parvovirus B19	16	16	0	0.00%
Anti-Rubella Virus	10	10	0	0.00%
Anti-*Toxoplasma gondii*	16	16	0	0.00%
Syphilis	10	10	0	0.00%
Anti-VZV	15	15	0	0.00%
Anti-WNV	23	23	0	0.00%
HAMA	15	15	0	0.00%
RF	21	21	0	0.00%
Yellow Fever Immunization	21	20	1	4.76%
Total	341	336	5	1.47%

b. Endogenous Interference:

The performance of the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays were evaluated with specimens containing potentially interfering endogenous substance. Stock solutions of each interferent were prepared and spiked into three (3) different pools with varying Zika Virus IgM concentrations. A control sample was prepared for each interfering substance by spiking with the appropriate diluent at the same volume as the interfering substance. All samples were run in triplicate and doses were calculated using 2-point data reduction. The mean percent interference was calculated for mid-positive pool and high-positive pool samples across matrices.

The following substances were evaluated at the concentration listed:

Total Protein	12 g/dL
Hemoglobin	1000 mg/dL
Conjugated Bilirubin	40 mg/dL
Unconjugated Bilirubin	60 mg/dL
Biotin	3500 ng/mL
Cholesterol	500 mg/dL
Triglycerides	3000 mg/dL

None of the tested endogenous substances cause a change in clinical interpretation for ADVIA Centaur Zika Ab or ADVIA Centaur Zika IgM. All samples had interference of less than 15%, most were less than 10%. The percent interference averaged across matrices was less than 10% for all conditions.

4. Assay Reportable Range:

Not applicable

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

a. Traceability/Analytical Sensitivity:

The analytical sensitivity at the cut-off values for the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays was determined using WHO 1st International standard for anti-Asian lineage Zika virus antibody (human) (NIBSC 16/352). This preparation contains antibodies reactive to Dengue virus. The standard was used to prepare a dilution series which

was tested using linear regression. The concentration of the reference standard that corresponds to the cut-off value of 0.80 Index for ADVIA Centaur Zika Ab is 23.18 IU/mL. The concentration of the reference standard that corresponds to the cut-off value of 1.00 Index for ADVIA Centaur Zika IgM is 1000 IU/mL. Therefore, dilutions are not informative for the ADVIA Centaur Zika IgM assay.

Results for WHO Dilutions (ADVIA Centaur Zika Ab)

WHO Standard 16/352 Dilution	Expected WHO Concentration (IU/mL)	Observed ADVIA Centaur Zika Ab Index
Neat	1000	12.32
1:2	500	6.72
1:4	250	3.89
1:8	125	2.40
1:16	62.50	1.42
1:32	31.25	0.90
1:64	15.63	0.53
1:128	7.81	0.35
Negative Basepool	0.00	0.13

b. Stability:

Stability studies have been performed to support the following claims:

Sample Stability:

The study data supports specimen stability at the following storage temperatures and storage times:

- Stored capped and upright at 2–8°C for up to 5 days
- Stored separated samples at room temperature for up to 24 hours
- Stored on the instrument system for up to 8 hours
- Stored at ≤ -20°C for up to 150 days
- No more than 3 freeze-thaw cycles

Reagent kit, Calibrators & Controls Stability:

Stability Claims for ADVIA Centaur Zika Ab/IgM Reagents, Calibrators, Controls

Stability Type	Claim
Zika Ab Reagent Shelf-Life Stability (2-8 °C)	12 months
Zika IgM Reagent Shelf-Life Stability (2-8 °C)	12 months
Zika Ab Calibrator Shelf-Life Stability (2-8 °C)	12 months
Zika IgM Calibrator Shelf-Life Stability (2-8 °C)	12 months
Zika Ab Control Shelf-Life Stability (2-8 °C)	12 months
Zika IgM Control Shelf-Life Stability (2-8 °C)	12 months
Zika Ab Reagent Onboard Stability (On System)	28 days
Zika IgM Reagent Onboard Stability (On System)	28 days
Zika Ab Reagent Onboard Stability (Calibration Interval)	14 days

Zika IgM Reagent Onboard Stability (Calibration Interval)	14 days
Zika Ab Calibrator Onboard Stability	8 hours
Zika IgM Calibrator Onboard Stability	8 hours
Zika Ab Control Onboard Stability	8 hours
Zika IgM Control Onboard Stability	8 hours
Zika Ab Calibrator Open Vial Stability	60 days
Zika IgM Calibrator Open Vial Stability	60 days
Zika Ab Control Open Vial Stability	60 days
Zika IgM Control Open Vial Stability	60 days

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   The assay standardization for the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays is based on agreement with known Zika positive samples. Assigned values of calibrators and controls are traceable to this standardization. The ADVIA Centaur Zika Ab assay has been standardized such that the clinical cutoff is set at 0.80 Index. The ADVIA Centaur Zika IgM assay has been standardized such that the clinical cutoff is set at 1.00 Index.

8. Class Specificity:
   An IgM blocking study was used to evaluate the potential of cross-reactivity to Zika IgG by the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays. A Zika IgG serial dilution study using a monoclonal antibody IgG specific to Zika NS1 was undertaken to determine the cross-reactivity of ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM to Zika-specific IgG.

   The results from the IgM blocking study indicate that while Zika IgG cross-reacts with ADVIA Centaur Zika Ab, ADVIA Centaur Zika IgM does not appear to bind human Zika IgG. The IgG serial dilution study showed that while some Zika IgG cross-reactivity is seen with ADVIA Centaur Zika Ab, the ADVIA Centaur Zika IgM assay does not cross-react with Zika specific IgG up to a concentration of 1 μg/mL.

9. Performance with FDA Zika Panel

   Performance of the ADVIA Centaur Zika test was evaluated by testing a panel of samples provided by the FDA. The FDA's panel consists of plasma samples from individuals infected with Zika, West Nile, or Dengue viruses at various stages of infection. Sample demographics and results were randomized and blinded to diagnostic developers to assess the proficiency of their tests. Performance was assessed from the subset of panel members for which a consensus of serostatus was established:

		ADVIA Centaur Zika test		
		Presumptive Zika Positive	**Negative for Antibodies to Zika Virus***	**Negative for IgM Antibodies to Zika Virus**
Zika IgM Consensus	**Positive (n=24)**	21	1	3
	Negative (n=12)	0	10	2

*Total anti-Zika antibodies
PPA= 21/24, 87.5%
NPA= 12/12, 100%

		ADVIA Centaur Zika test		
		Presumptive Zika Positive (False Positives)	**Negative for Antibodies to Zika Virus***	**Negative for IgM Antibodies to Zika Virus**
Cross-reactivity Evaluation	**West Nile** (n=11)**	0	11	0
	Dengue (n=10)**	0	6	4

*Total anti-Zika antibodies
**Note these were single bleeds that were positive for West Nile Virus or Dengue and negative for Zika.

This evaluation was performed using samples provided by Blood Systems Research Institute (BSRI, now Vitalant Research Institute) from a study supported by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health. The panel composition and consensus results are the responsibility of the FDA and do not necessarily represent the official views of BSRI, the NHLBI, or the National Institutes of Health.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   See section "C" below.

2. Matrix Comparison:

   The performance of the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays was evaluated using different matrices and sample collection tube types. Matched sample sets spanning the assay range for serum, EDTA plasma, and lithium heparin plasma used for the matrix comparison studies. For each matrix, twenty samples were prepared. Five (5) patient samples were spiked to make four (4) samples per patient (unspiked negative, high negative/borderline, low positive, mid positive). All the samples were run in singlicate. The

doses were calculated using a 2-point data calibration. Data were analyzed by Deming regression and results from plasma samples were compared to results of serum samples.

Results with ADVIA Centaur Zika AB assay:

Specimen (y)	Reference Specimen (x)	Regression Equation	Sample Interval	N[a]	r[b]
Lithium heparin (plasma)	Serum	y = 1.02x - 0.04	0.00–3.86	20	1.00
Potassium EDTA (plasma)	Serum	y = 0.98x - 0.01	0.00–3.67	20	1.00

[a] Number of samples tested.
[b] Correlation coefficient.

Results with ADVIA Centaur Zika IgM assay:

Specimen (y)	Reference Specimen (x)	Regression Equation	Sample Interval	N[a]	r[b]
Lithium heparin (plasma)	Serum	y = 1.06x + 0.00	0.00–5.44	20	1.00
Potassium EDTA (plasma)	Serum	y = 1.06x - 0.00	0.00–5.78	20	1.00

[a] Number of samples tested.
[b] Correlation coefficient.

C Clinical Studies:

1. Assay Performance with Zika-Positive Populations:

   a. Single-Draw Specimens:

   The performance of the ADVIA Centaur Zika test was evaluated using single-draw specimens from individuals who tested positive by PCR. A single blood draw was obtained from 49 individuals who tested positive for Zika virus by PCR. Samples were tested at three sites in accordance with the algorithm of the ADVIA Centaur Zika test. Results from the ADVIA Centaur Zika test were compared to the predicate device.

   Discordant results between ADVIA Centaur Zika test and the predicate device were further evaluated using Plaque Reduction Neutralization Tests (PRNT) for Zika virus and Dengue virus and the current CDC algorithm for the interpretation of Zika virus antibody test results.

   ADVIA Centaur Zika test was Reactive for 47 of the 49 confirmed-positive samples. ZIKV Detect 2.0 IgM Capture ELISA was Presumptive Zika Positive in all 49 samples.

Positive Percent Agreement with Predicate Device

Days After Symptom Onset	Predicate Device Negative			Predicate Device Positive		
	ADVIA Centaur Zika Test Reactive	ADVIA Centaur Zika Test Nonreactive	Negative % Agreement	ADVIA Centaur Zika Test Reactive	ADVIA Centaur Zika Test Nonreactive	Positive % Agreement
0-7	0	0	---	0	0	---
8-14	0	0	---	19	2	90.48%
15-28	0	0	---	15	0	100.00%
29-42	0	0	---	3	0	100.00%
43-56	0	0	---	1	0	100.00%
57-70	0	0	---	0	0	---
≥71	0	0	---	0	0	---
Variable*	0	0	---	9	0	100.00%
TOTAL	0	0	---	**47**	**2**	**95.92%**
TOTAL (≥ Day 8)	0	0	---	**47**	**2**	**95.92%**

* Specimens were collected between 4 to 8 weeks after symptom onset. However, the symptom onset is unknown.

b. Serial-Draw Specimens:

The performance of the ADVIA Centaur Zika test was evaluated using serial-draw specimens from individuals who tested positive by PCR. Eight serial blood draws (timing of draws unique to each patient) were obtained from 36 individuals who tested positive for Zika Virus by PCR methods. Samples were tested in singlicate by ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM. Performance of the ADVIA Centaur Zika test was compared against results obtained from testing with the predicate device.

Summary of ADVIA Centaur Zika Test Seroconversion Sensitivity

ADVIA Centaur Zika test Reactive at ***Same*** Bleed as predicate	27
ADVIA Centaur Zika test Reactive ***Later*** than predicate	4
ADVIA Centaur Zika test Reactive ***Earlier*** than predicate	5
NET (Earlier – Later Reactivity)	1
Total Reactive Samples (Out of 288 Total Samples)	249

The percent agreement of ADVIA Centaur Zika test to the predicate device was determined by stratifying the serial bleed samples into groups based on days after symptom onset.

Positive Percent Agreement with Predicate Device

Days After Symptom Onset	Predicate Negative			Predicate Positive		
	ADVIA Centaur Zika Test Reactive	ADVIA Centaur Zika Test Nonreactive	Negative % Agreement	ADVIA Centaur Zika Test Reactive	ADVIA Centaur Zika Test Nonreactive	Positive % Agreement
0-7	5	21	80.77%	7	4	63.64%
8-14	0	0	---	26	0	100.00%
15-28	1	0	0.00%	56	1	98.25%
29-42	3	0	0.00%	61	2	96.83%
43-56	3	0	0.00%	59	4	93.65%
57-70	5	0	0.00%	18	4	81.82%
≥71	0	0	---	5	3	62.50%
TOTAL	**17**	**21**	**55.26%**	**232**	**18**	**92.80%**
TOTAL (≥ Day 8)	**12**	**0**	**0.00%**	**225**	**14**	**94.14%**

The overall positive percent agreement was calculated by combining the results from the Single Bleed and Serial Draw studies.

Positive Percent Agreement with Predicate

Days After Symptom Onset	Predicate Negative			Predicate Positive		
	ADVIA Centaur Zika Test Reactive	ADVIA Centaur Zika Test Nonreactive	Negative % Agreement	ADVIA Centaur Zika Test Reactive	ADVIA Centaur Zika Test Nonreactive	Positive % Agreement
0-7	5	21	80.77%	7	4	63.64%
8-14	0	0	---	45	2	95.74%
15-28	1	0	0.00%	71	1	98.61%
29-42	3	0	0.00%	64	2	96.97%
43-56	3	0	0.00%	60	4	93.75%
57-70	5	0	0.00%	18	4	81.82%
≥71	0	0	---	5	3	62.50%
Variable	0	0	---	9	0	100.00%
TOTAL	**17**	**21**	**55.26%**	**279**	**20**	**93.31%**
TOTAL (≥ Day 8)	**12**	**0**	**0.00%**	**272**	**16**	**94.44%**

2. Assay Performance with Zika-Negative Populations:

The clinical specificity of the ADVIA Centaur Zika test was evaluated using specimens from individuals categorized as follows:

- Individuals from areas of low Zika virus prevalence (non-endemic areas)
  - Healthy blood donors
  - Pregnant women
  - Pediatrics
- Individuals from areas of high Zika virus prevalence (endemic areas)
  - Residents of endemic areas who are symptomatic
  - Residents of endemic areas who are asymptomatic
  - Travelers to endemic areas

Samples were tested at three sites in accordance with the ADVIA Centaur Zika test algorithm. The negative percent agreement of the ADVIA Centaur Zika test in the various specificity populations is presented in the following table.

Negative Percent Agreement with Predicate

Category	Samples Negative by Predicate	ADVIA Centaur Zika Test		
		Number Reactive	Number Nonreactive	Negative Percent Agreement
Traveler to Zika-Endemic Area	47	0	47	100.00%
Symptomatic Resident of Zika-Endemic Area	46	1	45	97.83%
Asymptomatic Resident of Zika-Endemic Area	262	19	243	92.75%
Healthy Donor from Non-Endemic Area	1365	0	1365	100.00%
Pregnant Donor from Non-Endemic Area	485	2	483	99.59%
Pediatric Donor from Non-Endemic Area	128	0	128	100.00%
All Endemic Area Specimens	355	20	335	94.37%
All Non-Endemic Area Specimens	1978	2	1976	99.90%
Total	**2333**	**22**	**2311**	**99.06%**

3. Pediatric Sample Spiking Study

Pediatric samples (ages ranged between 4 and 17) were spiked with samples from adults with known Zika IgM concentrations to demonstrate that the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays yield similar results with spiked pediatric samples compared to spiked adult samples.

Seven Zika IgM samples were used to spike pediatric and adult specimens. Each of the Zika IgM positive samples was used to spike up to three pediatric and adult specimens. Spiking was targeted between 1.00 and 1.50 Index as measured using the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays. Observed doses in both the spiked pediatric and adult samples were compared to the expected target doses for each sample.

The recovery patterns for spiked pediatric samples were similar, and statistically equivalent, to those observed for spiked adult samples. The study demonstrates that the pediatric sample matrix is unlikely to interfere with Zika IgM measurements by ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM.

An additional study evaluated five native pediatric samples from patients identified as having Zika virus infection. The samples, obtained from donors who ranged in age from 11 to 17, were tested with the ADVIA Centaur Zika Test and the predicate device. Four of the samples tested Presumptive Zika Positive by both assays and one sample tested Negative for Zika Antibodies and Presumptive Zika Positive by the predicate device.

D Expected Values/Reference Range:

The prevalence of Zika virus infection varies by geographic location.
In a population of 2018 volunteer blood donors, pregnant females and pediatric subjects from an area of low prevalence of Zika virus infection (mainland U.S.), 2016 (99.90%) samples were found to be nonreactive and 2 of these samples were Presumptive Zika Positive using the ADVIA Centaur Zika test.

In a population of 85 patients reactive for Zika IgM, 83 (97.65%) were found to be Presumptive Zika Positive using the ADVIA Centaur Zika test. Four of the five samples tested Presumptive Zika Positive while the fifth sample tested Negative for Zika antibodies by the ADVIA Centaur Zika test and Presumptive Zika Positive by the predicate device.

E Other Supportive Instrument Performance Characteristics Data:

Not applicable.

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.