Siemens Healthcare Diagnostics Inc.
Matthew Gee
Senior Manager, Regulatory Affairs
511 Benedict Avenue
Tarrytown, New York 10591

July 17, 2019

Re: K191578
Trade/Device Name: 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
Regulation Number: 21 CFR 866.3935
Regulation Name: Zika Virus Serological Reagents
Regulatory Class: Class II
Product Code: QFO, QCH
Dated: June 12, 2019
Received: June 14, 2019

Dear Matthew Gee:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal

statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*

K191578

Device Name
ADVIA Centaur Zika test

Indications for Use *(Describe)*

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 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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of 21 CFR 807.92 and the Safe Medical Device Act of 1990.

The assigned 510(k) Number is: K191578

1. Date Prepared

July 15, 2019

2. Applicant Information

Contact: Matthew Gee, M.Sc.
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3. Regulatory Information

Table 1. Regulatory Information for ADVIA Centaur Zika Test

Trade Name	ADVIA Centaur® Zika test
Model Numbers	ADVIA Centaur Zika Ab (100 tests): 11202473 ADVIA Centaur Zika IgM (50 tests): 11202471 ADVIA Centaur Zika Ab Quality Control: 11202474 ADVIA Centaur Zika IgM Quality Control: 11202472
Regulation Number	866.3935
Regulation Name	Zika Virus Serological Reagents
Regulation Definition	Zika virus serological reagents are devices that consist of antigens and antisera for the diagnosis of Zika virus infection in human clinical specimens from individuals that have signs and symptoms consistent with Zika virus infection and/or epidemiological risk factors. The device aids in the presumptive clinical diagnosis of Zika virus infection in conjunction with other clinical and laboratory findings.
Product Code	QFO
Regulatory Class	Class II
Review Panel	Microbiology (83)

4. Predicate Device Information

Predicate Device Name: ZIKV Detect 2.0 IgM Capture ELISA

De Novo Request Number: DEN180069

5. 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 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.

6. Device Description

The ADVIA Centaur Zika test consists of the components described in the following table.

Component	Volume	Ingredients
ADVIA Centaur Zika Ab Primary Reagent ReadyPack (included in Zika Ab assay kit)		
ADVIA Centaur Zika Ab Lite Reagent	5.0 mL/pack (x1)	NS1 Antigen labeled with acridinium ester (0.4 µg/mL) in buffered saline with surfactant, blockers, sodium azide (< 0.1%) and preservatives
ADVIA Centaur Zika Ab Solid Phase Reagent	25.0 mL/pack (x1)	Streptavidin-coated paramagnetic microparticles preformed with biotinylated anti-human IgM antibody (~0.1 mg/mL) in buffered saline with surfactant, blockers, sodium azide (< 0.1%) and preservatives
ADVIA Centaur Zika Ab Ancillary Well Reagent	5.0 mL/pack (x1)	Buffered saline with surfactant, blockers, sodium azide (< 0.1%) and preservatives
ADVIA Centaur Zika Ab Calibrators (included in Zika Ab assay kit)		
ADVIA Centaur Zika Ab High Calibrator	1.0 mL/vial (x1)	Processed human plasma negative for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.
ADVIA Centaur Zika Ab Low Calibrator	1.0 mL/vial (x1)	Processed human plasma positive for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.

Component	Volume	Ingredients
ADVIA Centaur Zika Ab Controls (included in Zika Ab QC kit)		
ADVIA Centaur Zika Ab Negative Control	1.0 mL/vial (x2)	Processed human plasma negative for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.
ADVIA Centaur Zika Ab Low Calibrator	1.0 mL/vial (x2)	Processed human plasma positive for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.
ADVIA Centaur Zika IgM Primary Reagent ReadyPack (included in Zika IgM assay kit)		
ADVIA Centaur Zika IgM Lite Reagent	2.5 mL/pack (x1)	NS1 Antigen labeled with acridinium ester (0.4 µg/mL) in buffered saline with surfactant, blockers, sodium azide (< 0.1%) and preservatives
ADVIA Centaur Zika IgM Solid Phase Reagent	12.5 mL/pack (x1)	Streptavidin-coated paramagnetic microparticles preformed with biotinylated anti-human IgM antibody (~0.1 mg/mL) in buffered saline with surfactant, blockers, sodium azide (< 0.1%) and preservatives
ADVIA Centaur Zika IgM Ancillary Well Reagent	2.5 mL/pack (x1)	Buffered saline with surfactant, blockers, sodium azide (< 0.1%) and preservatives
ADVIA Centaur Zika IgM Calibrators (included in Zika IgM assay kit)		
ADVIA Centaur Zika IgM High Calibrator	1.0 mL/vial (x1)	Processed human plasma negative for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.
ADVIA Centaur Zika IgM Low Calibrator	1.0 mL/vial (x1)	Processed human plasma positive for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.
ADVIA Centaur Zika IgM Controls (included in Zika IgM QC kit)		
ADVIA Centaur Zika IgM Negative Control	1.0 mL/vial (x2)	Processed human plasma negative for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.
ADVIA Centaur Zika IgM Low Calibrator	1.0 mL/vial (x2)	Processed human plasma positive for Zika IgM antibodies with sodium azide (< 0.1%) and preservatives.

7. Purpose of the Submission

The purpose of this premarket notification is to submit a new device (ADVIA Centaur Zika test) to FDA for consideration for clearance.

8. Comparison of Candidate Device and Predicate Device

Table 2. Comparison of ADVIA Centaur Zika Test to Predicate

Item	ADVIA Centaur Zika Test (Candidate Device)	ZIKV Detect 2.0 IgM Capture ELISA (Predicate Device)
Intended 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 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.	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, 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.
Methodology	Antibody capture immunoassay using chemiluminescence detection	ELISA
Detection Label	Acridinium ester	Horseradish peroxidase
Calibration	2-point calibration	N/A
Analyte	Zika virus IgM antibodies	Same
Specimen Type	Serum and Plasma (EDTA, LiHep)	Serum
Measurement Type	Qualitative	Same
Automation	Fully automated	Manual
Instruments	ADVIA Centaur XP ADVIA Centaur XPT	N/A
Incubation Time	ZikaAb Only: 36.25 minutes Full Algorithm: 108.75 minutes	~200 Minutes

Table 2. Comparison of ADVIA Centaur Zika Test to Predicate

Item	ADVIA Centaur Zika Test (Candidate Device)	ZIKV Detect 2.0 IgM Capture ELISA (Predicate Device)
Required Washes	ZikaAb Only: 2 washes Full Algorithm: 6 washes	32 (4 x 6) washes
Interpretations	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 OD_{450} ≥ Threshold Zika Ag OD_{450} **AND** Zika ISR value > 1.90: Presumptive Zika Positive Initial: Zika Ag OD_{450} ≥ Threshold Zika Ag OD_{450} **AND** 1.50 ≤ Zika ISR ≤ 1.90: Retest in duplicate Retest: Zika Ag OD_{450} ≥ Threshold Zika Ag OD_{450} **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

9. Standard/Guidance Document References

The following recognized standards from Clinical Laboratory Standards Institute (CLSI) were used as a basis of the study procedures described in this submission:

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Third Edition (CLSI EP05-A3, 2014; Recognition No. 7-251)
- Interference Testing in Clinical Chemistry. 3rd Edition (CLSI EP07-A3, 2018; Recognition No. 7-275)
- Supplemental Tables for Interference Testing in Clinical Chemistry. 1st Edition (CLSI EP37, 2018; Recognition No. 7-284)
- Medical devices – Application of risk management to medical devices (ANSI/AAMI/ISO 14971:2007/(R)2010; Recognition No. 5-40)

10. Performance Characteristics

10.1 Precision/Reproducibility

Precision of the ADVIA Centaur Zika Ab assay was evaluated according to the CLSI protocol EP05-A3. A two-member panel and controls were assayed in 2 replicates twice a day for 20 days (n = 80 for each sample). The following representative results were obtained:

Sample	Mean (Index)	Repeatability		Within-Lab	
		SD	%CV	SD	%CV
Negative Control	0.05	0.03	---	0.04	---
Positive Control	3.26	0.06	2.0	0.13	3.9
Plasma Pool 1	0.63	0.03	4.0	0.03	5.0
Plasma Pool 2	1.98	0.05	2.6	0.08	4.3

Precision of the ADVIA Centaur Zika IgM assay was evaluated according to the CLSI protocol EP05-A3. A two-member panel and controls were assayed in 2 replicates twice a day for 20 days (n = 80 for each sample). The following representative results were obtained:

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

Multi-site precision of the ADVIA Centaur Zika Ab assay was evaluated on the ADVIA Centaur XP system. A five-member panel, including negative samples, and low and high positive samples, was assayed in 3 replicates twice a day for 5 days at 3 sites with 3 different lots of ADVIA Centaur Zika Ab reagents (n=270 for each sample). The following results were obtained:

Sample	Mean (Index)	Repeatability		Between-Run		Between-Day		Between-Lot		Between-Site		Reproducibility	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Pool 1	0.05	0.03	---	0.02	---	0.03	---	0.00	---	0.00	---	0.05	---
Pool 2	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
Pool 3	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
Pool 4	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
Pool 5	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

Multi-site precision of the ADVIA Centaur Zika IgM assay was evaluated on the ADVIA Centaur XP system. A five-member panel, including negative samples, and low and high positive samples, was assayed in 3 replicates twice a day for 5 days at 3 sites with 3 different lots of ADVIA Centaur Zika IgM reagents (n=270 for each sample). The following results were obtained:

Sample	Mean (Index)	Repeatability		Between-Run		Between-Day		Between-Lot		Between-Site		Reproducibility	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Pool 1	0.09	0.07	---	0.04	---	0.02	---	0.04	---	0.04	---	0.10	---
Pool 2	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
Pool 3	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
Pool 4	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
Pool 5	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

10.2 Linearity / Assay Reportable Range

Linearity is not applicable to the ADVIA Centaur Zika test. The ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays are qualitative methods. The reportable range for the assays is 0.00 to 10.00 Index.

10.3 Detection Limits

Detection Limits (Limit of Blank, Limit of Detection, Limit of Quantitative) are not applicable to the ADVIA Centaur Zika test. The ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays are qualitative methods.

10.4 Analytical Sensitivity / Assay Cut-off

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 reagent 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 reagent that corresponds to the cut-off value of 1.00 Index for ADVIA Centaur Zika IgM is 1000 IU/mL.

10.5 Analytical Specificity / Cross-Reactivity and Interference

The ADVIA Centaur Zika test was evaluated for potential cross-reactivity with specimens containing IgM antibodies against other flavivirus specimens and disease state specimens. The following results were obtained using the ADVIA Centaur Zika test.

Disease State	Number of Samples Tested	ADVIA Centaur Zika Test Nonreactive Samples	ADVIA Centaur Zika Test Reactive Samples	Cross-Reactivity
ANA	19	19	0	0.00%
Adenovirus	1	1	0	0.00%
Borrelia sp. (Lyme)	11	11	0	0.00%
Chikungunya Virus	21	21	0	0.00%
CMV	12	12	0	0.00%
Dengue Virus	41	39	2	4.88%
EBV	11	11	0	0.00%
HAMA	15	15	0	0.00%
HBV	11	11	0	0.00%
HCV	15	15	0	0.00%
HSV-1/2	26	26	0	0.00%
Leptospira	16	16	0	0.00%
Malaria	10	8	2	20.00%
Parvovirus B19	16	16	0	0.00%
RF	21	21	0	0.00%
Rubella Virus	10	10	0	0.00%
Toxoplasma gondii	16	16	0	0.00%
Syphilis	10	10	0	0.00%
VZV	15	15	0	0.00%
WNV	23	23	0	0.00%
Yellow Fever Immunization	21	20	1	4.76%
Total	341	336	5	1.47%

The ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays were evaluated for potential interference with endogenous substances Testing was performed separately with both the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays in accordance with CLSI Documents EP07-A3 and EP37.

Endogenous Substance	Highest Concentration Tested with ≤10% Interference
Hemoglobin	1000 mg/dL
Triglycerides (Intralipid)	3000 mg/dL
Protein	12 g/dL
Conjugated Bilirubin	40 mg/dL
Unconjugated Bilirubin	60 mg/dL
Biotin	3500 ng/mL
Cholesterol	500 mg/dL

10.6 Comparison Studies

10.6.1 Method Comparison with Predicate Device

See Clinical Studies section.

10.6.2 Matrix Comparison

Specimen equivalency was determined using the Deming linear regression model in accordance with CLSI Document EP09-A3. No significant difference was observed between tube types.

The following results were obtained using the ADVIA Centaur Zika Ab assay:

Specimen (y)	Reference Specimen (x)	Regression Equation	Sample Interval	N	Correlation Coefficient
LiHep Plasma	Serum	y = 1.02x - 0.04	0.00–3.86	20	1.00
EDTA Plasma	Serum	y = 0.98x - 0.01	0.00–3.67	20	1.00

The following results were obtained using the ADVIA Centaur Zika IgM assay:

Specimen (y)	Reference Specimen (x)	Regression Equation	Sample Interval	N	Correlation Coefficient
LiHep Plasma	Serum	y = 1.06x + 0.00	0.00–5.44	20	1.00
EDTA Plasma	Serum	y = 1.06x - 0.00	0.00–5.78	20	1.00

10.7 FDA Zika Performance 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 an established consensus of sero-status was established:

Zika IgM Consensus Result	Total Samples	ADVIA Centaur Zika Test Presumptive Zika Positive	ADVIA Centaur Zika Test Negative*	% Agreement
Positive	24	21	3	PPA = 87.50% (21/24)
Negative	12	0	12	NPA = 100.00% (12/12)

* Includes samples that were nonreactive with either ADVIA Centaur Zika Ab or ADVIA Centaur Zika IgM.

Results from the cross-reactivity evaluation are shown below:

Disease State*	Total Samples	ADVIA Centaur Zika Test Presumptive Zika Positive	ADVIA Centaur Zika Test Negative*	% Cross-Reactivity
West Nile Virus	11	0	11	0.00% (0/11)
Dengue Virus	10	0	10	0.00% (0/10)

* These were single bleeds that were positive for West Nile Virus or Dengue virus and negative for Zika virus.

** Includes samples that were nonreactive with either ADVIA Centaur Zika Ab or ADVIA Centaur Zika IgM.

This evaluation was performed using samples provided by Blood Systems Research Institute (BSRI, now Vitalant Research Institute) from a study supported by 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.

10.8 Clinical Studies

Specimens from patients infected with Zika virus and uninfected individuals were collected from areas of low and high Zika virus prevalence. Testing was performed at 3 sites, with samples distributed approximately evenly across sites. Samples were tested with the ADVIA Centaur Zika test and a commercially-available Zika IgM assay.

10.8.1 Seroconversion Sensitivity

Eight (8) serial draws from 36 Zika PCR-positive patients from the Dominican Republic were prospectively collected and evaluated using the ADVIA Centaur Zika test and the ZIKV Detect 2.0 IgM Capture ELISA. The following seroconversion sensitivity results were obtained:

Series ID	First Reactive (Presumptive Zika Positive) Bleed Number*			Number of Reactive (Presumptive Zika Positive) Bleeds	
	ZIKV Detect 2.0 IgM Capture ELISA	ADVIA Centaur Zika Test	Difference in Bleed Numbers**	ZIKV Detect 2.0 IgM Capture ELISA	ADVIA Centaur Zika Test
TDS0067	1 (Day 3)	2 (Day 27)	-1	8	4
TDS0123***	3 (Day 13)	3 (Day 13)	0	6	6
TDS0173	2 (Day 10)	2 (Day 10)	0	7	7
TDS0220	1 (Day 6)	1 (Day 6)	0	8	8
TDS0246	2 (Day 19)	1 (Day 5)	+1	7	8

Series ID	First Reactive (Presumptive Zika Positive) Bleed Number*			Number of Reactive (Presumptive Zika Positive) Bleeds	
	ZIKV Detect 2.0 IgM Capture ELISA	ADVIA Centaur Zika Test	Difference in Bleed Numbers**	ZIKV Detect 2.0 IgM Capture ELISA	ADVIA Centaur Zika Test
TDS0249	2 (Day 20)	1 (Day 5)	+1	7	8
TDS0257	2 (Day 19)	2 (Day 19)	0	6	7
TDS0263	2 (Day 18)	2 (Day 18)	0	7	7
TDS0271	1 (Day 4)	2 (Day 10)	-1	8	4
TDS0279	2 (Day 11)	2 (Day 11)	0	7	7
TDS0281	2 (Day 14)	2 (Day 14)	0	7	7
TDS0282	1 (Day 2)	2 (Day 13)	-1	8	7
TDS0284	2 (Day 17)	2 (Day 17)	0	7	7
TDS0292	2 (Day 13)	1 (Day 4)	+1	6	8
TDS0296	2 (Day 9)	2 (Day 9)	0	7	7
TDS0306	1 (Day 4)	1 (Day 4)	0	8	8
TDS0310	2 (Day 8)	2 (Day 8)	0	7	7
TDS0314	1 (Day 6)	1 (Day 6)	0	8	8
TDS0322	1 (Day 5)	1 (Day 5)	0	8	8
TDS0328	2 (Day 10)	2 (Day 10)	0	7	2
TDS0341	2 (Day 10)	2 (Day 10)	0	7	5
TDS0343	2 (Day 18)	2 (Day 18)	0	7	7
TDS0345	2 (Day 10)	2 (Day 10)	0	5	7
TDS0362	2 (Day 25)	2 (Day 25)	0	2	7
TDS0372	2 (Day 9)	2 (Day 9)	0	7	7
TDS0376	2 (Day 14)	2 (Day 14)	0	7	7
TDS0379	1 (Day 6)	1 (Day 6)	0	8	7
TDS0396	1 (Day 2)	1 (Day 2)	0	8	8
TDS0421	2 (Day 9)	1 (Day 2)	+1	7	8
TDS0422	1 (Day 8)	1 (Day 8)	0	7	8
TDS0437	2 (Day 12)	2 (Day 12)	0	7	7
TDS0440	2 (Day 12)	2 (Day 12)	0	7	7
TDS0458	2 (Day 12)	2 (Day 12)	0	7	7
TDS0468	2 (Day 14)	1 (Day 6)	+1	5	8
TDS0480	2 (Day 12)	2 (Day 12)	0	7	7
TDS0499	1 (Day 5)	2 (Day 12)	-1	8	7
Total Reactive Bleeds				**250**	**249**

* The number of days is in relation to the initial draw date.

** The difference in bleed numbers is relative to the comparator assay. For example, a +1 means that the comparator assay required 1 additional bleed before reactivity was determined as compared to the time-point when the ADVIA Centaur assay confirmed positive.

*** There was insufficient volume for testing with ZIKV Detect 2.0 IgM Capture ELISA for Bleed 3 of TDS0123. This analysis assumes that ZIKV Detect 2.0 IgM Capture ELISA was Presumptive Zika Positive at this Bleed.

10.8.2 Agreement in Zika-Positive Populations

Single draws from 49 Zika PCR-positive patients from the Dominican Republic and mainland U.S. were prospectively collected and evaluated using the ADVIA Centaur Zika test and the ZIKV Detect 2.0 IgM Capture ELISA. The positive percent agreement of the ADVIA Centaur Zika test in this population was 95.92% (47/49).

Eight (8) serial draws from 36 Zika PCR-positive patients from the Dominican Republic were prospectively collected and evaluated using the ADVIA Centaur Zika test and the ZIKV Detect 2.0 IgM Capture ELISA. The positive percent agreement of the ADVIA Centaur Zika test in this population for specimens collected at 8 days or later after symptom onset was 94.14% (225/239).

The positive percent agreement of the ADVIA Centaur Zika test in the combined single draw and serial bleed population for specimens collected at 8 days or later after symptom onset was 94.44% (272/288).

Days After Symptom Onset	ZIKV Detect 2.0 IgM Capture ELISA Negative			ZIKV Detect 2.0 IgM Capture ELISA 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%**

* This timeframe is not supported. IgM antibodies to Zika virus develop during the first week of illness.

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

10.8.3 Agreement in Zika-Negative Populations

A population of residents and travelers to areas of high prevalence for Zika virus infection (Dominican Republic, Honduras and Puerto Rico) that were negative by the ZIKV Detect 2.0 IgM Capture ELISA were tested using the ADVIA Centaur Zika test. The categories included residents with symptoms associated with Zika infection but were PCR-negative for Zika virus (N = 46), asymptomatic residents (N = 262) and travelers (N = 47).

The negative percent agreement of the ADVIA Centaur Zika test in this population was 94.37% (335/355).

A population of residents from an area of low prevalence of Zika virus infection (mainland U.S.) that were negative by the ZIKV Detect 2.0 IgM Capture ELISA were tested using the ADVIA Centaur Zika test. The categories included apparently healthy male and female blood donors (N = 1365), pregnant females (N = 485), and pediatric subjects 2 to 21 years

of age (N = 128). The negative percent agreement of the ADVIA Centaur Zika test in this population was 99.90% (1976/1978).

The negative percent agreement of the ADVIA Centaur Zika test in the combined non-endemic and endemic population was 99.06% (2311/2333).

Category	ADVIA Centaur Zika Test Result			
	Nonreactive	Reactive	Total	Negative Percent Agreement
Endemic Area Travelers	47	0	47	100.00% (47/47)
Endemic Area Symptomatic Residents	45	1	46	97.83% (45/46)
Endemic Area Asymptomatic Residents	243	19	262	92.75% (243/262)
Non-Endemic Healthy Blood Donors	1365	0	1365	100.00% (1365/1365)
Non-Endemic Pregnant Women	483	2	485	99.59% (483/485)
Non-Endemic Pediatrics (2-21 years)	128	0	128	100.00% (128/128)
Total Endemic Population	**335**	**20**	**355**	**94.37% (335/355)**
Total Non-Endemic Population	**1976**	**2**	**1978**	**99.90% (1976/1978)**
Total	**2311**	**22**	**2333**	**99.06% (2311/2333)**

10.9 Traceability

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.

10.10 Stability

The onboard stability of the ADVIA Centaur ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM reagents on ADVIA Centaur XP and ADVIA Centaur XPT systems is 28 days with a calibration interval of 14 days.

The onboard stability of the ADVIA Centaur ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM calibrators and controls on ADVIA Centaur XP and ADVIA Centaur XPT systems is 8 hours.

The open vial stability of the ADVIA Centaur ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM calibrators and controls is 60 days.

The reagents, calibrators and controls are stable until the date printed on the box label when stored at 2-8°C.

11. Conclusions

The ADVIA Centaur Zika test is substantially equivalent in principle and performance to the currently-marketed predicate device, the ZIKV Detect 2.0 IgM Capture ELISA, granted De Novo classification under DEN180069.